Use of exclusive enteral nutrition in children and adolescents with Crohn's disease in Auckland, New Zealand: clinical practice and outcomes over a 10-year period

A mixed-methods study

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Abstract

Background

In 2014 the Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline (IBDCG) was introduced, outlining exclusive enteral nutrition (EEN) as the first-line induction therapy in children with newly diagnosed Crohn's disease (CD). The aim of this thesis was to review disease remission and clinical outcomes at Starship Child Health (SCH) before and after IBDCG implementation to determine if modifications are required to improve outcomes, and to explore patient, whānau and health care professional (HCP) views and experience of the guideline.

Methods

A mixed-methods approach was used. A retrospective medical note audit of children diagnosed with CD between June 2010 and July 2020 was completed. Patients were grouped into those diagnosed before January 2015 (pre-2015) and after January 2015 (post-2015). Demographics, disease characteristics, anthropometry, biochemistry, medications, and HCP contacts were collected at diagnosis, weeks 8, 13, 26, and 52. Semi-structured interviews were conducted with patients and their whānau and HCPs to determine the barriers and facilitators to EEN and solid food reintroduction. Thematic analysis was conducted.

Results

Ninety-one children met the inclusion criteria: pre-2015, *n*=40 (median age 12.3 years) and post-2015, *n*=51 (median age 11.9 years). Following induction therapy, 77.3% and 26.9% of children were in remission (p=0.001), and after 52 weeks, 84.6% and 43.3% of children were in remission (pre-2015 and post-2015, respectively; p=0.003). Albumin was significantly different at diagnosis and across the follow-up period between the groups (p≤0.001). Interviews with patients and whānau (*n*=10) revealed three major themes 1) a difficult and emotional time, 2) food confusion, and 3) support, with sub-themes clinical support and social support. Interviews with HCPs (*n*=7) revealed a single theme: a multidisciplinary team is needed.

Conclusion

Implementing the IBDCG has not improved outcomes in children with CD managed by SCH. Modifications to current practice and the IBDCG are recommended, including support groups, a dedicated nurse specialist and dietetic support beyond EEN.

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Glossary

ADHB	Auckland District Health Board
anti-TNF	Anti-tumour necrosis factor
BMI	Body mass index
CD	Crohn’s disease
CF	Consent form
CRP	C-reactive protein
CS	Corticosteroids
ECCO-ESPGHAN	European Crohn's and Colitis Organization – European Society for Paediatric Gastroenterology, Hepatology and Nutrition
EEN	Exclusive enteral nutrition
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology, and Nutrition
ESR	Erythrocyte sedimentation rate
FC	Faecal calprotectin
FODMAP	Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
GI	Gastrointestinal
GP	General practitioner
HCP	Health care professional
IBD	Inflammatory bowel disease
IBDCG	Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline
IBD-NS	Inflammatory bowel disease nurse specialist
IBD-U	Inflammatory bowel disease unclassified
IQR	Interquartile range
MDT	Multidisciplinary team
MH	Mucosal healing
mod-PCDAI	Modified paediatric Crohn’s disease activity index
NHI	National health index numbers
NZ	New Zealand
PCDAI	Paediatric Crohn’s disease activity index
PGA	Physician global assessment

PIS	Participant information sheet
post-2015	Patients diagnosed after January 2015
pre-2015	Patients diagnosed before January 2015
QoL	Quality of life
RCT	Randomised controlled trial
SCH	Starship Child Health
SD	Standard deviation
SES-CD	Simple endoscopic score for Crohn's disease
UC	Ulcerative colitis

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction to inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of chronic conditions characterised by inflammation of the mucosal lining in the gastrointestinal (GI) tract, which follows a pattern of relapse and remission (1-3). IBDs are predominantly made up of Crohn's disease (CD) and Ulcerative Colitis (UC), with a third classification IBD-unclassified (IBD-U), used where there is an inability to distinguish between CD and UC (4). CD can involve any part of the GI tract from the mouth to the anus (the rectum is rarely involved), is transmural and typically involves various portions of the GI tract in a discontinuous fashion (**Table 1.1**) (2,3,5). CD is a progressive disease; therefore can develop from simple GI inflammation and ulceration to stenosing or penetrating disease over time, typically developing complications including fistulas, strictures, bowel obstruction, and abscesses (1,2,6,7).

Table 1.1 | Signs, symptoms and pathological characteristics of Crohn's disease (1-6,8,9)

Signs and symptoms	Gastrointestinal symptoms that are persistent or recurrent, such as: Diarrhoea, abdominal pain, weight loss, anorexia, growth failure, fever, rectal bleeding, poor appetite, malaise, fatigue, and anaemia.
Laboratory findings	Decreased haemoglobin, elevated white cell and platelet counts, low serum albumin, raised faecal markers of inflammation, e.g., faecal calprotectin, raised inflammatory markers, e.g., C-reactive protein, Erythrocyte Sedimentation Rate
Endoscopic findings	Inflammation is discontinuous with intervening ulcers and normalcy, strictures, stenosis, fistulas, cobblestone appearance, and skip lesions.
Histologic findings	Transmural and submucosal inflammation, deep ulceration, patchy distribution, granuloma, chronic ileitis/colitis, crypt distortion and abscesses.
Radiologic findings	Discontinuous or segmented ulceration that is deep and has a submucosal extension, fissures, strictures, fistulas, rigid stenotic segments, sinus tracts, and submucosal fibrosis.
Intestinal complications	Strictures, fistulas, stenosis, cancer, fissures, abscesses, and obstruction.

Typically more CD than UC is diagnosed during childhood and adolescence; however, adult-onset IBD predominates UC (10-12). CD can be diagnosed at any age; however, up to 25% of patients are diagnosed during childhood (i.e., before 18 years of age) (5,6,12), with a large proportion of diagnoses occurring during puberty and the pubertal growth spurt (13), and peaking in in incidence between 20 and 30 years of age (10,11,14). In paediatric CD, more males are diagnosed than females (1.2-2.5:1), which is in contrast to adult CD, where fewer males are diagnosed compared to females (0.57-0.98:1) (10-12).

1.1.1 Epidemiology of inflammatory bowel disease

Incidence and prevalence of IBD vary by region around the world, and over the last few decades, the incidence has risen in all age groups (14). Globally, the incidence of paediatric CD is increasing in both developed and developing nations (15); however, accurate population-based data is lacking. Recent

population-based comparison data has revealed that there has been a rapid rise in incidence in the East, whilst incidence is plateauing in the West (14). Environmental factors are suggested to play a significant role in IBD incidence, particularly in developing nations where industrialisation and the western lifestyle appear to be linked to its rising incidence (15,16).

Global incidence rates for CD range from 0.2 to 13.9 in every 100,000 children (15), with most statistics originating from North America and Europe; however, the rates vary across these regions (14). Incidence rates in North America range from 0.66 to 13.9 in every 100,000 children (Texas, United States and Quebec, Canada, respectively), and in Europe, from 0.2 in every 100,000 children in Copenhagen County, Denmark, to 12.4 in every 100,000 children in Corsica, France (15). In New Zealand (NZ), a substantial increase in paediatric IBD incidence is reported in Canterbury, where the region has experienced a 4-fold increase from 2.88 (1996) to 13.06 (2015) in every 100,000 children (17). NZ-wide, CD diagnoses make up approximately two-thirds of all IBD cases annually (18). In 2015, the incidence of CD in NZ was 3.5 in every 100,000 children under 16 years of age (18), which is low compared to countries such as Canada and France.

IBD is a chronic disease with fairly early-onset and low mortality; therefore, the prevalence increases as the population ages (14). Globally, the prevalence of CD ranges, with higher rates seen in Europe and North America. Prevalence rates in Europe range from 8.2 (East Denmark) to 60 (Hungary) in every 100,000 children (19), and in America are up to 58 in every 100,000 children (16). In NZ, the point prevalence of paediatric IBD was 21.7 in every 100,000 children, and CD was 16.5 in every 100,000 children (30/6/2015); however, the prevalence rates of IBD in NZ vary by region (20). The Bay of Plenty has the lowest prevalence, and Marlborough has the highest prevalence (1.5 and 57.9 in every 100,000 children, respectively) (20). In the Auckland region, IBD prevalence is 19.9 in every 100,000 children, lower than the national average (20). A larger number of boys are affected by CD compared to girls (1.8:1), and Māori and Pacific children are underrepresented in IBD statistics (**Table 1.2**), with lower rates of CD diagnoses compared to the general population (20).

Table 1.2 | Ethnic proportion of New Zealand paediatric inflammatory bowel disease population compared to the New Zealand Census data (20)

Prioritised ethnicity	IBD 2015	Census 2013
European	86.8%	74%
Māori	4.2%	15%
Asian	9.9%	12%
Pacific	1.4%	7%
Middle Eastern, Latin American and African	1.4%	1%

1.1.2 Development of Crohn's disease

Disease aetiology and pathophysiology of CD are not completely understood; however, it is thought that interactions between the environment, the host's genetic susceptibility, immune-mediated tissue injury, and the role of intestinal microflora are key mediators (1,3,7,13). Genome-wide association studies have identified several genes/loci that contribute to IBD susceptibility (3,10,21,22). These genes are involved in immune homeostasis, as they code for proteins involved in mucosal barrier integrity, autophagy, and adaptive and innate immunity (3). However, genetic factors are only estimated to contribute between 30% and 40% to CD development (23), making environmental elements major influences on CD risk.

There is a growing evidence-base that changes in gut microbiota may be an important factor in the development of CD (9,24). Reduced diversity, altered composition, and changes to the epithelial barrier function commonly caused by antibiotic exposure or dietary intake are observed in patients with CD (3,24,25). When combined with genetic predisposition, alterations in gut microbiota and a dysregulated immune response can lead to the development of chronic inflammation and, ultimately, CD (3). Over time, sanitation and environmental hygiene have improved, leading to the 'hygiene hypothesis', whereby in order to establish and maintain the commensal microbiome, appropriate microbial exposures are required (26). It is proposed that less exposure to environmental antigens has altered immune cell balance, which then favours the development of autoimmune diseases such as IBD (14). Environmental factors reported to reduce the risk of CD include childhood contact with pets or farm animals, home-sharing, bed-sharing (27) and Helicobacter pylori infection (28).

1.1.2.1 The role of genetics in the development of Crohn's disease

Genetics plays a clear role in paediatric IBD, with familial links in 19% to 41% of cases compared to 5% to 10% in adult IBD, and is a strong predictor of CD diagnosis before 11 years of age (3). Patients diagnosed with IBD early in their lives show an increased prevalence of familial links and less influence from environmental factors and gut microbiota, whereas older patients have had more exposure to environmental modifiers; therefore, their influence on disease development is more significant (**Figure 1.1**) (10).

1.1.2.2 The role of diet in the development of Crohn's disease

The role the diet plays in the development of CD remains unclear due to limited and conflicting evidence (29,30). In a 2011 systematic review of 2,609 IBD patients (1,269 CD patients) and more than 4,000 controls, a diet high in total fats, polyunsaturated fatty acids, omega-6 fatty acids, and meat conferred an increased risk of CD, whilst dietary intakes high in fruit and fibre conferred a decreased

risk of CD (31). At this time, only one of the nineteen studies investigating pre-illness diet was in paediatric CD patients.

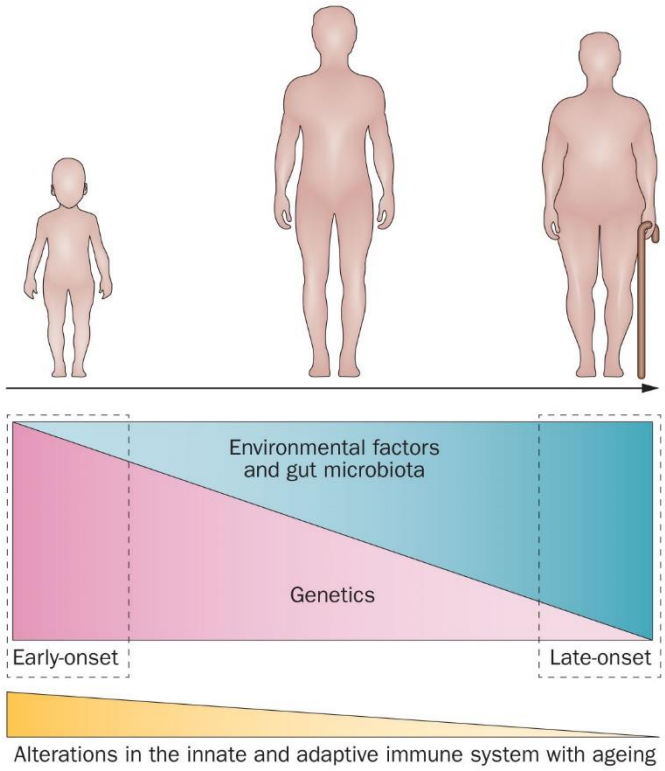

Figure 1.1 | Age differences in genetic and environmental factors and their contribution to the development of inflammatory bowel disease (10)

Reprinted by permission from Springer Nature: Nature. Nature Reviews Gastroenterology & Hepatology. IBD across the age spectrum—is it the same disease? Ruel J, Ruane D, Mehandru S, Gower-Rousseau C, Colombel J. Macmillan Publishers Limited (2014).

Few studies have investigated diet composition and the development of CD in paediatric populations (**Table 1.3**). Data suggests that higher intakes of fruits and vegetables, omega-3 fats, and fish have a protective effect, whilst high soft drink and white bread intake confer an increased risk of developing CD (32-35). A western dietary pattern (e.g., meats, fatty foods, desserts, fast food and snacks) was positively associated with CD development in girls, while a prudent dietary pattern (e.g., vegetables, fruits, olive oil, grains, dairy products, eggs, fish, dark bread and nuts) was inversely associated with CD development in both genders (34). Although paediatric data is limited, similar relationships are observed in adult populations, where dietary intakes high in fruits and fibre may be protective of CD development (31).

Table 1.3 | Studies investigating dietary factors associated with the development of Crohn's disease in children and adolescents

Author	Study design	Population	Age	Outcomes	Conclusions
Gilat *et al.*, 1987 (32)	International case-control study; 14 centres in 9 countries (USA, Canada, Israel, Sweden, Italy, Denmark, UK, Holland, France)	499 IBD; 302 CD, 197 UC cases (251 male, 248 female) 998 matched controls	20.0±5.2 y. [a] at time of study (Disease started before age 20y.)	Cases with CD consumed fewer vegetables and fruits than the controls Low consumption (0 and <1/day) vs high consumption (1-3 and >4/day) OR=0.58 (95%CI 0.37-0.91 p<0.001) Cases with CD consumed less wholemeal bread (p<0.001) and oat cereals (p<0.01) than controls	Children that consumed high quantities of fruits and vegetables were 42% less likely to develop CD than those with low intakes.
Amre *et al.*, 2007 (33)	Case-control study; 3 paediatric gastroenterology clinics across Canada	130 CD cases (77 male, 53 female) 202 controls (90 male, 112 female)	14.2±2.7 y. [a] at diagnosis	Highest compared to lowest intake of: Vegetables OR=0.69 (95%CI 0.33-1.44 p=0.03) Fruit OR=0.49 (95%CI 0.25-0.96 p=0.02) Fish OR=0.46 (95%CI 0.20-1.06 p=0.02) Consumption of long-chain ω-3 OR=0.44 (95%CI 0.19-1.0 p<0.001) Higher ω-3:ω-6 long-chain fatty acids OR=0.32 (95%CI 0.14-0.71 p=0.02)	Comparing the highest to the lowest categories of intake, children consuming higher amounts of vegetables, fruits, and fish had a lower risk of developing CD (31%, 51%, and 54%, respectively). Higher consumption of ω-3 and a higher ratio of ω-3 to ω-6 were associated with 56%, and 68% decreased risk of CD, respectively.
D'Souza *et al.*, 2008 (34)	Case-control study; 3 hospitals across Canada	149 CD cases (91 male, 58 female) 251 controls (120 male, 131 female)	13.3±2.3 y. [a] at diagnosis	Comparing highest versus lowest tertiles for dietary patterns Positive association with CD: Western diet pattern – Meat, fatty foods, desserts, fast food and snacks OR=4.7 (95%CI 1.6-14.2, p=0.006) (girls) Negative association for CD: Prudent diet pattern – Vegetables, fruits, olive oil, grains, dairy products, eggs, fish, dark bread and nuts OR=0.3 (95%CI 0.1-0.9, p=0.029) girls; OR=0.2 (95%CI 0.1-0.5, p<0.001) boys	Comparing the highest to the lowest intake of an overall diet pattern showed that a western dietary pattern had 4.7-times greater odds of CD development in girls, while a prudent dietary pattern was associated with a 70-80% decreased risk of CD development in both sexes.
Jakobsen *et al.*, 2013 (35)	Case-control study; Denmark (3 geographical regions	118 IBD; 59 CD (39 male, 20 female), 56 UC cases, 3 IBD-U	CD: 13.3 (2.9 – 14.9) y. [b]	Risk factors for CD: Soft drink consumption ≥4 times/week: OR=2.9 (95%CI 1.0-8.5, p<0.0001)	High soft drink and white bread consumption were strong risk factors for the development of CD

	- Eastern Denmark, Funen, Aarhus)	477 healthy controls (246 male, 231 female)	White bread consumption more than once per week: OR=4.9 (95%CI 1.0-23.4, p=0.05) <u>Protective factors for CD:</u> Vegetable consumption more than once per week: OR=0.3 (95%CI 0.1-1.0, p=0.05) Wholemeal bread consumption more than once per week: OR=0.4 (95%CI 0.2-0.9, p=0.02)	(2.9- and 4.9-times greater odds, respectively). Consuming vegetables or wholemeal bread more than once per week compared to less than once per week conferred a protective effect against developing CD (70% and 60%, respectively).

Abbreviations: CD: Crohn's disease; CI: Confidence interval; IBD: Inflammatory bowel disease; IBD-U: Inflammatory bowel disease unclassified; OR: Odds ratio; SD: Standard deviation; UC: Ulcerative colitis; UK: United Kingdom; USA: United States of America; y.: Year; ω-3: omega-3 fatty acids; ω-6: omega-6 fatty acids

[a] Mean ± SD; [b] Median (range)

1.2 Clinical presentation of paediatric Crohn's disease

Presenting symptoms for children with CD are heterogeneous and wide-ranging (Table 1.1) and may indicate many different diagnoses (1,3,7,36). This may lead to a considerable time lapse between the development of symptoms and pathological diagnosis, reported to range from 1.3 to 105 months (37-41). Symptoms can depend on the location, severity, and disease behaviour experienced by the child (1). Typical presenting symptoms in children and adolescents are pain, diarrhoea and weight loss, while atypical symptoms include extraintestinal manifestations of the skin, eye or joints (1,3,7), and more general symptoms such as anaemia, malaise, and fever (3).

1.2.1 Diagnosis of Crohn's disease

Experts in paediatric IBD, mainly from the Porto IBD Working Group of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), have collaborated to develop criteria for diagnosing IBD in children and adolescents (4). Diagnosis of CD is based on clinical suspicion, which is then confirmed through laboratory, endoscopic, histologic, and radiologic findings (Table 1.1) (4). Initial tests should exclude any bacterial or parasitic infections, such as Salmonella, Shigella, Yersinia, Campylobacter, and Clostridium difficile (4). Once intestinal inflammation is confirmed pathologically, the recommendation is for the paediatric gastroenterologist to perform an endoscopy and ileocolonoscopy, including taking multiple biopsies of the GI tract regardless of whether the appearance is normal (4). Magnetic resonance enterography is required to determine small bowel involvement and estimate the degree of intestinal inflammation and damage (4). The findings of these tests allow the gastroenterologist to differentiate and therefore diagnose children with CD, UC or IBD-U. This differentiation is critical as treatment regimens vary between IBD modalities.

1.2.2 Crohn's disease classification

Following a diagnosis of CD, the gastroenterologist will classify the disease location and behaviour and determine any growth delay. Prior to 2011, the Montreal classification was used to classify CD in both adults and children; however, there were several weaknesses in classifying children (42). Weaknesses of the Montreal classification and important elements of the paediatric CD phenotype include; 1) the extent of small bowel involvement, a critical component due to poorer outcomes associated with small bowel disease (e.g., growth failure, stricturing disease and weight loss), 2) the inability to distinguish patients with penetrating and stricturing disease, 3) growth abnormalities, which are present in up to 30% of children, and 4) age, as location and disease extent differs by age (42). In 2011, the Montreal classification of CD was modified to overcome these weaknesses and is termed the Paris classification. The modifications include differentiation of children into two age bands, the addition of growth delay classifications, and further location and behaviour classifications (**Table 1.4**).

Table 1.4 | Montreal and Paris classifications of Crohn's disease (42)

	Montreal classification	Paris classification
Age at diagnosis	A1: <17 y	A1a: 0 to <10 y A1b: 10 to <17 y
	A2: 17–40 y	A2: 17–40 y
	A3: >40 y	A3: >40 y
Location	L1: Terminal ileal ± limited cecal disease	L1: Distal 1/3 ileum ± limited cecal disease
	L2: Colonic	L2: Colonic
	L3: Ileocolonic	L3: Ileocolonic
	L4: Isolated upper disease	L4a: Upper disease proximal to the ligament of Treitz L4b: Upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum
Behaviour	B1: Non-stricturing non-penetrating	B1: Non-stricturing non-penetrating
	B2: Stricturing	B2: Stricturing
	B3: Penetrating	B3: Penetrating B2B3: Penetrating and stricturing disease either at the same or different times
	p: Perianal disease modifier	p: Perianal disease modifier
Growth	n/a	G0: No evidence of growth delay G1: Growth delay

Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, *et al*. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17(6):1317, by permission of Oxford University Press.

Disease location is reported to differ by age, with very early onset CD (age 0-6 years) tending towards pure colonic disease (L2) (11,43), whereas older children tend towards ileocolonic disease (L3) (11,44), and adults exhibit a mix (12,41,45) (**Table 1.5**). Paediatric patients have more widespread intestinal involvement, including both ileocolonic and upper GI tract disease (L3 + L4) (Table 1.5) (11,12), and perianal disease is more common in paediatric CD than in adults (41) (**Table 1.6**). Disease extension is more frequent in paediatric CD than adult-onset, with more widespread, complicated disease behaviour (11), including changes from an inflammatory disease at diagnosis to stricturing and penetrating disease over time (Table 1.6) (1,2,12,44). Although the data is limited, a longitudinal analysis of children with CD in France reported complicated disease in 29% of children at diagnosis, increasing to 59% at maximal follow-up (52 to 124 months) (44). The occurrence of disease extension and complications in paediatric onset CD and associated changes in mucosal integrity can result in severe nutritional and metabolic consequences (12,44,46).

Table 1.5 | Studies comparing disease location in paediatric and adult Crohn's disease

Author, year, study population	Data differentiation	Montreal Classification					Summary
		Disease location					
		L1 (%)	L2 (%)	L3 (%)	L4 (%)	L3 + L4 (%)	
Van Limbergen *et al*. 2008 (12) Scotland Paediatric onset *n*=276, age at diagnosis 11.5 (8.9-13.2) y. [a], 164 male:112 female, follow-up 1.7 – 6.0 y.	Diagnosis *n*=273 Follow-up ≥ 4 y. *n*=132 At last follow-up *n*=273	3.7 3.0 2.6	20.9 18.2 15.0	19.4 15.2 19.0	2.2 1.5 0.7	31.1 38.6 43.2	Location changed over time 39% increased anatomic extent in 2 y. 46% required immunomodulatory therapy within 12 months of diagnosis
Adult-onset *n*=596, age at diagnosis 29.7 (23.7-43.5) y. [a], 216 male:380 female, follow-up 3.8 – 20.6 y.	Adult-onset *n*=507 At last follow-up	31.5*	36.1*	19.5	2.6	3.2*	A higher proportion of panenteric CD (L3+L4) in children than in adults
Vernier-Massouille *et al*. 2008 (44) France Paediatric onset *n*=472, age at diagnosis 14 y. [a◊] (range 11-16 y.), 256 male:216 female, follow-up 52-104 months	Diagnosis *n*=472 Maximal follow-up *n*=404 (range 52 – 124 months)	9.6 4.3	11.7 5.7	42.3 42.3	36.0 47.7[#]	69.0 81.2	31% increased anatomic extent at maximal follow-up Extraintestinal manifestations increased from 23% at diagnosis to 48% at maximal follow-up
Jakobsen *et al*. 2011 (45) Denmark Paediatric onset *n*=29, age at diagnosis 12.9 (10.2-13.8) y. [a], 15 male:14 female, follow-up 4.4 – 6.0 y.	Diagnosis paediatric	14	31	34	0	7	No significant difference in disease location, treatment or disease course
Adult-onset *n*=67, age 33.4 (26.8-49.5) y. [a], 33 males:34 females, follow-up 4.3 – 5.6 y.	Diagnosis adults	19	13	10	4	8	
Guariso *et al*. 2010 (41) Italy Paediatric onset *n*=67, age at diagnosis 11.3 y. [b◊] (range 0-17 y.), male:female ratio 1.03:1,	At diagnosis	6	19.4	74.6	41.8		Delayed linear growth recorded in 23.5% of children
Adult-onset, *n*=65, age 29.1 y. [b◊] (range 18-40 y.), male:female ratio 1.5:1	At diagnosis	21.5	24.6	26.2	15.4		Extraintestinal manifestations were higher in children than in adults 14.3% vs 7.3% p=0.04 (respectively)

		Disease distribution categories			
		Proximal and Ileal	Colonic[Δ]	Ileo-colonic	
Paul *et al*. 2006 (43) United States of America Paediatric onset at diagnosis *n*=254, age at diagnosis 11 y. [a◊] (range 0.42-14.98 y.), male: female ratio 1.6:1	Early-onset 0-5 y. Later onset 5-15 y.	0 26	76** 26	24 48	Children with CD had growth impairment (compared to the reference population)

Abbreviations: CD: Crohn's disease; IQR: Interquartile range; L1: Distal 1/3 ileum ± limited cecal disease; L2: Colonic disease; L3: Ileocolonic disease; L4: Upper gastrointestinal tract disease (Proximal, oesophagus, stomach, duodenum, jejunum); SD: Standard deviation; y.: Years

[a] Median (IQR); [b] Mean ± SD; [◊] IQR or SD not reported

*p<0.0001 (adults compared to children at last follow-up); **p<0.0001 (early versus later onset); # p<0.01 (diagnosis compared to maximal follow-up for L4 disease)

[Δ] includes perianal disease

Table 1.6 | Studies comparing disease behaviour and progression in paediatric and adult Crohn's disease

Disease behaviour: (±perianal disease) Montreal classification	Data differentiation	Inflammatory disease (B1) %	Stricturing disease (B2) %	Penetrating disease (B3) %	Perianal disease (p) %	Conclusions
Van Limbergen *et al*. 2008 (12)	At diagnosis	91.2	4.4	4.4	13.9	Significant disease progression from diagnosis p=0.001
Scotland	2-year follow-up	82.7	9.6	7.6		
Paediatric onset	4-year follow-up	75.8*	12.9#	11.4†	22.2##	24% developed stricturing and penetrating disease at 4 y. compared to 9% at diagnosis (p<0.0001)
		72.7	14.7	12.6		
Adult-onset	At maximal follow-up	66.0	14.3	19.7		No significant difference between children and adults in disease behaviour (p=0.17)
Vernier-Massouille *et al*. 2008 (44)	At diagnosis	71	25	4	9	Evolution of disease behaviour from B1 to B2 or B3.
France	10-year follow-up	41**	44**	15**	27**	B1 to B2 32%, B1 to B3 11%, B2 to B3 16%
Paediatric onset						
Guariso *et al*. 2010 (41)	Paediatric patients				25.4	More perianal disease was observed at disease onset in paediatric patients than in adult patients
Italy	6 – 12 y. old				50	
Paediatric onset	13 – 17 y. old				30.8	
	0 – 5 y. old				19.2	
	4.8 y. (mean) follow-up				44.8	
Adult-onset	Adult patients				12.3††	
	3 y. (mean) follow-up				21.5 ***	

Abbreviations: y.: Years
Behaviour changes diagnosis to 4-year follow-up * p<0.0001, # p=0.001, † p=0.008, ## p=0.04,
Behaviour changes to 10-year follow-up ** p<0.01
Behaviour comparison at diagnosis children compared to adults †† p=0.0001
Behaviour changes at follow-up children compared to adults *** p=0.006

1.2.2.1 Extraintestinal manifestations of paediatric Crohn's disease

Signs, symptoms and clinical features of CD at diagnosis are similar for children, adolescents and adults (Table 1.1); however, faltering growth or growth failure and pubertal delay are two extraintestinal manifestations specific to children and adolescents (11,13). Literature on CD typically uses the term growth failure; for example, a Cochrane review suggests that 15% to 40% of children are affected by growth failure (47). However, definitions of growth failure across studies vary and include weight, height, the velocity of linear growth, height velocity, height for age below a defined centile (3^{rd} or 5^{th}), a z-score below -2 standard deviations (SD) on the growth chart, retardation of bone age by 2 years, and chronological age more than two SD above bone age (47), making comparisons difficult.

The Paris classification for CD uses the term growth impairment, which looks at the adequacy of linear growth velocity over time (**Table 1.7**). It recognises that growth retardation should be diagnosed using different metrics (42). In NZ, the Starship Child Health (SCH) Clinical Guideline (48) uses the term faltering growth to describe growth that is "much lower than expected or has crossed two major centile lines". This can be seen in **Figure 1.2**, where growth velocity is observed to alter from age 10, approximately 2 years prior to symptom onset, and continue for another 2 years until diagnosis at age 14. Growth velocity improved after diagnosis and careful disease management; therefore, target height was achieved at age 18 (49).

Table 1.7 | Paris classification of linear growth impairment in paediatric Crohn's disease **(42)**

Impaired linear growth as defined by at least one of the following criteria
1) Height z-score at diagnosis or subsequently significantly less than expected height z-score A) Difference between observed height z-score and predicted height z-score using the 'Mid-parental Heights' formula is >2.0 or B) Difference between the observed height z-score and the 'pre-illness' height z-score is >1.0
2) Current height z-score significantly less than height z-score at diagnosis Reduction in height z-score since diagnosis is ≥ 0.75

Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, *et al*. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17(6):1319, by permission of Oxford University Press.

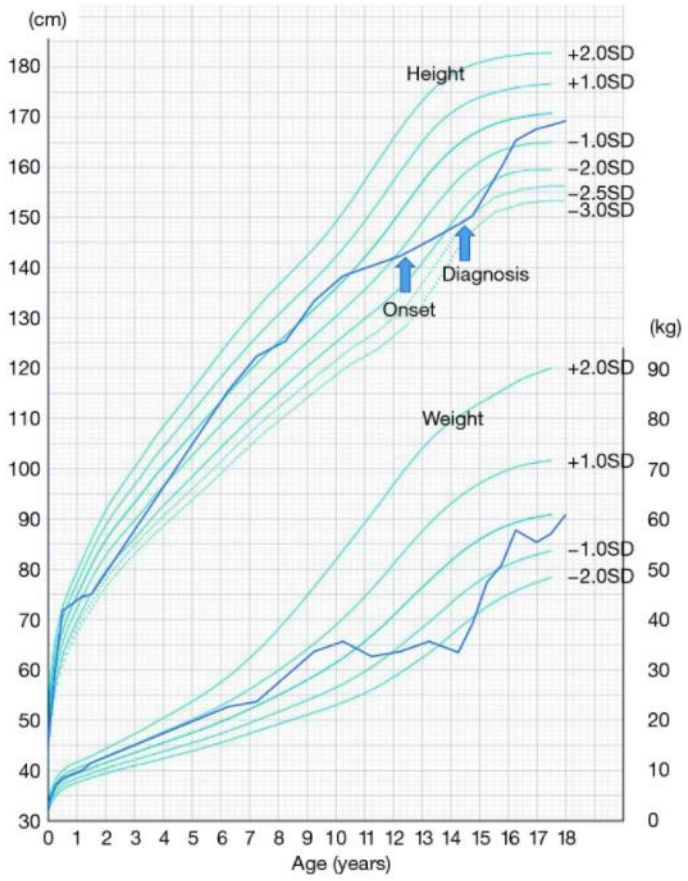

Figure 1.2 | Growth chart showing growth velocity alterations in a patient with paediatric onset Crohn's disease (49)

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Growth failure, defined as a height below the third percentile or a z-score below -2 SD on the growth chart, is a significant nutrition-related complication of CD, affecting 5% to 21% of children at diagnosis (49-55) (**Table 1.8**). In addition, 20% to 30% of children have disrupted or impaired linear growth, a change in height of -1 to -2 standard deviations on the growth chart (3). Growth failure in CD results from the disease process itself, whereby the inflammatory process is thought to suppress insulin-like growth factor I levels directly, and when coupled with nutrient malabsorption and poor oral nutrition, leads to suboptimal growth (47,49). The undesirable effects of chronic steroid treatments also play a role in growth failure (3). Growth failure in adulthood, a final height of less than -2 SD on the growth chart, has been reported in 6% to 37% of paediatric onset CD cases (49,55-58) (Table 1.8). Growth impairment can continue into adulthood, with approximately 50% of adults with adolescent-onset CD attaining a 10% shorter height than their parent and the general population of the same sex, and approximately 25% attaining a 5% shorter height (16,59).

Pubertal delay is common in adolescents with chronic inflammatory disease, with possible consequences manifesting as decreased bone mineralisation and reduced sexual maturation affecting their long-term quality of life (QoL) (13). The mechanisms are not fully understood, but it is thought that malnutrition, pro-inflammatory cytokines and insulin-like growth factor all play a role in

suppressing sex steroids (13,60,61). In females, it is hypothesised that a certain level of body fat and weight is required for menarche; therefore, given the occurrence of malnutrition and weight loss, a pubertal delay may occur (62).

CD is inflammatory in nature; therefore, inflammation of the musculoskeletal, dermatologic and oral, hepatopancreatobiliary, ocular, metabolic and renal systems can also occur (63,64). The prevalence of these extraintestinal manifestations in the literature varies depending on the definition used but is reported to affect between 25% and 40% of IBD patients (63). Musculoskeletal manifestations are the most common and include pain and conditions such as arthritis and osteoporosis (63).

Table 1.8 | Growth failure at diagnosis and final adult height in paediatric Crohn's disease

		Growth failure at diagnosis		Growth failure at final adult height	
Author, year, country	Study population	Growth failure definition	Growth failure (%)	Growth failure definition	Growth failure (%)
Griffiths *et al*. 1993 (50) Canada	*n*=100 (66 male, 64 female; age at diagnosis 11.3±2.3 y. [a])	Height below 3rd centile	21		
Markowitz *et al*. 1993 (56) United States of America	*n*=38 (male, female data not provided; age at diagnosis (IBD) 11.8±2.4 y. [a])			Growth curve / BP method / RWT method *	37
Hildebrand *et al*. 1994 (57) Sweden	*n*=46 (28 male, 18 female; age at diagnosis 12.7±2.4 y. [a])	Height velocity < -2 SD between age 3 and end of puberty	65	Final height < -2 SD Final height < -1 SD	7 29
Spray *et al*. 2001 (51) United Kingdom	*n*=64 (36 male, 28 female; age at diagnosis 10.1 y. [b◊] [range 1-17.6 y.])	Height for age z-score < -2 SD Height for age z-score < -3 SD	19 8		
Wine et at. 2004 (52) Israel	*n*=93 (56 male, 37 female; age at diagnosis 12.1±3.6 y. [a])	Diagnosis Height z-score < -2 SD Weight z-score < -2 SD At lowest disease severity Height z-score < -2 SD Weight z-score < -2 SD	 12 14 19 27		
Gupta *et al*. 2007 (65) United States of America	*n*=989 (566 male, 423 female, age at diagnosis11.5±3.8 y. [a])	Height for age below the 5th centile or decrease in height velocity below the 5th centile	9.8 Cumulative incidence over 10 y.		
Sawczenko *et al*. 2006 (66) United Kingdom	*n*=123, (65 male, 58 female, age at diagnosis 12.2±2.8 y. [a])			Final height >8cm below target	19
Pozler *et al*. 2006 (58) Czech Republic	*n*=223 (130 male, 93 female; age at diagnosis 14 y. [b◊])			Height z-score < -2 @ age 18 y.	6.4
Pfefferkorn *et al.* 2009 (53) United States of America	*n*=176 (114 male, 62 female; age at diagnosis 10.1±2.8 y. [a])	Height z-score < -2 SD Abnormal height velocity z-score < -2 SD	10 (diagnosis) 1 y.: 8 2 y.: 6.5 1 y.: 29 2 y.: 23		

Mesker *et al*. 2009 (67) The Netherlands	*n*=43 (28 male, 15 female; age at diagnosis 13.2 y. [b◊] [range 2.4-16.7 y.])	Height for age z-score < -1.64	9.5 (diagnosis)	Growth impairment after 5 y.	16.7
Vasseur *et al*. 2010 (54) France	*n*=261 (156 male, 105 female; age at diagnosis 13 [11.2-15.4] y. [b])	Height < -2 SD Weight < -2 SD BMI < -2 SD	9.5 27 32	Maximal follow-up 6 y.	Height: 6.9 Weight: 15
Lee *et al*. 2010 (68) United States of America	*n*=317 (196 male, 121 female; age at diagnosis 12 [10-14] y. [b])	Growth impairment height for age z-score < -1.64 SD	20.5		
Ley *et al*. 2016 (55) France	*n*=107 (63 male, 44 female; age at diagnosis 11.7 [9.8-13.5] y. [b])	Height for age z-score < -2 SD Growth impairment (height for age z score between -1 and -2)	8 13 (Prevalence)	Height for age z-score < -2 Growth impairment	5 17 (Prevalence)
Ishige 2019 (49) Japan	*n*=2,090 (male 1,446, female 644; age data not provided, diagnosed <20 y. and current age ≥20 y.)	Height z-score < -2	Male: 6.6 Female: 5.4	Height z-score <-2	Male: 6.8 Female: 4.7

Abbreviations: IBD: Inflammatory bowel disease; IQR: Interquartile range; SD: Standard deviation; y.: Years

* Methods: Growth Curve – final adult height centile 2 or more major growth channels below pre-illness or time of IBD diagnosis height centile; BP (Bayley-Pinneau) method – actual adult height ≥5cm less than predicted adult height; RWT (Roche-Wainer-Thissen) Method – actual adult height below the 90% confidence (5.5-7cm) of the predicted height)

[a]: Mean ± SD; [b]: Median (IQR); ◊ IQR not reported

1.3 Management of paediatric Crohn's disease

1.3.1 Treatment goals

The priority in managing a new paediatric CD diagnosis is the induction of disease remission, ideally leading to mucosal healing (1,3). Over the longer-term, maintenance of remission is the key goal and is critical to managing ongoing CD symptoms, preventing complications and improving QoL (5).

