DIET THERAPY FOR PEDIATRIC CROHN'S DISEASE

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Importance of Pediatric CD

- Childhood is a time of dynamic physical changes, bone accrual and growth along with emotional maturation.

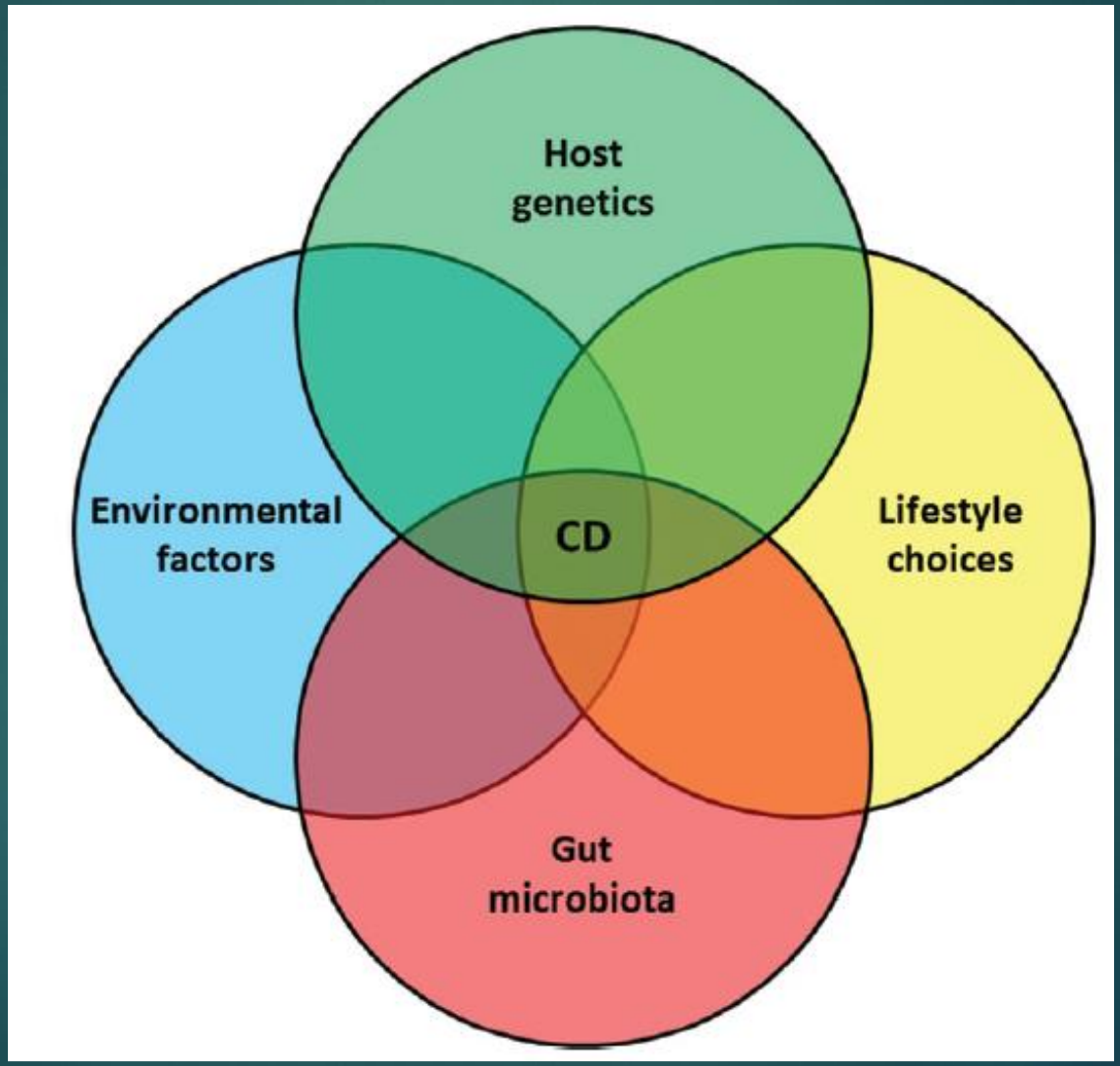
- Pediatric inflammatory bowel disease (IBD) is more often extensive and is associated with a more aggressive disease course.

Pigneur B, et al. Inflamm Bowel Dis 2010;16(6):953–61.

Micronutrient deficiency

- Zinc
- Folate
- B12
- Iron
- Vitamin D
- Ca

Pathogenesis of Crohn's disease



Diet

- Western diet
- High fat, n-6, high sugar, gluten, emulsifier
- Animal protein, processed food
- fibre