1.3.2 Health professional involvement in paediatric Crohn's disease care

The primary health care professional (HCP) is a gastroenterologist, with dietitians typically involved in patient care during exclusive enteral nutrition (EEN) (69,70); however, this varies by region from 100% in Canada and the United Kingdom to 18% in Spain (69). Nurses were involved during EEN in 50% to 65% of programs/centres (69-71), whereas psychologists were never or rarely involved during EEN (70-73). Dietitians were considered the most critical of these health professionals during EEN therapy (72).

1.3.3 Guidelines for the medical management of Crohn's disease

The European Crohn's and Colitis Organization – European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ECCO-ESPGHAN) is the leading authority on IBD management and has authored guidelines for the medical management of paediatric CD (74). Following diagnosis with CD, the gastroenterologist decides which treatments are applicable for inducing and maintaining remission (3). ECCO-ESPGHAN details a range of interventions depending on the type and severity of disease, summarised in **Table 1.9** and the flowchart used to determine therapy pathways for active CD is displayed in **Figure 1.3**. The interventions should be tailored to the child; for example, the recommended induction treatment is either EEN or corticosteroids (CS) for a child with low-risk disease and no growth delay. Once remission is achieved, maintenance options are methotrexate, thiopurines, or maintenance enteral nutrition (Table 1.9, Figure 1.3) (74). A child with high-risk disease, or induction/maintenance failure, should be managed with anti-tumour necrosis factor (anti-TNF) therapy. In children with severe growth delay, anti-TNF therapy alongside nutritional support may provide the best outcome (74). If, after using anti-TNF therapy, induction of remission failure persists, then alternate biologic agents may be considered (not shown) (74).

Table 1.9 | Summary of treatment options for paediatric Crohn's disease

	ECCO-ESPGHAN guideline (74)	Mechanism of action and benefits
Exclusive enteral nutrition (EEN)	- First-line therapy to induce remission in children with active luminal CD	- The exact mechanism is uncertain, thought to be a combination of restoration of epithelial barrier function, reduction of the inflammatory response and intestinal inflammation, and normalisation of intestinal microbiota (75) *Efficacy of clinical remission induction* - Cochrane Review 83% (76) - Mucosal healing: 89% (77), 74% (78) - Benefits include steroid avoidance, nutritional improvements, correction of growth failure (72,73,79,80)
Corticosteroids (CS)	- May be considered to induce remission in children where EEN is not an option - Should not be used as a maintenance therapy	- Exerts an anti-inflammatory effect - Exact mechanism is uncertain; thought to enter the nuclease and interact with glucocorticoid response locations on the chromosomal DNA (81) *Efficacy of clinical remission induction* - Cochrane Review 61% (76) - Mucosal healing: 17% (77), 33% (78)
Thiopurines	- Maintenance of steroid-free remission - Should not be used as an induction therapy	- Immunosuppressive medications - Delayed onset of action, up to 16 weeks
Methotrexate	- Maintenance of clinical remission as the first choice or after thiopurine failure or intolerance	- Immunosuppressive medication
Aminosalicylates	- Are no longer recommended for use in CD patients	- Mechanism of action is unknown; thought to act topically, not systemically, as immunomodulators and anti-inflammatory agents (82) - Compared to a placebo aminosalicylates have very modest (if any) benefit (83,84)
Biological (Anti-TNF)	- For inducing remission in complicated disease course or failing to achieve/maintain remission with an immunomodulator. - For inducing and maintaining remission in active perianal fistulising disease	- Biological agents bind to TNF-α, which disrupts the inflammatory cascade in CD (85) - Highly effective in inducing clinical and endoscopic remission - Decreases risk of complications (74)
Maintenance enteral nutrition	- Partial enteral nutrition may be used to maintain remission (i.e., meeting at least 50% of daily estimated energy requirements)	- Mechanism of action as for EEN - Benefits include a reduction in the use of CS and immunosuppressive drugs and the adverse effects of these medications (86)

Abbreviations: CD: Crohn's disease; DNA: Deoxyribonucleic acid; ECCO: European Crohn's and Colitis Organization; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; TNF-α: Tumour necrosis factor-alpha

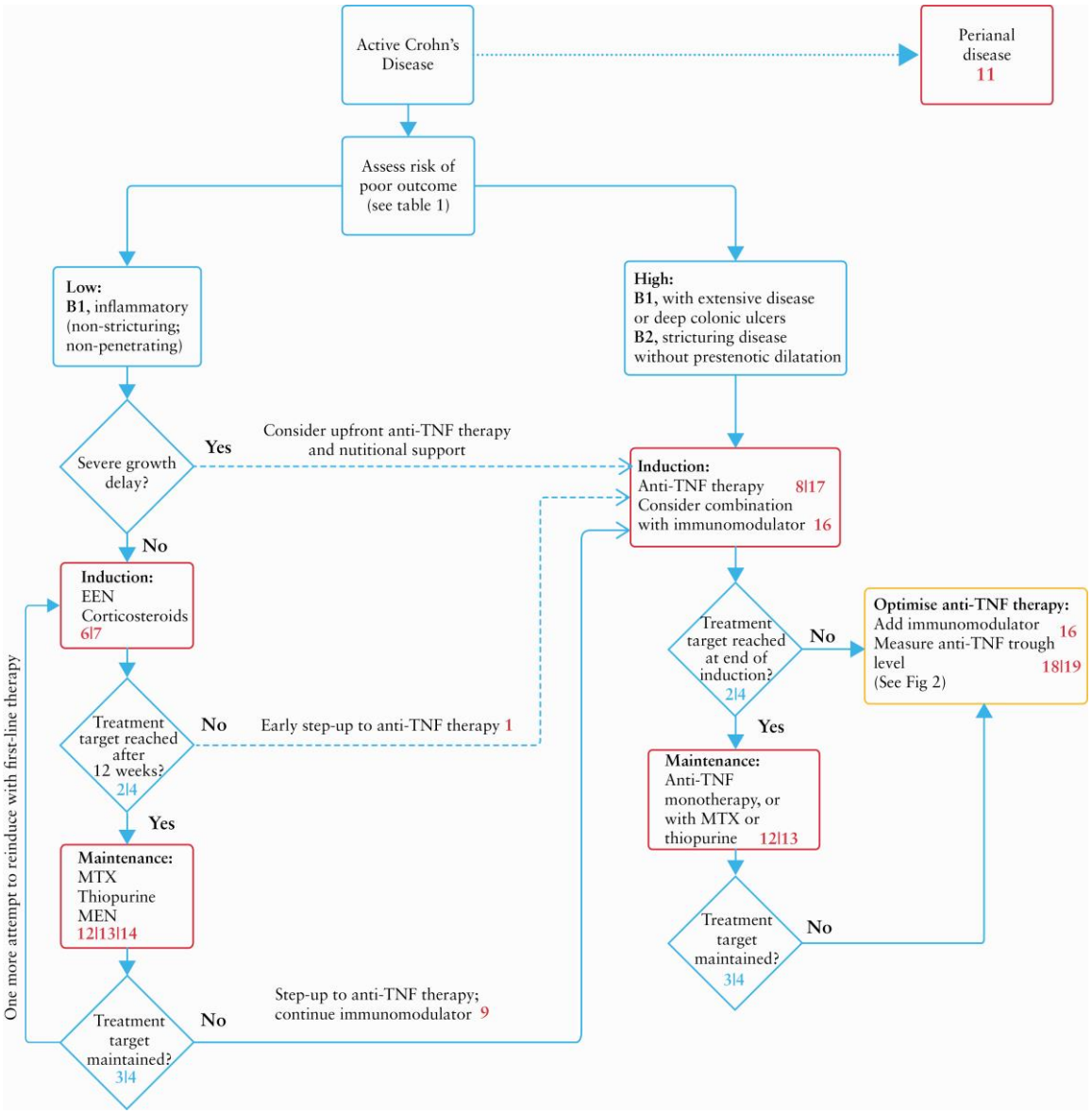

Figure 1.3 | Flow chart summarising ECCO-ESPGHAN guidelines for the medical management of paediatric Crohn's disease (74)

van Rheenen PF, Aloi M, Assa A, Bronsky J, Escher JC, Fagerberg UL, *et al*. The medical management of paediatric Crohn's disease: an ECCO-ESPGHAN guideline update. Journal of Crohn's and Colitis 2021;15(2):173, by permission of Oxford University Press

Abbreviations: Anti-TNF: Anti-tumour necrosis factor; ECCO: European Crohn's and Colitis Organization; EEN: Exclusive enteral nutrition; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; MEN: Maintenance enteral nutrition; MTX: Methotrexate; Note: the numbers on the flowchart refer to statements in the guideline

1.3.4 Therapeutic agents for induction therapy

1.3.4.1 Exclusive enteral nutrition as induction therapy

EEN is one of the recommended first-line therapies for inducing remission in paediatric CD (74). EEN therapy is usually an enhanced caloric intake of around 120% of estimated nutritional requirements, taking into account any need for catch-up growth and nutrient deficiencies (87). EEN is typically completed for 6 to 8 weeks (**Table 1.10**), after which gradual reintroduction of the patient's regular diet is commenced. Other foods or fluids (commonly known as cheats) allowed vary by centre or HCP (Table 1.10). Typically, water was freely allowed; however, Whitten *et al*. (70) found that 16% of HCPs did not allow water to be consumed. Common cheats are chewing gum, boiled lollies, clear fluids such as ice blocks, clear soups or broths, tea and fruit juices. If clinical improvement is not seen after 2-4 weeks of EEN with compliance to the EEN protocol (i.e., drinking the prescribed volume and excluding all foods except cheats) or symptoms are exacerbated, other treatment options are considered (Table 1.9).

EEN therapy varies across gastroenterology centres and disease locations (Table 1.10). More recent studies report regular EEN use in over 80% of patients (70,72,79,88), compared to studies pre-dating the ECCO-ESPGHAN guideline, where regular use of EEN was lower (57% of patients) (73) (Table 1.10). In a recent survey of paediatric IBD specialists (*n*=146) from 26 countries, the most common disease locations EEN was used for was ileocolonic (92%) and distal small bowel ± limited cecal disease (88%), whereas only 52% used EEN for isolated colonic disease and less than 31% used EEN for perianal disease (69). NZ and Australian gastroenterologists (*n*=37) reported similar responses, with 92% always or often using EEN in ileocolonic disease and 25% in perianal disease; however, use in isolated colonic disease was higher (72%) (72).

Table 1.10 | Summary of studies using questionnaires to determine clinical practice for Crohn's disease

Author, year, study details	EEN use	Type of formula used	Other factors allowed "cheats"
Burgess *et al*. 2020 (80) Paediatric gastroenterology units in tertiary public hospitals Paediatric dieticians working with gastroenterologists, *n*=18 Australia *n*=10, NZ *n*=8 Response rate not stated	Duration: At least 6 weeks, 100% 6-8 weeks, 50% 8 weeks, 39%	Polymeric used by 100%, between 2 and 5 different formulas on offer	- Water only, 44% (88% NZ), - Small amounts of extra food and drink, 56% (90% Australian) - Added flavourings, 44%. Cheats allowed: - Chewing gum, 50% - Boiled lollies, 33% - Jelly, 28% - Cordial, lemonade/lemonade ice blocks, jelly lollies, 22% - Clear apple juice, clear broth and caffeine-free tea, <20%
Bronsky *et al*. 2019 (88) Paediatric IBD centres, *n*=106 USA *n*=14, Canada *n*=8, Australia and NZ *n*=3, Japan *n*=1, Europe and Israel *n*=80 Response rate 65.4%	Used as first-line induction therapy in 82% of centres (CS: 9%, Other: 9%) Regional differences: Canadian and European centres primarily use EEN USA centres use EEN to a lesser extent	Not reported	Not reported
Ho & Day 2018 (72) Paediatric gastroenterologists, *n*=37 Australia *n*=31, NZ *n*=6 Response rate 54% 72% male 95% public hospital academic	Regular or frequent EEN use, 94% (Australia), Frequent EEN use 100% (NZ). Always use EEN with: Ileocolonic, 92%, Upper and lower gut, 86%, Isolated upper gut, 73%, Isolated colonic, 72%, Perianal, 25% Used 5.5-fold more in moderate rather than mild disease activity (OR 5.5 [95% CI 2.7–11.3], p < 0.01). Duration: 6-8 weeks, 95% 8-12 weeks, 5%	Polymeric used by 95%, Reasons for use: - Taste 78% - Availability 68% - Cost 27% - Composition 19%	- Added flavourings, 50% - Extra fluids, 27% (black tea, soft drinks, diluted fruit juice, barley water, jelly) - Boiled lollies and chewing gum allowed (frequency not stated)

Lawley *et al*. 2018 (69) Paediatric IBD gastroenterologists and dietitians, 26 different countries *n*=146 (Europe *n*=89, North America *n*=41, Rest of the world *n*=16) Response rate 73% (completed more than 80% of the survey)	Used in: Ileocolonic disease, 91% Distal small bowel ± limited caecal disease, 88% Isolated colonic disease, 52% Perianal disease, <31% Used beyond initial diagnosis, 82% Duration: 6 weeks 31% 8 weeks 57%, UK and Europe other favoured 6 weeks Canada, USA, Spain favoured 8 weeks,	Polymeric used by 88%	- Water only, 63% (Spain 88%, Europe other 86%, UK 55%) Cheats allowed by: USA 74%, Canada 57% Common cheats: - Candy and chewing gum, 16% - Clear fluids 12%
Whitten *et al*. 2012 (70) Attendees at the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Annual Scientific Meeting in 2006, *n*=35 UK *n*=16, Europe *n*=9, North America *n*=2, Asia-Pacific *n*=8 Response rate 42%	Duration: 6 to more than 12 weeks (mean 8.5 ± 1.7 weeks) < 6 weeks 3%, 6-8 weeks 81%, 8-12 weeks 16%	Polymeric, 90% Semi-elemental, 32% Elemental, 48% Formula choice: Palatability, 66% Clinical effectiveness, 49%, Composition, 35%	- Flavouring permitted, 81%, - Water for thirst (84%; 16% did not allow water) Cheats allowed: - Clear fluids, 68% (carbonated beverages, ice blocks, clear soup) - Boiled sweets, 48% - Chewing gum, 39% - Tea or coffee, 39%, - 1 centre allowed bread or rice and low-fat foods, 1 centre allowed 10% of caloric intake as food or fluid
Gråfors & Casswall 2011 (79) Paediatric units in Sweden that treat IBD, *n*=29 Response rate 78%	Used as primary therapy 65%, Used as a treatment option 96% Duration: 4 weeks 8% 4-6 weeks 4% 6 weeks 52% 6-8 weeks 32% 8 weeks 4%	Polymeric, 54% Polymeric and elemental, 38% Polymeric, semi-elemental, and elemental, 8% Formula choice: Taste, 59% Cost, 33% Availability, 26% Nutritional constitution, 22%, Documented effect, 22%	Cheats allowed: (81%) - Lollipops, 71% - Chewing gum, 52% - Juice, 52% - Popsicles, 43% - Tea, 43% - Broth, 33% - 1 unit allowed coffee, sugar and rusks

Stewart *et al*. 2011 (71) North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition, *n*=326 (86% USA, 14% Canada) Response rate 30.7%	Practitioners using EEN: Ileocolonic disease, 79% Isolated upper gut disease, 76% Colonic disease,33% Perianal disease, 20% Duration: <6 weeks 30% 6-8 weeks 46% >8 weeks 25%	Polymeric, 47% Semi-elemental, 55% Elemental, 47% Some physicians used more than one type	Not reported
Day *et al*. 2009 (73) Australian paediatric gastroenterologists, *n*=21 Response rate 58%	Practitioners currently using EEN: (57%) Always or sometimes consider EEN: - Ileocolonic or upper and lower gut involvement, 75% - Upper gut, 50% - Rarely or never use EEN: - Perianal disease, 25%, - Isolated colonic disease, 33% As an induction therapy, EEN was: - Very appropriate, 57% - Sometimes appropriate, 43%. Duration: 6-8 weeks 92% 8-10 weeks 8% Practitioners currently not using EEN: (43%) Reasons: compliance 78%, lack of efficacy 67%, lack of understanding of mechanisms 56%, lack of experience 33%.	92% regularly used polymeric formula, 7 separate brands used	Not reported

Abbreviations: CI: Confidence interval; CS: Corticosteroids; EEN: Exclusive enteral nutrition; IBD: Inflammatory bowel disease; NZ: New Zealand; OR: Odds ratio; UK: United Kingdom; USA: United States of America

Most HCPs or centres surveyed used a polymeric formula, with taste or palatability, cost and composition influencing the decision (Table 1.10). Elemental and semi-elemental formulas were also reported to be used, but by fewer HCPs or centres. A recent Cochrane review combining adults and children with CD concluded that there was no significant difference in remission rates between elemental and non-elemental formulae (64% compared to 62%, respectively; [RR = 1.02 95% CI 0.88-1.18; p=0.83]) (76). Two paediatric studies evaluating polymeric compared to elemental formulae, included in this review, reported no significant differences in inducing remission after 6 weeks (89,90). In adults, non-adherence due to palatability issues with elemental formulae have been reported in up to 41% of participants (91). Data on paediatric patients with CD is sparse; however, a study comparing children with Cystic Fibrosis, healthy children, and healthy adults found that taste preferences were not different between the groups (92). Therefore, as with adults, using a more palatable polymeric formula in paediatric EEN therapy, unless medically indicated to use an elemental formula (74,87), is likely to enhance compliance.

1.3.4.2 Corticosteroids as induction therapy

CS therapy is typically administered orally and uses prednisone, prednisolone or budesonide as the steroid family of choice. CS therapy is used short-term for up to 10 weeks, commencing at the maximal dose, and once remission is achieved (up to a maximum of 4 weeks), the CS dose is tapered off slowly until it can be discontinued (74).

1.3.4.3 Comparing exclusive enteral nutrition and corticosteroid induction therapy

EEN has been reported to be as effective in inducing clinical remission in paediatric CD as CS (76-78,93-100). However, remission determined using clinical variables such as disease activity index or anthropometric data does not consider mucosal healing (MH) (78). MH is reported to have several benefits, including more prolonged CS free remission, enhanced linear growth and bone health (95,98,99,101), fewer hospitalisations and reduced surgical resections (102).

MH is determined through endoscopic and histologic data; however, follow-up endoscopy is rarely completed in the clinical setting (78) due to costs, the time involved, and the burden on the patient (103). Several paediatric studies have highlighted differences in clinical remission and MH rates (77,78,99) (**Figure 1.4**). Most recently, Pigneur *et al.* (77) reported complete MH in 8 of 9 (89%) EEN patients and 1 of 6 (17%) CS patients on follow-up endoscopy, in contrast to patients deemed to be in clinical remission, 100% and 83%, respectively. The differences are in line with findings from two earlier paediatric trials in 2006 by Borrelli *et al.* (78) and Berni Canani *et al.* (99), as well as in adults (104), reporting improved MH with nutritional therapy compared to CS use.

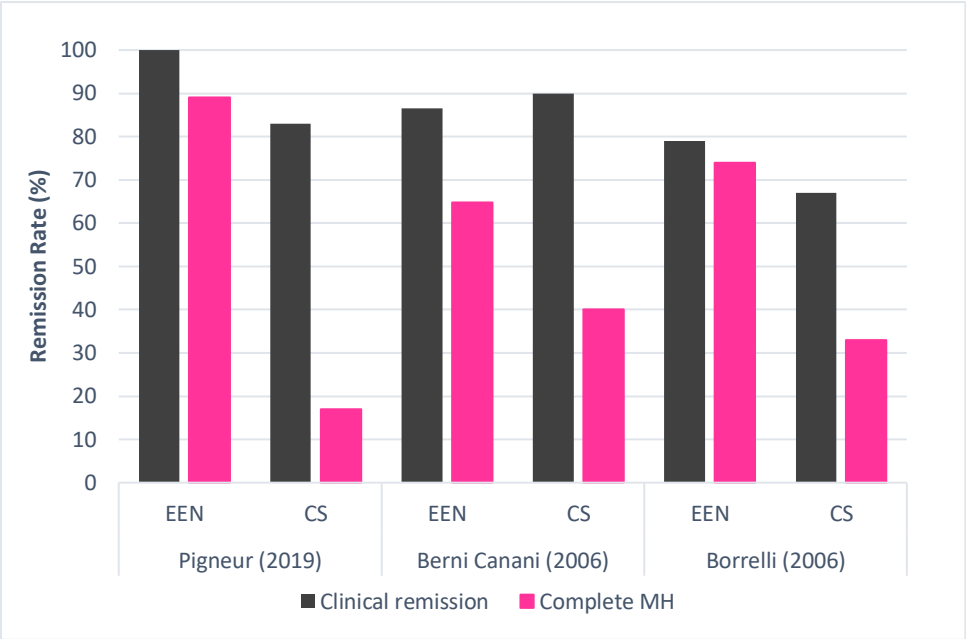

Figure 1.4 | Comparison of children with Crohn's disease achieving clinical remission versus mucosal healing after exclusive enteral nutrition or corticosteroid therapy (77,78,99)

Abbreviations: MH: Mucosal Healing; MH determined via Crohn's disease endoscopic index of severity (Pigneur, Borrelli), and previously validated endoscopic score (Berni Canani)

Direct comparison between EEN and CS on remission rates found no significant differences over the longer-term (6 months to 2 years) (97,98,105). However, survival analysis curves have shown greater protection from relapse with EEN (95,99,106,107), and EEN has been found to have fewer relapse episodes at 24 months compared to CS (mean relapse episodes 0.5 [range 0-2] and 1.5 [range 0-8], respectively; p=0.01) (106). Therefore, first-line induction therapy would ideally use EEN in preference to CS.

1.3.4.3.1 Benefits and advantages of exclusive enteral nutrition compared to corticosteroids

Advantages of EEN as a treatment modality include correction of micronutrient deficiencies and malnutrition, improved z-scores, and a decreased need for steroid and anti-TNF therapy (108). The benefits of using EEN have been reported to continue past its duration and include increased mucosal healing and growth stimulation (**Table 1.11**) (97). Paediatric Crohn's disease activity index (PCDAI) scores were also reported to be lower, and weight gain higher in children taking EEN compared to CS (mean difference -3.67, [95% CI -4.91– -2.43]; p<0.00001 and 1.92, [95% CI 0.02-3.83]; p=0.05, respectively) (109). The ability of EEN to be steroid-sparing means that the short- and long-term side effects associated with their use can be avoided. In comparison, CS are a much simpler regime, resulting in lower levels of patient withdrawal from treatment.

Table 1.11 | Summary of exclusive enteral nutrition and corticosteroids advantages, disadvantages, side effects and adverse events in paediatric Crohn's disease (38,39,44,74,76,78,81,82,87,93,95,97,99,100,108,110-112)

	Advantages	Disadvantages	Side effects	Adverse events
Exclusive enteral nutrition (EEN)	- Improvement in lean muscle mass, weight, and height - Improved nutritional status – macro and micronutrients - Reduction of growth failure - Steroid-sparing <u>Compared to CS:</u> - Higher rates of mucosal healing (OR = 4.5 [95% CI 1.64-12.32]; p=0.003) (100) - A trend towards more durable remission (100) - Higher rates of endoscopic MH (OR=5.24 [95% CI 2.06-13.37]; p=0.0005) (109) - Higher rates of histological MH (OR=4.78 [95% CI 1.89-12.08]; p=0.0009) (109)	- Unpalatable formulations - Formula monotony/fatigue - Nasogastric feeding may be necessary - Low compliance/adherence (i.e., consumption of restricted foods or drinks or difficulties in drinking the prescribed volume) - More likely to withdraw from treatment - Lack of response/treatment failure - Willingness/motivation of the patient - Requires more follow up and resources than CS	- Diarrhoea/flatulence - Nausea/vomiting - Abdominal discomfort/pain - Abdominal bloating - Constipation (uncommon) - Refeeding syndrome (very uncommon)	- Vomiting, diarrhoea, flatulence, heartburn 25% (76) - CS vs. EEN RR = 1.39 (95% CI 0.62-3.11); p=0.42 (76)
Corticosteroids (CS)	Less likely to withdraw from treatment	- Induces clinical but not always an endoscopic response - Increased susceptibility and risk of infection - Body image dissatisfaction - Acne - Swollen ankles - Insomnia - Easy bruising - Cushingoid appearance	- Associated with an increased risk of surgery HR 2.98 (95%CI 1.64-5.41; p<0.01) (44) - Stunted growth - Osteopenia - Osteoporosis - Insulin resistance - Steroid dependence - Glucose intolerance - Growth failure/retardation - Adrenal suppression - Cataracts	- Acne, hypo or hyperglycaemia, Cushingoid facies, muscle weakness 16% (76)

Abbreviations: CI: Confidence interval; HR: Hazard ratio; MH: Mucosal healing; OR: Odds ratio; RR: Risk ratio

1.3.4.3.2 Disadvantages and adverse effects of exclusive enteral nutrition compared to corticosteroids

There are no reported differences in the number of adverse events experienced by children using EEN compared to CS (RR = 1.39 [95% CI 0.62-3.11]; p=0.42) (76); however, the type of adverse events experienced by children differs (Table 1.11). Short term side effects of CS use can include a Cushingoid appearance, acne, swollen ankles, insomnia, and easy bruising (110). Comparatively, the short-term side effects of EEN tend to be mild gastrointestinal discomfort and are usually related to treatment initiation, with resolution on discontinuation of the therapy (Table 1.11).

There are a number of significant long term side effects related to CS use, including osteopenia (78,81,82,97,100,110) and growth failure (Table 1.11) (78,82,87,97). CS resistance and dependence are two complications that must be considered with this treatment modality. CS resistance rates have been reported to be between 5% and 17%, while reported dependence rates ranged from 25% to 41% (110). CS use does not necessarily lead to mucosal healing (78,98); therefore, patients often display disease activity flare as their CS dosage is reduced (99).

Finally, for EEN to succeed, the family and child need to be willing and motivated to persevere with treatment over a 6-to-8-week period. Factors that impact adherence/compliance to the EEN treatment pathway include difficulties in drinking the prescribed volume, formula fatigue, dislike of the taste, and monotony of the dietary pathway. Low compliance may necessitate nasogastric feeding or a change in treatment modality, which requires more follow up and resources (95).

1.3.5 Therapy outcomes

1.3.5.1 Induction of disease remission

CD clinical remission is typically determined via the PCDAI (113), a weighted PCDAI (114), or a physician global assessment (PGA) (115), +/- the inclusion of biochemical, histological, or transmural remission parameters and complete MH. The PCDAI includes a 1-week history of symptoms and general patient well-being, a physical examination and biochemical measures (113,115). Clinical remission is defined as a PCDAI<10 (115) and biochemical remission as a PCDAI ≤10, and C-reactive protein (CRP) <5mg/L (39,116). Transmural remission uses validated magnetic resonance imaging disease activity scores to score transmural disease activity, with 0-1 indicating no activity, 2-6 mild activity, and >7 moderate to severe activity (39). Complete MH is scored following endoscopy using the validated simple endoscopic score for CD (SES-CD), with a score of 0 indicating complete MH, 1-3 indicating near-complete healing, and >3 indicating incomplete healing (SES-CD 4–10 mild, 11–19 moderate and >19 severe disease activity) (39,116). Histologic scoring based on tissue biopsy determines histologic remission, and scores range from normal or minor chronic inflammation (score 0) through to inflammation with ulceration (score 3) (117).

In the last 25 years there have been 4 randomised controlled trials (RCTs) (77,78,89,90), 11 prospective studies (37,39,95,96,111,112,116-120) and 15 retrospective studies (38,97-99,102,105,106,121-128) which have reported remission rates using EEN in paediatric CD (**Table 1.12**). Remission following a course of EEN is reported to range from 47% to 100% (Table 1.12). Remission rates are determined using a variety of criteria, and those measured with the PCDAI tended to be higher, with most studies reporting rates between 70% and 90% (37-39,78,89,96-99,102,106,112,116-121,125-127), compared to more subjective measures, such as patient global assessment, which tended to be lower (47% (111), 53% (124), 60% (122), 80% (128)). Direct comparisons between studies are problematic due to the heterogeneity of disease remission criteria and the individual study populations (Table 1.12).

Clinical practice surveys have reported that paediatric gastroenterologists and dietitians use EEN less often with isolated colonic disease than ileocolonic or isolated upper gut disease (Table 1.10) (69,71-73). One prospective (117) and three retrospective (121,124,128) studies have investigated disease location on induction of clinical remission, and a second prospective study investigated disease location on a patient's endoscopic response (39) (Table 1.12). These studies have reported conflicting results; therefore, further investigations are needed to elucidate if disease location influences the induction of remission.

Table 1.12 | Summary of studies investigating the effect of exclusive enteral nutrition on Crohn's disease remission in children

Author, year	Study population		Length of EEN (weeks)	Data differentiation	Response to EEN		
	Study design Population Exclusions EEN protocol, extra's allowed	*n* (male:female); Age +/- age range			Clinical remission [Δ] (%)	Response but not clinical remission (%)	Remission defined as
Randomised Controlled Trials							
Pigneur *et al.* 2019 (77)	Single-centre RCT Efficacy comparison of EEN and CS for MH, microbiota composition and cytokine profiles Newly diagnosed CD with active disease Exclusions: antibiotic use in the previous 4 weeks, CS, biologic and immunosuppressive therapy, isolated perianal or oral disease, surgery risk, non-adherence to protocol risk, steroid refusal EEN protocol: EER (including basal requirements plus catch-up growth if required), extras not reported	N=19 EEN only 13 (3:10) 11.7±2.5 y. [a]	8	Clinical remission	100		HBI <5
				MH	89		CDEIS <3 or >60% point drop
Grogan *et al.* 2012 (89)	Single-centre RCT Efficacy of polymeric vs elemental formula for inducing remission Newly diagnosed with active CD, treated with EEN Exclusions: children with only large bowel disease EEN protocol: minimum EAR, clear fluids only	15 (7:8) 12.5±2.2 y. [a]	6	EF (ITT) EF (PP)	70 93		PCDAI<11
		19 (13:6) 11.3±2.9 y. [a]		PF (ITT) PF (PP)	71* 79*		

Borrelli *et al.* 2006 (78)	Single-centre open-label RCT Efficacy of EEN and CS on intestinal inflammation and clinical outcomes Newly diagnosed, treatment-naïve, moderate to severe disease only Exclusions: fistulising, anorectal stenosing disease, pre-existing lung disease, systemic disease, renal or hepatic dysfunction, possible pregnancy and contraindication to CS EEN protocol: calculated to provide 120-130% of RDA, clear fluids allowed	N=37 EEN only 19 (8:12) [+] 11.0 y. [b•] (range 4-16 y.)	10		79	PCDAI ≤10 and an absence of symptoms
Ludvigsson *et al*. 2004 (90)	Multicentre RCT Efficacy of polymeric vs elemental formula as primary EEN therapy New or relapsing with PCDAI >12, treated with EEN Exclusions: planned medication change, presence of bowel obstruction, short bowel syndrome or high flow fistulae, previous bowel resection EEN protocol: calories calculated using a formula by Ruuska (94), water only	16 (11:5) 14.9±2.7 y. [a] 17 (11:6) 13.5±2.6 y. [a]	6	EF PF	69 82*	PCDAI <10 or Decrease in PCDAI of 40%, or Decrease in PCDAI of 15 points of the initial level
Prospective Cohort Trials						
Strisciuglio *et al*. 2020 (112)	Prospective single-centre observational study Impact of EEN on body composition, bone mineral density, and nutritional status at 8, 26 and 52 weeks Newly diagnosed CD and started EEN therapy Exclusions: co-morbidities known to affect nutritional status, bone metabolism, growth, or pubertal development EEN protocol: individual based on RDA energy, extras not reported	CD: 18 (14:4) 13 y. [b•] (range 8-16 y.) HC 15 (5:10) 11 y. [b•] (range 7-14 y.)	8		72	PCDAI (no definition)

Rolandsdotter *et al.* 2019 (118)	A prospective single-centre cohort study Effect of EEN on mucosal cytokine profiles Newly diagnosed CD, treated with EEN Exclusions: Immunosuppressive medications 6 mo. prior EEN protocol: 120% of RDA energy, allowed to drink clear fluids, eat a few popsicles and hard mints per day	13 (7:6) 12.5 (10.5-14.5) y. [b]	6		83		PCDAI <10
Cohen-Dolev *et al.* 2018 (95)	Prospective multicentre open-label Longer-term comparison of EEN and CS on clinical outcomes Newly diagnosed, treatment-naïve, with mild to moderate disease only Exclusions: PCDAI ≥40, induced with therapy other than EEN or CS EEN protocol: not reported	N=147 EEN only 60 (36:24) 12.0±3.1 y. [a]	6-8	ITT	63		Physician global assessment and PCDAI <10
Grover *et al.* 2016 (116)	Prospective single-centre open-label Efficacy of EEN in inducing long term sustained remission (Extension of 2013 study, below) Newly diagnosed CD, treated with EEN Exclusions: inability to tolerate EEN for a minimum of 6 weeks, steroid induction, stricturing disease with proximal bowel dilatation and obstructive symptoms, previous exposure to steroids, thiopurines, biological agents EEN protocol: based on Scofield's equation, small amounts of clear fluids and jelly allowed	54 Complete MH: n=18 (12:6) 12.2 y. [a•] aED n=36 (21:15) 12.67y. [a•]	6	Clinical remission	83		PCDAI ≤10
				Biochemical remission	72		CRP< 5mg/L & PCDAI ≤ 10
				complete MH	33	19	SES=0, Response SES 1-3
Levine *et al.* 2014 (96)	Prospective multicentre open-label Comparison of different medical therapies to induce remission Newly diagnosed, treatment-naïve	N=222 EEN only 43 (16:27) 12.3±3.9 y. [a]	6-8	Clinical remission	79		PCDAI <10 or PCDAI <7.5 without height
				Biochemical remission	51		CRP< 5mg/L & PCDAI ≤ 10

	Exclusions: patients starting therapy before enrolment, missing 12-week data, undergoing surgical resection, IBD-U EEN protocol: not reported						
Grover *et al*. 2013 (39)	Prospective single-centre open-label Efficacy of EEN in inducing clinical, biochemical, mucosal, and transmural remission over 12 mo. Newly diagnosed CD, treated with EEN Exclusions: inability to tolerate EEN for a minimum of 6 weeks, steroid induction, stricturing disease with proximal bowel dilatation and obstructive symptoms, previous exposure to steroids, thiopurines, biological agents EEN protocol: based on Scofield's equation, small amounts of clear fluids and jelly allowed	34 (21:13) 13.10 (9.5-15.75) y. [b]	6	Clinical remission	84		PCDAI<10
				Biochemical remission	76		CRP< 5mg/L & PCDAI ≤ 10
				Complete MH	42	46	SES=0 (complete mucosal healing)
				Transmural remission	21	64	MRI DAS 0-1
				L1 L2	54* 62*		SES <3 (complete or near-complete mucosal healing)
Gerasimidis *et al*. 2012 (111)	Prospective cohort Micronutrient changes during EEN New CD diagnoses or relapsed disease, treated with EEN Exclusions: not reported EEN protocol: RDA, water, tea, coffee, lemonade, and clear mints.	17 (8:9) 12.7 y. [b•] (range 7-14.8 y.)	6-8		47		Classified by consensus of multidisciplinary health professional team including paediatric gastroenterologists, specialist gastroenterology dietitians and IBD nurse specialists
Whitten *et al*. 2010 (37)	Prospective single-centre Effect of EEN on markers of bone turnover Newly diagnosed CD, treated with EEN only Exclusions: severe colitis in the previous 4 weeks requiring intensive medical or surgical management, or the use of anti-inflammatories and antibiotics EEN protocol: EER, water and sugarless gum	CD: 23 (17:6) 10.72±3.77 y. [a] Control: 20 (13:7) 8.64±3.23 y. [a]	8		70		PCDAI <15

Afzal *et al.* 2005 (117)	Prospective two centre review Clinical and biochemical response to EEN in different disease locations Newly diagnosed CD, treated with EEN only Exclusions: corticosteroids or immunosuppressants 4 mo. prior to enrolment, currently on antibiotics or immunomodulatory therapy, stricturing disease with associated prestenotic dilatation EEN protocol: 110 – 120 % of RDA, extras not reported	65 (45:20) 13.6 y. [b•] (range 8-17 y.) (54 newly diagnosed)	8	L1 (*n*=12) L2 (*n*=14) L3 (*n*=39)	92 50[◊] 82		PCDAI <20
Lionetti *et al.* 2005 (119)	Prospective single-centre investigation Is faecal microflora modified through EEN induced remission New and relapsing patients treated with EEN only Exclusions: not reported EEN protocol: not reported	9 (4:5) Range 9 – 17 y. Mean or median not reported	8		89		PCDAI ≤15
Fell *et al.* 2000 (120)	Prospective single-centre Effect of EEN on the mucosal inflammatory processes New and relapsed disease, treated with EEN only Exclusions: Drug therapy changed in the past mo., prednisolone >0.5mg/kg, immunosuppressive therapy, stricturing EEN protocol: matched to daily nutritional requirements, extras not recorded	29 (21:8) 13.6 y. [b•] (range 8.1-17.1 y.)	8		79		PCDAI <10
Retrospective Studies							
Moriczi *et al.* 2020 (38)	Retrospective multicentre cohort Efficacy of EEN over 12 mo. treated with EEN for first flare up Exclusions: concomitant steroids or anti-TNF during EEN	222 (140:82) 11.6±2.5 y. [a]	6-8		83	12	wPCDAI <12.5 points

	EEN protocol: caloric needs of patient, water					
Scarpato *et al.* 2020 (105)	Retrospective single-centre Review of EEN compared to CS on short- and long-term outcomes Newly diagnosed CD Exclusions: induction therapy not EEN or CS, complex perianal fistula EEN protocol: not reported	N=68 EEN only 47 (27:20) 129 mo. [b•] (range 37-212) mo.	6-8	68		PCDAI ≤10, in the absence of physical symptoms
Lafferty *et al.* 2017 (98)	Retrospective single-centre case-matched analysis Comparison of outcomes of EEN and CS treatments Newly diagnosed, first induction treatment Exclusions: previous CD treatment, EEN not at protocol by day 7, biologics, combined EEN and CS, EEN protocol: negligible amounts of boiled sweets, jelly and chewing gum	N=56 EEN only 28 (20:8) < 10 y. *n*=4 10-17 y. *n*=24 Mean or median not reported	6-8	86		PCDAI ≤10
Connors *et al.* 2017 (102)	Retrospective single-centre propensity-score matched analysis Long term analysis of clinical outcomes for patients treated with EEN and CS as induction therapy Newly diagnosed CD Exclusions: treatment stopped before 4 weeks of therapy EEN protocol: not reported	N=111 EEN only 76 (28:48) 11.9 y. [b•] (range 3.3-16.3 y.)	8-16	87	3	PCDAI ≤7.5 Clinical response PCDAI change ≥12.5 points
Luo *et al.* 2015 (126)	Retrospective single-centre Short-term efficacy of EEN compared to CS Newly diagnosed mild to moderate CD Exclusions: previous CS, immunosuppressive drug, biological agent use, inadequate follow-up, children who could not adhere to the protocol EEN protocol: not reported	N=38 EEN only 10 (7:3) 11.1 (5-15) y. [b]	8	90		PCDAI <10

Frivolt *et al.* 2014 (123)	Retrospective single-centre Short- and long-term outcomes of the first vs second course of EEN New or relapsing (on stable medications, AZA or ASA) disease, treated with EEN only Exclusions: disease onset <6 y. of age, history of systemic or local steroid treatment 3 mo. prior, history of anti-TNF therapy, EEN protocol: Individual calorie requirements, chewing gum and water	52 (31:21) 12.6±3.2 y. [a]	6-8	First EEN Second EEN	92* 72*		wPCDAI <12.5 for at least 28 days after reintroduction of everyday foods (week 12)
Cameron *et al*. 2013 (122)	Retrospective case note review Short- and long-term effects of EEN on clinical outcomes and anthropometry Newly diagnosed CD, treated with EEN only Exclusions: significant co-morbidity affecting growth, no baseline measurements, EEN discontinuation within 15 days EEN protocol: EAR energy, extras not reported	109 (68:41) 11.2 ± 2.4 y. [a]	8		60	29	Patient global assessment
Soo *et al.* 2013 (97)	Retrospective single-centre medical chart review Compare the efficacy of EEN and CS on remission and relapse Newly diagnosed CD Exclusions: less than 12 mo. follow-up EEN protocol: actual weight or ideal body weight for patients with weight loss, plus activity or stress factor based on patient's activity level and disease severity	N=105 EEN only 36 (21:15) 12.9 (7.4-16.2) y. [b]	6		89		PCDAI ≤10

de Bie *et al.* 2013 (124)	Retrospective two centre record review Short- and long-term outcomes after EEN to identify factors predicting success Newly diagnosed CD, treated with EEN only Exclusions: CS induction therapy, relapsed disease EEN protocol: 110-120% RDA for energy and protein, water	77 (57% male) 13.9 (11.1–15.7) y. [b]	6	ITT PP L1 (*n*=19) L2 (*n*=18) L3 (*n*=39)	53 71 88[◊◊] 53 51	20 26	Remission ≤2 stools/day (no blood, pus, mucus, abdominal pain, and weight loss). Partial remission ≤4 stools/day (less than daily loss of blood, pus, mucus, abdominal pain, weight loss)
Lambert *et al.* 2012 (106)	Retrospective case review Comparison of EEN and CS to outcomes over 24 mo. Newly diagnosed CD treated with EEN or CS Exclusions: combination EEN and CS, or alternate induction therapy EEN protocol: EER, extras not reported	N=57 EEN only 31 (21:10) 10.0±4.7 y. [a]	6-8		84		PCDAI<15
Rubio *et al.* 2011 (127)	Retrospective review The efficiency of EEN comparing fractionated oral and enteral feeding New or first relapse disease, treated with EEN Exclusions: Steroid or therapy modification during treatment period EEN protocol: basal caloric requirements plus catch-up growth, no additional food or liquid intake	45 (31:14) 11.3±3.4 y. [a] Newly diagnosed *n*=34	8	Oral	75*		PCDAI <10
		61 (39:22) 10.9±3.4 y. [a] Newly diagnosed *n*=41		Continuous enteral feeding	85*		
Buchanan *et al.* 2009 (128)	Prospective single-centre review Effect disease location has on the effectiveness of EEN A primary treatment course of EEN Exclusions: not reported EEN protocol: EAR or above if underweight, extras not reported	110 (65:45) 11.12 (9.84-13.49) y. [b]	7	Cohort L1 (*n*=4) L2 (*n*=19) L3 (*n*=29) L4 (*n*=49)	80 25** 79* 86* 88*		Improvement in all domains of the global patient assessment; combining inflammatory markers, stool frequency, weight gain and general well being

Berni Canani *et al.* 2006 (99)	Retrospective single-centre Comparing the efficacy of EEN and CS on clinical remission and MH Newly diagnosed CD Exclusions: intestinal surgery, CS or immunosuppressive drugs 3 mo. prior to diagnosis, incomplete data, poor compliance EEN protocol: Polymeric, elemental and semi-elemental formulas used, unsweetened tea and water allowed	N=47 EEN only 37 (21:16) 12.1 y. [b•] (range 7-16 y.)	8		87	PCDAI <10
Day *et al.* 2006 (125)	Retrospective case note review Benefits of EEN on disease activity and nutrition parameters over 24 mo. New and longstanding disease, treated with EEN only Exclusions: enteral feeds supplementing the diet EEN protocol: EER, extras not reported	27 (17:10) 11.8 ± 3.3 y. [a]	8	Cohort (ITT) New diagnosis (PP) (*n*=15) Long standing disease (PP) (*n*=12)	70 80 53	PCDAI ≤15 (Groups not compared)
Wilschanski *et al.* 1996 (121)	Retrospective record review Effect of nocturnal EEN on length of remission Active disease, treated with EEN Exclusions: immunosuppressive drugs started concurrently EEN protocol: nocturnal NG feeding only, clear fluids only	65 (36:29) 3.6 ± 2.1 y. [a]	≥ 4	Cohort L1 (*n*=27) L2 (*n*=33) L3 (*n*=5)	72 80 20[◊] 78	PCDAI <20

Abbreviations: aED, Active endoscopic disease; anti-TNF: Anti-tumour necrosis factor ASA: 5-aminosalicylate; AZA: Azathioprine; CD: Crohn's disease; CDEIS: Crohn's disease endoscopic index of severity; CRP: C-reactive protein; CS: Corticosteroid; EAR: Estimated average requirement (for age and gender); EEN: Exclusive enteral nutrition; EER: Estimated energy requirements; EF: Elemental formula; HBI: Harvey-Bradshaw index; HC: Healthy controls; IBD-U: Inflammatory bowel disease-unclassified; IQR: Interquartile range; ITT: Intention to treat; L1: Distal 1/3 ileum ± limited cecal disease; L2: Colonic disease; L3: Ileocolonic disease; L4: Upper disease proximal to the ligament of Treitz; MH: Mucosal Healing; mo.: Months; MRI DAS: Magnetic resonance imaging disease activity score; PCDAI: Paediatric Crohn's disease activity index; PF: Polymeric formula PP: Per protocol; RCT: Randomised controlled trial; RDA: Recommended daily allowance (for age and gender); SES: Simple endoscopic scoring; wPCDAI: weighted Paediatric Crohn's disease activity index; y.: Years

[Δ] Clinical remission is stated unless data is differentiated by other remission measures; [+] reported statistics for total population and male female split do not add up in the study report

* Not significant between-group comparison; ** p=0.02 compared to other groups; [◊] p<0.05 compared to L1 and L3; [◊◊] p<0.04 compared to L2 or L3

[a] Mean ± SD; [b] Median (IQR); • IQR or SD not reported

Response: The patient did not meet the clinical remission criteria but had a response to the treatment

It is thought that children who experience complete MH compared to just clinical remission will have better long-term outcomes (39). Complete MH in early-stage CD has been reported to have higher steroid-free remission rates (129) and a reduction in surgical resections (130). In a 2013 prospective cohort of 21 children, Grover *et al*. (39) compared endoscopic, transmural, clinical, and biochemical remission rates after a minimum period of 6 weeks of EEN. Remission rates determined by clinical or biochemical measures were much higher than endoscopic or transmural measures (84% and 76% vs 42% and 21%, respectively) (**Figure 1.5**). In a follow-up study (2016, *n*=54) (116), 83% of the children were in clinical remission, 72% were in biochemical remission, and 33% had complete MH (Figure 1.5). Disease activity has been reported to correlate poorly with symptoms (129,131,132); therefore, using clinical measures of remission, which rely heavily on symptoms, is likely to differ from remission determined endoscopically. This highlights that children may reach clinical remission based on a PCDAI <10; however, this does not necessarily translate to complete healing of the gut, thus increasing the frequency of clinical relapse, hospitalisations, surgical resections, and risk of fistulising disease (39).

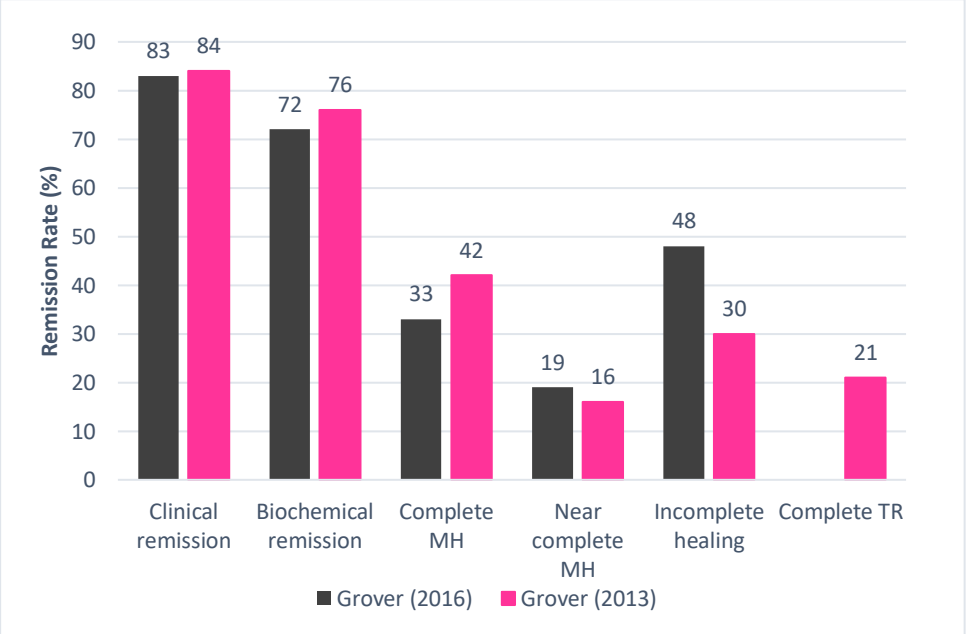

Figure 1.5 | Comparison of children with Crohn's disease achieving clinical and biochemical remission versus mucosal healing after a minimum 6-week course of exclusive enteral nutrition (39,116)

Abbreviations: MH: Mucosal Healing; TR: Transmural Remission (activity in the small bowel) MH was determined through simple endoscopic activity score (SES); SES = 0, MH; SES 1-3, near-complete MH; SES >3, incomplete healing; TR was determined via Magnetic Resonance Imaging disease activity score (0-1, no activity; 2-6, mild activity; >7, moderate to severe activity

MH has been identified as the goal of treatment and is crucial to maintaining an improved disease course (103,133-136). Currently, non-invasive models to predict disease remission or individual biomarkers such as faecal calprotectin (FC) or CRP do not accurately reflect the level of mucosal inflammation; therefore, endoscopic procedures assessing mucosal activity are the most effective way to determine mucosal healing (103,135,136). Whilst an ileocolonoscopy is the gold standard in predicting mucosal activity in CD, use in clinical practice is limited due to high cost, availability, the patient burden, and the risk of complications (103,135,137). Further well-designed prospective studies are required to elucidate an effective non-invasive model or biomarker/s that can assess mucosal activity, thus reducing the need for ongoing ileocolonoscopies for patients with CD. Non-invasive measures are critical in a clinical context to monitor and manage patients with CD more effectively (136).

1.3.5.2 Maintenance of disease remission

After inducing remission, the goal becomes long-term remission maintenance, which is critical for a child's growth, well-being, QoL and disease course (3,138). Maintenance of remission is achieved using secondary pharmacological therapies, i.e., thiopurines (azathioprine and 6-mercaptopurine) or methotrexate (Table 1.9, Figure 1.3) (74). Typically, in studies, maintenance of remission is measured as relapse rate. Relapse rates based on patients who achieved clinical remission after EEN treatment are reported to range from 0% (i.e., no relapse) to 72% after 1 year (39,97,98,105,106,112,116,120,121,123), 62% to 92% after 2 years (89,95,105,106,116,122,124), and 94% after 3 years (116) (**Table 1.13**). Relapse was reported to occur 3 to 16 months (mean or median) following induction therapy (89,95,98,106,122-124) (Table 1.13). Complete MH has been reported to lead to a 52% lower relapse rate compared to active endoscopic disease at one, two, and three years (**Figure 1.6**) (OR 0.48 [95% CI 0.23-0.98]; p=0.04) (116), highlighting that complete MH is crucial for improved long-term outcomes and remission of CD. However, follow-up endoscopy to determine MH in clinical practice is rarely used due to cost, availability and the invasive nature of the procedure (103,135,137).

Table 1.13 | Summary of studies reporting clinical relapse rate following exclusive enteral nutrition in paediatric Crohn's disease

Author, year	Length of EEN, weeks	Clinical relapse of children who achieved remission following EEN (during the specified time) (Time to relapse (if reported))
Scarpato *et al*. 2020 (105)	6-8	6 months: 26%, *n*=47 1 year: 41%, *n*=46 2 years: 51%, *n*=37
Strisciuglio *et al*. 2020 (112)	8	1 year: 0% (no relapse), *n*=18
Cohen-Dolev *et al.* 2018 (95)		2 years: 45%, *n*=60 (16.05±1.1 mo.) [a]
Lafferty *et al*. 2017 (98)	6-8	1 year: 46%, *n*=28 (3 (4) mo.) [b]
Grover *et al*. 2016 (116)	6	1 year: aED: 72%, *n*=36 / MH: 28%*, *n*=18 2 years: aED: 92%, *n*=24 / MH: 50%*, *n*=16 3 years: aED: 94%, *n*=19 / MH: 50%*, *n*=16
Frivolt *et al*. 2014 (123)	6-8	1 year: First EEN: 67%, *n*=48 (4.8 mo.) [b•] Second EEN: 70%, *n*=20 (7.6 mo.) [b•]
Grover *et al.* 2013 (39)	6	1 year: 71%, *n*=24 SES≤3: 53%, *n*=15 SES >3: 100%*, *n*=11
Cameron *et al.* 2013 (122)	8	2 years: 58%, *n*=109 (6.5 (7) mo.) [b]
de Bie *et al.* 2013 (124)	6	2.5 years: >3 months follow-up after EEN completion: 62%, *n*=37 (20.6 (10-39) wks.) [b]
Soo *et al.* 2013 (97)	6	1 year: 41%, *n*=32
Grogan *et al.* 2012 (89)	6	2 years: Elemental Formula, *n*=15 67% (183 (range 63-286) days) [a•] Polymeric Formula, *n*=19 68% (162 (range 53-301) days) [a•]
Lambert *et al.* 2012 (106)	6-8	1 year: 61%, *n*=31 (5.25 mo.) [b•] 2 years: 61%, *n*=31
Fell *et al.* 2000 (120)		10 months: 39%, *n*=23
Wilschanski *et al.* 1996 (121)	8	6 months: 43%, *n*=47 1 year: 60%, *n*=47

Abbreviations: aED: Active endoscopic disease; EEN: Exclusive enteral nutrition; IQR: Interquartile range; MH: Mucosal healing; mo.: months; SD: Standard deviation; SES: Simple endoscopic score for Crohn's disease; SES≤3 includes complete and near-complete mucosal healing; SES>3 includes mild, moderate and severe disease; wks.: Weeks
[a] Mean ± SD; [b]: Median (IQR); •: SD or IQR not reported
*: P<0.05

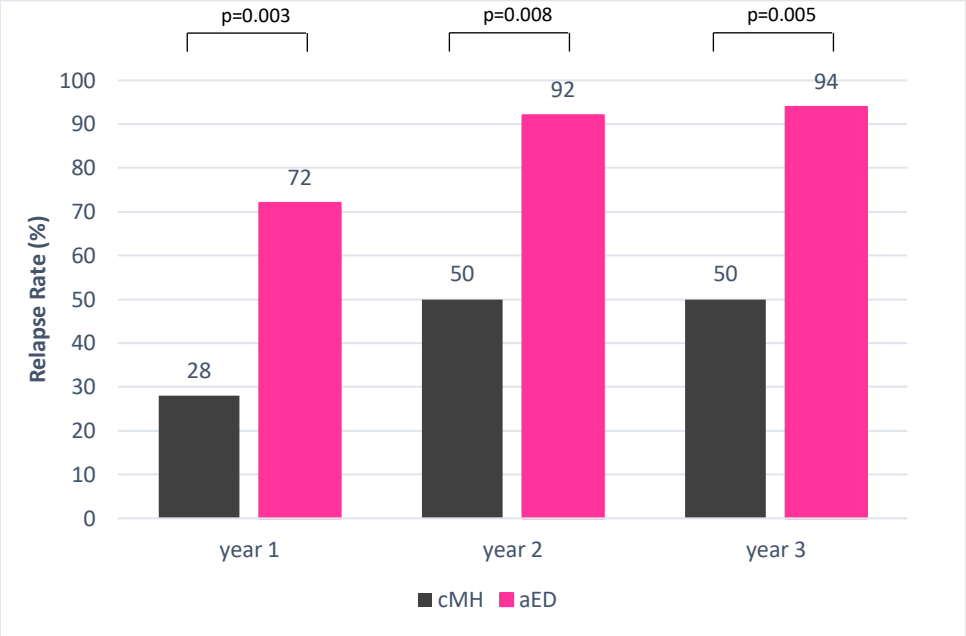

Figure 1.6 | Comparison of relapse rates between complete mucosal healing compared to active endoscopic disease in children with Crohn's disease (116)

Abbreviations: aED: Active endoscopic disease; cMH: Complete mucosal healing

1.3.5.3 Changes to anthropometry

Typically, there is a delay between the onset of CD symptoms and diagnosis, meaning that children often present with malnutrition, weight loss and disrupted linear growth (Figure 1.2) (36). Therefore, in addition to inducing long-term disease remission, catch-up growth is a crucial goal of nutrition therapy.

EEN, typically administered over a 6-8 week period is effective in making significant improvements in weight z-scores in children with CD (37,39,89,98,111,112,120,122,125). In contrast, improvements in height z-scores are not significantly different following treatment (37,39,93,98,111,112,123,125,126,128). There is less data on the long-term impact (6 to 24 months) of EEN on height and weight. Data suggests that weight z-score continues to maintain the significant improvements seen following treatment, whereas height z-score results vary, showing significant and non-significant changes (98,106,112,122,128). A retrospective case audit reported improved weight z-score, but not height z-score, in 109 children with CD over 24 months (122). In contrast, a prospective study by Strisciuglio *et al*. (112) investigating body composition changes reported significant improvements in weight and height z-scores at 26 and 52 weeks following an 8-week EEN course. This study provides evidence that improvements in height may be seen beyond the initial

course of EEN (i.e., take longer to appear), whereas improvements in weight can be seen at completion of the initial course of EEN (apparent in the short term). Further research is required to confirm this.

1.3.5.4 Changes to biochemical markers

When diagnosing and monitoring children with CD, biochemical markers albumin, CRP, erythrocyte sedimentation rate (ESR), and FC may be used (139). At diagnosis, biochemical markers cannot be used alone but are suggestive of IBD, allowing the gastroenterologist to rule out other diagnoses before progressing to endoscopic evaluation (4). Typically, CRP, FC and ESR are elevated before diagnosis, while albumin is diminished (4).

Following EEN therapy albumin levels in the blood are seen to increase (37,38,93,98,111,118,122-125), whereas CRP (37-39,98,111,116,118,120,122-125) and ESR (37,38,98,111,118,122-125) levels are observed to decrease. FC is not commonly reported in studies researching the effect of EEN; however, when it is available, it is reported to decline following treatment (38,105,118,123).

In studies comparing children with active and inactive CD, CRP (116,139) and ESR (139) are reported to be significantly lower, whereas albumin (139) is significantly higher in children in remission compared to active disease. Compared to reference standards used in NZ, children with active disease are reported to have CRP and ESR outside of the reference range (9.4-57.0 mg/L, reference 0-8 mg/L and 21-31 mm in 1 hour, reference 1-10 mm in 1 hour; respectively) (116,139,140). In contrast, albumin results in children with active disease are generally within the reference range (31-37 g/L, reference 32-48 g/L) but are lower than those with inactive disease (38-42 g/L) (139,140).

1.3.6 Reintroduction of solid food following exclusive enteral nutrition therapy

Once remission is induced in children with CD, EEN is slowly reduced over 2-3 weeks, while a patient's regular diet is reintroduced (75). Several therapeutic diets have been reported to be beneficial in maintaining remission and preventing relapse in CD, such as the specific carbohydrate diet, Crohn's disease exclusion diet, Mediterranean diet, fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet and the IBD-anti-inflammatory diet. However, studies investigating therapeutic diets lack RCTs, are heterogeneous, often have small populations and investigate mixed populations of patients with IBD, i.e., CD and UC, rather than CD specifically (141,142).

A recent Cochrane Review of dietary interventions for either inducing or maintaining remission reported conclusions were unable to be drawn due to limited data from small samples and heterogeneous studies (diets were varied) (141). In 2018, the Nutrition cluster from the International Organisation for the Study of IBD met to develop evidence-based recommendations for dietary patterns in relapse management of IBD (142). Due to a lack of RCTs testing specific dietary patterns,

recommendations were unable to be made. In most cases, the evidence level for the recommendations was low; however, CD consensus recommendations suggest:

> *Regular intake of fruits and vegetables (in the absence of symptomatic strictures) and reduced intake of saturated, trans, and dairy fat; additives, such as P80 and carboxymethylcellulose; processed dairy or foods rich in maltodextrins; artificial sweeteners containing sucralose or saccharine; and processed food containing nanoparticles* (142).

In this space, more well-designed RCTs investigating dietary patterns in CD are required for evidence-based recommendations to be made to patients with CD.

1.4 Limitations to literature reporting on exclusive enteral nutrition outcomes

There are several limitations to the evidence for the effectiveness of EEN in inducing and maintaining remission alone (*n*=19) or when compared to CS (*n*=11) in paediatric CD. Most studies in this clinical area are prospective (*n*=11) or retrospective (*n*=15) cohort trials, which can inherently introduce bias. Inclusion or participant bias is evident in some studies, whereby exclusion criteria such as children with CD who have previous exposure to or are currently treated with concomitant medications (37-39,78,99,101,116-118,120,121,123,126) or have complicated disease behaviour, e.g., stricturing (78,90,101,105,117,120) are excluded from individual studies. These and other less common exclusion criteria such as more severe (PCDAI >30) (95,126), or less severe disease (PCDAI <30) (78), previous or possible surgeries (77,90,96,99), or polytherapy (101,106) results in study populations that differ; therefore, making direct comparisons of outcomes between individual studies is challenging. Due to exclusion criteria, the findings of individual studies may not be representative of the paediatric CD population, thus lacking generalisability.

In terms of study design, most studies (*n*=26) were not randomised; therefore, treatment choice is primarily determined by the physician and patient, including a reluctance to take steroids as an alternate induction treatment, which contributes to selection bias. Twenty-four (80%) studies were carried out within a single institution and the majority had small numbers, 13 studies (43%) had fewer than 50 participants (37,39,77,78,89,90,111,112,118-120,125,126) and 9 studies (30%) had between 50-100 participants (98,99,105,106,116,117,121,123,124). Prospective studies can be influenced by factors such as refusal of repeat endoscopies (as a measurement of pathological remission) linked to improvements in symptoms, which impacts data completeness according to treatment protocols, resulting in missing data. Whilst retrospective studies were reported to exclude children with missing data.

Whilst most studies had a primary outcome of determining whether clinical remission is reached, measurements and definitions of clinical remission varied. In most studies, a PCDAI score ≤ 10 is utilised as the definition of clinical remission (39,78,89,90,95-99,105,116,118,120,126,127); however, PCDAI ≤ 7.5 without height (96), PDCAI < 15 (37,106,119,125), PCDAI < 20 (117,121) or decreases of set percentages or PCDAI points (e.g., decrease of PCDAI of 40% or 15 points of initial level) (90,102) are also utilised. Differing measures such as a weighted PCDAI (38,123), endoscopic scoring (39,77,116) or subjective measures such as a PGA (95,111,122,124,128) are also used; therefore, the lack of standardisation makes it difficult to compare clinical remission outcomes accurately. Furthermore, the PCDAI as a measure of clinical remission is regarded as a fallible measure (100), as symptoms and biomarkers of disease activity do not necessarily indicate mucosal healing (103,129,131,132,135,136) as previously discussed (section 1.3.5.1).

1.5 Crohn's disease and exclusive enteral nutrition summary

CD is a chronic lifelong relapsing disease involving any part of the GI tract (2,3,5,7,26). Incidence is rising globally; however, disease pathophysiology and aetiology are still not completely understood. The current consensus is that genetic predisposition combined with altered intestinal microflora and a dysregulated immune response leads to the development of chronic inflammation and, ultimately, CD in some individuals (1,3,7,13).

The principal goal of therapy for patients with CD is to induce and maintain remission (1,3). Several treatment pathways for remission induction in paediatric CD are available, with EEN as the recommended first-line therapy (74). In paediatric CD patients, EEN is reported to be as effective in inducing remission as CS; however, it has additional benefits over remission induction, including MH, normalisation of inflammatory markers, growth stimulation, correction of micronutrient deficiencies, and a decreased need for steroids (108). Growth stimulation is an essential element of therapy as diagnosis of CD can often occur during adolescence, impacting key stages of pubertal development such as height (3,13). Long-term outcomes are also improved when remission is induced via EEN, as MH is crucial for long-term remission, which results in lower relapse rates than in active endoscopic disease (39,116). All of which provide significant evidence of the benefits of utilising EEN as the preferred treatment modality compared to CS in paediatric patients.

1.6 Patient and whānau perspectives

1.6.1 Information needs of patients and whānau affected by inflammatory bowel disease

An important aspect when an IBD diagnosis is made and during the disease course is receiving appropriate and timely information or education regarding the disease and its management (143).

Literature investigating the information needs of IBD patients is limited and is frequently the IBD disease modalities of CD and UC combined as a single group. Information needs of children or their whānau are lacking; however, eight studies have investigated the information needs of adults with IBD (143-150). Whilst these adults are IBD patients, it could be hypothesised that the information needs of the parents of children with CD may be similar; however, further research into paediatric patient and whānau information needs is required.

Adults have identified a wide variety of topics that they classed as very important in newly diagnosed IBD. However, there was a disconnect between finding the information important and receiving the right amount of information; only 8% to 36% of adults with IBD received the right amount of information on these topics (**Table 1.14**) (143,145,146,148). Therefore, to manage a patient's disease, there needs to be a partnership between the patient, whānau and the health professional (143,148). Effective communication is critical during IBD management so the HCPs can understand and be aware of the patient's needs or concerns (150).

Information needs for adults, determined via quantitative surveys, fell into three broad categories; 1) general disease knowledge, 2) treatment of IBD, and 3) self-management. General disease knowledge included common symptoms, complications, aetiology, cancer development risk, how fertility may be affected and the genetic predisposition of a child developing IBD (143,145,148). The treatment of IBD includes medications and common side effects, surgical treatments, managing pain and other symptoms, altering medications when symptoms are troublesome, and when to contact a HCP (143,145,148). Self-management includes topics of; changes to diet when CD is active or inactive, foods that offer the best nutritional value, risks of nutritional deficiencies, when supplements may be required, how to talk to family about IBD, managing time away from school or work, support if sick days run out, and sources of support in order to cope with IBD (143,145,148). The importance rating varied by topic and those rated as very important by over 80% of participants are displayed in Table 1.14.

Sources of information include the patient's gastroenterologist and general practitioner (GP), the internet, newspapers, books, television and magazines, patients associations, pharmacists, paramedics, family and friends, and educational programs (147,149). The most common sources of information were the patient's gastroenterologist and GP and the internet (143,147,149,150). When symptoms first developed, the gastroenterologist was reported to be the most common source of information (68% of adults); however, this dropped at diagnosis to 37%, whereas using the internet as the most common source of information increased from 31% to 42%, respectively (149). Significantly more males searched the internet than females, and women were significantly less satisfied with information from their physicians and the internet than males (149).

Table 1.14 | Summary of studies investigating the information needs of patients with inflammatory bowel disease

Author, year, study population	Summary of study findings related to information	
	Topics rated important by > 80% of participants Patients who received the right amount of information	Information received at diagnosis
Bernstein *et al* 2011 (143) Single-centre survey Canada N=74 IBD, *n*=34 CD Male 35, female 39 Age: 37.8±14.9 y. [a] Age at diagnosis: 36.4±14.7 y. [a] Disease duration: 3-24 months	General disease knowledge: prognosis 14% Treatment: medications and side effects, managing pain and other symptoms, medications adjustment when symptoms cause problems, when to contact a HCP 12%-31% Self-management: changes to diet when CD is active or inactive, foods offering the best nutritional value, risk of nutritional deficiencies 14%-19%	Patients described that they received little or no information on topics that they considered important 24% were dissatisfied with the amount of information received at diagnosis The right amount of information was received by a modest number of patients
Wong *et al.* 2012 (148) Population-based research registry, self-report survey Canada N=271 IBD, *n*=132 CD Male 106, female 165 Age: 46.5±14.5 y. [a] Disease duration: Average 11 y.	General disease knowledge: symptoms, complications, prognosis 11-36% Treatment: medications and side effects, managing pain and other symptoms, medications adjustment when symptoms cause problems, when to contact a HCP 10%-32% Self-management: changes to diet when CD is active or inactive, foods offering the best nutritional value, risk of nutritional deficiencies 8%-16%	The right amount of information was received by a modest number of patients 38% were dissatisfied with the amount of information received at diagnosis
Wu & Zhong 2018 (145) Cross-sectional survey China *n*=159 CD Male 114, female 45 Age range 14-70 y. ≤25 y. 39%, 26-35 y. 37%, 36-45 y. 13% ≥46 y. 11% Age at onset: <17 y. 12%, 17-40 y. 77%, >40 y. 11% Disease duration: <1 y. 35%, 1-5 y. 46%, >5 y. 19%	General disease knowledge: complications, prognosis Treatment: drug treatment, adjusting medications, regular follow-up Self-management: diet choice in active and inactive disease, life management Information received was not studied	
Daher *et al.* 2019 (146) Online questionnaire Israel N=571 IBD, *n*=392 CD	General disease knowledge: symptoms, complications, prognosis, cancer risk, how IBD affects fertility Importance mean rating >4.0/5.0 Information received mean rating 0.4-1.7/5.0	A wide variety of topics were considered to be very important for a patient with newly diagnosed IBD; however, participants felt that they had

Male 190, female 162 Age 33.8±15.1 y. [a] Age at diagnosis: 24.1±10.8 y. [a]	Treatment: medications and side effects, managing pain and other symptoms, medications adjustment when symptoms cause problems, when to contact a HCP, alternative medications; Importance mean rating >4.0/5.0, Information received mean rating 0.5-1.5/5.0 Self-management: changes to diet when CD is active or inactive, foods offering the best nutritional value, risk of nutritional deficiencies, when supplements are required, managing time away from school or work, support if sick, sources of support in order to cope with IBD, how to cope psychologically with an IBD diagnosis, tools to deal with stress related to diagnosis or affecting disease Importance mean rating >4.0/5.0 Information received mean rating 0.3-1.5/5.0	received little or no information on the topics that they regarded as important

Abbreviations: CD: Crohn's disease; GP: General practitioner; HCP: Health care professional; IBD: Inflammatory bowel disease; y.: Year

[a] Mean ± Standard Deviation

Knowledge requirements change during the disease course and are higher at diagnosis and relapse than when the disease is in remission (144). Many adults with IBD wanted more information than was provided; however, others felt that additional knowledge would not be beneficial and could increase their anxiety (144). Two studies in Canada, one evaluating the information needs in long-duration IBD (average age 11 years, *n=271*) (148) and the second evaluating information needs in recently diagnosed IBD cases (3-24 months, *n*=74) (143), found similarities in what the participants felt was very important as well as the number of patients who receive the right amount of information (Table 1.14).

1.6.2 Patient and whānau experiences of exclusive enteral nutrition

Few studies (*n*=3) have investigated patient or whānau experiences during EEN use or their perceptions of the EEN protocols (151-153). Patient and whānau experiences using EEN for IBD are diverse; however, in paediatric and adult IBD patients, the food restrictions imposed by EEN can be challenging (152,154). Children and adolescents reported that they could feel excluded from family meals and other enjoyable occasions connected with food and eating due to the restrictions put in place by the EEN protocols (154). They could also feel isolated, different or ostracised from their peers, which can cause a negative self-image during adolescence based on the child's interpretation of how others perceive them (151,154). The social impact on adults was divergent; some needed to avoid activities during EEN therapy, while others maintained usual involvement to normalise their situation (152). Adults reported that EEN was difficult at first while getting used to not eating; however, a reduction in gut symptoms aided adherence, but difficulty increased towards the end when returning to regular consumption of food again (152).

Parents of current EEN users reported cost/finances (33%) and difficulty in social situations (27%) as the main barriers to EEN use, and the therapy was not working (37%) or it was complete (21%) as the main reasons for stopping EEN (153). Adherence to the EEN treatment protocol, drinking the prescribed volume, pain, nausea, and night-time waking with nasogastric overnight feeding are factors reported by patients as contributing to difficulties associated with EEN therapy (118,121,124). Social support from whānau and friends was found to be critical to enabling the success of treatment, alongside support from HCPs (152).

1.6.3 Food practices and dietary strategies patients with inflammatory bowel disease use

Eight studies have investigated dietary strategies and food practices of children (*n*=1) and adults (*n*=7) living with IBD (155-162). Using a semi-structured interview format, Chuong *et al.* (158) reported that children and adolescents with IBD and their caregivers (*n*=28) used food avoidance and moderation as a possible way to gain control over their illness. They took an active role in manipulating food

practices to manage their IBD, and their relationship with food was dynamic and would change depending on whether their disease was active or inactive (158). Identifying foods that may trigger symptoms was accomplished using trial and error, i.e., "how does this food make my stomach feel?" (158). The participants reported avoiding a wide variety of foods or food groups that they thought exacerbated symptoms, such as; fast foods, fried foods, spicy foods, processed foods, foods containing gluten, foods high in fibre such as raw vegetables, corn and popcorn (158).

Similar food practices and dietary strategies are reported in adults; however, adults also avoided carbonated beverages, alcohol, coffee and tea, dairy and red meat (156,157,160,161). Foods reported to improve symptoms or have no effect included carrots, potatoes, white bread, rice, biscuits, candy, steamed vegetables, banana and yoghurt; however, many more foods are reported to worsen symptoms than improve them. However, whether these foods impact bowel inflammation or just patient symptoms is not known (157,159,161). A French cross-sectional study used a self-administered questionnaire to determine dietary knowledge and choices in 50 CD patients (mean age 44.7, range 18-70 years) (162) and reported that 80% had changed their eating habits since diagnosis. In 27% of cases, the dietary change was initiated by a HCP; however, only 69% were reported to follow the HCP advice; therefore, nearly three-quarters of patients had made a dietary change without HCP advice (162).

Navigating their diet was considered a lifelong struggle for some adults with IBD, while others feel that food does not play a role in their symptoms (157). For some, food has become an uncertain experience or agonising problem rather than a pleasurable or enjoyable social experience (156,157). Nutritional status may be compromised due to the dietary restrictions imposed by the patient (159); however, a questionnaire survey of IBD patients (*n*=244) reported that only 36% of participants felt that a nutrient deficiency could result from their dietary behaviours (156). Poor food-related QoL has been associated with decreased intake of fibre, calcium, magnesium and phosphorus, nutrients vital for bone and gut health (155).

Dietary advice from a HCP has been reported as confusing, generic, non-specific and unhelpful (157,160). Studies report that HCPs have advised patients that dietary intake does not affect IBD and that eating a variety of foods in moderation is appropriate, whereas other HCPs have recommended a gluten-free diet, a low fibre diet or restrictions during a flare (157,160,162). Some adults with IBD have voiced that they find it hard to accept that their diet is not connected to their IBD symptoms (160). Over 80% of adults with IBD rated changes to the diet when IBD is active and inactive, foods that offer the best nutritional value, and risk of nutritional deficiencies as very important; however, only 8% to 19% felt they received the right amount of information on these topics (Table 1.14) (143,148). For these reasons, IBD patients turn to the internet to find advice from internet forums,

discussion groups, or websites on IBD (160). Therefore, patients impose dietary changes without professional advice, leading to a possible risk of nutritional deficiencies or inadequacies (157).

Due to a lack of strong evidence-based dietary guidelines, one of the most common sources of information for IBD patients is the internet (143,147,149,150). Online sources provide various dietary options for a patient with IBD; however, these are unverified nonmedical resources, and the information can be contradictory (163). Hou *et al.* (163) published a review in 2014 of patient targeted dietary recommendations, where they ran an internet search for "CD diet" and "UC diet", finding 47 unique sites for CD and 55 unique sites for UC. All sites recommended excluding cruciferous vegetables, alcohol, carbonated beverages, and sugars, and >80% recommended excluding raw vegetables, citrus, red meat, coffee and tea, fatty and fried foods, spicy food, seeds and popcorn (163). Recommended inclusions by all sites were cooked vegetables, poultry and lean protein, while fish, tofu and a high protein diet were recommended by >80% (163). Conflicting advice was found both between sites and within site, and the highest conflicting advice was for nuts (17%), whole grains (18%), any vegetables (21%), and any fruits (32%) (163).