Corticosteroids in the Treatment of Pediatric IBD

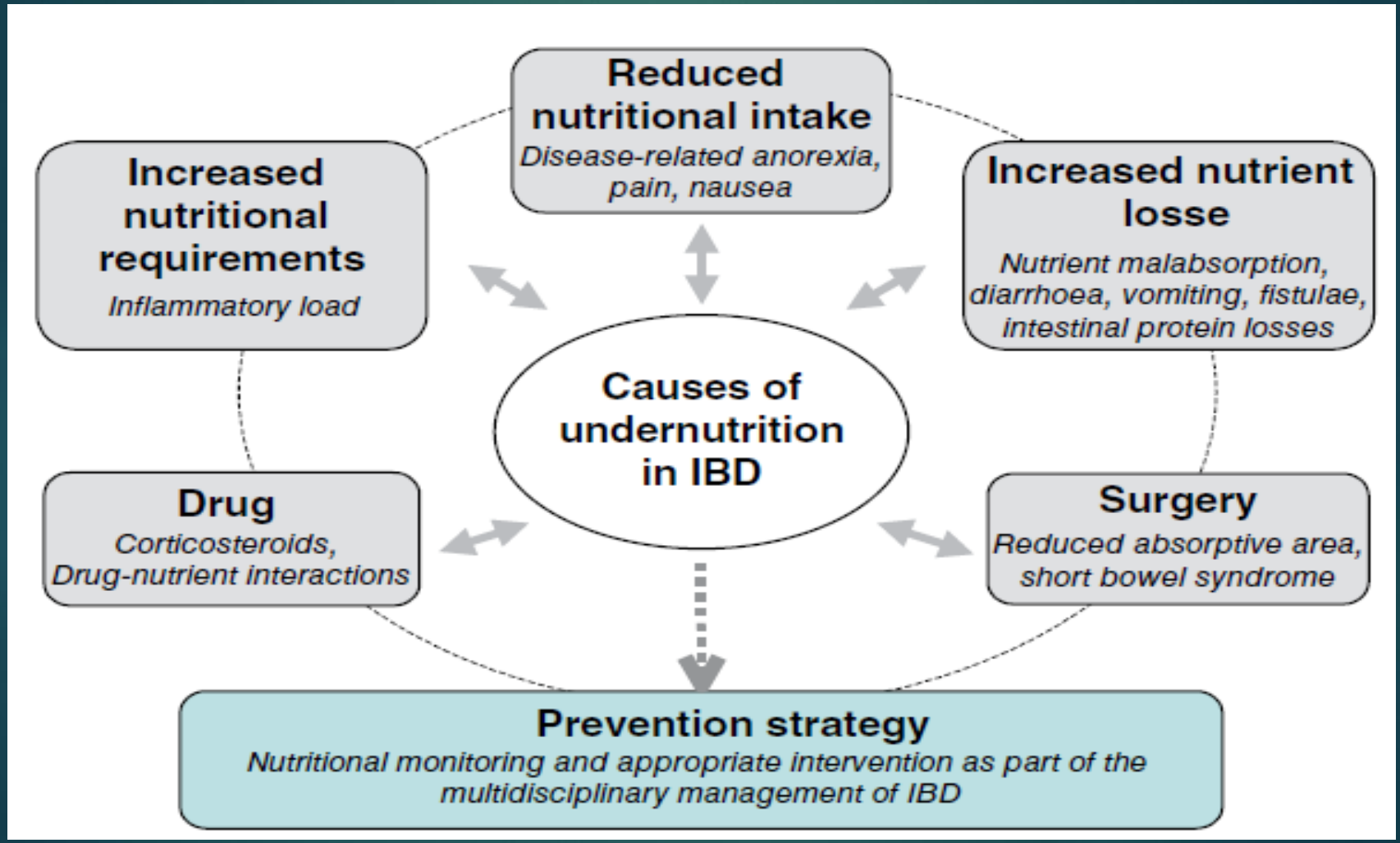
- Very effective short-term
- Psychosocial problems common
  - depression, anxiety, memory loss, loss of concentration, irritability, sleep disturbances
- Adverse effects on growth, bone metabolism

A stunted, cushingoid child without gastrointestinal symptoms is not a success story

What about anti-TNF Abs?

- Acute infusion reactions (AIR)
- Delayed hypersensitivity reactions
- Risk of Ab Formation
- Increased risk of serious infection
- Potential risk for malignancy

Causes of undernutrition in IBD



O'Sullivan M. Proceedings of the NutritionSociety 2009; **68**: 127–134.

"But doctor - can't we treat this with diet, all my friends say so..."

Rationale For Nutritional Therapy

- Increased caloric intake—improved BMI
- Anti-inflammatory properties
- Modification of gut microflora

BMI=body mass index

Beattie, *J Parenteral Enteral Nutr* 2005; 29:S151-5
Fell, *J Parenteral Enteral Nutr* 2005; 29:S126-8

Meta-analysis: Exclusive Enteral Nutrition in Pediatric CD

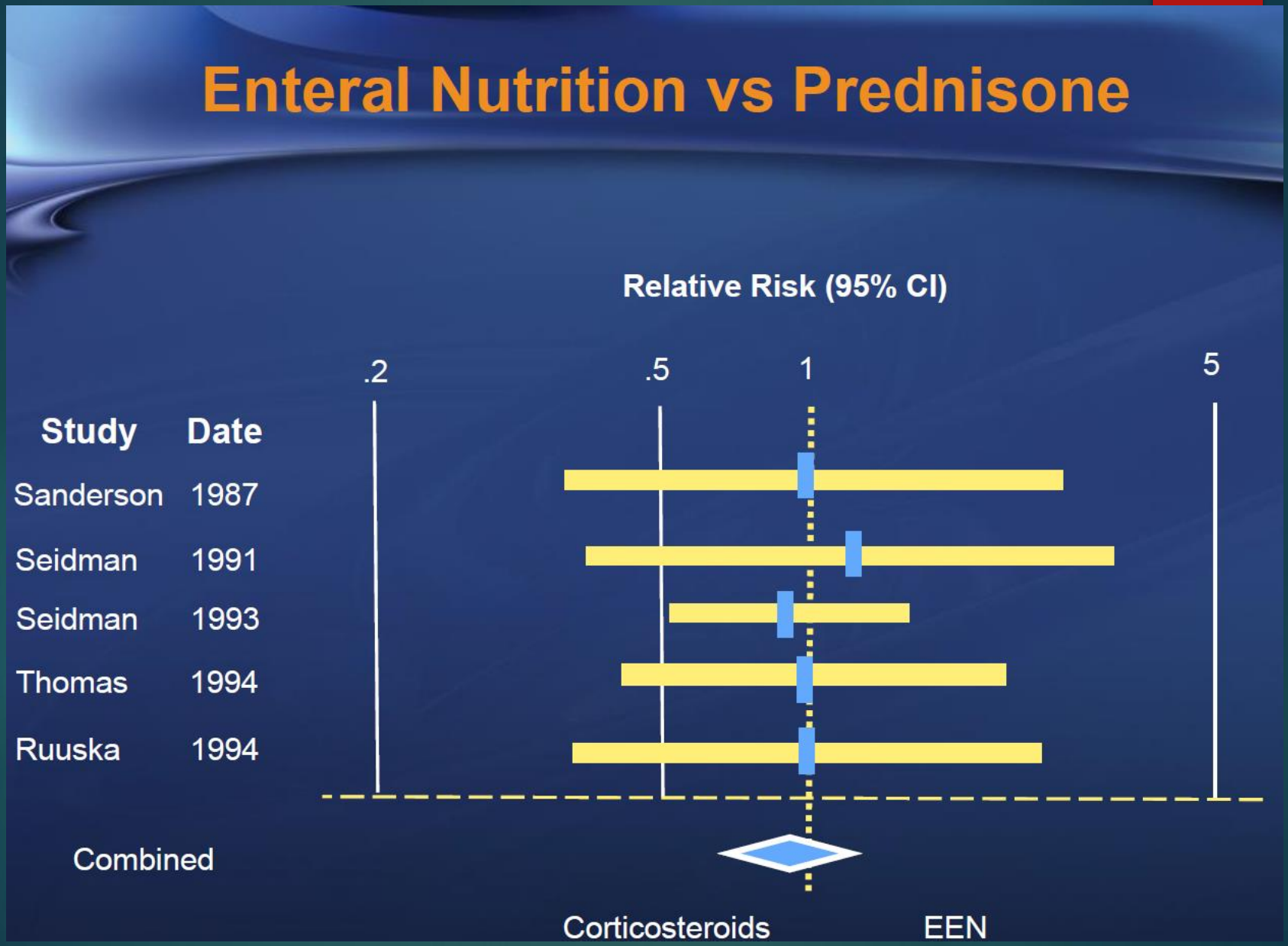
- 5 prospective randomized clinical trials comparing exclusive enteral nutrition vs. steroids in children
  - Study population of 166
  - Interventions
    - Elemental, semi-elemental, polymeric x 4 – 8 weeks (exclusive)

      OR

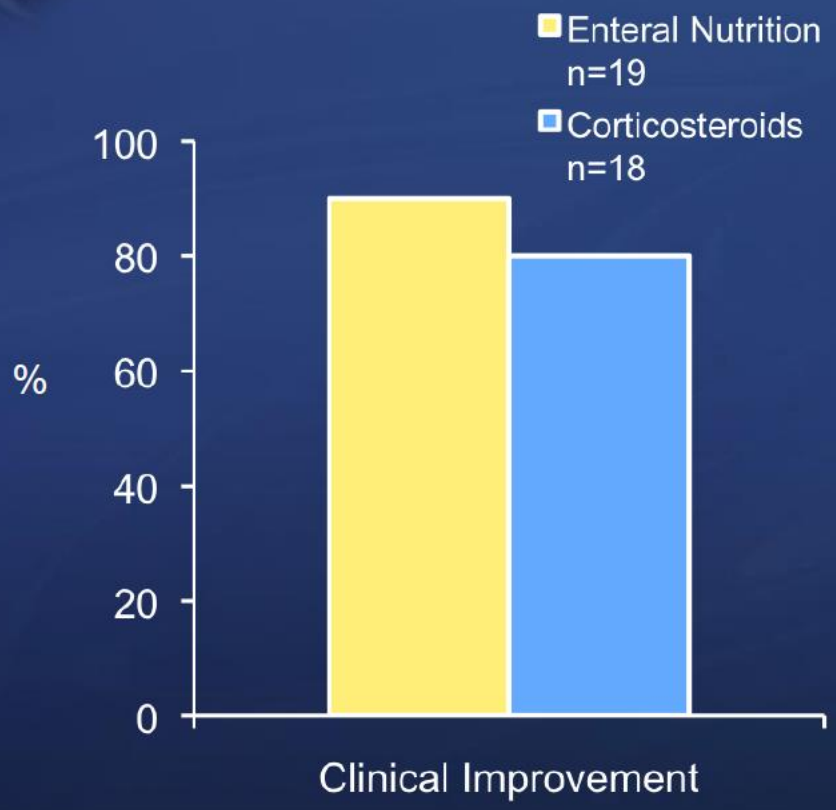
    - Prednisone/prednisolone 1 – 2 mg/kg/day x 1 – 3 weeks & then taper

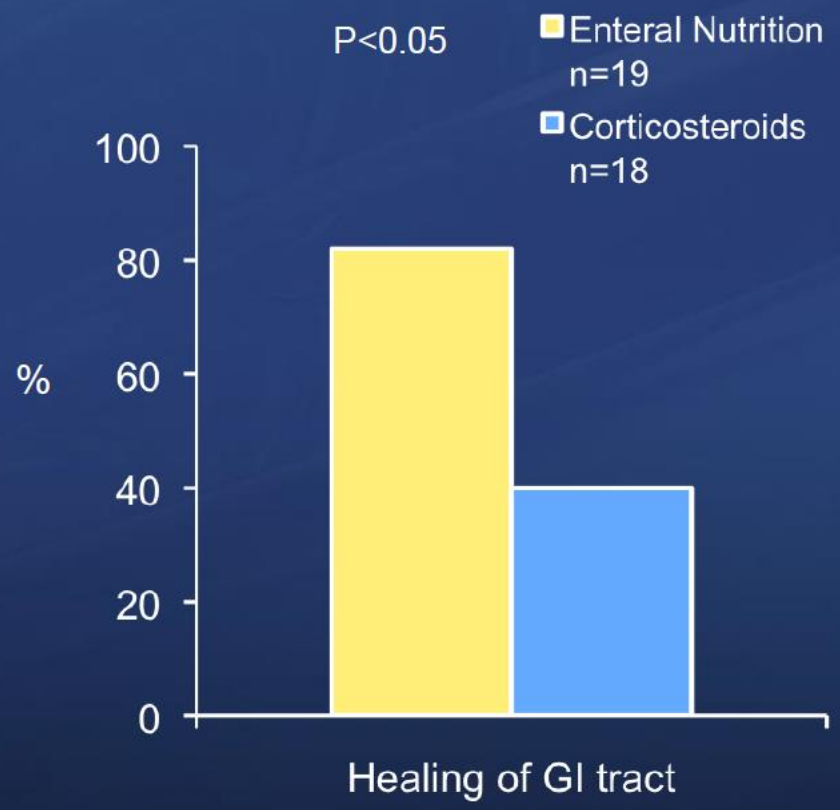
Seidman et al *Gastroenterology* (abstract) 1986
Tomas et al *JPGN* 1993
Seidman et al AGA abstract 1993

Enteral Nutrition vs Prednisone



Polymeric Diet vs. Steroids for Induction





Cochrane Review: Effect of Protein Type

- 7 trial meta-analysis
- 113 patients elemental
- 109 patients polymeric
- No difference between groups
  - (OR 1.37; 95% CI 0.80—2.35; p = 0.24)

Australian Retrospective: Effect of Disease Location

Day AS, et al. *Journal of Gastroenterology and Hepatology* 2006;21:1609–1614

Exclusive enteral nutrition(EEN)

- Exclusive Enteral Nutrition (EEN) is recommended as first line therapy to induce remission in children with low risk active luminal CD.