1.6.4 The impact of inflammatory bowel disease on quality of life and psychosocial health

Due to the chronicity of CD with alternating periods of relapse and remission, patient QoL can be severely affected. Whilst the literature in this space is limited, QoL in adults and children with CD is associated with disease activity; the higher the disease activity index, the lower the QoL (155,164-168). While QoL is reported to be affected by active disease, Keeton *et al.* (*n*=294, mean age 47.8 years) (167) reported that 95% of participants reported significant IBD associated concerns, despite the majority of participants (74%) being in remission. Lix *et al.* (169) reported patterns of disease activity impacted QoL but not psychological function over 2 years, suggesting that IBD exerts a continuous effect on patients' lives.

Development of IBD during the life course is challenging; however, the development of IBD during childhood and adolescence, a time of psychological, physical and social change, can put patients at risk of psychological and psychosocial problems (170). In a comparison of Australian adolescents and young adults with IBD to young people with other chronic diseases (*n*=51, mean age 21.4), young people with IBD were significantly more likely to be at risk of depression on the Kessler psychological distress scale than those with other chronic illness (37.2% compared to 23.2%, respectively; p=0.04) (171). In adults, Fu *et al.* (165) reported anxiety and depressive symptoms in more than 40% of the studies 199 IBD participants, and Mules *et al.* (172) reported severe depressive symptoms in 36.1% (95% CI 26.8-45.5%), and severe anxiety symptoms in 23.8% (95% CI 15.5-32.1%) of CD patients (*n*=107). The association between endoscopic disease activity and stress, depressive or anxiety

symptoms was not significant; however, increased or worsening symptoms were significantly associated with stress, depressive or anxiety symptoms ($p<0.05$) (172). Prior diagnoses of depression or anxiety (15% and 10%, respectively) did not mirror those who were experiencing severe symptoms of depression or anxiety (31% and 22%, respectively) (172), and 54% of IBD patients report wanting psychological help; however, only 28% have had prior therapy (173). This information suggests that psychosocial screening should be an essential part of treatment and care pathways in patients with IBD (171).

IBD is a heavy burden for children, and the disease changes both how they view themselves (perception as different to their peers) and how they interact with their peers (difficulties in engaging in typical peer group activities, changing friendships) (154). Children with IBD perceive that they have limited control over their bodies and lives due to their IBD, the possibility of a flare occurring at any time, the need for ongoing monitoring, and help with toileting and hygiene (154,174). Social support from a child's family is critical in enabling the child to cope with their disease, while children without a supportive family can feel helpless and worried about their disease (154). Participating in a summer camp for children with IBD improved children's overall health-related QoL, possibly due to increased social support from similar peers, thus normalising their experiences (175). Attending camp is a personal experience, with some children envisaging the camp as depressing and centred on their disease, whereas campers reported feeling understood as they bonded with peers (154,176). This and other peer support programs enable children with CD to engage with "kid's like me" (176), helping them to adjust to living with IBD (177-179).

An extensive survey investigation to determine the impact of IBD on patients' lives (*n*=4,670, 25 European countries) has reported gaps in healthcare delivery and communication (180). Only one-third of patients are diagnosed within six months of symptom development, with nearly half taking longer than 1 year (180). Most of the respondents (85%) had been hospitalised in the last 5 years, only 56% were very or somewhat satisfied with their treatment plan, 56% felt that they could not disclose a potentially important point about their illness to their gastroenterologist, and 64% felt that the gastroenterologist should probe more to understand the patient's disease status better (180). Friendships are affected, they have to consider toilets when planning an outing, can be unfairly judged by others regarding toileting, and their work or school life can be affected due to pain, fatigue, and medical appointments; therefore, IBD has a significant impact on a person's life (180).

1.7 Summary of patient and whānau perspectives

Patients with IBD require a wide variety of information on their disease at diagnosis; however, there appears to be a disconnect between what patients deem important and the information they receive

(143,145,148). Information is acquired from various sources, most commonly their gastroenterologist or GP and the internet (143,147,149,150). Prior to diagnosis, more information comes from the patient's gastroenterologist or GP; however, after diagnosis, they gain more information online (143,147,149,150).

Patients and whānau report diverse experiences with EEN; however, the food restrictions are challenging and create social isolation from both friends and family during treatment, which is also a barrier to use (151,153,154). Following induction treatment, manipulation of dietary intake through food avoidance or moderation is common in children and adults with IBD (156-158,160,161). Navigating nutrition is reported as a lifelong struggle for these patients, which decreases the enjoyment and pleasure associated with food (156,157). Most patients have not had advice from a HCP when making their dietary changes, which could lead to nutritional inadequacy or deficiency (157,159). Patients have reported receiving confusing, non-specific or unhelpful advice from a HCP, while conflicting advice can be found online (157,160,163).

CD affects QoL of both adults and children, with poorer QoL reported during active disease, while worries and concerns continue to affect QoL during disease remission (155,164-168). Higher levels of depressive and anxiety symptoms are found in children and adults with IBD, suggesting screening for psychosocial symptoms should be part of care pathways (165,171,172). Social support from friends and family is an essential element in coping with IBD, and children who attended an IBD summer camp found the experience helped in adjusting to living with IBD (154,175,176).

1.8 Health professional perspectives

1.8.1 Multidisciplinary support during Crohn's disease treatment

IBD services differ worldwide in both structure and the disciplines involved in the care of the patients (181). A report detailing international health professional views on IBD care reported that ideally, the IBD service would involve an IBD nurse specialist (IBD-NS), a dietitian and a psychologist working to identify and prevent serious problems developing (182). Ideally, a specialist clinic would have all the HCP at the same location and be accessible to patients; however, funding was the primary barrier to establishing the service (182).

The nature of IBD as a chronically relapsing and remitting disease means that long-term follow-up is required, and hospitalisations are common (180). In Australia, inpatient healthcare costs are reported as lower in IBD patients who are managed proactively by a formal IBD service than in non-IBD controls (183). Before the service change, IBD patients had higher costs than non-IBD age and sex-matched controls (184). The change to a formal service included a named lead gastroenterologist, an IBD-NS, a specialist IBD clinic, a joint surgical and medical clinic and a regular radiology review schedule as well

as a phone helpline, protocol for monitoring, scheduled phone follow-ups, active management according to disease status, support and education such as leaflets, newsletters and encouragement to join Crohn's and Colitis Australia (183). IBD-NSs are described as having a "pivotal role in IBD management, supporting both patients and the multidisciplinary team (MDT)" (185). Two studies investigating the benefit of a dedicated IBD-NS, one in France (186) and one in Australia (187), reported a reduction in hospital presentations and admissions and outpatient reviews resulting from an IBD-NS. The IBD-NS was an established point of contact for patients, conducted patient education and reviews, and facilitated access to the IBD team (185-187). Access to IBD-specific healthcare via an IBD-NS (in-person or via phone) enabled a patient-focused, flexible approach to disease management, resulting in cost savings and improved patient contact (186,187).

IBD United Kingdom, a multidisciplinary collaboration of patient and professional organisations, recently published consensus standards for healthcare in IBD (188). The IBD service is recommended to include a MDT, including senior HCPs, an IBD-NS and a service coordinator to monitor and manage the service (188). It was agreed that all newly diagnosed patients should have a named gastroenterologist and an IBD-NS as a contact point and have a full assessment of their mental health, nutritional status, bone health and disease status, with reviews carried out on an appropriate schedule (188). The literature varies on the specialities included in an IBD MDT; typical inclusions are gastroenterologists, IBD-NS, a service coordinator, dietitians, psychologists, pharmacists, and surgeons (181,188).

1.9 Management of paediatric Crohn's disease in New Zealand

In New Zealand until 2014, treatment for CD was determined by the patient's gastroenterologist. EEN was often used, but there was variation in the treatments used to induce and maintain remission in this patient group. In 2013, a retrospective case-note review of 109 CD patients aged 3.3 to 15.7 years reported that an 8-week course of EEN induced remission in 60% of patients, with a further 29% experiencing an improvement in their patient global assessment (122). Weight, body mass index (BMI) z-scores, and inflammatory markers were also reported to improve during EEN (122).

This research instigated a country-wide review of NZs management of paediatric IBD. In 2014, the Paediatric Gastroenterology Clinical Network published the Management of IBD in children and adolescents in New Zealand clinical guideline (IBDCG) (189). This set out a framework for and formalised the use of EEN as the first-line treatment to induce remission in paediatric CD patients in NZ (**Figure 1.7**). The guideline states that EEN should be used as the first-line therapy for 8 weeks unless fistulising disease is present (189). After inducing remission, a maintenance cascade is

described in detail to maintain remission (Figure 1.7). If treatment or maintenance fails, then alternate pathways are followed.

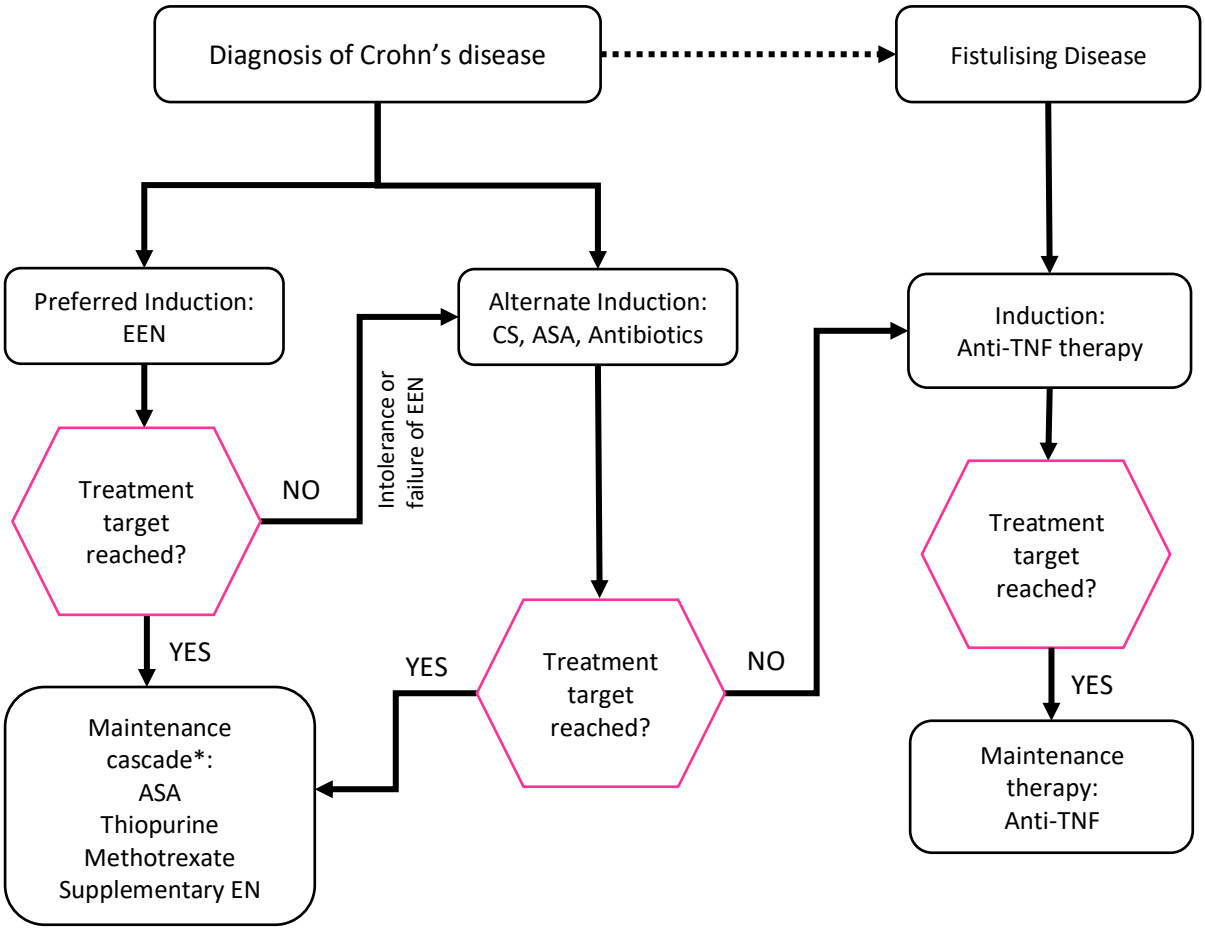

Figure 1.7 | Summary of the Management of Inflammatory Bowel Disease in Children and Adolescents in New Zealand Clinical Guideline (189)

Maintenance cascade description:
- Aminosalicylates may have a role in inducing or maintaining remission in children with mild disease
- Thiopurines are used when aminosalicylates are not sufficient to maintain remission or with moderate to severe disease
- Methotrexate is used when children do not tolerate thiopurines or have failed thiopurine therapy

Abbreviations: Anti-TNF: Anti-tumour necrosis factor-alpha; ASA: Aminosalicylate; CS: Corticosteroids EEN: Exclusive enteral nutrition; EN: Enteral nutrition

1.9.1 Thesis rationale, aims and objectives

Since the introduction of the IBDCG in 2014, changes in disease remission and clinical outcomes such as growth have not been reviewed; therefore, it is unclear whether its implementation has improved disease remission rates and clinical outcomes in paediatric CD patients at SCH. Patient, whānau and HCP views and experiences of EEN treatment, education, and support via the IBDCG are also unknown. Therefore, this thesis aims to 1) determine if the implementation of the IBDCG has improved disease remission rates and clinical outcomes in paediatric CD patients managed by SCH, 2) determine if the IBDCG needs modification to improve clinical practice or support for the future, and has the following objectives:

1. To complete a retrospective process and impact evaluation of the IBDCG, dietetic input, and patient outcomes in 103 children and adolescents with Crohn's disease managed by SCH from 2010 to 2020;
2. To evaluate current clinical practice under the IBDCG and assess whether the pathway has impacted clinical outcomes to inform clinical practice and support;
3. To determine patients, whānau and HCP experiences and perspectives on education, support, EEN practices and solid food reintroduction.

CHAPTER 2: METHODOLOGY

This research utilises a mixed-methods approach; therefore, this methods chapter is divided into two sections. Section one details the design and procedure of a retrospective medical note audit of paediatric CD patients at SCH. Section two details the methodology for semi-structured interviews with patients, whānau, and health professionals to determine their perspectives on EEN and the IBDCG pathway.

2.1 Ethical considerations and consent processes

Ethical approval for this study was obtained from the Auckland Health Research Ethics Committee (Reference: AH3434), and institutional approval was obtained by the Auckland District Health Board (ABHB) Research Office (Reference: A+8241).

A waiver of consent was approved for patients identified in the retrospective medical note audit. These patients continued to receive standard care through SCH, and their inclusion in the audit did not impact their treatment. All recorded personal health information was de-identified using an independent identifier code specific to this research project that did not allow linking to patient national health index numbers (NHIs). All data was stored in a password protected file only accessible to the research team. All data collection variables were pre-defined, and only medical notes relevant to the audit were reviewed.

Patients, their whānau, and health professionals were invited to participate in semi-structured interviews. All participants were provided with a participant information sheet (PIS) (**Appendix 1, 2, 3**) before giving informed consent. Participation was voluntary, and participants had the right to withdraw without giving any reason or impacting their treatment through SCH. The semi-structured interviews were completed according to a pre-defined protocol, and participants were given a coded identifier. All interviews were recorded using a voice recorder app (version 21.3.30.23), Zoom (https://zoom.us/) or Otter.ai (version 2.1.60-3125) and transcribed verbatim into a password-protected Microsoft® Word document. Following transcription, audio files were destroyed. All files were stored on a password-protected computer.

Section one: Retrospective medical note audit

2.2 Research design

In 2014, the IBDCG was introduced, which provided a framework and formalised the treatment cascade for paediatric patients diagnosed with CD (Figure 1.7). A retrospective medical note audit of newly diagnosed paediatric patients with CD was completed between May and August 2021. In this audit, patients were grouped into those diagnosed *prior* to January 2015 (*n*=45) and those diagnosed *after* January 2015 (*n*=58). A comparison of clinical outcomes pre IBDCG implementation (2010-2014, termed 'pre-2015') and post IBDCG implementation (2015-2020, termed 'post-2015') was used to determine whether the IBDCG has improved patient outcomes such as disease activity, biochemical markers and z-scores.

2.3 Participants

Senior paediatric gastroenterology dietitians Amy Andrews and Kim Herbison identified 103 patients diagnosed with CD and managed by the SCH paediatric gastroenterology between June 2010 and July 2020 in a previous research project investigating the clinical outcomes of EEN as a first-line treatment. Demographic information such as age, gender, ethnicity, socioeconomic status, disease location and behaviour, remission, treatment, EEN duration and method, anthropometry and nutritional status 6 to 8 weeks following diagnosis have been collected and previously described (190). This data formed the base for the current research project.

2.4 Inclusion and exclusion criteria

Inclusion and exclusion criteria were pre-defined in the study protocol (**Appendix 4**).

Inclusion criteria:

- Patients aged 1 to 18 years
- Confirmed CD diagnosis
    - Between June 1st 2010, and July 1st 2020
    - Diagnosis of CD was based upon standard clinical, histologic, endoscopic, and radiologic criteria, determined via upper GI endoscopy, ileocolonoscopy and small bowel imaging as per the Porto criteria for diagnosis of IBD in children and adolescents (4)
- A minimum of 12 months follow-up from diagnosis
- Managed by the SCH paediatric gastroenterology team

Exclusion criteria:

- A diagnosis of UC or IBD-U
- Less than 12 months of follow-up data from the commencement of treatment

2.5 Data collection

Data on the 103 identified NHIs was collected from the ADHB patient management system (Regional Clinical Portal and 3M ChartView®). ADHB Clinical Records provided access to the patients' records. The student researcher developed a project-specific data collection tool in Microsoft® Excel® for the clinical audit. Each patient's case notes, including medical, dietetic and laboratory records, were searched according to the pre-defined data collection variables displayed in **Table 2.1**.

Table 2.1 | Retrospective medical note audit data collection variables

Variable	Data parameters	Search methods
Demographic information	*Gender (male/female)* *Ethnicity* *Socioeconomic status* *Date of birth*	*Collected and previously described by Rajasekaran et al. 2022 (190)*
Crohn's disease	*Date of diagnostic scope* *Disease location* *Disease behaviour* *Growth Delay* *Extraintestinal manifestations*	*Collected and previously described by Rajasekaran et al. 2022 (190)*
Anthropometric	*Reported weight loss pre-diagnosis* Weight Height	*Collected and previously described by Rajasekaran et al. 2022 (190)* Collected from the ADHB patient management system (Éclair) using search filter/text within observation name "weight". Reviewed cumulative data, which provided weight and height measurements across multiple collection points to determine the time point closest to the data collection time parameter
Laboratory values	C-reactive protein Erythrocyte sedimentation rate Haemoglobin Haematocrit Albumin Faecal calprotectin	All laboratory parameters collected from ADHB patient management system (Éclair) using search filter tab/text within observation name: "CRP" / "ESR" / "haemoglobin" / "albumin" / "calprotectin". Reviewed cumulative data, which provided measurements across multiple collection points to determine the time point closest to the data collection time parameter
EEN Treatment	*Start and finish date* *Route* *Failure reason*	*Collected and previously described by Rajasekaran et al. 2022 (190)*
	Further courses of EEN	Determined via ADHB patient management system (collected from clinic letters)
	Maintenance EN	Determined via ADHB patient management system (collected from clinic letters)
Concomitant medication started (date)	Aminosalicylates Azathioprine Steroids	Determined via: - ADHB patient management system (Éclair) using by service tab/pharmacy: pharmacy dispensing determined the start date of medication.

		- Clinic letters were also scanned for medication start dates.
	Infliximab and Adalimumab	Determined via ADHB patient management system (collected from clinic letters and discharge summaries)
Other	*Remission status determined by the gastroenterologist*	*Collected and previously described by Rajasekaran et al. 2022 (190)* Current practice is based on a physician global assessment, i.e., the clinical impression of whether the disease is well controlled by assessing several factors such as symptomatic response, growth and blood markers (+/- faecal calprotectin) carried out by the gastroenterologist.
	Medical conditions at baseline and after diagnosis	Determined via ADHB patient management system (collected from clinic letters)
	Paediatric Crohn's disease activity index	Determined via ADHB patient management system (collected from clinic letters)
	Medical points of contact and dietetic points of contact	Doctor and dietetic points of contact (encounters) were determined from 3M ChartView® based on the diagnostic scope date. If the patient was hospitalised, medical contact points included ward rounds (abbreviations included WR, RWR, PWR, SWR, FWR, CWR), if the house officer was called (abbreviations included HO, SHO, OCHO), paper rounds and infliximab infusions. Iron infusions and nasogastric tube insertions were not included. If the 52-week review was within two weeks of the expected time point, this was included as a point of contact. Encounters could include inpatient hospitalisations, emergency department presentations, outpatient clinics, day stay, phone calls, and emails.
	Hospitalisations	Determined via ADHB patient management system (collected from discharge summaries). Hospitalisations were classed as at least 1-night stay. Day-stay or same-day discharge for emergency department presentations were not classed as a hospitalisation.
	Surgical procedures	Determined via ADHB patient management system (collected from discharge summaries).

Abbreviations: ADHB: Auckland District Health Board; CRP: C-reactive protein; CWR: Consultant ward round; EEN: Exclusive enteral nutrition; EN: Enteral nutrition; ESR: Erythrocyte sedimentation rate; FWR: Fellow ward round; HO: House officer; OCHO: On-call house officer; PWR: Paper ward round; RWR: Registrar ward round; SHO: Senior house officer; SWR: Surgical ward round; WR: Ward round

Data collection points included diagnosis, weeks 8, 13, 26, and 52; definitions are included in **Table 2.2**. Time differential to data collection points was recorded.

Table 2.2 | Data collection time point definitions for the retrospective medical note audit

Collection period	Definition
Diagnosis	Data that was closest to the EEN start date was used. In cases where two options were available, one before and one after the EEN start date, the one before the start date was chosen.
Week 8	Data from weeks 6 to 12, classed as post-treatment
Week 13	Data from weeks 13 to 17
Week 26	Data from weeks 22 to 30
Week 52	Data from weeks 50 to 65
Where multiple data points were available in a collection period, the data point closest to weeks 8, 13, 26, and 52 were chosen.	

Abbreviations: EEN: Exclusive enteral nutrition

2.5.1 Anthropometric measurements

Weight (kg) and height (cm) measurements at each time point were extracted from the ADHB patient management system and used to calculate BMI and standardised z-scores via the website https://apps.cpeg-gcep.net/quickZ_WHO/ (191) by the student researcher.

Height and weight measurements are taken according to standardised protocols based on the Royal College of Nursing Standards for the Weighing of Infants, Children and Young People in the Acute Health Care Setting (192) and World Health Organisation measuring guidelines (193).

2.5.2 Clinical assessment of disease activity

Disease activity was calculated in Microsoft® Excel® 2016 using the modified paediatric CD activity index (mod-PCDAI) (194). The mod-PCDAI uses CRP, ESR, haematocrit, and albumin (parameters and corresponding scores are displayed in **Table 2.3**). These four laboratory parameters are combined to give a score that provides an objective measure of the patient's disease activity that is reported to correlate well with a PGA and the PCDAI (194). A mod-PCDAI score of <7.5 indicates remission, 7.5 – 10 mild disease activity, 12.5 – 17.5 moderate disease activity, and >17.5 severe disease activity (194).

Sixty-one (19%) CRP data points were reported as <0.6, <1.0 or <5.0. In order to determine a mod-PCDAI score, the CRP values were altered to 0.5, 0.9 and 4.9. In addition, these altered values were used in analyses of biochemical markers, including the repeated measures analysis.

Table 2.3 | Modified paediatric Crohn's disease activity index parameters required to determine a patients score (194)

Laboratory measure	Mod-PCDAI parameters	Score
Haematocrit, %	<10y (>33), 11–19y F (≥34), 11–14y M (≥35), 15–19y M (≥37)	0
	<10y (28–32), 11–19y F (29–33), 11–14y M (30–34), 15–19y M (32–36)	2.5
	10y (<28), 11–19y F (<29), 11–14y M (<30), 15–19y M (<32)	5
ESR, mm/hr	<20	0
	20 – 50	2.5
	> 50	5
Albumin, g/dL	≥ 3.5	0
	3.1 – 3.4	5
	≤ 3.0	10
CRP, mg/L	< 5	0
	5 – 10	2.5
	> 10	5

Used with permission from Wolters Kluwer Health, Inc.: Leach ST, Nahidi L, Tilakaratne S, Day AS, Lemberg DA. Development and Assessment of a Modified Pediatric Crohn Disease Activity Index. J Pediatr Gastroenterol Nutr. 2010;51(2):232-236, URL: https://journals.lww.com/jpgn/Abstract/1991/05000/Development_and_Validation_of_a_Pediatric_Crohn_s.5.aspx.

2.5.3 Determination of relapse rate

The relapse rate was calculated using clinic letters, dispensing and medical record (hospitalisations) data for corticosteroids, and clinic letters and discharge summaries for biologic treatment. Dispensed corticosteroids or progression to biologic treatment, such as infliximab, was classed as disease relapse if this occurred after week 8. A change to corticosteroids or biologic therapy prior to week 8 was classed as treatment failure.

2.5.4 Missing data

Following data collection, it was found that a considerable amount of data was missing for week 13 across the measures of weight, height, CRP, ESR, albumin and haematocrit (39.6% to 69.2% of available data points). This time point was removed from the repeated measures analysis, as it could not be determined whether this data was missing at random. All other time points were included in the model.

2.6 Statistical analysis

Data was collected in Microsoft® Excel® 2016 and imported into SPSS Statistics for Windows, version 27 (SPSS Inc., Chicago, Ill., USA) for analysis. Continuous variables (e.g., age, anthropometry, biochemistry, mod-PCDAI score) were visually evaluated for normality via histograms, with all variables found to follow non-normal distributions. Descriptive statistics are reported as frequency and percentage, and continuous variables are reported as median and interquartile range (IQR). As appropriate, comparisons between groups for categorical data were assessed using Pearson's chi-

square analysis or Fisher-Freeman-Halton Exact test. Between-group comparisons for continuous data were assessed using the Mann Whitney U-test.

A fixed linear mixed model was used for repeated anthropometric and biochemical measures on the same patient and to account for missing data, assuming data were missing at random. A model adjusted treatment effect was estimated using an interaction between the treatment group and time point. Multiple comparisons were completed post hoc to compare values within groups at each time point since diagnosis (paired). The mixed model results are reported as the mean and standard error of the mean. Statistical significance was defined as $p < 0.05$.

Section two: Semi-structured interviews

Semi-structured interviews were carried out in two groups: 1) children and whānau who had completed a course of EEN, and 2) gastroenterology HCPs. These interviews aimed to obtain patient and whānau experiences during EEN treatment and discuss the implementation of the IBDCG with gastroenterology HCP involved in the care pathway. Interviews were carried out between June and October 2021 using convenience sampling.

2.7 Patient and whānau interviews

2.7.1 Data collection

CD patients with upcoming appointments (between June 28th and August 1st 2021) either in the gastroenterology outpatient clinic or day stay clinic were identified by Amy Andrews (senior paediatric gastroenterology dietitian). The student researcher approached potential participants attending the day stay clinic, who introduced them to the research and provided the child and whānau member with a PIS (Appendix 1, 2). Participants were given time to read the PIS and ask further questions before agreeing or declining to participate. If the child and whānau member agreed to participate, they were given a consent form (CF) to complete (**Appendix 5, 6**) before the interview began. Potential participants attending a gastroenterology outpatient clinic appointment were approached by Amy Andrews, who introduced the research and gained consent for the student researcher to contact the parent or caregiver to arrange an interview.

Potential participants not approached during their clinic appointment or who had recently completed their EEN but did not have an appointment booked were emailed an invitation to participate in the research (**Appendix 7**), together with the PIS and CF. Two weeks after being sent the email invitation, parents were followed up with a phone call to discuss participation, answer any questions that may arise, and if agreeable, schedule a suitable time to meet for the interview. Due to COVID-19 restrictions (in Auckland) from August to October 2021, in-person interviews could not be completed,

so interviews were conducted via zoom. All participants were asked to complete the CF prior to the interview.

The interview guide was pre-defined and based on consideration of the topic and literature. Interview questions were developed to gather information on the education provided prior to commencing EEN and solid food reintroduction, the patient and whānau experience with EEN and solid food reintroduction, and any barriers and facilitators to completing EEN treatment (**Figure 2.1**). Specific question prompts provided are displayed in **Appendix 8**. A questionnaire was used to collect demographic data from interview participants (**Appendix 9**). Interviews took place at SCH during infliximab treatment or via zoom. Interviews lasted between 11 and 29 minutes and were recorded via a voice recorder app, zoom or Otter.ai and transcribed verbatim into a Microsoft® Word 2016 document. Transcripts were checked for accuracy, but participants were not asked to check them.

2.7.2 Inclusion and exclusion criteria

Inclusion criteria:

- Patient is aged 1 to 18
- Patient and/or the parent or caregiver of the patient can be interviewed
- Confirmed CD diagnosis
    - Diagnosis of CD was based upon standard clinical, histologic, endoscopic, and radiologic criteria, determined via upper GI endoscopy, ileocolonoscopy and small bowel imaging as per the Porto criteria for diagnosis of IBD in children and adolescents (4)
- Patient was managed with EEN as first-line induction therapy following diagnosis

Exclusion criteria:

- Diagnosis of UC or IBD-U
- Patient did not receive EEN induction therapy as first-line therapy following diagnosis

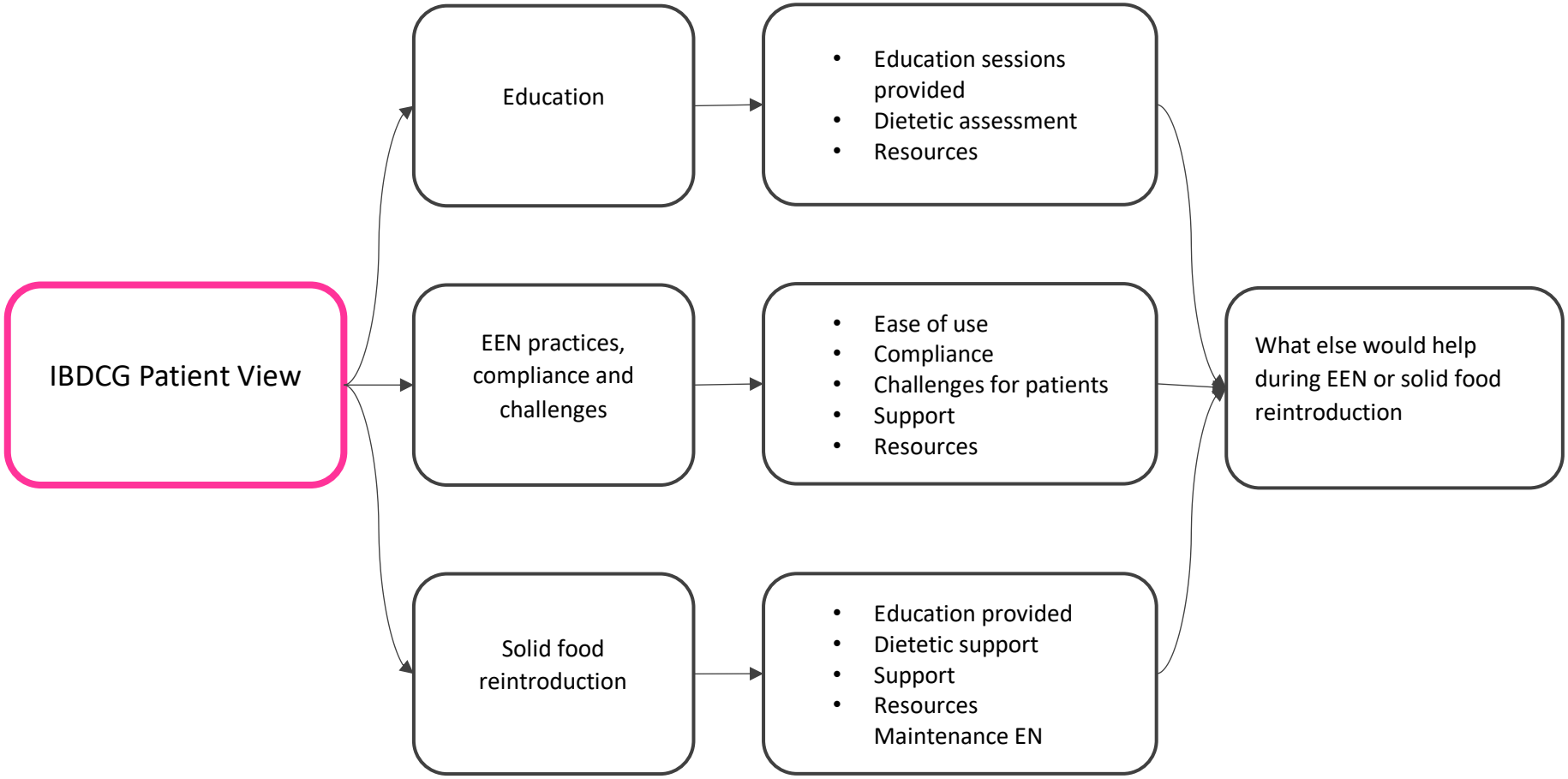

Figure 2.1 | Semi-structured interview content for children with Crohn's disease and their whānau

Abbreviations: EEN: Exclusive enteral nutrition; EN: Enteral nutrition; IBDCG: Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline

2.8 Health care professional interviews

2.8.1 Data collection

Key gastroenterology HCPs (e.g., consultants, nurse specialists, and dietitians) were invited via email to participate in a short semi-structured interview discussing their experiences with CD patients and EEN (**Appendix 10**). The email consisted of a short description of the research, a PIS (Appendix 3) and a CF (**Appendix 11**). If the HCP consented to be interviewed, a suitable time for the interview was arranged, and the CF was completed and returned to the student researcher. Due to COVID-19 restrictions (August 2021), interviews were changed from in-person to via zoom.

The interview questions were developed to gather information on the clinician's current practice in enacting the IBDCG pathway (**Figure 2.2**). Specific question prompts provided are displayed in **Appendix 12**. Interviews took place via zoom, lasted between 15 and 40 minutes and were recorded via zoom and Otter.ai and transcribed verbatim into a Microsoft® Word document. Transcripts were checked for accuracy, but participants were not asked to check them.

2.8.2 Inclusion and exclusion criteria

Inclusion criteria

- Part of a IBD gastroenterology team
- Practising at SCH

Exclusion criteria

- Does not work in an IBD gastroenterology team
- Does not practise at SCH

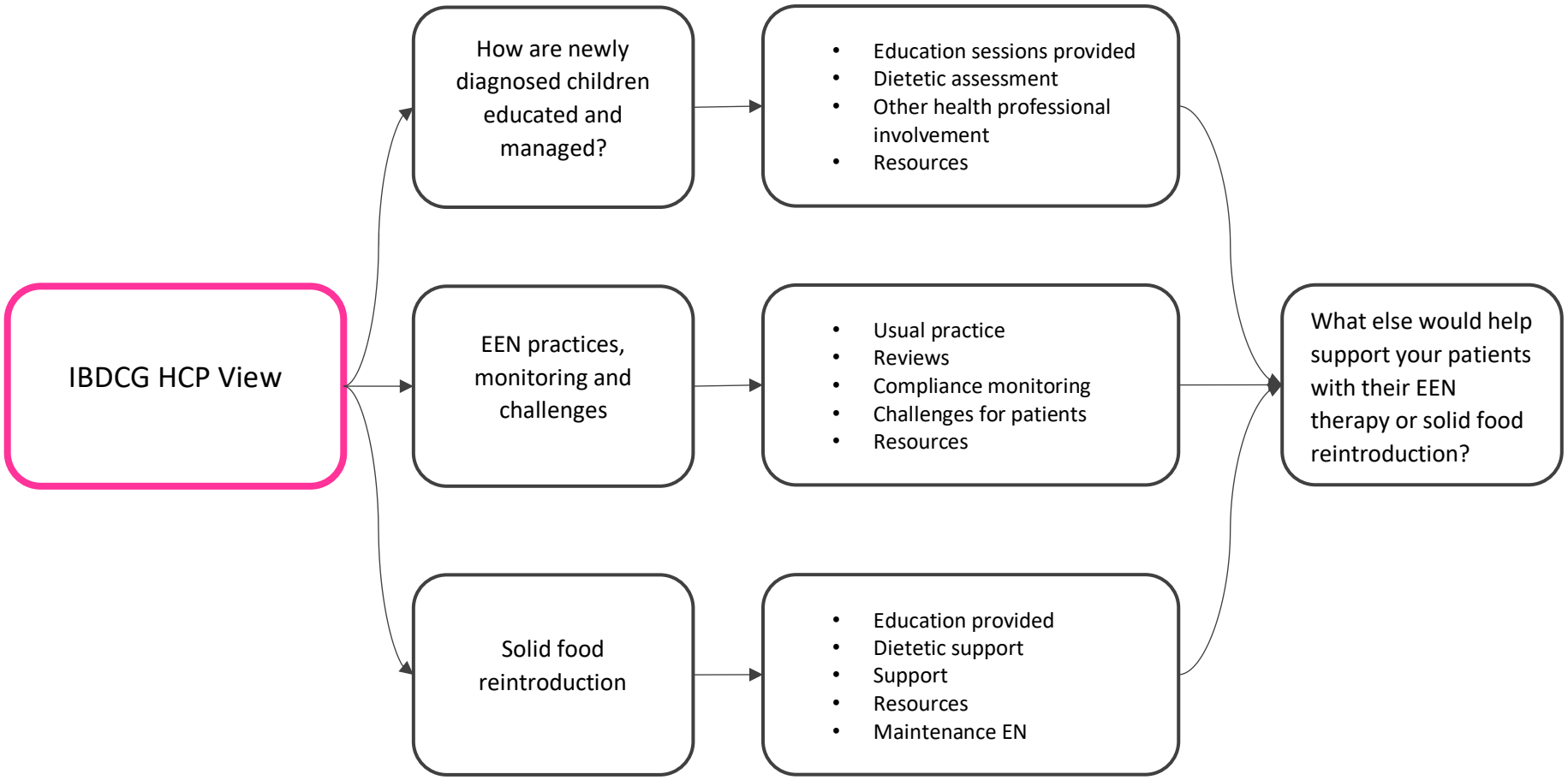

Figure 2.2 | Semi-structured interview content for health care professionals in the Crohn's disease treatment pathway

Abbreviations: EEN: Exclusive enteral nutrition; EN: Enteral nutrition; HCP: Health care professional; IBDCG: Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline

2.9 Data analysis

Two different analyses were carried out on the patient and whānau and key HCP interview data.