How long?

- EEN as induction therapy is usually prescribed for 6 to 8 weeks.
- If EEN does not induce clinical response within 2 weeks an alternative treatment should be considered

Schofield equation

- There are a number of formulas to calculate resting energy expenditure, but the Schofield equation is the one most commonly utilized.

- For males

Age	W=weight in kg; H=height in cm.
< 3 years	0.167W + 15.174H - 617.6
3-10 years	19.59W + 1.303H + 414.9
10-18 years	16.25W + 1.372H + 515.5

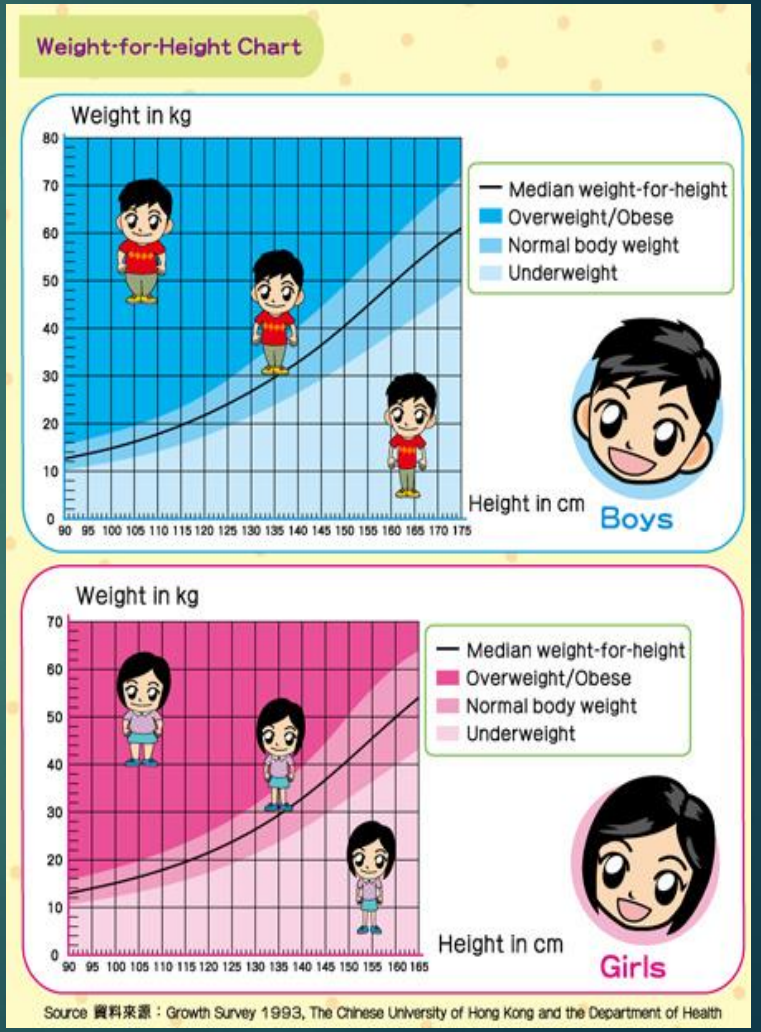
- For females

Age	W=weight in kg; H=height in cm.
< 3 years	16.252W + 10.232H - 413.5
3-10 years	16.969W + 1.618H + 371.2
10-18 years	8.365W + 4.65H + 200.0
18-30 years	13.623W + 2.83H + 98.2

Schofi eld WN. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5–41.
Mouzaki M, Griffiths AM.. In Pediatric Nutrition in Practice 2015 13;113

Infrastructure Needed for a Successful EN Regimen

In the setting of malnutrition, ideal body weight (the weight for the patient's age that corresponds to the same percentile on the growth chart as their height percentile) should be used instead of actual weight to prevent underfeeding.



Mouzaki M, Griffiths AM.. In Pediatric Nutrition in Practice 2015 Apr 13 (Vol. 113, pp. 239-243). Karger Publishers.

Infrastructure Needed for a Successful EN Regimen

- Some children can drink the formula by mouth, especially polymeric formulas which are more palatable.
- Many, however, will be unable to drink the large volumes of liquid required (often 1.5–2.5 L), and will prefer to receive a portion of the formula while asleep through a nasogastric tube.

Ananthakrishnan AN. Nutritional Management of Inflammatory Bowel Diseases.

Proposed protocol for the initiation of EEN

Initial rate of feeds	Start with half of the target hourly volume and give continuously over 24 h
Increasing feeds	Increase by 10 ml/h every 3 – 6 h, depending on symptoms
Cycling feeds	Decrease the overall feed duration by 2 – 3 h every day; the rate is determined by the total volume to be given over the desired number of hours
Final goal of feeds	The maximum rate is usually 6 – 8 ml/kg/h; the final duration of feeding is 10 – 14 h

Mouzaki M, Griffiths AM. In Pediatric Nutrition in Practice 2015 Apr 13 (Vol. 113, pp. 239-243). Karger Publishers.

For children who are active and can't receive all the formula overnight, there are small pumps that can be hidden in

Choice of Formula

- The choice of formula is determined by the provider and patient.
- The primary factor determining which formula to use is if the patient is willing to drink it.
- We can utilize both polymeric formulas (e.g. Pediasure, Fastmeal®) and partially hydrolyzed formulas (e.g. Peptamen®).

- according to the recent pediatric guidelines, always offer oral feeds with a polymeric formula, while EEN via a nasogastric tube remains reserved for patients unable to achieve the desired caloric intake, approximately120% of daily caloric need, or who refuse oral feeding due to taste or texture.

- Elemental feeds should only be reserved for patients allergic to cow's milk protein

Ruemmele FM. Ann Nutr Metab 2016;68:33–41.

the fat composition of formula

- An analysis comparing low-fat (<20 g fat/1000 kcal) vs high-fat (>20 g fat/1000 kcal) formulas found no difference in outcomes, nor did a further analysis of very-low fat formula (<3 g fat/1000 kcal).