2.9.1 Thematic analysis

Thematic analysis followed the six phases of thematic analysis described by Braun and Clarke (195). Data familiarisation was carried out through repeated reviewing of the transcripts. Transcriptions were uploaded into Microsoft® Excel® 2016, which was used to code the transcripts and develop the themes. Following initial theme development, transcripts were reviewed again to finalise the themes before naming the themes and producing the report. Patient and whānau interviews were reviewed separately to the HCPs, and themes for each were developed.

2.9.2 Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline practice and experiences

In addition to thematic analysis, the interview data were scanned to determine the clinician's current practice in enacting the IBDCG pathway and patient and whānau experiences while taking EEN and during solid food reintroduction.

Two sections, titled EEN experience and patient education, were used to explain patient and whānau experiences during treatment, while similar sections titled the treatment pathway and patient education summarise stakeholder practices. In these sections, interview data were categorised to explore practice and experiences navigating the IBDCG EEN pathway.

CHAPTER 3: RESULTS

Section one: Retrospective medical note audit

Medical records for 103 children with CD receiving treatment at SCH, previously identified by Rajasekaran et al. 2022 (190), were reviewed. Ninety-one patients met the inclusion criteria; pre-2015 *n*=40 and post-2015 *n*=51. Twelve patients did not meet the inclusion criteria; six had no definitive CD diagnosis, and six had less than twelve months follow-up; therefore, they were excluded from this analysis (**Figure 3.1**).

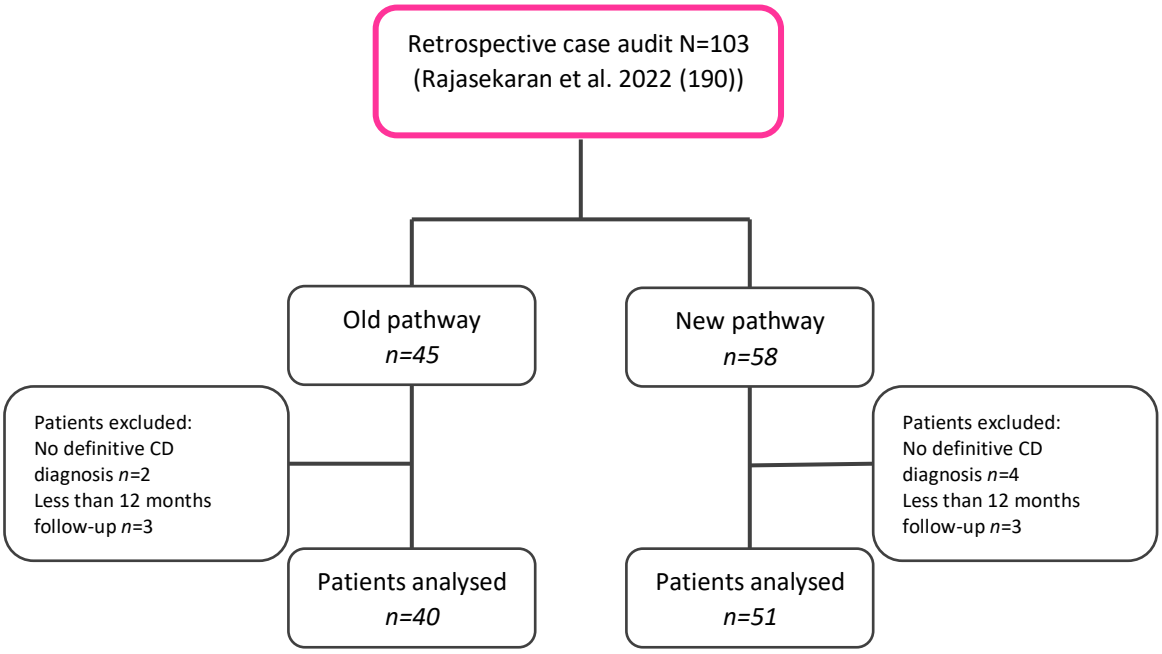

Figure 3.1 | Flow chart summary of children receiving treatment at Starship Child Heath selected for the retrospective case audit

Abbreviations: CD: Crohn's disease

3.1 Patient characteristics

3.1.1 Demographic characteristics

There were no differences between the groups for key demographics, shown in **Table 3.1**. The cohort had a median (IQR) age of 12.3 (4.3) years (pre-2015) and 11.9 (4.0) years (post-2015), and there were more males diagnosed with CD compared to females in both groups; 63% and 57% (pre-2015 and post-2015, respectively). CD was more prevalent in patients identified as NZ European ethnicity in both groups; 73% (pre-2015) and 53% (post-2015) and in areas of the least deprivation, with quintiles 1 and 2 making up 60% of all CD cases managed by SCH.

Table 3.1 | Demographic characteristics at diagnosis of children with Crohn's disease receiving treatment at Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		
	Pre-2015 *n*=40	Post-2015 *n*=51	p-value
Gender, *n* (%)			0.743[a]
Male	25 (62.5)	29 (56.9)	
Female	15 (37.5)	22 (43.1)	
Age, median (IQR)	12.3 (4.3)	11.9 (4.0)	0.716[b]
Ethnicity, *n* (%)			0.147[c]
NZ European	29 (72.5)	27 (52.9)	
Māori	0 (0.0)	1 (2.0)	
Pasifika	1 (2.5)	0 (0.0)	
Asian	1 (17.5)	16 (31.4)	
Other*	3 (7.5)	7 (13.7)	
NZDEP, *n* (%)			0.090[c]
Q1	11 (27.5)	19 (37.3)	
Q2	13 (32.5)	12 (23.5)	
Q3	11 (27.5)	5 (9.8)	
Q4	2 (5.0)	7 (13.7)	
Q5	3 (7.5)	8 (15.7)	

Abbreviations: IQR: Interquartile range; NZ: New Zealand: NZDEP: New Zealand Index of Deprivation; Q1: Quintile 1 – Decile 1 and 2; Q2: Quintile 2 – Decile 3 and 4; Q3: Quintile 3 – Decile 5 and 6; Q4: Quintile 4 – Decile 7 and 8; Q5: Quintile 5 – Decile 9 and 10 (196)

* 'Other' ethnicity includes: Middle Eastern, Other European, European not further defined and African

[a] Chi-squared test; [b] Mann Whitney U-test; [c] Fisher-Freeman-Halton Exact test

3.1.2 Disease classification characteristics

The Paris classification was used to categorise disease location and behaviour, growth delay, and age according to set criteria (Table 1.4). Comparisons between groups are displayed in **Table 3.2**. There were no differences between groups for disease location or behaviour, perianal disease, growth delay or extraintestinal manifestations.

Table 3.2 | Disease characteristics at diagnosis using the Paris classification of children with Crohn's disease receiving treatment at Starship Child Heath pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		p-value
	Pre-2015	Post-2015	
	n=40	*n*=51	
Paris Classification			
Age, *n* (%)			0.682[a]
A1a	11 (27.5)	11 (21.6)	
A1b	29 (72.5)	40 (78.4)	
Disease Location, *n* (%)			0.421[a]
L1	4 (10.0)	10 (19.6)	
L2	10 (25.0)	13 (25.5)	
L3	26 (65.0)	28 (54.9)	
Upper GIT disease, *n* (%)			0.734[a]
L4a	9 (22.5)	10 (19.6)	
L4b	9 (22.5)	15 (29.4)	
Disease behaviour, *n* (%)			1.000[b]
B1	27 (67.5)	34 (66.7)	
B2	10 (25.0)	12 (23.5)	
B2B3	3 (7.5)	4 (7.8)	
B3	0 (0.0)	1 (2.0)	
Perianal disease, *n* (%)	10 (25.0)	14 (27.5)	0.981[a]
Growth delay, *n* (%)	10 (25.0)	8 (15.7)	0.400[a]
Extra intestinal manifestations, *n* (%)	4 (10.0)	6 (11.8)	1.000[b]

Abbreviations: A1a: 0 to <10 y; A1b: 10 to <17 y; B1: Non-stricturing non-penetrating; B2: Stricturing; B2B3: Both penetrating and stricturing disease either at the same or different times; B3: Penetrating; GIT: gastrointestinal tract; L1: Distal 1/3 ileum ± limited cecal disease; L2: Colonic disease; L3: Ileocolonic disease; L4a: Upper disease proximal to the ligament of Treitz; L4b: Upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum.

[a] Chi-squared test; [b] Fisher-Freeman-Halton Exact test

3.1.3 Clinical characteristics at diagnosis

The clinical characteristics of the study population are shown in **Table 3.3**. There were no significant differences between the groups for anthropometric measurements. Inflammatory markers CRP and ESR showed no significant differences between the groups (p=0.383 and p=0.596, respectively); however, they were elevated compared to reference standards (140). Albumin was significantly lower in the post-2015 group compared to the pre-2015 group (median 29.5 g/L, and 36 g/L, respectively; p=0.001) and was outside the reference range (32-48 g/L (140)). FC, a measure of inflammation of the intestine, showed that all patients had a result above the reference value, 50 µg/g (140).

Table 3.3 | Clinical characteristics at diagnosis (anthropometry, biochemical markers, and disease activity) of children with Crohn's disease receiving treatment at Starship Child Heath pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		p-value
	Pre 2015 *n*=40	Post 2015 *n*=51	
Anthropometry, median (IQR)			
Reported weight loss (kg)	1.58 (4.79)	1.30 (5.00)	0.598[a]
Weight			
kg	33.0 (14.2)	35.4 (17.4)	0.655[a]
z-score*	-0.55 (1.59)	-0.67 (1.20)	0.617[a]
Missing, n	*1*	*1*	
Height			
cm	145.4 (27.3)	147.3 (20.1)	0.745[a]
z-score*	0.01 (1.36)	-0.33 (1.67)	0.896[a]
Missing, n	*2*	*7*	
BMI			
kg/m^2	16.2 (3.1)	15.9 (4.0)	0.443[a]
z-score*	-0.63 (1.67)	-0.78 (1.62)	0.313[a]
Missing, n	2	*7*	
Biochemical markers, median (IQR)			
CRP, mg/L	31.5 (48.6)	24.0 (37.4)	0.383[a]
Missing, n	*2*	*6*	
ESR, mm in 1 hr	40.5 (31.8)	34.0 (31.3)	0.596[a]
Missing, n	*4*	*15*	
Albumin, g/L	36.0 (11.0)	29.5 (25.0)	**0.001**[a]
Missing, n	*5*	3	
Faecal calprotectin◊, *n*, (%)			0.143[b]
>50 µg/g	31 (100.0)	49 (100.0)	
Missing, n	*9*	*2*	
Disease Activity			
Mod-PCDAI, median (IQR)	12.5 (12.5)	15.0 (12.5)	0.253[a]
Missing, n	*7*	*16*	
Disease activity, *n* (%)			0.391[b]
Remission	5 (15.2)	5 (14.3)	
Mild	10 (30.3)	5 (14.3)	
Moderate	7 (21.2)	8 (22.9)	
Severe	11 (33.3)	17 (48.6)	
Missing, n	*7*	*16*	

Abbreviations: BMI: body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IQR: interquartile range; Mod-PCDAI: Modified paediatric Crohn's disease activity index.

* The z-score was calculated using the WHO growth standards (191)

◊ Median Faecal calprotectin results were unable to be computed due to 36 results reported as >500, >2000 or >8000

[a] Mann Whitney U-test; [b] Fisher-Freeman-Halton Exact test

There were no differences in median disease activity scores, measured by the mod-PCDAI (194), between pre-2015 and post-2015 groups (median (IQR) 12.5 (12.5), range 0-22.5 and 15 (12.5), range 0-25, respectively; p=0.253) (Table 3.3). While not significant, one-third of the pre-2015 and nearly

50% of the post-2015 groups had severe disease activity, and 14 to 15% of patients were classed as in remission at diagnosis (**Figure 3.2**).

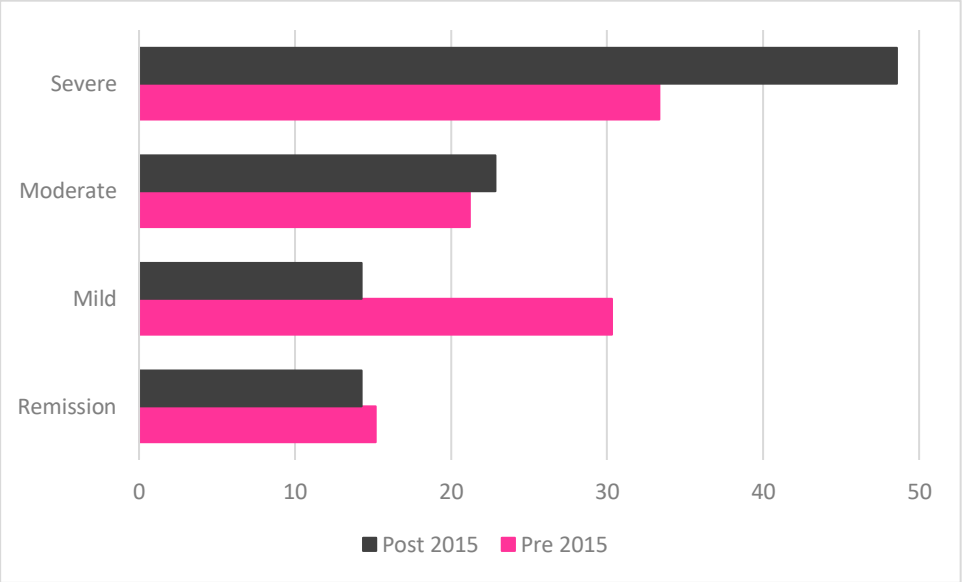

Figure 3.2 | Disease activity comparison at diagnosis of children with Crohn's disease treated at Starship Child Health, segmented by group; pre-2015 and post-2015, and disease severity classification using the modified paediatric Crohn's disease activity index

Key: Remission, <7.5; Mild disease activity, 7.5 – 10; Moderate disease activity, 12.5 – 17.5; Severe disease activity, >17.5 using Modified paediatric Crohn's disease activity index (194)

3.1.4 Malnutrition status at diagnosis

There were no significant differences between the malnutrition status of the groups before treatment (BMI z-score; p=0.379) (**Appendix 13, Table A1**). At diagnosis, approximately 40% of the cohort were classed as having mild to severe malnutrition (BMI z-score ≤ -1.0 SD (197)).

3.2 Treatment

EEN was used to induce remission in over 90% of the study population (**Table 3.4**), including one patient who received dual EEN and CS as their induction therapy. Eight children (pre-2015 *n*=3, post-2015 *n*=5) did not receive EEN as an induction treatment and received CS (pre-2015 *n*=1, post-2015 *n*=1), aminosalicylate anti-inflammatory agent (pre-2015 *n*=2, post-2015 *n*=2), or biological drug and antimetabolite thiopurine analogue drug (post-2015 *n*=2) as their induction treatment. All subjects were included in the outcomes analysis for the two groups regardless of their treatment modality.

Table 3.4 | Comparison of treatment methods, including administration route, exclusive enteral nutrition completions, reasons for treatment failure and duration of treatment in children with Crohn's disease managed by Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		p-value
	Pre-2015 *n*=40	Post-2015 *n*=51	
Treatment following diagnosis, *n* (%)			1.000[a]
EEN	37* (92.5)	46 (90.2)	
Other treatment	3 (7.5)	5 (9.8)	
Administration route, *n* (%)			0.004[b]
Oral	40 (100.0)	51 (100.0)	
NGT	15 (40.5)	5 (10.9)	
Completion, *n* (%)			0.212[b]
Yes	31 (83.8)	32 (69.6)	
No	6 (16.2)	14 (30.4)	
No EEN	3	5	
EEN failure reasons, *n* (%)			0.267[a]
Adherence	0 (0.0)	4 (28.6)	
Insufficient clinical improvement	6 (100.0)	10 (71.4)	
EEN therapy duration[1], weeks	6.0 (1.1)	6.0 (2.9)	0.887[c]
EEN therapy duration[2], weeks	6.0 (1.1)	6.1 (1.9)	0.150[c]
Duration of completions, *n* (%)			0.086[a]
<5 weeks	1 (3.2)	0 (0.0)	
5-6 weeks	9 (29.0)	2 (6.3)	
6-7 weeks	13 (41.9)	18 (56.3)	
7-8 weeks	4 (12.9)	4 (12.5)	
8 + weeks	4 (12.9)	8 (25.0)	

Abbreviations: EEN: Exclusive enteral nutrition; NGT: Nasogastric tube.

* One patient received dual EEN and corticosteroid as induction therapy; this patient was included in the EEN group as they completed the required duration

[1] EEN therapy duration for all patients who started EEN

[2] EEN therapy duration for all patients who were deemed to have completed treatment

[a] Fisher-Freeman-Halton Exact test; [b] Chi-squared test; [c] Mann Whitney U-test.

The flow of patients through the two pathways for treatment and outcomes is shown in **Figure 3.3**. Sixty-three children completed EEN treatment (pre-2015 *n*=31 (84%), post-2015 *n*=32 (70%)), and twenty children failed to complete EEN treatment due to lack of adherence (post-2015 *n*=4) or insufficient clinical improvement (pre-2015 *n*=6, post-2015 *n*=10). All children used oral EEN therapy, while 20 of 83 (24%) children also used a nasogastric tube. Nasogastric therapy was used by 40.5%

(pre-2015) compared to 10.9% (post-2015; p=0.004). The median treatment duration between groups was not significantly different between children who started EEN or those classed as completing EEN treatment (Table 3.4). CRP levels at diagnosis were significantly higher in children who did not complete EEN treatment than those who did (median 44.0 mg/L versus 24.0 mg/L, respectively; p=0.045) (**Appendix 13, Table A2**). There were no significant differences in other disease characteristics or demographics between children who failed to complete treatment and those who completed treatment (Appendix 13, Table A2).

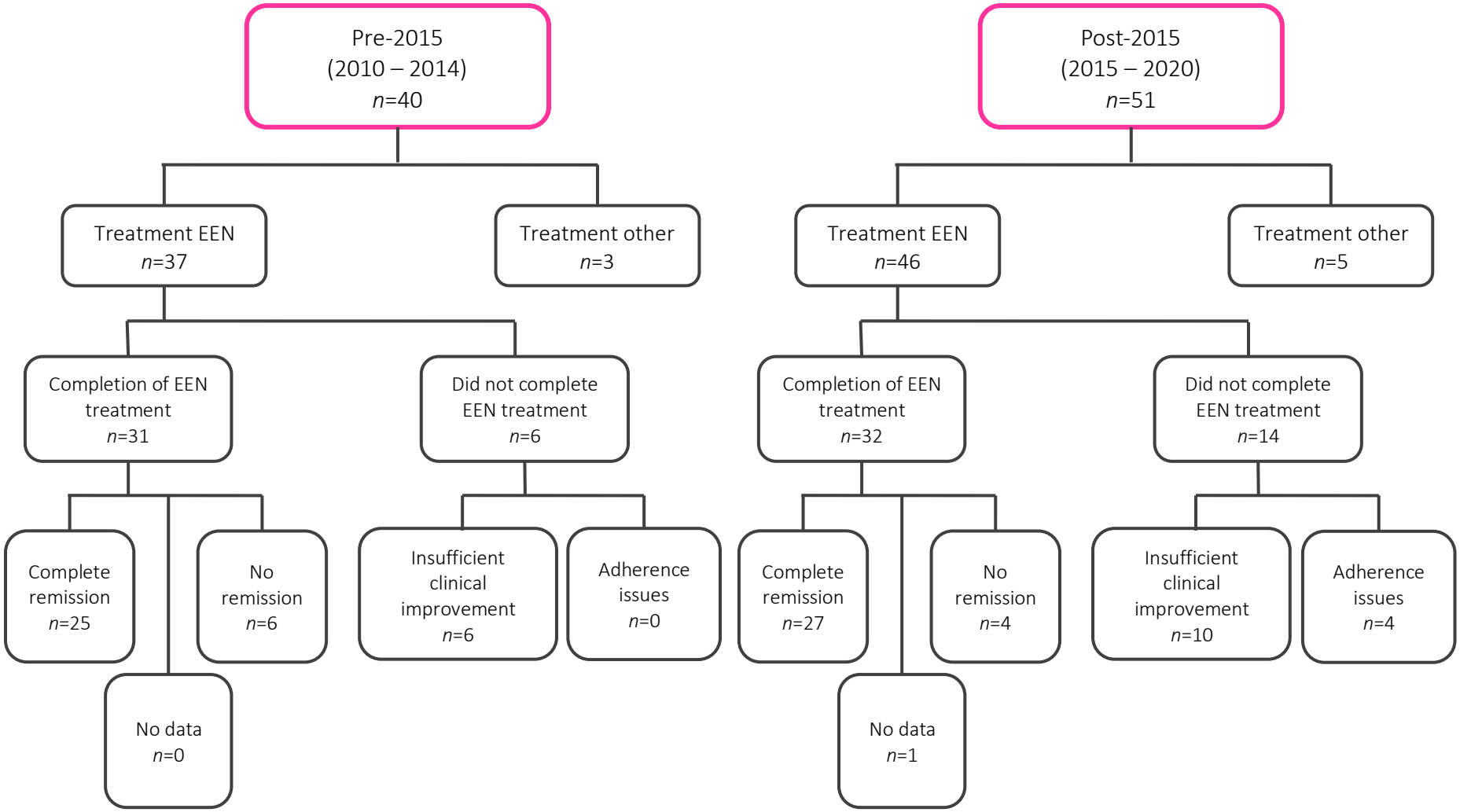

Figure 3.3 | Flow chart summary detailing treatment and treatment outcome progression of children with Crohn's disease treated at Starship Child Health pre-2015 and post-2015

Note: Remission data is based on gastroenterologist determined remission

3.3 Response to treatment and outcomes over the first year

3.3.1 Clinical disease activity and the induction of remission

3.3.1.1 At week 8

Mod-PCDAI scores could only be calculated for 48 of 91 (52.7%) children (55.0% pre-2015, 51.0% post-2015) due to missing data. Mod-PCDAI disease activity and the corresponding remission status post-treatment were significantly different between the groups (**Table 3.5**). Seventeen children (77.3%) were in remission, and no children reported severe disease activity pre-2015, compared to seven children (26.9%) in remission and ten children (38.5%) continuing to report severe disease activity post-2015 (p=0.001) (**Figure 3.4**). Moderate disease activity was similar between the groups, while mild disease activity was higher post-2015, 30.8% (*n*=8) compared to 18.2% (*n*=4) pre-2015. Of the twenty-four children who did not achieve remission (Table 3.5), twelve had improved mod-PCDAI scores, three had no change, and seven had worsening disease activity. Disease activity improved more in the pre-2015 no remission sub-set than the post-2015 sub-set (median 15.0 and 5.0, respectively; p=0.038). There were no significant differences at diagnosis in demographics, disease phenotype or severity for children deemed to be in remission via the mod-PCDAI and those that were not. At diagnosis, albumin was significantly lower in the children who did not achieve remission than in those who achieved remission (median 28.0 and 33.0, respectively; p=0.042) and was lower than the reference range (32-48 g/L (140)).

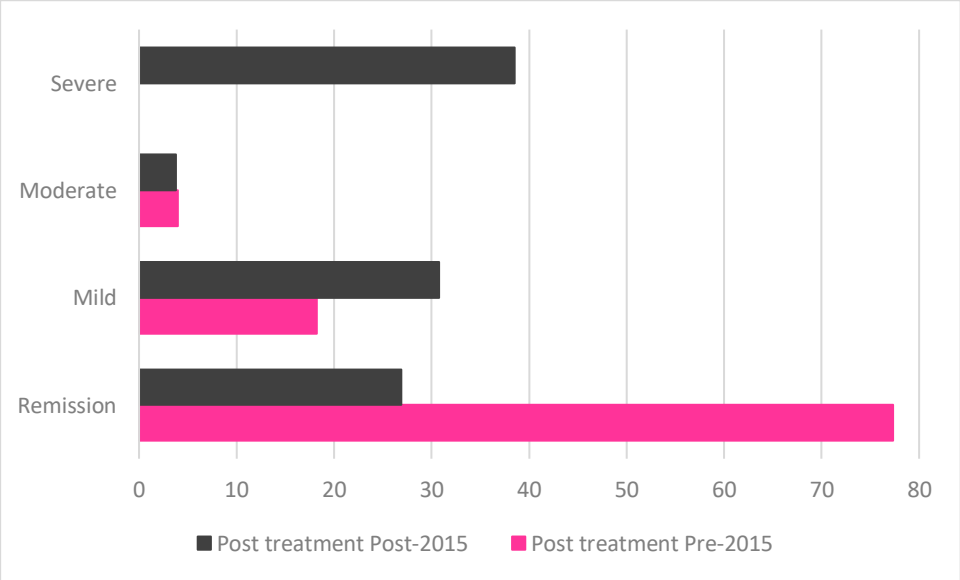

Figure 3.4 | Post-treatment disease activity comparison of children with Crohn's disease treated at Starship Child Health, segmented by group; pre-2015 and post-2015, and disease severity classification using the modified paediatric Crohn's disease activity index

Key: Remission, <7.5; Mild disease activity, 7.5 – 10; Moderate disease activity, 12.5 – 17.5; Severe disease activity, >17.5 using Modified paediatric Crohn's disease activity index (194)

Table 3.5 | Comparison of disease activity and remission status following induction treatment in children with Crohn's disease treated at Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		p-value
	Pre 2015 *n*=40	Post 2015 *n*=51	
Mod-PCDAI score, median (IQR)	5.0 (3.1)	10.0 (13.8)	0.002[a]
Missing, n	*18*	*25*	
Remission determined by Mod-PCDAI, *n* (%)			0.001[b]
In remission	17 (77.3)	7 (26.9)	
No remission	5 (22.7)	19 (73.1)	
Disease activity determined by Mod-PCDAI, *n* (%)			<0.001[c]
Remission	17 (77.3)	7 (26.9)	
Mild	4 (18.2)	8 (30.8)	
Moderate	1 (4.5)	1 (3.8)	
Severe	0 (0.0)	10 (38.5)	
Remission status determined by gastroenterologist, *n* (%)			0.877[c]
Clinical	23 (62.2)	24 (55.8)	
Serological	2 (5.4)	3 (7.0)	
No remission	12 (32.4)	16 (37.2)	
Missing, n	*3*	*8*	
Patients not achieving remission			
Response but not remission (Mod-PCDAI), *n*	3	9	
Median point change (min-max)	15.0 (12.5-15.0)	5.0 (2.5-15.0)	0.038[a]
Median % change	66.7	22.2	
No change in Mod-PCDAI, *n*	1	2	
Decline in Mod-PCDAI score, *n*	1	6	
Missing, n	*0*	*2**	

Abbreviations: IQR: interquartile range; Mod-PCDAI: Modified paediatric Crohn's disease activity index.

[a] Mann Whitney U-test; [b] Chi-squared test; [c] Fisher-Freeman-Halton Exact test

* Unable to calculate response due to mod-PCDAI missing at diagnosis

Following treatment completion, the gastroenterologist assesses disease activity, categorising it into clinical remission, serological remission, or no remission. Gastroenterologist-determined remission status was not significantly different between groups (p=0.877), with 62.2% and 55.8% of patients in clinical remission, 5.4% and 7.0% in serological remission, and 32.4% and 37.2% not in remission (pre-2015 and post-2015, respectively) (Table 3.5). Of those who achieved remission compared to those who did not, there were no significant differences in demographic or disease characteristics at diagnosis except for CRP, where values were significantly higher in children who did not achieve remission (median 41.5 mg/L) versus those who did (median 23.0 mg/L; p=0.004).

3.3.1.2 Longitudinally to week 52

Fifty-two weeks after diagnosis, disease activity continued to show significant differences between the groups (**Appendix 13, Table A3**). Mod-PCDAI scores were lower in the pre-2015 group than in the post-2015 group (mean 3.27 versus 8.42, respectively; p=0.003); however, at 26 weeks, there was no significant difference between the groups (p=0.509) (**Figure 3.5**). Children diagnosed post-2015 had

more severe disease, one-third had moderate or severe disease compared to zero pre-2015, and 43.3% were in remission (post-2015), compared to 84.6% pre-2015 (p=0.002) (**Figure 3.6**). There was no significant interaction between the treatment pathway and time (p=0.142).

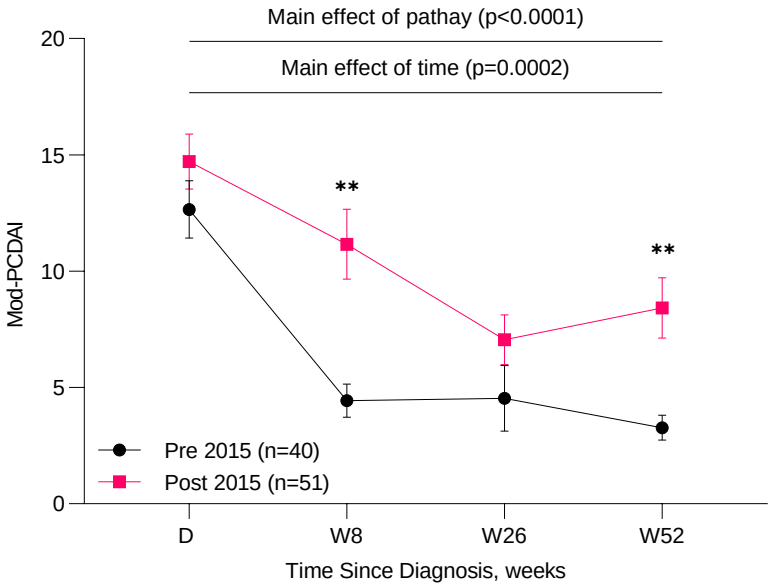

Figure 3.5| Comparison of modified paediatric Crohn's disease activity index (mean ± SEM) at diagnosis, weeks 8, 26, and 52 of treatment. Fixed linear model to account for missing data compared at time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions

** p≤0.01

Abbreviations: D: diagnosis; W8: week 8; W26: week 26; W52: week 52

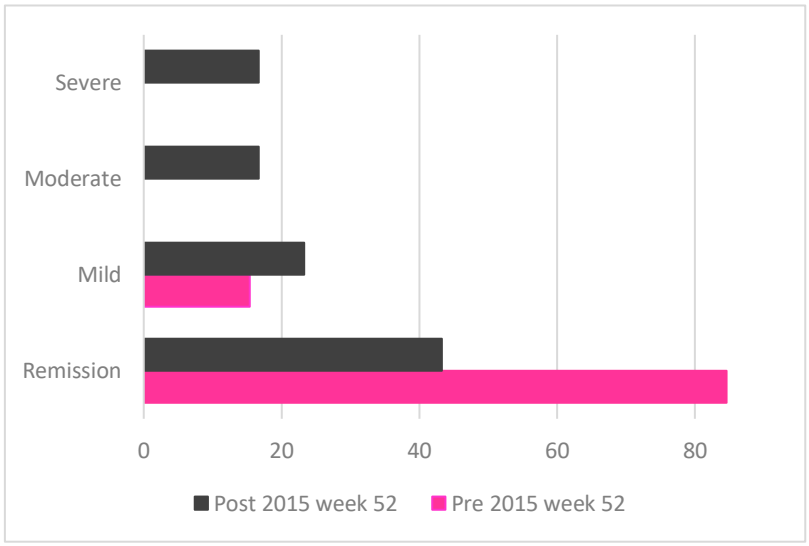

Figure 3.6| Disease activity comparison 52 weeks after treatment of children with Crohn's disease treated at Starship Child Health, segmented by group; pre-2015 and post-2015, and disease severity classification using the modified paediatric Crohn's disease activity index

Key: Remission, <7.5; Mild disease activity, 7.5 – 10; Moderate disease activity, 12.5 – 17.5; Severe disease activity, >17.5 using modified paediatric Crohn's disease activity index (194)

3.3.1.3 Disease relapse

During the follow-up period, disease relapse occurred in 35% of children pre-2015 and 59% post-2015 (p=0.041).

3.3.2 Anthropometry

3.3.2.1 At week 8

There were no significant differences between groups for weight, height, BMI or corresponding z-scores following induction treatment (**Appendix 13, Table A4**).

3.3.2.2 Longitudinally to week 52

Weight and height and corresponding z-scores increased over time (**Figure 3.7**); however, there were no significant differences between the pathways (p>0.05) (Appendix 13, Table A4). Weight z-score increased steadily over the 52 weeks of follow-up, trending towards zero z-score (mean weight z-score for children of the same age and sex) at week 26 and trending higher than zero z-score at week 52. Within-group (paired) comparisons (diagnosis to week 52) show significant improvements in weight z-score (pre-2015; p=0.002, post-2015; p<0.001). Height z-score remained relatively static for the first 26 weeks, then increased over the second 26 weeks, trending higher than zero z-score at week 52. Diagnosis to week 52 comparisons revealed that height z-score within-group (paired) comparisons had improved significantly post-2015 (p=0.001), whereas pre-2015 had not (p=0.066). Anthropometric measurements and z-scores showed no significant interaction between treatment pathway and time (p>0.05).

3.3.3 Biochemical markers

3.3.3.1 At week 8

Post-treatment, there were no significant differences in mean CRP and ESR values (**Appendix 13, Table A5**); however, both biochemical markers continued to sit above the reference ranges (140). Albumin levels for the post-2015 group were significantly lower at diagnosis and continued to be significantly lower post-treatment (mean, pre-2015 41.6 g/L, post-2015 33.7 g/L; p<0.0001) (Appendix 13, Table A5, **Figure 3.8**). Following treatment, the post-2015 group albumin values had improved and were within the reference range (32-48 g/L (140)) (Appendix 13, Table A5). Following induction treatment, albumin values were significantly higher in children classed as "in remission" by their gastroenterologist (median 38.0 g/L) compared to children who were not in remission (median 35.5 g/L; p<0.001), whereas albumin values at diagnosis for these groups were not significantly different (**Appendix 13, Table A6**). The pre-2015 group had significantly higher albumin levels than the post-2015 group, whether the children were in remission or not (Appendix 13, Table A6).

3.3.3.2 Longitudinally to week 52

There were no significant differences between the pathways for CRP or ESR across all time points (Figure 3.8). There were significant differences between pathways for albumin, with higher values seen pre-2015 than post-2015 across all time periods (Figure 3.8). Across the follow-up period, mean ESR and CRP values were outside the reference range (140) (except for pre-2015 week 26 CRP), while mean albumin values (except post-2015 diagnosis) were within the reference range (140) (Appendix 13, Table A5). There was no significant interaction between treatment pathway and time for CRP, ESR or albumin ($p>0.05$).

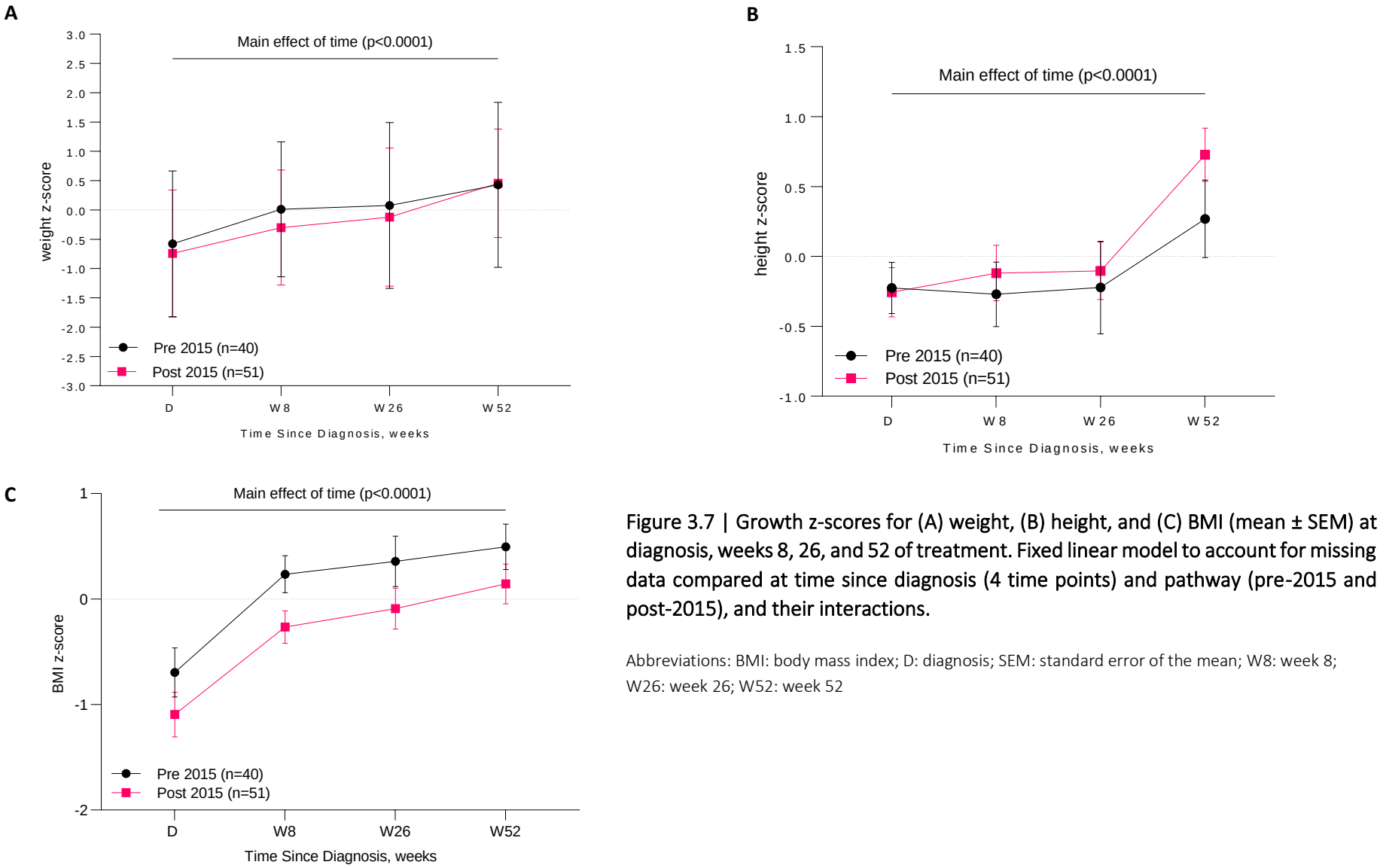

Figure 3.7 | Growth z-scores for (A) weight, (B) height, and (C) BMI (mean ± SEM) at diagnosis, weeks 8, 26, and 52 of treatment. Fixed linear model to account for missing data compared at time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions.

Abbreviations: BMI: body mass index; D: diagnosis; SEM: standard error of the mean; W8: week 8; W26: week 26; W52: week 52

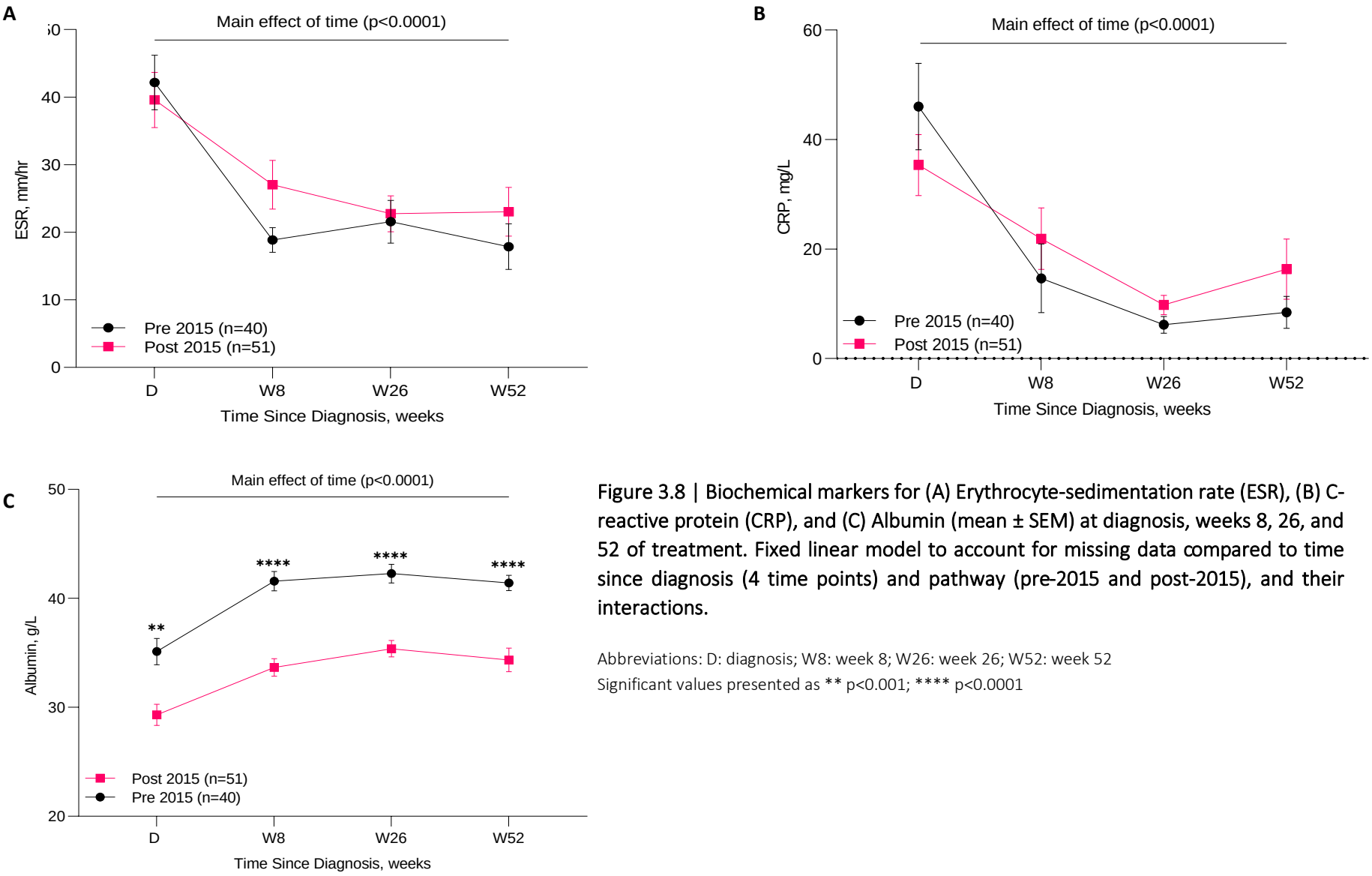

Figure 3.8 | Biochemical markers for (A) Erythrocyte-sedimentation rate (ESR), (B) C-reactive protein (CRP), and (C) Albumin (mean ± SEM) at diagnosis, weeks 8, 26, and 52 of treatment. Fixed linear model to account for missing data compared to time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions.

Abbreviations: D: diagnosis; W8: week 8; W26: week 26; W52: week 52
Significant values presented as ** p<0.001; **** p<0.0001

3.3.4 Malnutrition status

Post-treatment, malnutrition status was not significantly different between the groups (Appendix 13**,** Table A1); however, there was a significant difference between time points within groups (paired). From diagnosis to week 8 the number of children classified as having no malnutrition (BMI z-score > -1.0 SD (197)) increased from 60.5% to 93.8% (p=0.005; pre-2015) and 59.1% to 82.4% (p=0.012; post-2015) (**Figure 3.9**)**.**

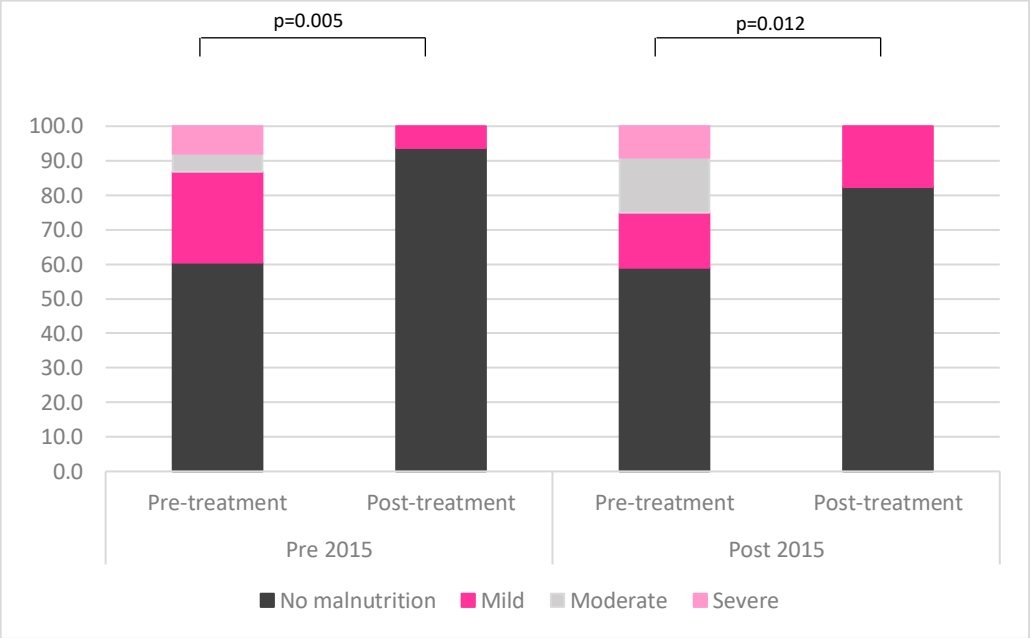

Figure 3.9 | Comparison of malnutrition classification (assessed using BMI z-score) at diagnosis and following treatment of children with Crohn's disease treated at Starship Child Health pre-2015 and post-2015

Note: p-values calculated via Fisher-Freeman-Halton Exact test

Abbreviation: BMI: Body mass index

3.4 Medical and dietetic points of contact and hospitalisations

In the 52 weeks following diagnosis, there were no significant differences in the median number of medical or dietetic contacts per child (p=0.742 and p=0.428, respectively; **Appendix 13 Table A7**). Both groups had more medical contact points than dietetic contact points per child. There were no significant differences between groups at most time points, except for the medical contacts between weeks 26 and 52; this was higher post-2015 (p=0.029), with 12 hospitalisations compared to no hospitalisations pre-2015. When hospitalised children were excluded from the analysis, there were no significant differences between groups for the number of medical or dietetic points of contact at any time point (Appendix 13, Table A7).

The number of hospitalisations were similar between groups (p=0.710) (Appendix 13, Table A7); however, the reasons varied and were significantly different (p=0.032) (**Table 3.6**). Pre-2015, most children (46.2%) were hospitalised for their diagnosis, compared to 20.9% post-2015. Pain and/or vomiting were the primary cause of children being hospitalised post-2015 compared to pre-2015 (32.6%, vs 7.7%, respectively). Five patients had surgery in the 12 months of follow-up. Reasons for surgery pre-2015 included examination under anaesthesia (EUA), proctoscopy and curette of a fistula tract (*n*=1*)*, and post-2015 included EUA, drainage of an abscess and insertion of setons (*n*=1), right hemicolectomy (*n*=1), laparoscopic ileocolic resection and limited right hemicolectomy (*n*=1), and ileocaecal resection and formation of an end ileostomy (*n*=1).

Table 3.6 | Reasons for hospitalisation events in children with Crohn's disease treated at Starship Child Health during the 52-week follow-up pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		
	Pre-2015 *n*=40	Post-2015 *n*=51	p-value
Hospitalisation reasons, *n* (%)			0.032[a]
For diagnosis	18 (46.2)	9 (20.9)	
Exacerbation of CD	5 (12.8)	6 (14.0)	
Pain and/or vomiting	3 (7.7)	14 (32.6)	
EEN induction/NGT insertion	2 (5.1)	2 (4.7)	
EEN problems	3 (7.7)	1 (2.3)	
Surgery	1 (2.6)	4 (9.3)	
Other CD related	7 (17.9)	7 (16.3)	

Abbreviations: CD: Crohn's disease; EEN: Exclusive enteral nutrition; NGT: nasogastric tube.
[a] Fisher-Freeman-Halton Exact test.

3.5 Concomitant medications

Aminosalicylate, CS, azathioprine, and biological therapies (infliximab, adalimumab or certolizumab [via clinical trial]) were recorded for this case audit (**Table 3.7**). Significantly more children were prescribed aminosalicylate therapy pre-2015 compared to post-2015 (77.5% vs 31.4%, respectively; p<0.001), but the median time to therapy was not significantly different. There was no significant difference in the prescription of azathioprine maintenance therapy or CS between groups, including the median time to therapy (Table 3.7). The number of children requiring biologic therapy trended towards significance (p=0.052), with more children needing the therapy post-2015 (35%) than pre-2015 (15%).

Table 3.7 | Concomitant medications used during the 52-week follow-up pre-2015 (*n*=40) and post-2015 (*n*=51)

	Pathway		p-value
	Pre-2015 *n*=40	Post-2015 *n*=51	
Aminosalicylate, *n* (%)	31 (77.5)	16 (31.4)	<0.001[a]
Time to therapy, weeks, median (min-max)	0.6 (-4.9 – 41.1)	4.1 (-3.0 – 48.6)	0.076[b]
Corticosteroids, *n* (%)	19 (47.5)	32 (62.7)	0.214 [a]
Time to therapy, weeks, median (min-max)	6.4 (0.6 – 54.9)	8.8 (0.4 – 50.7)	0.953 [b]
Azathioprine, *n* (%)	36 (90.0)	45 (88.2)	1.000 [a]
Time to therapy, weeks, median (min-max)	4.5 (-2.0 – 50.7)	4.7 (1.0 – 54.0)	0.801 [b]
Biologic therapy, *n* (%)	6 (15.0)	18 (35.3)	0.052 [a]
Time to therapy, weeks, median (min-max)	38.7 (10.4 – 57.1)	20.6 (3.1 – 49.4)	0.096 [b]

[a] Chi-squared test; [b] Mann Whitney U-test

Children were detailed as having between one and three supplement drinks or having Fortisip as snacks, for weight loss, increasing weight, growth failure, and problematic food reintroduction. In two cases where parents were reluctant to start azathioprine, two 200 mL Fortisip drinks were recommended. There was no significant difference in the number of children recorded as having maintenance enteral nutrition pre-2015 and post-2015. A second course of EEN was recorded in 6 children (*n*=4 pre-2015 and *n*=2 post-2015), commencing between weeks 13 and 45 following diagnosis.

3.6 Deviations from data collection time points

Due to the retrospective nature of the medical note audit, it was essential to determine if there were significant differences in the week of data collection between the two pathways. When the week of measurement was reviewed, there were no significant differences between the pathways for anthropometric measurements for any time point (**Table 3.8**). Biochemical measurements showed a significant difference between diagnosis and week 8 (Table 3.8). Median measurements for the groups following diagnosis were 0.3 weeks (pre-2015) and 1.3 weeks (post-2015) before EEN commencement (p=0.011). Median measurements at week 8 for the pre-2015 group were taken 1 week after the post-2015 group (8.7 weeks and 7.7 weeks, respectively; p=0.035).

Table 3.8 | Deviations from the expected week of measurement for anthropometric and biochemical data

	Pathway		
	Pre 2015 *n*=40	Post 2015 *n*=51	p-value
Anthropometric measurements, median (IQR)			
Deviation from expected time point, weeks			
Diagnosis	-0.1 (0.6)	-0.6 (0.8)	0.098
Week 8	1.0 (2.5)	-0.5 (2.2)	0.078
Week 13	1.7 (1.5)	2.0 (2.0)	0.718
Week 26	-0.6 (4.6)	-0.3 (4.2)	0.542
Week 52	5.2 (8.1)	3.7 (4.9)	0.889
Biochemical measurements, median (IQR)			
Deviation from expected time point, weeks			
Diagnosis	-0.3 (1.9)	-1.3 (2.5)	**0.011**
Week 8	0.7 (1.7)	-0.3 (1.7)	**0.035**
Week 13	1.4 (1.2)	1.4 (1.7)	0.699
Week 26	0.5 (3.2)	0.0 (4.1)	0.958
Week 52	2.0 (4.6)	1.6 (4.1)	0.981

Abbreviations: IQR: interquartile range

3.7 Post hoc analyses

3.7.1 Aminosalicylate therapy

3.7.1.1 Disease remission at week 8

In a post hoc analysis investigating the effect of aminosalicylates on disease remission, children prescribed aminosalicylates within 6 weeks of diagnosis had significantly improved remission (72.2%) and lower mod-PCDAI scores (median 3.8) compared to those who were not (36.7%; p=0.037, median 7.5; p=0.017, respectively) (**Appendix 13, Table A8**). Characteristics at diagnosis for those prescribed aminosalicylate therapy and those who were not were similar.

In the sub-group of children prescribed aminosalicylate therapy, mod-PCDAI scores were lower, and disease remission was higher in the pre-2015 group than in the post-2015 group (p=0.006 and p=0.019, respectively) (**Appendix 13, Table A9**). Demographic or disease characteristics at diagnosis were not significantly different between the groups. The sub-group of children who were not prescribed aminosalicylate therapy showed no significant difference in disease remission or mod-PCDAI score between pre-2015 and post-2015 (**Appendix 13, Table A10**). At diagnosis, ethnicity and albumin showed significant differences (p=0.019 and p=0.004, respectively), but other characteristics did not.

3.7.1.2 Disease remission at week 52

Children who were prescribed aminosalicylate therapy did not have improved long-term disease remission (week 52) compared to those who were not (Appendix 13, Table A8). In the sub-group of children prescribed aminosalicylates, the pre-2015 group had better disease remission (90.9%) than post-2015 (28.6%; p=0.026), and mod-PCDAI scores were trending towards significance (p=0.069) (Appendix 13, Table A9).

Section two: Semi-structured Interviews

3.8 Child and whānau interviews

3.8.1 Participant characteristics

Twenty-four children with CD who had completed a course of EEN treatment were invited to participate in semi-structured interviews. Ten (42%) were interviewed, seven declined, and a further seven did not respond. Five interviews included the child with CD and a whānau member, and five were solely with the child's parent. Demographic characteristics are displayed in **Appendix 13, Table A11**. EEN treatment was completed during 2021 (*n*=2), 2020 (*n*=7) and 2019 (*n*=1), and five (50%) participants had progressed to requiring Infliximab treatment to control their CD.

3.8.2 Themes

There were three major themes identified from the interview data. These were 1) a difficult and emotional time, 2) food confusion, and 3) support. Support was further split into two sub-themes; clinical support and social support.

3.8.2.1 A difficult and emotional time

The emotions expressed during the interviews were predominantly negative. Their emotional angst was evident in their words; "*I'm sick of being different", "we bugged them a lot with questions", "we felt, I felt quite isolated", "it was horrific", "she was in tears, we were in tears".* Participants also verbalised their emotions via words; "*I was stupid", "there is an overwhelming guilt", "there was a sense of real failure for us like we had failed this", "the diagnosis… it's particularly traumatising for her", "it didn't feel like we were winning at all at that stage", "psychologically, that was really difficult for us as a family and for [name]".*

Guilt or concern over whether the foods provided to the child were contributing to ongoing inflammation was prominent and linked to food confusion.

> *It was just an emotional time, I guess, for all of us. You just feel this overwhelming guilt of what if he's eating something every day that's actually just contributing to the inflammation (P3, mother).*

3.8.2.2 Food confusion

The children and their whānau were clear on the treatment protocol for EEN; however, some experienced confusion regarding food reintroduction and most were unclear on ongoing dietary practices. Most participants received the step-by-step approach resource and a discussion around food reintroduction during a clinic appointment; however, some of the participants were provided with little or no information regarding food reintroduction during their EEN treatment. For some

children and whānau, confusion was created by health professionals advising removal of dietary elements such as dairy, gluten and additives, while others advised there was no need to remove any dietary elements following food reintroduction.

> *They gave me a little plan of how to start introducing foods back into her diet and what to start with. But that was kind of very confusing for me because half of the people were telling me to put her on a dairy-free gluten-free diet, and then half of the people weren't, and then the food lists she was giving me were absolutely not gluten-free or dairy-free, it was kind of a confusing time… That was the dietician, the registrar, another consultant that I saw, just before we were discharged from Starship, but when I specifically asked my consultant, it was no that's not important in her diet (P9, mother).*

Most parents had gone looking for further information regarding CD to help their child but found it challenging to navigate the wealth of information available to them, and they were unsure what information could be trusted. The information they found regarding diet was often contradictory and recommended the removal of certain foods or food groups. Parents had the impression that diet was important in managing CD and that they would need to identify foods or food groups that would exacerbate the disease for dietary removal.

> *I find the hardest part of the disease is the nutritional side of things. There's so much, you know, on to Google, there's so many things you can read, you know, one gastroenterologist is saying, a vegan diet is amazing, and another person is saying a FODMAP diet is amazing and you just don't know which one you should be doing… I find it a bit hard to navigate my way through (P3, mother).*

3.8.2.3 Support

3.8.2.3.1 Clinical support

During the initial treatment stages, participants mentioned that they were seen roughly every two weeks and experienced support from both the dietitian and gastroenterologist, who were available via phone or email throughout their EEN treatment and during the food reintroduction phase. They thought this support was important during treatment; however, some participants revealed that they had not received any or enough education or information, and in these cases, there was a sense of overwhelmingness in trying to navigate their own way through.

3.8.2.3.2 Social support

Social support was identified as important during the initial stages of CD diagnosis and treatment. Parents reported feeling isolated and were often overwhelmed during this time. Participants that were able to connect with others in similar situations found the support to be valuable.

The main actual bonus for us was that a friend of ours ... whose [child] was recently diagnosed. So, we just had coffee with her and we actually talked quite a lot. That was useful, but obviously not part of the program (P4, mother).

When I reached out to a friend … who has a [child] similar age and has been through it … So that was really helpful to have other people's experiences, like that was probably the most valuable thing (P10, mother).

Children navigating their CD treatment journey often did not want to discuss or know what was going on. Participants felt that it would have been beneficial to have a forum where children with CD could connect with others in a similar situation following diagnosis and during treatment.

She didn't want to bar of me talking to her about it, and would kind of fob me off when I tried to explain this is why are we doing this and justification for it all. So maybe if there was something for the kids at a kid level to kind of buy into it… A session, definitely, and even not necessarily one on one, like even just a group session. And even for me as a mum to talk to other mums and share ideas or views and things" (P9, mother).

We found now that he's made like friends with Crohn's; he's been to the camp purple. That really helps just to have people he could talk to, but obviously, when you go on that diet … it might have been helpful if there were other kids that he knew that he could talk to and have some fun with (P5, mother).

3.8.3 Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline experience

3.8.3.1 The exclusive enteral nutrition experience

The children's experiences when taking EEN varied and showed how individual the journey is for each child. The recommended and actual duration of EEN therapy, reasons for stopping, and how easy it was to comply with EEN requirements varied between the children (**Appendix 13, Table A12**).

I had to go through Christmas and New Years on the diet, but they gave me leeway [to eat] … and then I got sick again really bad, and it just put me all the way back, so I ended up going on steroids along with the ensure (P1, female).

We did eight weeks of fortisip, and that was hell (P2, male), it wasn't very easy because they were very gross (P4, female), he'd slam them down, so very easy (P6, father).

Most children had experienced a further flare or exacerbation of symptoms; however, none had a further course of EEN since finishing their initial treatment, and whether they could take a further course varied (Appendix 13, Table A12).

So, when the markers went back up, it wasn't till I got off the phone that I thought why didn't they offer EEN as an option instead (P4, mother)?

3.8.3.2 Patient education

Most children or whānau recalled having general discussions but not typical education sessions with their gastroenterologist directly after the diagnosis, during clinic appointments or while hospitalised regarding their treatment options and being provided with information such as resources or website links to review. The children and whānau were given resources; however, they described these as fairly basic; therefore, they always had lots of questions when meeting with the gastroenterologist and dietitian.

I guess I did. At the time, on the day of the colonoscopy, the specialist came out and showed me the scan photos, and sort of explained what we were looking at. So, I guess, if that's education. There was communication (P4, mother).

In addition, most recalled seeing a dietitian at or soon after diagnosis to discuss the EEN protocol and order the supplements. Participants mentioned that they would usually see the gastroenterologist and the dietitian at the same time in their clinic appointments during EEN treatment and food reintroduction.

3.9 Health care professional interviews

Nine key HCPs within the SCH CD treatment pathway were invited to participate in semi-structured interviews. Interviews were carried out with paediatric consultant gastroenterologists (*n*=4), senior paediatric gastroenterology dietitians (*n*=2), a gastroenterology nurse specialist (*n*=1), and two HCPs did not respond. The gastroenterologists and dietitians worked directly with CD patients, and the nurse specialist did not.

3.9.1 Theme

Only one theme was identified from HCP interviews; a multidisciplinary team is needed.

3.9.1.1 A multidisciplinary team is needed

At SCH, a team approach was involved in coordinating EEN treatment, including both gastroenterologists and dietitians. Other services such as psychology, social work, pharmacy or an IBD-NS were not involved; therefore, it was felt that a "*true*" MDT approach was not used for managing CD.

In terms of a MDT, there's two, two specialities, that work together to do this (Dietitian).

The underlying theme from these interviews was that there is a real need for a wider multidisciplinary team to make things "*a bit more streamlined and predictable*". It was felt that an IBD-NS is crucial as

"*an anchor"* for the service, who was able to dedicate time to education and could be a support for and liaise with children and whānau. In addition, it was deemed that psychology support would be beneficial to mitigate the potential impacts on QoL and self-image that may be a consequence of having a chronic disease diagnosis. The HCPs considered that there was a "*definite inequity*" when comparing the IBD service to the liver transplant service, "*which does not reflect the morbidity of IBD or the challenges that these children face".*

> *The obvious lack in our service is nursing support and the dedicated time, and education and liaison communication with the families that they are often able to provide that, in all honesty, we as medics are either not very good at or don't have the time to do so (Gastroenterologist).*

> *I wonder whether a lack of support, a lack of wraparound care account for some of the issues that we face in that, you know, in an ideal world, if the patient knew, within the first week they'd get two phone calls from a clinical nurse, within the first two weeks they'll get one face to face or telephone conversation with a dietitian, within the first three weeks they'll see the consultant, if there was that defined structure to what we do, so they knew that, if they're struggling or the parents knew the child is struggling, it's only two days or three days to the next contact (Gastroenterologist).*

3.9.2 Management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline practice

3.9.2.1 Patient education

When asked about education for children and whānau, the HCPs all described discussions with whānau immediately following the endoscopy while the child was in recovery. It was felt that discussions with children and whānau following endoscopies were "*less than ideal*" and "*often quite rushed*" (in between endoscopies), with whānau being *"anxious and stressed or distracted*" and "*no one's remembering very much at that point*". In addition to discussions with the gastroenterologist following the endoscopy, patients are seen in the outpatients' clinic soon after diagnosis.

> *The first time I see the patient and family again in clinic, I go over what we've talked about, but before I do, I often say, look I know we've talked about this I know there's a lot to take in, you've probably done some reading and some googling. Where are you up to what would you like to talk about, … and make sure there is opportunity to go over things again (Gastroenterologist).*

3.9.2.2 The treatment pathway

There was variation between gastroenterologists in the duration of EEN Treatment. EEN was prescribed for 6 to 8 weeks and could be stopped if patients have a good response and are in clinical remission at 6 weeks; otherwise, it is stopped after 8 weeks.

A lot of patients will get into clinical remission within six weeks alone, so I very rarely use the 8 weeks (Gastroenterologist).

So, eight weeks absolutely, it's not just 8 weeks is it … you eat one meal a day plus two of EEN (Gastroenterologist).

The gastroenterologists would typically see the patients 2 to 3 weeks into EEN and then towards the end of their EEN treatment.

What I usually aim to do is see them about two to three weeks into the course of treatment on the basis that if there's been absolutely no clinical response in two to three weeks, it's generally safe to assume that the EEN and is not going to work providing they're adhering to it (Gastroenterologist).

The gastroenterologists did not see the patient every two weeks; however, the patient or whānau would be in regular contact with the dietitian during their EEN treatment to ensure requirements were met and to help with troubleshooting. In addition, the gastroenterologists felt that dietetic input was crucial during this time and allowed regular contact that they could not provide due to time constraints.

A dietetic review is happening every two weeks, and the docs relying on us to say hey, things aren't going well, or the parents have questions (Dietitian).

I've alluded to already it's probably as important if not, arguably more important [than seeing the gastroenterologist] that the dietician is seeing the patients, at least regularly checking, you know, are they meeting requirements (Gastroenterologist).

CHAPTER 4: DISCUSSION

4.1 Overview

This study is the first to formally review patient outcomes (disease remission and growth) at SCH following the implementation of the IBDCG in 2014. Prior to implementing the IBDCG, treatment for newly diagnosed CD patients was determined by their primary gastroenterologist. In this audit, we grouped the patients into those diagnosed between June 2010 and December 2014 (termed pre-2015) and those diagnosed between January 2015 to July 2020 (termed post-2015). In addition, HCP practices and views of the IBDCG and patient and whānau experiences during CD treatment at SCH have not previously been identified. Therefore, this thesis used a mixed-methods approach to determine 1) if the implementation of the IBDCG has improved disease remission rates and clinical outcomes in paediatric CD patients managed by the SCH gastroenterology team and 2) if the IBDCG needs modifying to improve clinical practice or support for the future. Overall, this research found that the introduction of the IBDCG has not contributed to improved disease outcomes for children with CD managed by SCH. Improvement in education and support for patients with CD and their whānau is required, and an IBD-NS would be a valuable addition to the IBD service for this purpose.

4.2 Response to treatment

The primary objective for patients newly diagnosed with CD is to induce remission, followed by management to control inflammatory activity, thus enabling maintenance of remission and prevention of long-term complications such as growth failure, pubertal delay or long-term tissue injury (3,138). EEN is recommended as the preferred first-line therapy and is effective in inducing remission in patients with CD (74). Current literature reports disease remission rates between 47% and 92% using EEN therapy (37-39,89,90,111,112,116-125,127,128). At SCH, 77.3% of children with CD achieved remission *prior* to introducing the IBDCG, which is in line with the current literature. Following the introduction of the IBDCG, there was a significant decrease in the proportion of children with CD that achieved remission (26.9%), a result that is at least 20% lower than the current literature. However, published literature describing remission following EEN therapy is heterogeneous in both exclusion criteria and the definition of disease remission, making direct comparisons challenging. Common exclusions include steroid, immunomodulatory or anti-TNF medications (37-39,78,99,101,116-118,120,121,123,126), more complicated disease behaviour e.g., stricturing (78,90,101,105,117,120), and more severe disease e.g., PCDAI >30 (95,126). In addition, a large proportion of research investigates the effect of EEN only, rather than a range of induction therapies. The present cohort included *all* children with a confirmed CD diagnosis managed by SCH no matter the treatment modality, severity, or disease behaviour between June 2010 and July 2020. At

diagnosis, patients with stricturing and penetrating disease or a combination of both made up over 30% of the present cohort, and severe disease was experienced by 49% (post-2015), which may explain the variation seen.

This study shows that the introduction of the IBDCG did not result in improved outcomes for children with CD. Two factors, 1) albumin levels and 2) aminosalicylate use may have contributed to the observed differences in disease remission outcomes. Albumin is a parameter in determining remission via the mod-PCDAI, contributing up to 40% of the final value, while CRP, ESR, or haematocrit contribute up to 20% each. Lower albumin values contribute a higher proportion to the mod-PCDAI score, i.e., ≤ 30.0 g/L adds 10 to the score, while ≥ 35.0 g/L contributes no points. In the post-2015 group, albumin was significantly lower at diagnosis and across the follow-up period, leading to lower mod-PCDAI scores compared to the pre-2015 group. Children classified as "in remission" by their gastroenterologist had significantly higher albumin levels than children who had not attained remission following induction treatment. Grouping the children classed as in remission into pre-2015 and post-2015 revealed that the post-2015 group had significantly lower albumin values at diagnosis and following treatment. It has been demonstrated that patients with active CD have lower albumin levels than those in remission (139), which corroborates our finding of lower albumin levels in children classed as not attaining remission, i.e., still had active disease, compared to those who attained remission.

Aminosalicylates are no longer commonly used in treating CD due to a paucity of evidence demonstrating their benefit. Compared to a placebo, aminosalicylates were found to have very modest (if any) benefits for patients with CD (83,84). In the present study, the pre-2015 group was prescribed more aminosalicylate therapy than the post-2015 group (77.5% and 31.4%, respectively). Children prescribed aminosalicylates in the present cohort had significantly higher remission rates (72.2%) than those who were not prescribed aminosalicylates (36.7%). However, new ECCO-ESPGHAN guidelines (2021) (74) do not recommend aminosalicylate use in the induction or maintenance of remission in CD; therefore, the clinical significance is likely to be low.

Following induction treatment, the patient's gastroenterologist determines remission status via a PGA. This is based on the gastroenterologist's clinical impression using symptoms and growth, +/- inflammatory markers and FC to determine how well controlled the patient's disease is, rather than a tool validated in this population. Disease remission determined by the child's gastroenterologist, and the calculated mod-PCDAI scores were not significantly different. For this cohort, the gastroenterologist determined disease remission was at the low end of the range of the current published literature (62.2% pre-2015 and 55.8% post-2015). Typically, disease remission is determined via the PCDAI or a weighted PCDAI; however, limited studies use subjective measures such

as patient global assessment (122,128), MDT consensus classification (111), or patient-reported stool markers (124). In reports such as these, remission tends to be lower (47% (111), 53% (124), 60% (122), 80% (128)), whereas PCDAI or weighted PCDAI results tend to be higher (70 – 92% (37-39,89,90,112,116-121,123,125,127)). SCH gastroenterologists determine remission via a PGA, which could explain why current remission prevalence is toward the lower end of published literature.

Following induction of remission, immunomodulatory medications are prescribed to maintain remission from active CD (74). During the 52-week follow-up, azathioprine therapy was started at a median time of 4.5 and 4.7 weeks, with 90% and 88% of children beginning therapy (pre-2015 and post-2015, respectively). Treatment progressed to requiring biological therapy at a median time of 38.7 weeks in 15% of children (pre-2015) and 20.6 weeks in 35% of children (post-2015), which trended toward significance. Few studies report progression to biological therapy over time; however, this cohort is in line with current literature, reporting progression to biological therapy 52 weeks following treatment in up to 39% of cases (38,96,105).

Maintenance of remission is crucial for a child's growth and development (97,102) and holistic well-being (160,172). Longitudinal studies typically evaluate disease relapse following EEN treatment, with reported relapse rates between no relapse (0%) to 72% of children relapsed after one year (39,97,98,105,106,112,116,120,121,123). Due to the retrospective nature of this study, relapse rates were determined via prescribed corticosteroids or progression to biological therapy after induction treatment (i.e., after week 8). Based on this criteria, disease relapse rates were estimated at 35% (pre-2015) and 59% (post-2015), which is similar to other studies measuring disease relapse (95-98,105,106,116,120,122-124). Lower albumin values post-2015, as previously discussed, and hence more active disease (139,198), may account for the significantly higher relapse rates in this group. Disease remission 52 weeks following diagnosis remained significantly lower in the post-2015 group (43%) than in the pre-2015 group (85%), and disease activity score was significantly higher, indicating more active disease in these children.

For paediatric patients with CD, their disease must be well managed due to the effect insufficient nutrition can have on growth and pubertal development (47,60,126). Typically, children have lost weight prior to diagnosis (2,3,9,41,138), and using EEN to induce remission as opposed to corticosteroids, has the benefit of aiding in weight recovery and nutritional status (97,108,109). While not significantly different between the groups in this cohort, most children gained weight following induction treatment. Weight and BMI z-scores showed significant improvements from diagnosis to the end of induction treatment; however, height z-score did not. Typically children show increases in weight and BMI, but not height z-scores following induction treatment (89,98,111,120,123,125,128) as evidenced in this cohort. Disrupted or impaired growth results from the disease process as well as

nutritional status; therefore, an alteration in height velocity may have occurred prior to diagnosis (Figure 1.2) and requires effective disease management to maximise growth potential (49). This growth impairment can lead to a final adult height shorter than their parent and the general population of the same sex (16,59).

Over a more sustained period (6 – 24 months), changes in anthropometric measurements are sparse. Weight z-score shows significant increases from diagnosis over the longitudinal follow up period; however, height z-score results vary, exhibiting significant and non-significant changes over the longer term (98,106,112,122,128). The present cohort exhibited a slow, consistent increase in weight z-score across 52 weeks; however, height z-score remained relatively stable for the first 26 weeks, followed by an increase between weeks 26 and 52. After 52 weeks, weight and BMI z-score showed significant improvements from diagnosis in both groups, similar to the literature. Height z-score showed significant improvements for the post-2015 group and was trending to significance in the pre-2015 group. Inconsistent results have been reported for height z-score. A prospective study in 18 children aged 8 to 16 years reported significant improvements in height z-score 52 weeks following EEN treatment (112), while retrospective studies have reported non-significant changes in height z-score between 6 and 24 months (98,106,122,128), indicating that height changes may take longer to appear.

4.3 Experiences with the management of inflammatory bowel disease in children and adolescents in New Zealand clinical guideline

In the semi-structured interviews, participants were asked about their experiences following CD diagnosis and during treatment, which served as a proxy to determine experiences with the IBDCG. The IBDCG sets out steps for diagnosing and managing IBD, including education regarding a child's diagnosis and treatment, dietetic assessment, introduction to support groups, and ongoing monitoring (189). Patient and whānau experiences during EEN treatment and solid food reintroduction differed.

During the initial management of CD, the IBDCG states that children and their parents should be provided with two or more education sessions in order for them to understand their diagnosis (189). Each gastroenterologist provides education immediately following a patient endoscopy, although they recognised that this was "less than ideal". Patients and their whānau had a poor recollection of the content of these conversations; however, most recalled having a general conversation with their gastroenterologist directly after the diagnosis, during clinic appointments or while hospitalised. Lack of recall is not unexpected given the timing of these initial discussions and highlights how difficult it is to recall verbal information (148). In most instances, resources such as the EEN protocol and a booklet from Crohn's and Colitis NZ were provided to patients, which is an effective way to supplement oral information (148). During follow-up appointments, parents recalled they had many questions due to

the timing of education following the endoscopy and the provision of simple resources. Gastroenterologists were more than happy to answer patient or whānau questions as they arose; however, an opportunity exists to collate common questions and use evidence-based information to develop a more in-depth resource that can be given to patients and whānau following diagnosis. Alternatively, patients could be directed to reputable online resources for those who would like to find out more information regarding CD, treatments or side effects.

The IBDCG considers a multidisciplinary approach to education and support to be critical to the success of EEN (189). At SCH, children with CD were managed during EEN treatment and subsequent food reintroduction by a gastroenterologist in conjunction with a dietitian, a limited MDT approach. The gastroenterologists considered dietetic involvement crucial during EEN, and there was a heavy reliance on dietetic feedback to identify patients who may need additional medical support. Further support from psychologists, social work, or other allied health services was on an as-needed basis, and IBD-NS support was not available. Gastroenterologists, dietitians and parents indicated that psychological support for children with CD would be beneficial to mitigate the potential impacts on QoL and self-image that may be a consequence of having a chronic disease diagnosis. Psychological symptoms such as anxiety, stress or depression are significantly higher in paediatric and adult patients with IBD than healthy controls (165,172). IBD has been reported to exert a continuous effect on a patient's QoL (169), and during active disease, children are reported to have poorer psychological well-being and depression symptoms than during remission (168). SCH HCPs identified a lack of wrap-around care and support for the IBD patients through not having an IBD-NS who could actively check on the patients and their symptoms and drive disease-related education and support. IBD-NSs are commonly associated with IBD services worldwide as a standard of care (182,187,188). IBD-NSs are reported to decrease hospital admissions, aid in patient management through email and phone contact, improve patient education and support (181,186,187). Not every patient and whānau felt that they received timely information or support, or they faced challenges during their treatment that would have benefitted from further input; therefore, an IBD-NS supporting the current SCH gastroenterology dyad could ensure better education and coordination of care.