- an evaluation of long-chain triglyceride content at the thresholds 5%, 10%, and 15% of total energy similarly found no difference in outcomes.

Zachos M, et al. Cochrane Database Syst Rev 2007:CD000542.

EEN vs. PEN

- The most important point when using EN as induction therapy is to use it on an exclusive basis, without any additional foods.

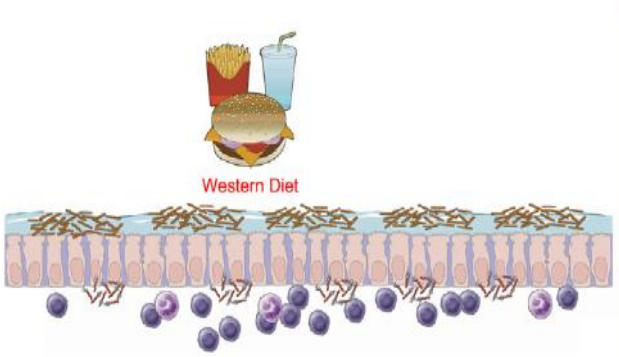
- Johnson et al. showed in a RCT (exclusive EN vs. partial EN with normal diet over 6 weeks using an elemental formula) clear superiority for full EEN over partial EN in remission rates at 6 weeks.

Johnson T, et al. Gut 2006; 55: 356–361.

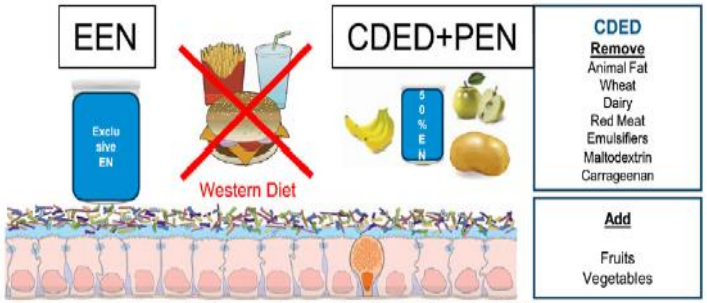
Svolos V, Hansen R, Nichols B, *et al.* Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition. *Gastroenterology* 2019;**156**:1354–67.e6.

Levine A, Wine E, Assa A, *et al.* Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology* 2019;**157**:440–50.e8.

Dietary Therapy: Crohn's Disease Exclusion Diet + Partial Enteral Nutrition vs. Exclusive Enteral Nutrition



Habitual Diet Triggering Crohn's Disease
Increased Proteobacteria Dysbiosis, Intestinal permeability, Inflammation,
Active Disease



Crohn's Disease Exclusion Diet+ PEN vs. EEN
Primary endpoint: CDED+PEN is better tolerated than EEN
Secondary endpoints:
Both CDED+PEN and EEN are effective to achieve remission at week 6
CDED+PEN is superior to sustain remission and reduce inflammation at week 12
CDED+PEN: associated with reduction in Proteobacteria and Intestinal Permeability

Gastroenterology

performed a 12-week prospective trial of children with mild to moderate CD. The children were randomly assigned to a group that received CDED plus 50% of calories from formula (Modulen, Nestlé) for 6 weeks (stage 1) followed by CDED with 25% PEN from weeks 7 to 12 (stage 2) (n = 40, group 1) or a group that received EEN for 6 weeks followed by a free diet with 25% PEN from weeks 7 to 12 (n = 38, group 2). Patients were

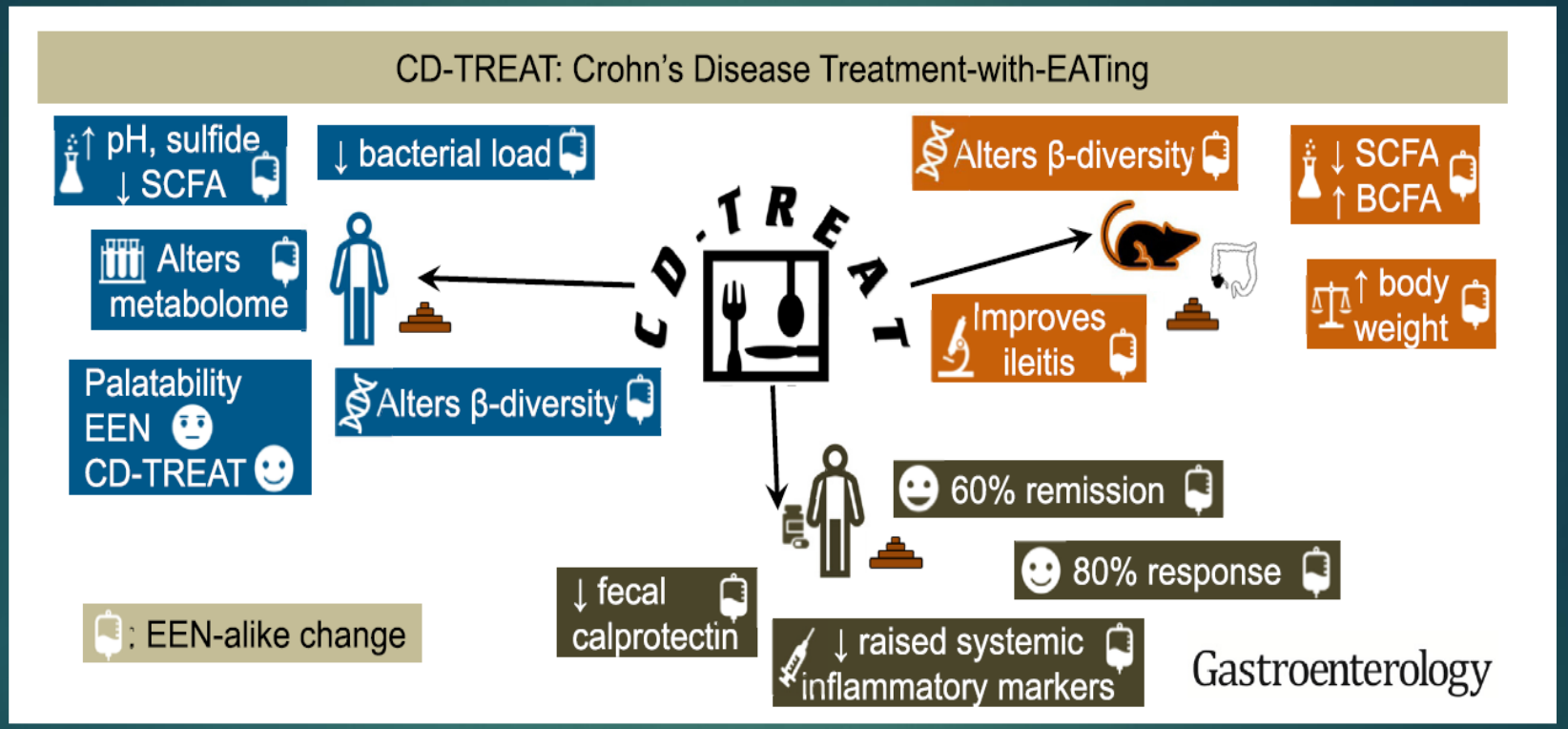
A novel Crohn's Disease Exclusion Diet, coupled with partial enteral nutrition, was better tolerated than exclusive enteral nutrition and demonstrated superior sustained remission and reduction in inflammation by week 12.