The experience of having a child diagnosed with CD was a challenging and emotional time for parents, the child and the whole family. The chronicity of the illness plays a role, and not knowing what to expect along the treatment continuum can exacerbate a family's difficulties. Support was seen as playing an essential role in helping patients and families through this time. Support from HCP at SCH was crucial and occurred approximately every two weeks during EEN treatment, but less so following food reintroduction. Shared experiences and connecting with parents in a similar situation were considered valuable, and support groups for whānau may benefit this patient group. Support groups

could be facilitated during early treatment, where children and their parents (separately) could connect with others in a similar situation. The ability to share ideas and discuss challenges could help parents navigate their child's life-changing diagnosis, whilst children could learn about their disease and have fun with other children in a similar situation. Peer support and support groups are recommended as part of the IBDCG during initial CD management (189); however, support is not currently in practice outside of the traditional patient-HCP relationship.

Focus groups of children with IBD and their parents have identified that peer support programs would ideally provide educational activities with a mentor who has been living with IBD for at least a year (179). Children and adults with CD find it easier to share their thoughts, experiences and feelings with others with CD, as they recognise a shared understanding (177,178). Crohn's and Colitis NZ run Camp Purple for children living with IBD to experience fun childhood activities within a supportive environment (199). Attending camps or away days for children with IBD helps acquire new perspectives about their IBD and can build up a new social network to provide additional support for living with a chronic condition such as IBD (154,175,176). At SCH, a coordinator is required to facilitate support groups to enable more effective support for children and their families living with CD. There is an opportunity to coordinate an informal "coffee group" type group for children newly diagnosed with CD and their whānau to provide support at this challenging time.

CD is a disease of the GI tract; therefore, there was a belief that manipulation of the diet would be required to manage symptoms and flares over the longer term. Most parents had independently searched for further information regarding CD to help their child but found it challenging to navigate the wealth of information available to them and were unsure what information could be trusted. Parents revealed that they were confused by what they should do as information on diet and CD was often contradictory and recommended removing specific foods or food groups. In a 2014 review of patient targeted recommendations for IBD, Hou *et al*. (163) found 47 unique websites containing recommendations for a "CD diet", where 11 food categories were recommended to be avoided by ≥80% of sites mentioning that food. Between sites, recommendations could be contradictory; however, individual sites also gave conflicting recommendations, i.e., both for and against inclusion or exclusion in the diet (163). During treatment at SCH, gastroenterologists and dietitians were seen to cause inadvertent confusion around food with conflicting advice to remove (or not) dietary elements such as dairy, gluten, and additives. This inadvertent advice could also contribute to the belief that dietary manipulations are necessary to manage symptoms and flares. Similar opinions have been portrayed in adults with IBD where limited dietary information or resources were provided by the gastroenterologist (152,157), patients did not feel supported with diet counselling (157), or they

received conflicting advice (157,160), all of which were experienced by the present study's patients and whānau.

Following remission induction, the patient returns to their usual diet; however, there are limited recommendations for diet manipulation in CD management (141,142). Diets such as the Specific Carbohydrate diet, IBD-anti-inflammatory diet and the FODMAP diet have shown promise; however, these studies were small; therefore, larger, well-designed RCTs and prospective cohort studies are required (141,142). Due to a lack of strong evidence, the SCH health professionals reassure parents that diet is not important in managing CD, but despite this, parents find it difficult to accept that food does not contribute to ongoing symptoms. This was demonstrated by Czuber-Dochan *et al*. (160), where adults with IBD are advised by their gastroenterologists that diet does not matter; however, they struggle to accept this advice as they cannot see how a digestive illness is not linked to the food they are consuming. In the present cohort, there was a belief that diet could manage symptoms and flares over the longer term, with parents restricting (or believing they should be restricting) certain foods or food groups and looking for foods that may be causing flares. This is concordant with several studies investigating the impact of a CD diagnosis on food intake, where individuals with CD often restrict their diet to manage symptoms (152,155,158-160) and make changes without any professional advice (157). An emerging theme in the present data was that patients and whānau would have liked a continued relationship with the dietitian following food reintroduction, where queries or concerns regarding a child's diet or food intake could be addressed. During EEN treatment, the gastroenterologist and dietitian work closely to monitor patients. However, once food reintroduction is complete, there is little dietetic input for reasons such as lack of time, non-targeted IBD clinics, reliance on medical staff to identify patients needing additional support and lack of strong dietary recommendations. Adults with CD consider dietary advice important; however, they feel that they do not receive the right amount of information (148). There is a lack of evidence for ongoing dietary advice in paediatric CD; however, as parents are primarily responsible for dietary management, their needs could be assumed to be similar; therefore, ongoing dietetic input for children with CD would be beneficial.

4.4 Strengths

The present study is the first in NZ to describe the paediatric CD cohort diagnosed and managed by SCH between June 2010 and July 2020 and formally review patient outcomes following the implementation of the IBDCG. This study included all children diagnosed with CD over a 10-year period with at least 12 months of follow-up; therefore, the sample is representative of the CD population in NZ. A project-specific data collection tool was designed for the clinical audit, capturing an extensive range of parameters to describe the cohort. Disease remission was calculated using the

mod-PCDAI, a validated measure of assessing disease severity that has been reported to correlate well with the PCDAI and a PGA (194).

This study is the first to identify SCH HCP, patient and whānau experiences of EEN treatment in NZ and their views of education and support provided via the IBDCG pathway. Pre-defined questions based on consideration of the topic and literature guided the interviews. In addition, participants were given the opportunity to contribute views outside of the questions at the end of the interview. During analysis, the final themes emerged from the data instead of being pre-defined; therefore, they represented patient, whānau and HCP opinions.

4.5 Limitations

Due to the retrospective nature of this study, there are several limitations. Typical clinical indices, such as PGA or PCDAI, were not recorded at week 52; therefore, biochemical markers were used to determine disease remission via the mod-PCDAI score. The mod-PCDAI is one of several abbreviations of the PCDAI since its development in 1990 (200). The mod-PCDAI is not commonly used as a measure of disease remission in CD literature, possibly due to the variety of disease remission options and because it has only been evaluated in a small cohort of children (*n*=62) in a single-centre (200). In comparison, the PCDAI was developed by 30 senior paediatric gastroenterologists, followed by validation in 12 North American gastroenterology centres (113). Larger validation studies are required to compare the mod-PCDAI to the PCDAI; until validations occur, direct comparisons are more challenging.

It was difficult to retrospectively determine the effectiveness of the change in the protocol because of missing data. During the clinical audit, missing data led to incomplete data sets; therefore, remission status could not be determined for 47% of the cohort (45% pre-2015 and 49% post-2015). The missing data may have led to the results being overstated, i.e., missing data had lower mod-PCDAI scores, therefore would lower the median result, or understated, i.e., missing data had higher mod-PCDAI scores, therefore would increase the median result. This study's results do not fully describe the cohort due to missing data; therefore, they should be treated with caution. Data used to determine clinical outcomes was not collected at uniform time points, e.g., week 8; instead, measured time points included data collected over a defined period (e.g., weeks 6-12, or weeks 50-65). Dispensing data used to determine relapse rate does not confirm that the child took the medication; therefore, relapse rates may be overstated.

The semi-structured interviews used a convenience sampling method; therefore, these results are open to selection bias and may not represent the CD population. Most participants in the patient and whānau interviews (80%) had completed EEN therapy during 2019 and 2020; therefore, their

recollection of experiences may differ from patients who completed therapy more recently and could be influenced by ongoing disease management. COVID-19 restrictions in the Auckland region from August to October 2021 required in-person interviews to be replaced with virtual interviews. Virtual interviews unintentionally excluded some children or whānau who did not feel comfortable communicating via an online platform but would have consented to an in-person interview or did not have access to a device or stable internet connection. The quality of information obtained during the interviews may have been compromised if a child or parent were uncomfortable using a virtual platform. Technical issues such as connectivity problems or low audio disrupted interviews and created transcribing difficulties.

4.6 Future directions

The findings from this study highlighted low remission rates compared to published literature. Reasons for this may be multifactorial; however, designing a prospective cohort study measuring disease remission compared to mucosal healing and clinical outcomes, such as growth in newly diagnosed children with CD over 52 weeks, would better elucidate outcomes for children in NZ. The pre-definition of data collection variables and time points would ensure that data variables are consistently measured, therefore limiting missing data. Ideally, this study could encompass all children diagnosed with CD at SCH and Christchurch Hospital, the two tertiary paediatric gastroenterology centres. In addition, the study design could be mixed-methods and include semi-structured interviews following EEN induction therapy to explore patient and whānau experiences with EEN and the IBDCG pathway.

Further analysis could be carried out using this study's data set. Children treated with sole EEN therapy could be evaluated to determine if there were any independent risk factors for the success or failure of EEN treatment. Segmenting the dataset by disease location, disease behaviour, and disease severity at diagnosis in children treated with EEN could determine if these characteristics contributed to the effectiveness of EEN as a treatment modality. However, this would reduce the sample size and potentially impact the effect size of the outcome. Data from paediatric CD patients managed by Christchurch Hospital could be added to this data set, further defining the NZ CD population and exploring disease remission rates and clinical outcome changes following the implementation of the IBDCG.

4.7 Conclusion

The change to a more formalised process of CD treatment via the IBDCG has not contributed to improved outcomes for children with CD at SCH. Disease remission following induction treatment was lower and albumin higher before the IBDCG introduction, and there were no differences between

pathways for anthropometric measures and inflammatory markers CRP and ESR. Future research could focus on a NZ wide prospective cohort study design to elucidate patient outcomes in NZ and allow comparisons with the current literature. Modifications to current practice and the IBDCG are required to better support patients and whānau with CD at SCH. A dedicated IBD-NS is required to provide improved wrap-around care such as active disease management, education and resources for children. Coordination of peer support or support groups for newly diagnosed children with CD and their whānau is required. Further dietetic support is required beyond EEN treatment and solid food reintroduction to help patients navigate their nutritional needs and the plethora of contradictory information online, often with no solid evidence base. Further review of how patients and whānau experience current practice is recommended.

APPENDICIES

Appendix 1: Participant information sheet patient <16 years of age

MEDICAL AND HEALTH SCIENCES

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PARTICIPANT INFORMATION SHEET

PARTICIPANT'S <16 YEARS OF AGE

Study Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

Why am I being asked to be in the study?

- You have had treatment through Starship Children's Hospital for Crohn's Disease
- You have finished your liquid diet (nutritional supplement drinks) treatment
- In this study, we will ask you questions about your experiences with the liquid diet and any support you received.
- We will also ask you questions about re-introducing solid foods back into your diet and whether you continued with your liquid food.

Your mum, dad, or the person taking care of you and the research team will tell you more about being in the study. The lead study researcher is Dr. Amy Lovell, and her phone number is 021 020 59300. You can call her any time you have questions.

What will happen if I agree to take part in this study.

- You will be asked to take part in a short interview, which involves talking about your experiences with the nutritional supplement drinks. We will also ask you about your experience in re-introducing solid foods after your liquid diet, and any nutrition information you have received. We will include your parent/caregiver in our discussions.
- You will only need to take part in one interview. This will take approximately 30 minutes.
- You will be asked a few questions to find out how easy or hard it was to take your nutritional drinks, and for how long you took them. We also want to find out if there were any things that made it easier to take your drinks. Lastly, we want to know how much support you received in taking your nutritional drinks and starting to eat solid foods again, and whether there was anything that could have helped you during this process.

A researcher will arrange a time to call you and your parent/caregiver. During the interview we will:

- Ask a few questions about you.
- Ask you some questions relating to when you drank your nutritional drinks and when you starting eating normal food again

- Ask you about any help or support you had and what you might have liked when you were taking your nutritional drinks and starting to eat normal food again.
- We will record our discussion to make sure we capture all the things you talk about.
- You do not have to answer a question if you don't want to, or can't remember the answer. If you feel uncomfortable at any time you are welcome to withdraw from the discussion.
- Any discussion that you have taken part in before deciding to withdraw will be used in our analysis.

Do I have to be in the study?

NO: You can choose if you want to be in this study or not. Also, you can change your mind at any time even if you have started the study. Even if your mum, dad or person taking care of you says YES, you can still say NO. If you decide not to be in the study, no one will be angry with you. All you have to do is tell your mum, dad or person taking care of you or your doctor that you don't want to be in the study anymore. This will not have any effect on your treatment plan.

Do my parents or person taking care of me have to be in the study?

NO: You can choose if you would like your parents or person taking care of you to take part in the interview discussion. Whilst it is helpful to understand the experiences of you and your whānau when you were taking your nutritional drinks and re-introducing normal foods, you can decide on who attends with you.

Will being in this study help me?

Taking part in this study will help us to determine whether any changes need to be made to how we make people better who have Crohn's Disease like you.

What if there is a problem?

If you are worried about anything to do with the study, please ask the research team, your doctor, or nurse who will do their best to answer your questions. Dr Amy Lovell (leading this study) can also be contacted on 021 020 59300.

Who do I contact for more information of if I have concerns?

If you, mum or dad or the person taking care of you have any questions, concerns or complaints about the study at any stage, you can contact:

Lead researcher: Dr Amy Lovell, Ph: 021 020 59300, E: a.lovell@auckland.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact the AHREC Chair on:

Auckland Health Research Committee, Ph: 09 373 7599 ext. 83711, E: ahrec@auckland.ac.nz

The University of Auckland, Private Bag, 92019, Auckland 1142.

For Maori Health support please contact :

He Kamaka Waiora (Māori Health Team), Ph: 09 486 8324 ext. 2324

Ethical Approval

Approved by the University of Auckland Health Research Committee on 15/02/2021 for three years. Reference number AH3434.

Appendix 2: Participant information sheet patient and whānau

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

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New Zealand

PARTICIPANT INFORMATION SHEET
PATIENT/WHĀNAU INTERVIEWS

Research Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

An invitation

My name is Toni, and I am a master's student at the University of Auckland in the Department of Nutrition and Dietetics. I am studying towards a Masters of Health Sciences in Nutrition and Dietetics. My supervisors are Dr Amy Lovell (University of Auckland), Amy Andrews and Kim Herbison (Starship Clinical Paediatric Dietitian's). The aim of this study is to determine whether the Inflammatory Bowel Disease National Clinical Pathway (IBDCP) which formalised the Crohn's Disease (CD) treatment pathway has made a difference to outcomes for children and adolescents. We will also be determining if the IBDCP needs modifying to improve clinical practice or support for the future.

You are being invited to participate in part of this research project because you are a member of the family or whānau of a child that has received treatment for their Crohn's Disease at Starship Child Health. Your input in this study will allow us to understand your experiences and views of exclusive enteral nutrition (EEN) in treatment of your CD. We hope that through speaking with you we will be able to determine and identify any changes that may be required to the treatment pathway. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason.

What is the purpose of this research?

The purpose of this part of our research is to provide you with the opportunity to give feedback on the use of EEN as first line therapy for CD. It will provide you with an opportunity to give feedback on your perception of how effective EEN is as a first line therapy for CD and discuss any facilitators or barriers you experienced. With your input we will discover if modifications are required in order to improve outcomes or support in the future.

This research will involve short interviews with patients, family and whānau to explore if there are any barriers to efficient implementation of the CD treatment protocol.

Why have I been invited to participate in this research?

You have been invited to participate in this study because you are:

- A patient over the age of 16 that has received treatment through Starship Child

- A member of the family or whānau of a child who has received treatment for their Crohn's Disease at Starship Hospital.

What does this study involve?

If you decide to participate, you will be asked to participate in a short interview with the research team to provide us with feedback on your experiences navigating the Crohn's treatment pathway. If you are older than 16 years, you can decide whether or not you would like your parents/caregivers to take part with you. If you are a parent/caregiver of a child between the ages of 7 to 16 years, you can decide whether you all take part in the interview. These options will be discussed with you when you provide consent.

The interview will be facilitated by student researcher, Toni Mitchell. We will ask you to discuss any nutrition and diet-related challenges you faced and any resources or extra support that may have been helpful during this time. You may ask the researcher's questions and express your opinions without judgement or penalty. Interviews will not last more than 20-30 minutes, and all discussions will be recorded.

What are the discomforts and risks? And how will these discomforts and risks be alleviated?

During the interview, you will be asked to discuss your opinions on your experience with the pathway of treatment for your Crohn's Disease. The discussion should not elicit any discomfort or risk as no personal identifying information will be sought. However, if any discomfort or risk felt, you can withdraw from the interview at any time. Participation or non-participation will have no effect on your relationship with the DHB or the University of Auckland.

Will I benefit from this study?

Taking part in this study will help us to determine whether modifications are required to the IBDCP in order to have the best outcomes for children and adolescents with CD. A summary of the research will be sent to if you indicated this on the consent form.

How will my privacy be protected?

The researchers will audio record the interview so that discussions can be transcribed verbatim (i.e., word-for-word) for analyses. This recording will be transcribed (de-identified) and used in data analysis. You will be asked to confirm your consent to the use of the recording following your recorded interview prior to analysis, On completion of your interview, you will be asked whether any recorded comments/discussions you have had with the interviewer are to remain 'off the record'. Should this be the case, you will be given the opportunity to review the transcript of your discussion prior to data analysis.

To protect your confidentiality, no real names will be used in transcriptions. Also, no other identifiable information will be requested or transcribed. After each interview has been transcribed and analysed, the digital recording will be erased. All data, including consent forms will be stored in a secure manner. Consent forms will be stored separate from the research data. All data will be destroyed after six years of completion of the study. You may refuse to answer any questions or withdraw from the interview at any time without penalty. If you withdraw, the information you have contributed up to that point cannot be withdrawn. The research team would never identify you as one of the research

participants. Your personal information will never be related to any of the study findings. The risks of participating in this study are minimal.

What are the costs of participating in this research?

The only cost for you is 20-30 minutes of your time to complete a single semi-structured interview. Interviews will take place at Starship Child Health.

How do I agree to participate in this research?

You will be provided with a Consent Form by the research team whilst attending your IBD Outpatient Clinic appointment at Starship Child Health. After reading through this Participant Information Sheet and discussing any questions you may have with the research team, you will be asked to sign the Consent Form to indicate your agreement to participate. Once signed, you will return the Consent Form to the research team in clinic.

Will I receive feedback on the results of this research?

The research team will provide you with a summary of the research. However, your personal information will never be related to any of the study findings. You are also always free to contact the research team via phone or e-mail or ask us not to contact you further after your interview.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Principal Investigator, Dr Amy Lovell, PhD, a.lovell@auckland.ac.nz or student researcher, Toni Mitchell, tmit472@aucklanduni.ac.nz.

Additional support

If you require Māori cultural support talk to your whānau in the first instance. Alternatively, you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext. 2324.

Contact details:

Student Researcher	Toni Mitchell, tmit472@aucklanduni.ac.nz
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ADHB	Amy Andrews (Clinical supervisor), AmyA@adhb.govt.nz
	Kim Herbison, KHerbison@adhb.govt.nz
Academic Head	Professor Clare Wall, c.wall@auckland.ac.nz
AHREC Chair	For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz, 09 373 7599 ext. 83711, Auckland Health Research Committee, The University of Auckland, Private Bag, 92019, Auckland 1142.

Ethical Approval

Approved by the Auckland Health Research Committee on 15/02/2021 for three years. Reference number AH3434.

Appendix 3: Participant information sheet health care professionals

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PARTICIPANT INFORMATION SHEET

STAKEHOLDER INTERVIEWS

Research Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

An invitation

My name is Toni, and I am a master's student at the University of Auckland in the Department of Nutrition and Dietetics. I am studying towards a Masters of Health Sciences in Nutrition and Dietetics. My supervisors are Dr Amy Lovell (University of Auckland), Amy Andrews and Kim Herbison (Starship Clinical Paediatric Dietitian's). The aim of this study is to determine whether the Inflammatory Bowel Disease National Clinical Pathway (IBDCP) which formalised the Crohn's Disease (CD) treatment pathway has made a difference to outcomes for children and adolescents. We will also be determining if the IBDCP needs modifying to improve clinical practice or support for the future.

You are being invited to participate in part of this research project. As you are a key stakeholder within the CD treatment pathway, your input in this study will allow us to understand your experiences and views of exclusive enteral nutrition (EEN) in treatment of CD with your families and patients. We hope that through speaking with you we will be able to determine and identify any changes that may be required IBDCP. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason.

What is the purpose of this research?

In 2014 the IBDCP was introduced, setting out a frame work for and formalising the use of EEN as the first line treatment to induce remission in paediatric CD patients. Since the introduction of the IBDCP in 2014, changes in disease remission, clinical outcomes and patient or clinician perceptions of the protocol have not been reviewed.

This study has three main objectives:

1. To complete a retrospective process and impact evaluation of the IBDCP, dietetic input and patient outcomes in approximately 100 children and adolescents with Crohn's Disease in Auckland from 2010-2020;

2. To evaluate current clinical practice under the IBDCP and assess whether the pathway has impacted clinical outcomes to inform clinical practice and support;
3. To present a report of the audit findings and future recommendations to the Starship Paediatric Gastroenterology team and Child and Youth Health Paediatric Gastroenterology Clinical Network

The purpose of this part of our research is to gain feedback on the use of EEN as first line therapy for CD. It will provide you with an opportunity to give feedback on your perception of how effective EEN is as a first line therapy for CD and discuss any strengths, weaknesses or challenges you have implementing the protocol. With your input we will discover if modifications are required in order to improve outcomes or support in the future. This part of the research project will use semi-structured interviews with key stakeholders (i.e. allied health professionals, consultants, nurse specialists,) to explore if there are any barriers to efficient implementation of the CD treatment protocol.

Why have I been invited to participate in this research?

You have been invited to participate in this study because you are a key stakeholder in the CD treatment pathway.

What does this study involve?

If you decide to participate, you will be asked to complete in a single semi-structured interview facilitated by researchers at the University of Auckland. We will ask you to provide us with feedback on the management of newly diagnosed CD patients. Questions relate to EEN and re-introduction of solid foods. We will refer to steps detailed in the IBDCP to determine current practice and identify any specific challenges your patients face in taking and completing the prescribed course of EEN, and whether you feel any changes would be useful. This information will help us to determine if modifications are required to the IBDCP in order to improve outcomes or support for the future. Interviews will not last more than 20-30 minutes, and all discussions will be audio-recorded. No further participation will be required.

What are the discomforts and risks? And how will these discomforts and risks be alleviated?

During the interview, you will be asked to discuss your opinions on your current practice with newly diagnosed CD patients and the use of EEN to induce remission. The discussion should not elicit any discomfort or risk as no personal identifying information will be sought. However, if any discomfort or risk felt, you can withdraw from the interview at any time. Participation or non-participation will have no effect on your relationship with the DHB or the University of Auckland.

Will I benefit from this study?

Taking part in this study will help us to determine whether modifications are required to the IBDCP in order to have the best outcomes for children and adolescents with CD. A summary of the research will be presented to the Starship Paediatric Gastroenterology team and Child and Youth Health Paediatric Gastroenterology Clinical Network.

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How will my privacy be protected?

The researchers will audio record the interview so that discussions can be transcribed verbatim (i.e., word-for-word) for analyses. This recording will be transcribed (de-identified) and used in data analysis. You will be asked to confirm your consent to the use of the recording following your recorded interview prior to analysis, On completion of your interview, you will be asked whether any recorded comments/discussions you have had with the interviewer are to remain 'off the record'. Should this be the case, you will be given the opportunity to review the transcript of your discussion prior to data analysis.

To protect your confidentiality, no real names will be used in transcriptions. Also, no other identifiable information will be requested or transcribed. After each interview has been transcribed and analysed, the digital recording will be erased. All data, including consent forms will be stored in a secure manner. Consent forms will be stored separate from the research data.

All data will be destroyed after six years of completion of the study. You may refuse to answer any questions or withdraw from the interview at any time without penalty. If you withdraw, the information you have contributed up to that point cannot be withdrawn. The research team would never identify you as one of the research participants. Your personal information will never be related to any of the study findings. The risks of participating in this study are minimal.

What are the costs of participating in this research?

The only cost for you is 20-30 minutes of your time to complete a single semi-structured interview. Interviews will take place at Starship Children's Health.

How do I agree to participate in this research?

You can agree to participate by informing Toni Mitchell (student researcher) tmit472@aucklanduni.ac.nz or Dr Amy Lovell a.lovell@auckland.ac.nz. You can also contact Dr Amy Lovell if you have general questions.

Will I receive feedback on the results of this research?

The research team will present a report of the research findings and future recommendations to the Starship Paediatric Gastroenterology team and Child and Youth Health Paediatric Gastroenterology Clinical Network . Your personal information will never be related to any of the study findings.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Principal Investigator, Dr Amy Lovell, PhD, a.lovell@auckland.ac.nz or student researcher, Toni Mitchell, tmit472@aucklanduni.ac.nz.

Additional support

If you require Māori cultural support talk to your whānau in the first instance. Alternatively, you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext. 2324.

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Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

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Contact details:	
Student Researcher	Toni Mitchell, tmit472@aucklanduni.ac.nz
University of Auckland	Dr Amy Lovell (Principal investigator), a.lovell@auckland.ac.nz
ADHB	Amy Andrews (Clinical supervisor), AmyA@adhb.govt.nz
	Kim Herbison, KHerbison@adhb.govt.nz
Academic Head	Professor Clare Wall, c.wall@auckland.ac.nz
AHREC Chair	For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz, 09 373 7599 ext. 83711, Auckland Health Research Committee, The University of Auckland, Private Bag, 92019, Auckland 1142.

Ethical Approval

Approved by the Auckland Health Research Committee on 26/05/21 for three years. Reference number AH3434.

Appendix 4: Study protocol

Project proposal

2021

MHSc Research Proposal

Use of Exclusive Enteral Nutrition in children and adolescent's with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

Toni Mitchell

Project proposal

New Zealand Inflammatory Bowel Disease Clinical guidelines: Comparison of outcomes and clinical efficacy pre- and post-implementation in paediatric Crohn's Disease.

Background

Crohn's disease (CD) is a lifelong condition of chronic inflammation of the gastrointestinal tract (GIT), which follows a pattern of relapse and remission (1-4). CD can progress from simple GIT inflammation to stenosing or penetrating disease over time (5). Disease pathophysiology and aetiology are not completely known, however it is thought that it is a combination of interactions between the environment, the host's genetic susceptibility, immune mediated tissue injury, and the role of intestinal microflora (2,6). CD can be diagnosed at any age, with approximately 25% of patients diagnosed during childhood (2,6,7). Symptoms that are common at presentation include weight loss, abdominal pain and diarrhoea (2,6). Approximately 85% of children present with weight loss at diagnosis, between 15%-40% with growth failure (1) and 20-30% have disrupted linear growth (8). Often paediatric patients have more widespread intestinal involvement than adult patients (2). Onset in childhood can be associated with severe nutritional and metabolic consequences. Paediatric patients are at risk of faltering growth and pubertal delay (7), therefore inducing long term remission is a key goal of therapy so as to promote and maintain optimal growth and pubertal development as well as quality of life.

However, patients have reported difficulty in adhering to the EEN treatment protocol, drinking the prescribed volume, pain, nausea and night time waking with nasogastric overnight feeding (9-11). Intention to treat compared to per protocol have showed that remission rates are higher in those participants who were able to maintain the protocol (10,12). Therefore, understanding barriers to adherence to treatment protocol will be important in determining the best path forward. There is very little evidence around patients' perceptions and opinions of EEN. Svolos and colleagues (2017) found that 79% of CD patients surveyed successfully

completed the 8-week course of EEN. However, 21% discontinued EEN treatment due to lack of response or palatability issues (13).

During 2014 Starship Children's health introduced the Inflammatory Bowel Disease National Clinical Pathway (IBDCP), which set out a framework for and formalised the use of exclusive enteral nutrition (EEN) as the first line treatment to induce remission in paediatric CD patients. EEN, also known as the 'liquid diet' involves 6-8 weeks of enteral feeding to meet full nutritional requirements, including any catch-up growth. EEN is the favoured treatment pathway as it induces mucosal healing in the gastrointestinal tract and has a positive effect on growth. Immunosuppressant medication is commenced during EEN as a maintenance therapy that maintains remission, however therapeutic effectiveness is not attained until 6-8 weeks following commencement, which usually coincides with completion of EEN. Induction of remission is critical in paediatric patients and is central to reducing the risk of faltering growth, malnutrition, growth retardation or pubertal delay (1,7,8). Since the introduction of the IBDCP in 2014, changes in disease remission and clinical outcomes have not been reviewed. It is not known if the implementation of the IBDCP has improved the effectiveness of disease remission and clinical outcomes in paediatric CD patients, or whether the support provided via this pathway is effective. The purpose of this research is to determine how the IBDCP has improved clinical outcomes and to make recommendations for future practice.

Research questions and objectives

The main aim of this project is to complete a retrospective audit of current clinical practice, dietitian input and outcomes for children and adolescents with Crohn's disease in Auckland, NZ over a 10-year period (2010-2020).

This study aims to answer the following research questions:

1. How has using the Inflammatory Bowel Disease National Clinical Pathway (IBDCP) improved disease remission and clinical outcomes for children and adolescents with Crohn's disease (CD) in Auckland from 2010 to 2020?

2. Does the IBDCP need modifying in order to improve clinical practice or support for the future?

This study has three main objectives:

1. To complete a retrospective process and impact evaluation of the IBDCP, dietetic input and patient outcomes in approximately 100 children and adolescents with Crohn's Disease in Auckland from 2010-2020;
2. To evaluate current clinical practice under the IBDCP and assess whether the pathway has impacted clinical outcomes to inform clinical practice and support;
3. To present a report of the audit findings and future recommendations to the Starship Paediatric Gastroenterology team and Child and Youth Health Paediatric Gastroenterology Clinical Network

Methodology

The purpose of this study is to determine whether the formalised framework of the IBDCP has made a positive impact on disease remission and clinical outcomes in newly diagnosed paediatric CD patients.

A retrospective clinical audit of medical charts in paediatric CD patients will compare outcomes from 2010 to 2014 with 2015 to 2020. Patients will be newly diagnosed with CD, and treated with EEN as their first line therapy.

A comparison of clinical outcomes pre IBDCP implementation (2010-2014) and post IBDCP implementation (2014-2020) will determine whether the IBDCP has improved patient outcomes. In cases where patients have failed to respond to treatment, potential mediating factors that may be responsible for this will be identified.

Develop a project specific data collection tool

The study will involve development of a project-specific data collection tool for use during the clinical audit. This tool will include key measures of disease remission and clinical outcomes such as growth (presence of stunting/wasting), anthropometric z scores (at diagnosis and

throughout), malnutrition status, doctor and dietetic contacts, relapse occurrence, Azathioprine start date, duration of illness prior to diagnosis, a modified Paediatric Crohn's Disease Activity Index (modified-PCDAI) using biochemical parameters at baseline, months 3, 6, and 12 following diagnosis.

Inclusion and exclusion criteria

Inclusion criteria:

- Age 1 – 18
- CD diagnosis
    - made between Jan 1st 2010 and July 1st 2019
    - made by upper gastrointestinal endoscopy and biopsies, ileo-colonoscopy and biopsies and small bowel imaging (e.g. MRI enterography)
- Minimum of 12 months follow up from diagnosis
- Managed by Starship Children's Health paediatric gastroenterology team
- Resident of Auckland metropolitan area

Exclusion criteria include:

- Diagnosis of ulcerative colitis or inflammatory bowel disease undefined
- Diagnosis of comorbid diseases including primary sclerosing cholangitis
- Diagnosis of CD and residing outside Auckland metropolitan area
- Less than 12 months follow up data

Participants and Recruitment

Previous research by Starship Clinical Supervisors Amy Andrews and Kim Herbison have identified 103 patients that were diagnosed with CD between 2010 and 2020. Demographic information such as age, gender, ethnicity, socioeconomic status, disease location and behaviour, remission, treatment, EEN duration and method, anthropometry and nutritional status have been collected and previously described (Andrews et al. 2019). The study has received Institutional Approval from the ADHB Research Review Committee (Ref: A+8241).

Methodology Amendment

The purpose of this amendment is to add in semi-structured interviews with patients and parents, and clinicians to provide feedback on experiences with use of EEN as first line therapy for CD.

Semi-structured interviews with patients and parents would be carried out separately to interviews with clinicians. Clinician views on how patients are educated and managed, what their EEN practices and monitoring are, any challenges that they or their patients face in adhering to the protocol and information on solid food re-introduction will be sought (see figure 1). Patients views on education, compliance challenges, support and resources associated with their CD diagnosis, EEN therapy and solid food re-introduction will be sought (see figure 2).

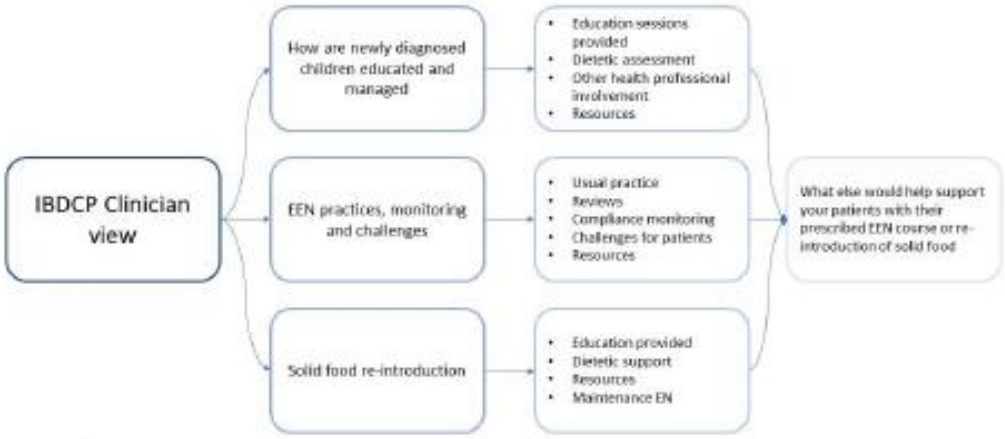

Figure 1: Semi-structured interview content for Clinicians

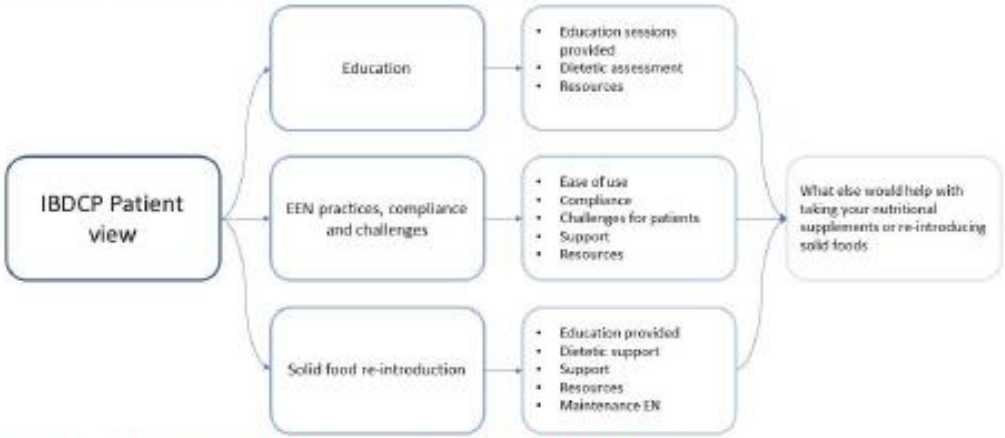

Figure 2: Semi-structured interview content for patients and parents

Project proposal

Inclusion and exclusion criteria

Inclusion criteria:

- Age 1 – 18
- CD diagnosis
    - made by upper gastrointestinal endoscopy and biopsies, ileo-colonoscopy and biopsies and small bowel imaging (e.g., MRI enterography)
- Minimum of 12 months follow up from diagnosis
- Managed by Starship Children's Health pediatric gastroenterology team
- Resident of Auckland metropolitan area
- Treated with EEN only

Exclusion criteria include:

- Diagnosis of ulcerative colitis or inflammatory bowel disease undefined
- Diagnosis of comorbid diseases including primary sclerosing cholangitis
- Diagnosis of CD and residing outside Auckland metropolitan area
- Less than 12 months follow up data
- Not treated with EEN as induction therapy

Participants and Recruitment

Patients who have been treated with EEN will be invited to participate in semi-structured interviews during outpatient clinic and day stay appointments. Interviews will be carried out in person. Current gastroenterology clinicians who are managing paediatric CD patients will be invited to participate in semi-structured interviews via email. Interviews will be carried out either in person.

Analysis Plan

Thematic analysis will be carried out on the patient and/or their parents separate to the clinicians. Analysis will follow the six phases of thematic analysis described by Braun and Clarke (14)

Ethics

An application for Ethical Approval for this research will be sought from the Auckland Health Research Ethics Committee (AHREC).

Project Management

This project will be managed by the student researcher Toni Mitchell with support from ADHB Dietitians – Amy Andrews and Kim Herbison. Toni's University Supervisor is Dr Amy Lovell who will provide oversight of the entire project.

References:

(1) Soo J, Malik BA, Turner JM, Persad R, Wine E, Siminoski K, et al. Use of Exclusive Enteral Nutrition Is Just as Effective as Corticosteroids in Newly Diagnosed Pediatric Crohn's Disease. Dig Dis Sci 2013;58(12):3584-3591.

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(6) Lambert B, Lemberg DA, Leach ST, Day AS. Longer-Term Outcomes of Nutritional Management of Crohn's Disease in Children. Dig Dis Sci 2012;57(8):2171-2177.

(7) Connors J, Basseri S, Grant A, Giffin N, Mahdi G, Noble A, et al. Exclusive Enteral Nutrition Therapy in Paediatric Crohn's Disease Results in Long-term Avoidance of Corticosteroids: Results of a Propensity-score Matched Cohort Analysis. J Crohns Colitis 2017;11(9):1063-1070.

(8) Ruuska T, Savilahti E, Mäki M, Ormälä T, Visakorpi JK. Exclusive whole protein enteral diet versus prednisolone in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr 1994;19(2):175-180.

(9) Rolandsdotter H, Jönsson-Videsäter K, L Fagerberg U, Finkel Y, Eberhardson M. Exclusive Enteral Nutrition: Clinical Effects and Changes in Mucosal Cytokine Profile in Pediatric New Inflammatory Bowel Disease. Nutrients. 2019;11(2):414.

(10) de Bie C, Kindermann A, Escher J. Use of exclusive enteral nutrition in paediatric Crohn's disease in The Netherlands. Journal of Crohn's and colitis. 2013;7(4):263-270.

(11) Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut 1996;38(4):543-548.

(12) Grogan JL, Casson DH, Terry A, Burdge GC, El-Matary W, Dalzell AM. Enteral feeding therapy for newly diagnosed pediatric crohn's disease: A double-blind randomized controlled trial with two years follow-up. Inflamm Bowel Dis 2012;18(2):246-253.

(13) Svolos V, Gerasimidis K, Buchanan E, Curtis L, Garrick V, Hay J, et al. Dietary treatment of Crohn's disease: Perceptions of families with children treated by exclusive enteral nutrition, a questionnaire survey. BMC gastroenterology 2017;17(1):1-6.

(14) Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology 2006;3(2):77-101.

Appendix 5: Consent form patients < 16 year of age

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CONSENT FORM

PARTICIPANT'S <16 YEARS OF AGE

Study Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

Locality: Auckland DHB

Ethics reference: AH3434

Lead investigator: Dr Amy Lovell

Ph: 021 020 59300

THIS FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

Participant's Name: _____ Date of Birth: _____

(full name in CAPITALS) *(Month/Year)*

Please circle all you agree with:

I have read this form (or have had it read to me)	Yes / No
The research team have explained the study to me	Yes / No
I understand what this study is about	Yes / No
I have asked all the questions I want	Yes / No
I am happy to take part in this research study	Yes / No
I understand that the interview will be recorded	Yes / No

If any answers are "no" or you don't want to take part, don't sign your name!

If you do want to take part in this study, please write your name and today's date below.

You will be given a copy of this signed form.

Participant's Full Name: _____

Participant's Signature for Assent: _____

Date: _____

Participant's Parent/Caregiver Full Name: _____

Parent/Caregiver Signature for Assent: _____

Date: _____

Statement of Person Obtaining Informed Assent

I, the undersigned, have fully explained the details of this research study to the participant named above.

Name of Person Conducting Assent Discussion (Print): _____

Signature of Person Conducting Assent Discussion: _____

Date: _____

Ethical Approval

Approved by the University of Auckland Health Research Committee on 15/02/2021 for three years. Reference number AH3434.

Appendix 6: Consent form patients and whānau

THE UNIVERSITY OF AUCKLAND
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MEDICAL AND HEALTH SCIENCES

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Auckland 1142
New Zealand

CONSENT FORM
PATIENTS/WHĀNAU

Study Title: Use of Exclusive Enteral Nutrition in children and adolescent's with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

THIS FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

I agree to take part in this research:

- I have read the Participation Information Sheet, and I have understood the nature of the research and why I have been selected to participate in semi-structured interviews. I have had the opportunity to discuss the research with the research team and have had my questions answered to my satisfaction;
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my relationship with the DHB or the University of Auckland;
- I understand that the semi-structured interviews will be recorded and that I cannot ask for the recorder to be turned off, but can choose to not answer any question and/or leave the room;
- I understand that I will be given the opportunity to identify any recorded statements that I wish to remain "off the record" and understand that these will be excluded from the transcription;
- I understand that should I request any comments be off the record, I will be given the opportunity to review the recording transcript;
- I give consent for the inclusion of my recorded interview in the data analysis;
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study;
- I understand that I am to complete a pre-interview questionnaire
- I have had time to consider whether to take part in the study;

- I wish to receive a summary of the research findings: Yes ☐ No ☐

  If yes, please indicate at which postal or email address you would like to receive this:

  _____

- I would be happy to be re-contacted for involvement in a later co-design project: Yes ☐ No ☐

I, _____ (full name) hereby consent to take part in this study.

Signed_____ Date _____

Ethical Approval

Approved by the University of Auckland Health Research Committee on 15/02/2021 for three years. Reference number AH3434.

Appendix 7: Email invitation patient and whānau

Dr Amy Lovell
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New Zealand

Research Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

The paediatric dietitians at Starship Child Health and researchers at the University of Auckland are interested in speaking with patients and their whānau about their experiences in receiving nutrition information and support during their treatment for Crohn's Disease. We hope that through speaking with you we will be able to determine whether the IBD Clinical Pathway needs modifying to improve clinical practice or support for the future.

As a parent/caregiver or patient that has received treatment for Crohn's Disease at Starship Child Health we would like to invite you to participate in a short interview discuss how you have navigated this treatment pathway and whether there was any additional support that would have been helpful to you. Your participation is voluntary and you will receive a voucher as thank you for your time. The interview will take approximately 20-30 minutes. Please read the Participant Information Sheet attached for more information.

The student researcher, Toni Mitchell will arrange a convenient time within your busy schedule to speak with you.

Contact details:

Student Researcher	Toni Mitchell, tmit472@aucklanduni.ac.nz
University of Auckland	Dr Amy Lovell (Principal investigator), a.lovell@auckland.ac.nz
ADHB	Amy Andrews (Clinical supervisor), AmyA@adhb.govt.nz
	Kim Herbison, KHerbison@adhb.govt.nz
Academic Head	Professor Clare Wall, c.wall@auckland.ac.nz
AHREC Chair	For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz, 09 373 7599 ext. 83711, Auckland

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HEALTH SCIENCES

Health Research Committee, The University of Auckland, Private Bag, 92019, Auckland 1142.

Ethical Approval

Approved by the Auckland Health Research Committee on 25/6/21 for three years. Reference number AH3434.

Appendix 8: Question prompts for patient and whānau semi-structured interviews

Patient Core Questions	Probes
Introduction	
Let's start with an introduction. Please tell me your name and age a short description of your/ your child's treatment journey.	
Experiences Navigating Nutrition	
Did you have any education sessions after you were diagnosed with Crohn's Disease?	
If so, can you remember who gave these to you and what did they tell you	Probe who provided this support
Did you see a dietitian for assessment after you were diagnosed?	
If so, can you remember what they told you	Probe for information
How long were you advised to take the nutritional supplement drinks for?	
How many weeks did you take the nutritional supplement drinks for?	
When you stopped taking the nutritional supplement drinks, what was the reason?	• I forgot to take them • They made me feel too full • My doctor told me to stop • My course was finished • I no longer needed them • Other: (please tell us any other reasons)
How easy was it to take the nutritional supplement drinks?	
Was there anything that helped you/your child to take their nutritional supplements?	
Do you have any other comments on your experience of the liquid only diet?	
Have you had any further courses of nutritional supplements? If so, how many?	
If you have a further flare of Crohn's disease, do you think you could complete another course of the liquid-only diet?	
What type of support did you receive when you were given your nutritional supplements?	
Was there any support you would have liked that would have helped you to take your nutritional supplements?	
What type of support did you receive after completing your course of nutritional supplements on food re-introduction?	
Was there any further support you would have liked around food re-introduction?	
Finally, is there anything about nutrition challenges and support that has not been discussed that you feel strongly about and would like to bring up now?	

Appendix 9: Questionnaire to collect demographic information from patients and whānau

Pre-interview questionnaire

1. What gender do you identify as?
    - Male
    - Female
    - Other (please specify) _____
    - Prefer not to say
2. What is your age?
    - Under 18
    - 18-24
    - 21-29
    - 30-39
    - 40-49
    - 50-59
    - 60 or older
3. What ethnicity do you identify with?
    - New Zealand European
    - Māori
    - Samoan
    - Cook Islands Māori
    - Tongan
    - Niuean
    - Chinese
    - Indian
    - Other (please specify) _____
4. In what region is your home located? _____
5. How many people are in your household? _____

6. What is your current employment status?
    - Employed
    - Self-employed
    - Out of work and looking for work
    - Out of work but not currently looking for work
    - A homemaker
    - A student
    - Retired
    - Unable to work
7. Who was the main carer for your child as they were going through their treatment for Crohn's Disease? _____

Appendix 10: Email invitation health care professionals

MEDICAL AND HEALTH SCIENCES

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INTERVIEWS WITH GASTROENTEROLOGY MDT

Research Title: Use of Exclusive Enteral Nutrition in children and adolescents with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year Period.

The paediatric dietitians at Starship Child Health and researchers at the University of Auckland are interested in speaking with key members of the Starship Gastroenterology Team (including nurses and allied health) to determine whether the Inflammatory Bowel Disease National Clinical Pathway (IBDCP) which formalised the Crohn's Disease (CD) treatment pathway has made a difference to outcomes for children and adolescents. We hope that through speaking with you we will be able to determine whether the IBDCP needs modifying to improve clinical practice or support for the future.

You are being invited to participate in part of this research project. As you are a key stakeholder within the CD treatment pathway, your input in this study will allow us to understand your experiences and views of exclusive enteral nutrition (EEN) in treatment of CD with your families and patients. We hope that through speaking with you we will be able to determine and identify any changes that may be required IBDCP. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason.

Your participation in these interviews is voluntary and will take approximately 20-30 minutes of your time. Please read the Participant Information Sheet below for more information.

Student researcher, Toni Mitchell will arrange a convenient time within your busy schedule to speak with you.

Contact details:

Student Researcher	Toni Mitchell, tmit472@aucklanduni.ac.nz
University of Auckland	Dr Amy Lovell (Principal investigator), a.lovell@auckland.ac.nz

ADHB	Amy Andrews (Clinical supervisor), AmyA@adhb.govt.nz
	Kim Herbison, KHerbison@adhb.govt.nz
Academic Head	Professor Clare Wall, c.wall@auckland.ac.nz
AHREC Chair	For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz, 09 373 7599 ext. 83711, Auckland Health Research Committee, The University of Auckland, Private Bag, 92019, Auckland 1142.

Ethical Approval

Approved by the Auckland Health Research Committee on 26/05/2021 for three years. Reference number AH3434.

Appendix 11: Consent form health care professionals

THE UNIVERSITY OF AUCKLAND
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MEDICAL AND HEALTH SCIENCES

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CONSENT FORM

STAKEHOLDER INTERVIEWS

Study Title: Use of Exclusive Enteral Nutrition in children and adolescent's with Crohn's Disease in New Zealand: Clinical Practice and Outcomes over a 10-Year

- I have read the Participation Information Sheet, and I have understood the nature of the research and why I have been selected to participate in semi-structured interviews. I have had the opportunity to discuss the research with the research team and have had my questions answered to my satisfaction;
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my relationship with the DHB or the University of Auckland;
- I understand that the semi-structured interviews will be recorded and that I cannot ask for the recorder to be turned off, but can choose to not answer any question and/or leave the room;
- I understand that I will be given the opportunity to identify any recorded statements that I wish to remain "off the record" and understand that these will be excluded from the transcription;
- I understand that should I request any comments be off the record, I will be given the opportunity to review the recording transcript;
- I give consent for the inclusion of my recorded interview in the data analysis;
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study;
- I understand I will also need to complete a pre-interview questionnaire;
- I have had time to consider whether to take part in the study;
- I wish to receive a summary of the research findings: Yes ☐ No ☐

If yes, please indicate at which postal or email address you would like to receive this:

_____

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

I, _____ (full name) hereby consent to take part in this study.

Signed_____ Date _____

Contact details:

Student Researcher	Toni Mitchell, tmit472@aucklanduni.ac.nz
University of Auckland	Dr Amy Lovell (Principal investigator), a.lovell@auckland.ac.nz
Academic Head	Professor Clare Wall c.wall@auckland.ac.nz
ADHB	Amy Andrews (Clinical supervisor), AmyA@adhb.govt.nz
	Kim Herbison, KHerbison@adhb.govt.nz
AHREC Chair	For concerns of an ethical nature, you can contact the Chair of the Auckland Health Research Ethics Committee at ahrec@auckland.ac.nz, 09 373 7599 ext. 83711, Auckland Health Research Committee, The University of Auckland, Private Bag, 92019, Auckland 1142.

Ethical Approval

Approved by the University of Auckland Health Research Committee on 26/05/21 for three years. Reference number AH3434.

Appendix 12: Question prompts for health care professionals semi-structured interviews

Health professional Core Questions	Probes
Introduction	
Please tell me your name, and a little about your role within the pediatric CD treatment pathway	
Experiences as a key stakeholder	
How are newly diagnosed patients educated about their condition?	The IBDCP says that at least 2 education sessions are provided
Is a multidisciplinary team approach used for managing CD? If so, who is involved?	Do all children have a formal dietetic assessment following diagnosis? Are there any other professions that are consistently used for CD patients?
EEN is usually recommended for 8 weeks. Is this your current/usual practice?	
The IBDCP suggests while completing EEN, multidisciplinary reviews should occur every two-weeks. Does this occur? If not why not?	
How do you monitor compliance to EEN over the 8-week period?	In person, via phone, via email
What typical challenges (that you are aware of) are faced by patients when taking the course of EEN?	
Are you involved in discussions regarding re-introduction of solid foods? If so, how is this discussed? What support is provided for patients in food re-introduction?	
Do you use maintenance EN?	Why? Or Why not? What is your protocol?
Finally, is there anything about EEN or support for CD patients that has not been discussed that you feel strongly about and would like to bring up now?	

Appendix 13: Supplementary material (Chapter 3)

Table A1 | Malnutrition status (calculated using z-scores) for children with Crohn's disease managed by Starship Child Health at diagnosis and following Crohn's disease treatment pre-2015 (n=40) and post-2015 (n=51)

	Pathway				
	Pre 2015 *n*=40	p-value[1]	Post 2015 *n*=51	p-value[1]	p-value[2]
Malnutrition based on weight z-score[3], *n* (%)					0.929
Pre-treatment		0.097		0.256	
No malnutrition	25 (64.1)		33 (66.0)		
Mild malnutrition	9 (23.1)		12 (24.0)		
Moderate malnutrition	4 (10.3)		3 (6.0)		
Severe malnutrition	1 (2.6)		2 (4.0)		
Missing, n	*1*		*1*		
Post-treatment					0.848
No malnutrition	29 (85.3)		35 (83.3)		
Mild malnutrition	4 (11.8)		6 (14.3)		
Moderate malnutrition	0 (0.0)		1 (2.4)		
Severe malnutrition	1 (2.9)		0 (0.0)		
Missing, n	*6*		*9*		
Malnutrition based on height z-score[3], *n* (%)					0.817
Pre-treatment		1.000		0.796	
No malnutrition	29 (76.3)		32 (72.7)		
Mild malnutrition	6 (15.8)		9 (20.5)		
Moderate malnutrition	2 (5.3)		3 (6.8)		
Severe malnutrition	1 (2.6)		0 (0.0)		
Missing, n	*2*		*8*		
Post-treatment					0.766
No malnutrition	25 (78.1)		26 (76.5)		
Mild malnutrition	5 (15.6)		5 (14.7)		
Moderate malnutrition	1 (3.1)		3 (8.8)		
Severe malnutrition	1 (3.1)		0 (0.0)		
Missing, n	*8*		*18*		
Malnutrition based on BMI z-score[3], *n* (%)					0.379
Pre-treatment		**0.005**		**0.012**	
No malnutrition	23 (60.5)		26 (59.1)		
Mild malnutrition	10 (26.3)		7 (15.9)		
Moderate malnutrition	2 (5.3)		7 (15.9)		
Severe malnutrition	3 (7.9)		4 (9.1)		
Missing, n	*2*		*8*		
Post-treatment					0.260
No malnutrition	30 (93.8)		28 (82.4)		
Mild malnutrition	2 (6.3)		6 (17.6)		
Moderate malnutrition	0 (0.0)		0 (0.0)		

Severe malnutrition	0 (0.0)	0 (0.0)
Missing, n	*8*	*18*

Abbreviations: BMI: body mass index

[1] Within group (paired) comparison, diagnosis and week 8 (Fisher-Freeman-Halton Exact test)

[2] Between group comparison (Fisher-Freeman-Halton Exact test)

[3] The z-score was calculated using the WHO growth standards (1)

Table A2 | Characteristics at diagnosis of children with Crohn's disease managed by Starship Child Health who completed exclusive enteral nutrition (*n*=63) and those that did not (*n*=20)

	EEN Completion		p-value
	Completed EEN	Did not complete EEN	
	n=63	*n*=20	
Demographics			
Gender, *n* (%)			0.084[a]
Male	41 (65.1)	8 (40.0)	
Female	22 (34.9)	12 (60.0)	
Age, median (IQR)	11.6 (2.6)	13.1 (2.4)	0.140[b]
Ethnicity, *n* (%)			0.798[c]
NZ European	39 (61.9)	11 (55.0)	
Māori	1 (1.6)	0 (0.0)	
Pasifika	1 (1.6)	0 (0.0)	
Asian	15 (23.8)	7 (35.0)	
Other*	7 (11.1)	2 (10.0)	
NZDEP, *n* (%)			0.079 [c]
Q1	22 (34.9)	5 (25.0)	
Q2	20 (31.7)	2 (10.0)	
Q3	10 (15.9)	5 (25.0)	
Q4	6 (9.5)	3 (15.0)	
Q5	5 (7.9)	5 (25.0)	
Paris Classification			
Age, *n* (%)			0.741[a]
A1a	17 (27.0)	4 (20.0)	
A1b	46 (73.0)	16 (80.0)	
Disease Location, *n* (%)			0.764[c]
L1	9 (14.3)	4 (20.0)	
L2	14 (22.2)	5 (25.0)	
L3	40 (63.5)	11 (55.0)	
Upper GIT disease, *n* (%)			0.631[c]
L4a	15 (23.8)	1 (5.0)	
L4b	20 (31.7)	4 (20.0)	
Disease behaviour, *n* (%)			0.356[c]
B1	43 (68.3)	12 (60.0)	
B2	15 (23.8)	5 (25.0)	
B2B3	5 (7.9)	2 (10.0)	
B3	0 (0.0)	1 (5.0)	
Perianal disease, *n* (%)	17 (27.0)	5 (25.0)	1.000[a]
Growth delay, *n* (%)	10 (15.9)	5 (25.0)	0.341[c]
Clinical characteristics			
Mod-PCDAI; median (range)	15.0 (6.92)	12.5 (7.61)	0.922[b]
BMI z-score[◊]	-0.68 (1.34)	-0.78 (1.54)	0.968[b]
Biochemical markers			

CRP, mg/L	24.0 (39.1)	44.0 (51.1)	**0.045**[b]
ESR, mm in 1 hr	36.0 (22.6)	38.0 (25.3)	0.517[b]
Albumin, g/L	31.0 (8.1)	34.0 (7.1)	0.612[b]

Abbreviations: A1a: 0 to <10 y; A1b: 10 to <17 y; B1: Non-stricturing non-penetrating; B2: Stricturing; B2B3: Both penetrating and stricturing disease either, at the same or different times; B3: Penetrating; BMI: body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; GIT: gastrointestinal tract; IQR: Interquartile range; L1: Distal 1/3 ileum ± limited cecal disease; L2: Colonic disease; L3: Ileocolonic disease; L4a: Upper disease proximal to the ligament of Treitz; L4b: Upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum; Mod-PCDAI: Modified paediatric Crohn's disease activity index NZ: New Zealand: NZDEP: New Zealand Index of Deprivation; Q1: Quintile 1 – Decile 1 and 2; Q2: Quintile 2 – Decile 3 and 4; Q3: Quintile 3 – Decile 5 and 6; Q4: Quintile 4 – Decile 7 and 8; Q5: Quintile 5 – Decile 9 and 10 (2)

* 'Other' ethnicity includes: Middle Eastern, Other European, European not further defined and African

◊ The z-score was calculated using the WHO growth standards (2)

[a] Chi-squared test; [b] Mann Whitney U-test; [c] Fisher-Freeman-Halton Exact test

Table A3 | Modified paediatric Crohn's disease activity index comparisons of children with Crohn's disease managed by Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51), using a mixed model analysis across 4 time points during the 52-week follow-up

	Pathway								
	Pre 2015			Post 2015					
	n	*Missing n*	Mean (SEM)	*n*	*Missing n*	Mean (SEM)	Adjusted difference[1] (95% CI)	p-value[2]	Interaction p-value[3]
Mod-PDCAI	40			51					0.142
Diagnosis		*7*	12.65 (1.23)		*16*	14.71 (1.18)	-2.06 (-6.43, 2.31)	0.650	
Week 8		*18*	4.43 (0.72)		*25*	11.15 (1.50)	-6.72 (-11.09, -2.36)	**0.001**	
Week 26		*24*	4.53 (0.86)		*17*	7.06 (1.07)	-2.53 (-7.20, 2.14)	0.509	
Week 52		*14*	3.27 (0.53)		*21*	8.42 (1.30)	-5.15 (-8.82, -1.48)	**0.003**	

Abbreviations: CI: Confidence interval; Mod-PCDAI: Modified paediatric Crohn's disease activity index; SEM: standard error of the mean

[1] Adjusted difference (pre-2015 – post-2015)

[2] Sidak's multiple comparisons test

[3] Fixed linear model to account for missing data compared at time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions.

Table A4 | Anthropometric measure comparison of children with Crohn's disease managed by Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51), using a mixed model analysis across 4 time points during the 52-week follow-up

	Pathway								
	Pre 2015			Post 2015					
	n	*Missing, n*	Mean (SEM)	*n*	*Missing, n*	Mean (SEM)	Adjusted difference[1] (95% CI)	p-value[2]	Interaction p-value[3]
Weight, kg	40			51					0.392
Diagnosis		1	35.81 (1.93)		1	36.24 (1.45)	-0.43 (-6.60, 5.74)	0.999	
Week 8		6	39.28 (1.98)		9	38.35 (1.82)	0.93 (-5.94, 7.80)	0.995	
Week 26		19	40.92 (3.20)		16	40.38 (1.80)	0.54 (-9.13, 10.21)	0.999	
Week 52		10	41.85 (2.45)		12	44.62 (2.16)	-2.77 (-11.14, 5.60)	0.870	
Weight z-score[4]	40			51					0.523
Diagnosis		1	-0.58 (0.20)		1	-0.74 (0.15)	0.17 (-0.48, 0.81)	0.944	
Week 8		6	0.01 (0.20)		9	-0.30 (0.15)	0.31 (-0.33, 0.95)	0.623	
Week 26		19	0.08 (0.31)		16	-0.12 (0.20)	0.20 (-0.77, 1.16)	0.973	
Week 52		10	0.43 (0.26)		12	0.46 (0.15)	-0.03 (-0.80, 0.74)	>0.999	
Height, cm	40			51					0.575
Diagnosis		2	144.9 (2.97)		7	146.8 (2.12)	-1.38 (-10.64, 7.89)	0.992	
Week 8		8	144.2 (3.20)		17	144.5 (2.44)	0.41 (-9.80, 10.62)	>0.999	
Week 26		19	144.5 (3.92)		16	148.7 (2.39)	-3.62 (-15.61, 8.38)	0.897	
Week 52		11	146.2 (2.97)		14	153.1 (2.48)	-6.47 (-16.38, 3.45)	0.341	
Height z-score[4]	40			51					0.877
Diagnosis		2	-0.23 (0.18)		7	-0.26 (0.18)	-0.03 (-0.62, 0.67)	>0.999	
Week 8		8	-0.27 (0.23)		17	-0.12 (0.20)	-0.15 (-0.93, 0.63)	0.979	
Week 26		19	-0.22 (0.33)		16	-0.10 (0.21)	-0.12 (-1.14, 0.90)	0.997	
Week 52		11	0.27 (0.28)		14	0.73 (0.19)	-0.46 (-1.33, 0.41)	0.523	
BMI, kg/m^2	40			51					0.648
Diagnosis		2	16.74 (0.44)		7	16.19 (0.39)	0.56 (-0.94, 2.05)	0.816	
Week 8		8	18.39 (0.39)		17	17.14 (0.39)	1.26 (-0.16, 2.67)	0.101	

Week 26		19	18.95 (0.70)		16	17.97 (0.41)	0.98 (-1.17, 3.13)	0.662	
Week 52		11	19.04 (0.64)		14	18.51 (0.50)	0.53 (-1.55, 2.61)	0.945	
BMI z-score[4]	40			51					0.966
Diagnosis		2	-0.70 (0.23)		7	-1.10 (0.21)	0.40 (-0.40, 1.20)	0.610	
Week 8		8	0.24 (0.18)		17	-0.27 (0.15)	0.50 (-0.10, 1.10)	0.137	
Week 26		19	0.36 (0.24)		16	-0.09 (0.19)	0.45 (-0.35, 1.25)	0.485	
Week 52		11	0.50 (0.22)		14	0.14 (0.19)	0.35 (-0.38, 1.09)	0.636	

Abbreviations: BMI: Body mass index; CI: Confidence interval; SEM: standard error of the mean

[1] Adjusted difference (pre-2015 – post-2015)

[2] Sidak's multiple comparisons test

[3] Fixed linear model to account for missing data compared at time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions

[4] The z-score is calculated using the WHO growth standards (1)

Table A5 | Biochemical marker comparison of children with Crohn's disease managed by Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51), using a mixed model analysis across 4 time points during the 52-week follow-up

	Pathway								
	Pre 2015			Post 2015					
	n	*Missing, n*	Mean (SEM)	*n*	*Missing, n*	Mean (SEM)	Adjusted difference[1] (95% CI)	p-value[2]	Interaction p-value[3]
CRP, mg/L	40			51					0.115
Diagnosis		2	46.03 (7.89)		6	35.34 (5.58)	10.69 (-14.03, 35.42)	0.720	
Week 8		13	14.66 (6.26)		19	21.88 (5.62)	-7.22 (-28.88, 14.44)	0.865	
Week 26		17	6.17 (1.53)		11	9.78 (1.76)	-3.61 (-9.60, 2.38)	0.418	
Week 52		9	8.43 (2.90)		12	16.03 (5.37)	-7.90 (23.91, 8.11)	0.609	
ESR, mm/hr	40			51					0.249
Diagnosis		4	42.17 (4.02)		15	39.58 (4.08)	2.58 (-12.07, 17.24)	0.986	
Week 8		14	18.85 (1.82)		22	27.03 (3.62)	-8.19 (-18.73, 2.36)	0.184	
Week 26		15	22.42 (3.18)		15	22.75 (2.66)	-1.19 (-11.86, 9.48)	0.997	
Week 52		7	17.88 (3.37)		17	23.03 (3.60)	-5.15 (-17.78, 7.48)	0.760	
Albumin, g/L	40			51					
Diagnosis		5	35.11 (1.21)		3	29.31 (0.97)	5.80 (1.85, 9.76)	**0.001**	0.449
Week 8		7	41.58 (0.89)		10	33.66 (0.81)	7.92 (4.86, 10.98)	**<0.0001**	
Week 26		14	42.27 (0.86)		9	35.38 (0.75)	6.89 (3.96, 9.82)	**<0.0001**	
Week 52		4	41.42 (0.70)		11	34.35 (1.08)	7.07 (3.77, 10.36)	**<0.0001**	

Abbreviations: CI: Confidence interval; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SEM: standard error of the mean

[1] Adjusted difference (pre 2015 – post 2015)

[2] Sidak's multiple comparisons test

[3] Fixed linear model to account for missing data compared at time since diagnosis (4 time points) and pathway (pre-2015 and post-2015), and their interactions diagnosis.

Table A6 | Comparison of median albumin values following induction treatment (week 8) in children with Crohn's disease managed by Starship Child Health for children deemed as in remission (*n*=52) and not in remission (*n*=28) by their gastroenterologist

	Remission status				
	Missing	Remission *n*=52	*Missing*	No Remission *n*=28	p-value[a]
Albumin, g/L, median (IQR)					
Diagnosis	*3*	32.0 (7.4)	*1*	31.0 (7.0)	0.261
Week 8	*8*	38.0 (5.6)	*4*	35.5 (7.4)	**<0.001**
	Children in Remission, *n*=52				
	Missing	Pre-2015 *n*=25	*Missing*	Post-2015 *n*=27	p-value[a]
Albumin, g/L, median (IQR)					
Diagnosis	*1*	36.5 (6.8)	*2*	29.0 (6.3)	**<0.001**
Week 8	*5*	43.0 (4.6)	*3*	35.0 (4.6)	**<0.001**
	Children not in Remission, *n*=28				
	Missing	Pre-2015 *n*=12	*Missing*	Post-2015 *n*=16	p-value[a]
Albumin, g/L, median (IQR)					
Diagnosis	*1*	34.0 (7.6)	*0*	29.5 (6.4)	0.182
Week 8	*0*	40.5 (5.8)	*4*	30.0 (5.0)	**<0.001**

Abbreviations: IQR: interquartile range

[a] Mann Whitney U-test

Table A7 | Medical and dietetic points of contact, and hospitalisation events in children with Crohn's disease managed by Starship Child Health pre-2015 (*n*=40) and post-2015 (*n*=51) during the 52-week follow-up

	Pathway		p-value
	Pre 2015 *n*=40	Post 2015 *n*=51	
Medical contacts			
Number per patient, median (IQR)			
Diagnosis to 52 weeks	13 (7)	10 (12)	0.742[a]
To diagnosis	2 (3)	2 (2)	0.788[a]
Diagnosis to wk. 8	3 (4)	3 (2)	0.262[a]
Wk. 8 to wk. 13	1 (1)	1 (1)	0.833[a]
Wk. 13 to wk. 26	1 (1)	2 (3)	0.128[a]
Wk. 26 to wk. 52	2 (2)	3 (4)	**0.029**[a]
Medical contacts (excl. hospitalised children)			
Number per patient, median (IQR)			
Diagnosis to 52 weeks	2 (2)	2 (2)	0.590[a]
To diagnosis	1 (1)	2 (1)	0.760[a]
Diagnosis to wk. 8	3 (3)	2 (1)	0.094[a]
Wk. 8 to wk. 13	1 (1)	1 (1)	0.761[a]
Wk. 13 to wk. 26	1 (1)	1 (2)	0.282[a]
Wk. 26 to wk. 52	2 (2)	2 (1)	0.398[a]
Dietetic contacts			
Number per patient, median (IQR)			
Diagnosis to 52 weeks	5 (6)	6 (4)	0.428[a]
To diagnosis	2 (1)	1 (1)	0.254[a]
Diagnosis to wk. 8	3 (3)	3 (3)	0.680[a]
Wk. 8 to wk. 13	1 (1)	1 (1)	0.626[a]
Wk. 13 to wk. 26	1 (1)	1 (2)	0.430[a]
Wk. 26 to wk. 52	2 (2)	1 (3)	0.519[a]
Dietetic contacts (excl. hospitalised children)			
Number per patient, median (IQR)			
Diagnosis to 52 weeks	2 (2)	2 (2)	0.274[a]
To diagnosis	1 (1)	1 (1)	0.885[a]
Diagnosis to wk. 8	3 (3)	3 (3)	0.145[a]
Wk. 8 to wk. 13	1 (1)	1 (1)	0.429[a]
Wk. 13 to wk. 26	1 (1)	1 (1)	0.922[a]
Wk. 26 to wk. 52	2 (2)	1 (0)	0.115[a]
Hospitalisations			
Hospitalisation events, *n*			
Diagnosis to 52 weeks	39	43	0.710[b]
To diagnosis	19	10	
Diagnosis to wk. 8	12	11	
Wk. 8 to wk. 13	5	3	
Wk. 13 to wk. 26	3	7	

Wk. 26 to wk. 52	0	12	

Abbreviations: Excl.: Excludes; IQR: interquartile range; Wk: Week
[a] Mann Whitney U-test; [b] Chi-squared test

Table A8 | Comparison of children with Crohn's disease managed by Starship Child Health prescribed aminosalicylate therapy (*n*=33) and those not who were not (*n*=58) between 2010 and 2020

	Aminosalicylate therapy				p-value
	Missing	Yes *n*=33	*Missing*	No *n*=58	
Mod-PCDAI score, median (IQR)					
Diagnosis	*8*	12.5 (6.9)	*15*	15.0 (7.2)	0.853[a]
Week 8	*15*	3.8 (4.4)	*28*	7.5 (7.5)	**0.017**[a]
Week 52	*15*	2.5 (6.3)	*20*	5.0 (6.0)	0.498[a]
Mod-PCDAI remission status, *n* (%)					
Diagnosis	*8*		*15*		1.000[b]
Remission		4 (16.0)		6 14.0)	
No remission		21 (84.0)		37 (86.0)	
Week 8	*15*		*28*		**0.037**[b]
Remission		13 (72.2)		11 (36.7)	
No remission		5 (27.8)		19 (63.3)	
Week 52	*15*		*20*		0.883[b]
Remission		12 (66.7)		23 (60.5)	
No remission		6 (33.3)		15 (39.5)	
CRP, mg/L, median (IQR)					
Diagnosis	*2*	23.0 (46.6)	*6*	27.0 (39.7)	0.862[a]
Week 8	*12*	1.1 (34.4)	*20*	10.0 (30.7)	**0.015**[a]
Week 52	*9*	2.2 (19.4)	*12*	3.0 (30.8)	0.906[a]
Albumin, g/L, median (IQR)					
Diagnosis	*6*	32.0 (7.3)	*2*	31.5 (7.3)	0.065[a]
Week 8	*9*	40.0 (5.7)	*8*	35.0 (6.3)	**0.008**[a]
Week 52	*4*	40.0 (5.1)	*11*	37.0 (7.2)	**0.028**[a]

Abbreviations: CRP: C-reactive protein; IQR: interquartile range; Mod-PDCAI: Modified paediatric Crohn's disease activity index
[a] Mann Whitney U-test; [b] Chi-squared test

Table A9 | Comparison of children with Crohn's disease managed by Starship Child Health prescribed aminosalicylate therapy, segmented by group; pre-2015 (*n*=23) and post-2015 (*n*=10)

	Pathway				p-value
	Missing	Pre-2015 *n*=23	*Missing*	Post-2015 *n*=10	
Mod-PCDAI score, median (IQR)					
Diagnosis	*5*	13.8 (7.4)	*3*	12.5 (6.1)	0.691[a]
Week 8	*8*	2.5 (2.4)	*7*	10.0 (4.3)	**0.006**[a]
Week 52	*12*	2.5 (2.2)	*3*	12.5 (7.7)	0.069[a]
Mod-PCDAI remission status, *n* (%)					
Diagnosis	*5*		*4*		1.000[b]
Remission		3 (16.7)		1 (14.3)	
No remission		15 (83.3)		6 (85.7)	
Week 8	*8*		*7*		
Remission		13 (86.7)		0 (0.0)	**0.019**[b]
No remission		2 (13.3)		3 (100.0)	
Week 52	*12*		*3*		**0.026**[b]
Remission		10 (90.9)		2 (28.6)	
No remission		1 (9.1)		5 (71.4)	
Albumin, g/L, median (IQR)					
Diagnosis	*4*	34.0 (8.1)	*2*	31.5 (4.7)	0.202[a]
Week 8	*4*	43.0 (4.9)	*5*	33.0 (1.6)	**0.002**[a]
Week 52	*3*	43.0 (4.1)	*1*	35.0 (4.4)	**0.003**[a]

Abbreviations: IQR: interquartile range; Mod-PDCAI: Modified paediatric Crohn's disease activity index

[a] Mann Whitney U-test; [b] Chi-squared test

Table A10 | Comparison of children with Crohn's disease managed by Starship Child Health not prescribed aminosalicylate therapy, segmented by group; pre-2015 (*n*=17) and post-2015 (*n*=41)

	Pathway				p-value
	Missing	Pre-2015 *n*=17	*Missing*	Post-2015 *n*=41	
Mod-PCDAI score, median (IQR)					
Diagnosis	*3*	10.0 (6.7)	*13*	16.3 (7.2)	0.106 [a]
Week 8	*9*	5.0 (4.4)	*18*	7.5 (8.0)	0.121 [a]
Week 52	*2*	2.5 (3.0)	*18*	7.5 (7.0)	0.102 [a]
Mod-PCDAI remission status, *n* (%)					
Diagnosis	2		13		1.000 [b]
Remission		2 (13.3)		4 (14.3)	
No remission		13 (86.7)		24 (85.7)	
Week 8	9		18		0.237 [b]
Remission		5 (62.5)		7 (30.4)	
No remission		3 (37.5)		16 (69.6)	
Week 52					
Remission	2	12 (80.0)	18	11 (47.8)	0.100 [b]
No remission		3 (20.0)		12 (52.2)	
Albumin, g/L, median (IQR)					
Diagnosis	*1*	36.0 (6.2)	*1*	28.5 (7.0)	**0.004** [a]
Week 8	*2*	41.0 (5.4)	*5*	34.0 (5.5)	**<0.001** [a]
Week 52	*1*	41.0 (4.4)	*10*	36.0 (7.4)	**0.001** [a]

Abbreviations: IQR: interquartile range; Mod-PCDAI: Modified paediatric Crohn's disease activity index

[a] Mann Whitney U-test; [b] Chi-squared test

Table A11 | Demographic characteristics of participants (*n*=15) in the child and whānau semi-structured interviews.

	Participants *n*=15
Participants, *n*	
Patients	5
Parent/caregiver	10
Patient Gender, *n*	
Male	4
Female	6
Participant Gender, *n*	
Male	4
Female	11
Age of participants, *n*	
Under 18	5
30 – 39	1
40 – 49	4
50 – 59	3
Ethnicity, *n*	
NZ European	10
Māori	4
Asian	1
Main Caregiver during treatment, *n*	
Mother	7
Both parents	3

Abbreviations: NZ: New Zealand

Table A12 | Exclusive enteral nutrition experiences of 10 children discussed during semi-structured child and whānau interviews

	Patients *n*=10
Administration route, *n*	
Oral	9
NGT	2
EEN duration[1], *n*	
6 weeks	5
6-8 weeks	1
8 weeks	4
EEN Duration[2], *n*	
<6 weeks	1
6 weeks	5
8 weeks	4
Reason for stopping EEN, *n*	
Course/Plan finished	5
Symptoms improved	4
Weight increased	2
Palatability issues	1
How easy was it to take the supplements?, *n*	
Really Hard	3
Fairly Easy	3
Initially hard, then became easier	1
Easy at first, then became harder	3
Would a further course of EEN be feasible?, *n*	
Yes	1
If I had to	3
Maybe	1
I'd/They'd need a NGT	2
No way	3

Abbreviations: EEN: Exclusive enteral nutrition; NGT: Nasogastric tube.

[1] EEN therapy duration recommended by the gastroenterologist before starting EEN

[2] Actual EEN duration, classed as completed treatment

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