LIMITATIONS

The authors did not directly assess mucosal healing by endoscopy within 3 months, as this is not a standard of care in most pediatric centers.

IMPACT

The study identifies a dietary option, which combines food and enteral nutrition, which can help with reducing inflammation in Crohn's disease.


CD-TREAT: Crohn's Disease Treatment-with-EATing
↑ pH, sulfide
↓ SCFA
↓ bacterial load
Alters metabolome
Palatability
EEN
CD-TREAT
Alters β-diversity
CD-TREAT
Alters β-diversity
↓ SCFA
↑ BCFA
Improves ileitis
↑ body weight
60% remission
80% response
↓ fecal calprotectin
↓ raised systemic inflammatory markers
: EEN-alike change
Gastroenterology

CD-TREAT, an ordinary food diet, had similar effects to those of exclusive enteral nutrition on the gut microbiome and metabolome of healthy participants; reduced ileitis in a rat model of disease; and reduced disease activity and colonic inflammation in children with active Crohn's disease.

LIMITATIONS

The efficacy of CD-TREAT in patients with active Crohn's disease requires replication in large clinical trials.

IMPACT

CD-TREAT is a diet-only treatment for active Crohn's disease that might be used interchangeably with exclusive enteral nutrition; particularly in adults.

Vaios Svolos, et al,
Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition, Gastroenterology, 2019

Table S1: A day's menu of CD-TREAT diet for a boy with CD, 15 y, 48 kg and 170cm.

Breakfast:
1 multivitamin tablet
Full fat milk (360ml)
Rice breakfast cereals (45g)
Apple juice (360ml)
Morning snack:
Pineapple juice (360ml)
1 peeled apple
Lunch:
1 sandwich with white bread (2 slices), cheddar (45g) and cream cheese (45g), lettuce (20g) and peeled cucumber (20g)
1 bowl chicken and rice soup
Afternoon snack:
1 rice pudding
Dinner:
1 portion grilled salmon (180g) with mashed potatoes (260g) and cheese sauce

All dairy products were lactose free; all cereal-based products were gluten free

Reintroduction of Solid Food

There is no evidence to guide reintroduction of normal food at the end of EEN. The consensus panel suggests gradual food re-introduction with concomitant decrease of formula volume every 2–3 days over a 2–3 week period

Foods are usually reintroduced gradually.

It may be prudent, particularly if there are intestinal strictures, to offer a low-fiber diet initially following completion of the enteral nutrition regimen.

Sample protocol for reintroduction of solid foods

Day of introduction	Type of food	Examples
1-4	Grains; low fibre	White flour bread, crackers, pasta, rice Hot cereal: cream of wheat Cold cereal (low fat, low fibre)
5-9	Meat, fish and alternatives; low fibre, low fat	Plain (not fried, not processed) lamb, veal, beef, chicken, turkey Fish (low fat) Tofu Eggs
10-14	Fruits and vegetables; low fibre, low fat	Raw fruits without skin/seeds Canned fruits without skin/seeds Cooked vegetables without skin/seeds
15-17	Dairy; low fat	Milk, yogurt, cheese
18	Regular diet	Slowly increasing fat and fiber content based on

Moraki M, Griffiths AM. In Pediatric Nutrition in Practice 2015 Apr 13 (Vol. 115, pp. 239-243). Karger Publishers.

Maintenance Diet

- Medications (MTX/ Azathiupourines)
- EEN One out of every 4 months
- PEN 4-5 days every week

ECCO-ESPGHAN statement 14

In children with low-risk CD who achieved clinical remission, monotherapy with maintenance enteral nutrition [at least 50% of daily energy requirements] can prolong remission. LoE: 3 | Agreement: 87%.

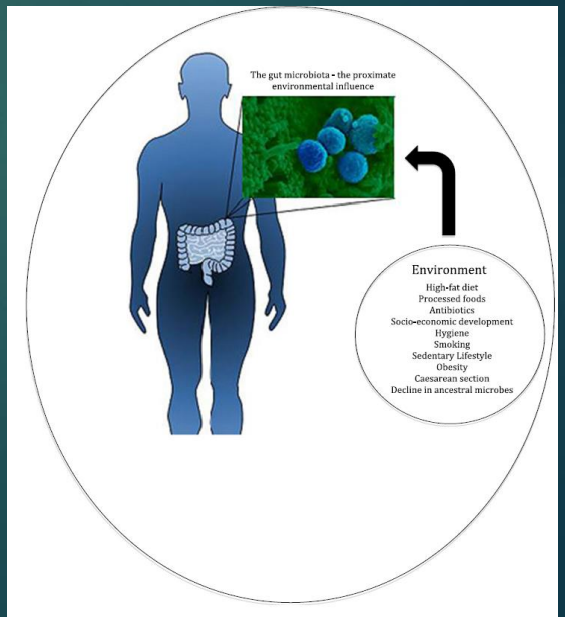
Mechanism of action

The mode of action of EN to treat CD is still not completely understood despite many ongoing studies. Several mechanisms have been proposed:

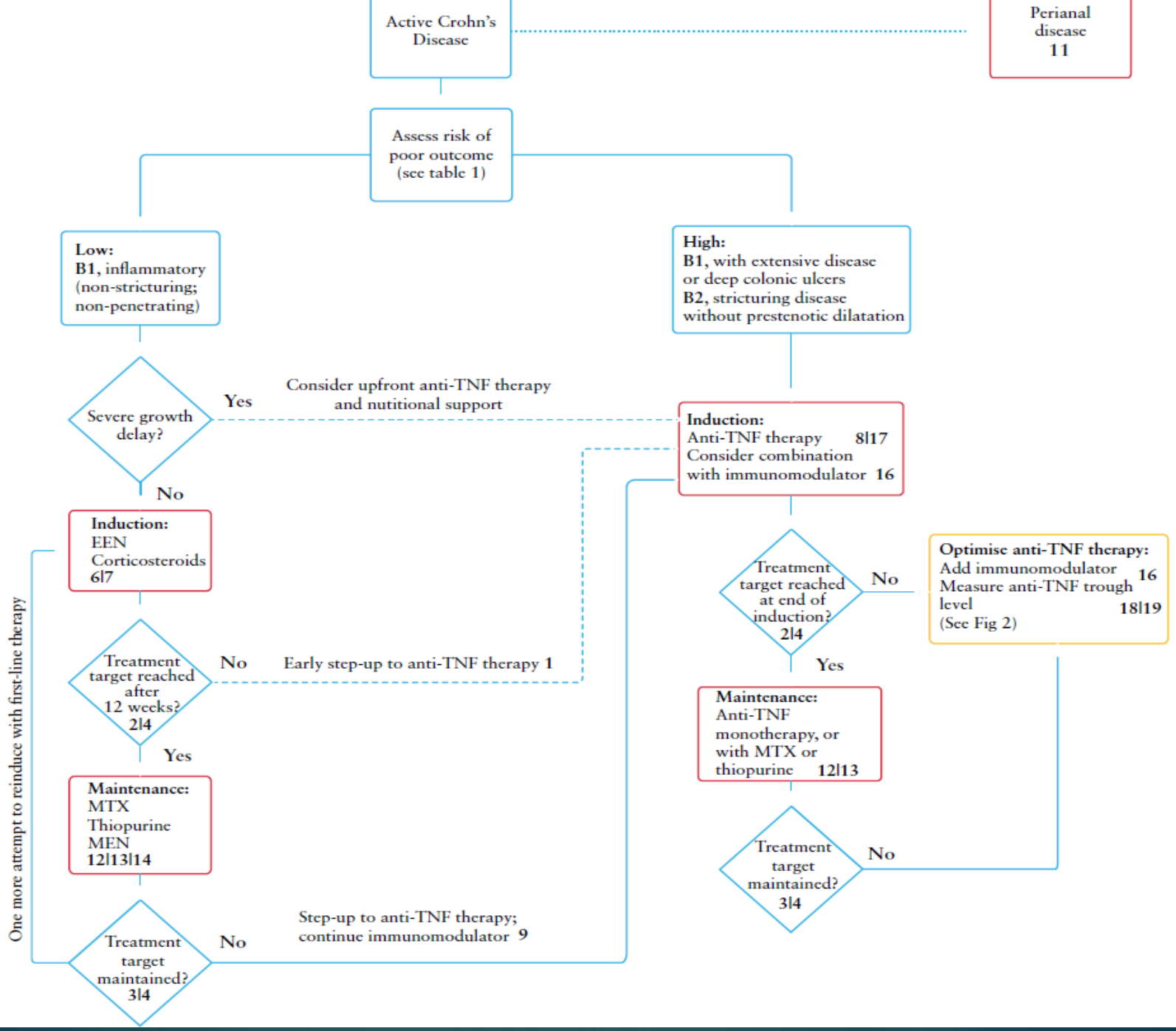
- ☑ reduced allergenic load,
- ☑ being nucleotide free,
- ☑ no addition of food additives,
- ☑ and an anti-inflammatory lipid composition

Ruemmele FM. Ann Nutr Metab 2016;68:33–41.

- In line with the mechanisms discussed, a new hypothesis has recently been developed in that EEN has a specific effect on the intestinal microbiome, positively interfering with the dysbiosis in CD patients.



Ruemmele FM. Ann Nutr Metab 2016;68:33–41.


Active Crohn's Disease
Perianal disease 11
Assess risk of poor outcome (see table 1)
Low: B1, inflammatory (non-stricturing; non-penetrating)
High: B1, with extensive disease or deep colonic ulcers B2, stricturing disease without prestenotic dilatation
Severe growth delay?
Yes
Consider upfront anti-TNF therapy and nutitional support
No
Induction: EEN Corticosteroids 6|7
Treatment target reached after 12 weeks? 2|4
No
Early step-up to anti-TNF therapy 1
Yes
Maintenance: MTX Thiopurine MEN 12|13|14
Treatment target maintained? 3|4
No
Step-up to anti-TNF therapy; continue immunomodulator 9
One more attempt to reinduce with first-line therapy
Induction: Anti-TNF therapy 8|17 Consider combination with immunomodulator 16
Treatment target reached at end of induction? 2|4
No
Optimise anti-TNF therapy: Add immunomodulator 16 Measure anti-TNF trough level 18|19 (See Fig 2)
Yes
Maintenance: Anti-TNF monotherapy, or with MTX or thiopurine 12|13
Treatment target maintained? 3|4
No

Probiotics

Trial Author	Number of Patients	Treatment	Duration	Results/*p* Value
Dore et al., 2018 [14]	200 patients (78 with CD, 122 with UC)	Probiotics given orally; VSL#3 (450 billion CFU/packet comprising strains of *Lactobacilli*, *Bifidobacteria*, and *Streptococcus*) once daily; *Lactobacillus reuteri* (DSM 17,938) 108 CFU/tablet once a day; and a mixture of *Streptococcus. thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, and *Bifidobacterium animalis* ssp. *lactis* for a total of 50 × 109 CFU/packet once a day	36 months	CD patients taking probiotics for 25–74% of disease, had a 64% reduction. Systemic steroid use and hospitalizations dropped to zero events for UC patients and decreased by 93% ($p < 0.001$) in CD patients taking probiotics for ≥75% of the disease duration.
Matthes et al., 2010 [19]	90 patients with UC	*Escherichia coli* Nissile 1917 enema	2 weeks	80 patients had positive effects.
Tursi et al., 2010 [15]	144 patients with UC	Mixture of 4 strains of *Lactobacilli*, 3 strains of *Bifidobacteria* and one strain of *Streptococcus thermophilus* (VSL#3) taken orally	8 weeks	Decrease in disease activity compared to the placebo group ($p = 0.010$).
Fedorak et al., 2015 [16]	120 patients with CD	1 packet of VSL #3 daily, taken orally	3 months	Control group had lowered mucosal levels of inflammatory cytokines and lower rate of recurrence.
Marteau et al., 2006 [20]	98 patients with CD with recent intestinal resection	1 packet *Lactobacillus johnsonii* bacteria daily taken orally	6 months	Concluded that there was not any sufficient effect.

polyphenols

Trial Author	Number of Patients	Substance Tested	Duration	Results/*p*-Value
Stan et al., 2019 [25]	100 male mice	*Thuja occidentalis* 25 or 50 mg/kg/per day	7 days	Shown to inhibit inflammatory processes induced by TNBS.
Dodda et al., 2014 [26]	6 rats	Quercetin 50 mg/kg/per day or 100 mg/kg/per day.	3 days	Significant improvement in ulcers in rats, and shown some protective role in IBD symptoms.
Hanai et al., 2006 [32]	89 patients with inactive UC	1 gram of curcumin after breakfast and 1 gram after dinner along with mesalamine.	6 months	4.65% relapsed on curcumin ($p = 0.40$).
Singla et al., 2014 [27]	45 patients with mild to moderate UC	Curcumin NCB-02 enemas containing 140 mg of NCB-02 (curcumin) preparation dissolved in 20 mL of water.	8 weeks	Higher improvements in disease activity noted in patients receiving the enema ($p = 0.14$).
Lang et al., 2015 [28]	50 patients with UC treated with mesalamine	5-aminosalicylate administered with curcumin capsules.	1 month	Curcumin addition helped to achieve clinical remission ($p \leq 001$).
Kedia et al., 2017 [29]	41 patients with mild to moderate UC	150 mg of curcumin added to 2.4 g of mesalamine	8 weeks	Not effective in inducing clinical remission or response in patients tested ($p = 0.75$).
Samsamikor et al., 2016 [31]	56 patients with UC	500 mg of resveratrol	6 weeks	Decreased serum level of malondialdehyde (MDA), which decrease disease activity ($p = 0.001$).

Fiber

Trial Author	Number of Patients	Substance Tested	Duration	Results/*p*-Value
Benjamin et al., 2011 [38]	103 patients with active CD	Chicory fructan supplementation Synergy 1 © product 15 g/day	4 weeks	Decreased disease activity, increased fecal bifidobacterial counts, and dendritic cell response ($p < 0.05$).
Casellas et al., 2007 [40]	19 patients with UC	Synergy 1©, administered in the dose of 4 grams, 3 times daily	14 days	Decrease in dyspeptic symptoms, decrease in calprotectin on day 7 ($p < 0.05$).
Fernandez-Banares et al., 1999 [41]	102 patients with UC	Psyllium 10 g, twice daily	1 year	Comparable results of remission as mesalamine ($p = 0.67$).
Hallert et al., 1991 [42]	29 people with UC	Psyllium (3.52 g ispaghula husk)	4 months	Improved gastrointestinal symptoms ($p < 0.001$).
Hallert et al., 2003 [43]	32 patients with inactive UC	60 g of oat bran daily	12 weeks	Increased restoration of intestinal homeostasis and gut barrier function ($p < 0.05$).
Faghfoori et al., 2014 [46]	46 patients with inactive UC	Barley foodstuff supplementation 30 grams, 3 times daily)	2 months	Decreased CRP, and symptoms improvements ($p = 0.017$).
Kanauchi et al., 2002 [47]	18 patients with moderate UC	Germinated barley foodstuff (20–30 grams daily)	4 weeks	Decrease in clinical disease activity and increase in *Bifidobacterium* numbers in feces, aiding intestinal microbial homeostasis ($p < 0.05$).
Liu et al., 2015 [45]	80 mice	Oat beta-glucans, 500 mg/kg /day or 1000 mg/kg/day	7 days	Clinical symptoms such as weight loss, diarrhea and colon shortening significantly reduced ($p < 0.05$).

Fatty Acids

Trial Author	Number of Patients	Substance Tested	Duration	Results/*p* Value
Scaioli et al., 2018 [49]	60 UC patients	EPA–FFA (eicosapentaenoic acid as free fatty acid), of 500 mg 2×/day	6 months	Clinical remission was noted in 50% compared to placebo ($p = 035$).
Prossomariti et al., 2017 [50]	20 patients with UC	EPA–FFa 2 g/daily	3 months	Reduced mucosal inflammation, promoted goblet cell differentiation, and modulated intestinal microbiota.
Chan et al., 2014 [51]	229, 705 patients across 9 European centers	DHA intake and risk of CD	7 years	A significant relationship between DHA intake and the development of CD was noted.
Bassaganya-Riera et al., 2012 [52]	13 patients with mild to moderate CD	6 g/day of CLA (conjugated linoleic acid)	12 weeks	Reduced the production of TNF-α, IFN-γ, IL-17, lymph proliferation and significant drop in CDAI at week 12 ($p = 0.013$).
Seidner et al., 2005 [53]	50 patients	2.5 g of EPA and 1.0 g of DHA per day	6 months	EPA and DHA group were less likely to take steroids and did not exceed baseline dose ($p < 0.001$).
Feagan et al., 2008 [54]	365 adult patients in remission of active CD	Enteric coated capsules with 2–2.4 g of EPA and 0.6–1 g of DHA per day	4 years	Relapse rate was lower (36.1%) in control group ($p = 0.30$).


Thank You!
Any Question?