Diet and IBD

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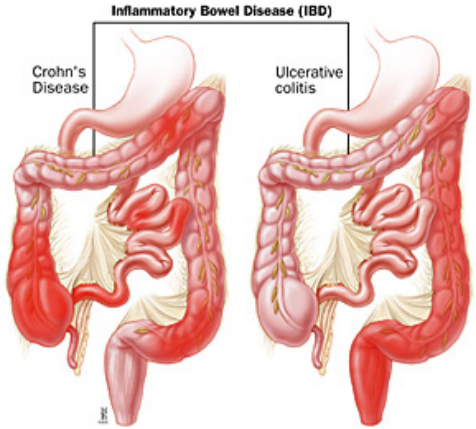
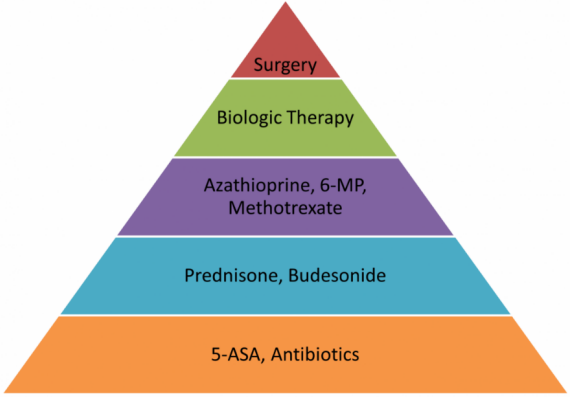
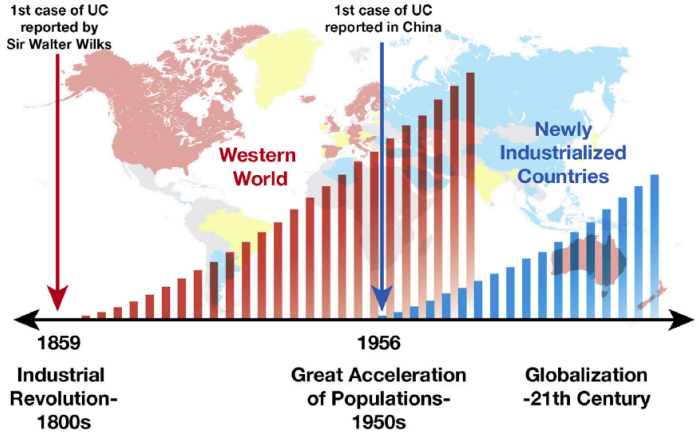
Inflammatory Bowel Disease: Environmental Contribution

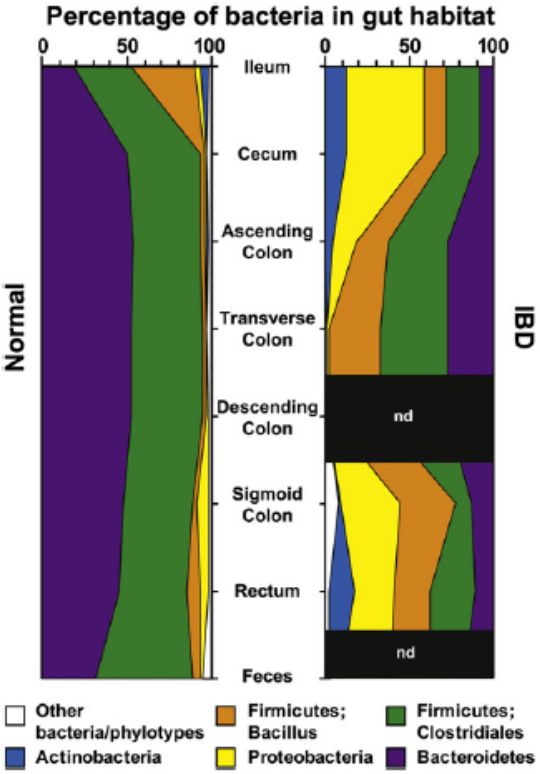




- The genetic contribution to the development of Crohn's disease is at most 30-40%
- In total, the contribution of IBD associated genetic loci account for only 13% of Crohn's disease variance
- Thus environmental factors are the largest contributor to the pathogenesis of IBD



Microbiota Dysbiosis in IBD: Both Cause and Effect



Peterson et al. Cell Host & Microbe 2008;3:417-427

Mice

Potentially injurious species in susceptible hosts	Protective species
Bacteroides vulgatus, B. thetaiotaomicron	*Lactobacillus species*
Escherichia coli (adherent/invasive)	*Bifidobacterium species*
Enterococcus faecalis (nonpathogenic)	*Escherichia coli*
Klebsiella pneumoniae	*Bacteroides thetaiotaomicron*
Fusobacterium varium	*Faecalibacterium prausnitzii*
Helicobacter hepaticus and other intestinal species	
Bifidobacterium animalis	

PNAS 2008;105:16413

Precision editing of the gut microbiota ameliorates colitis

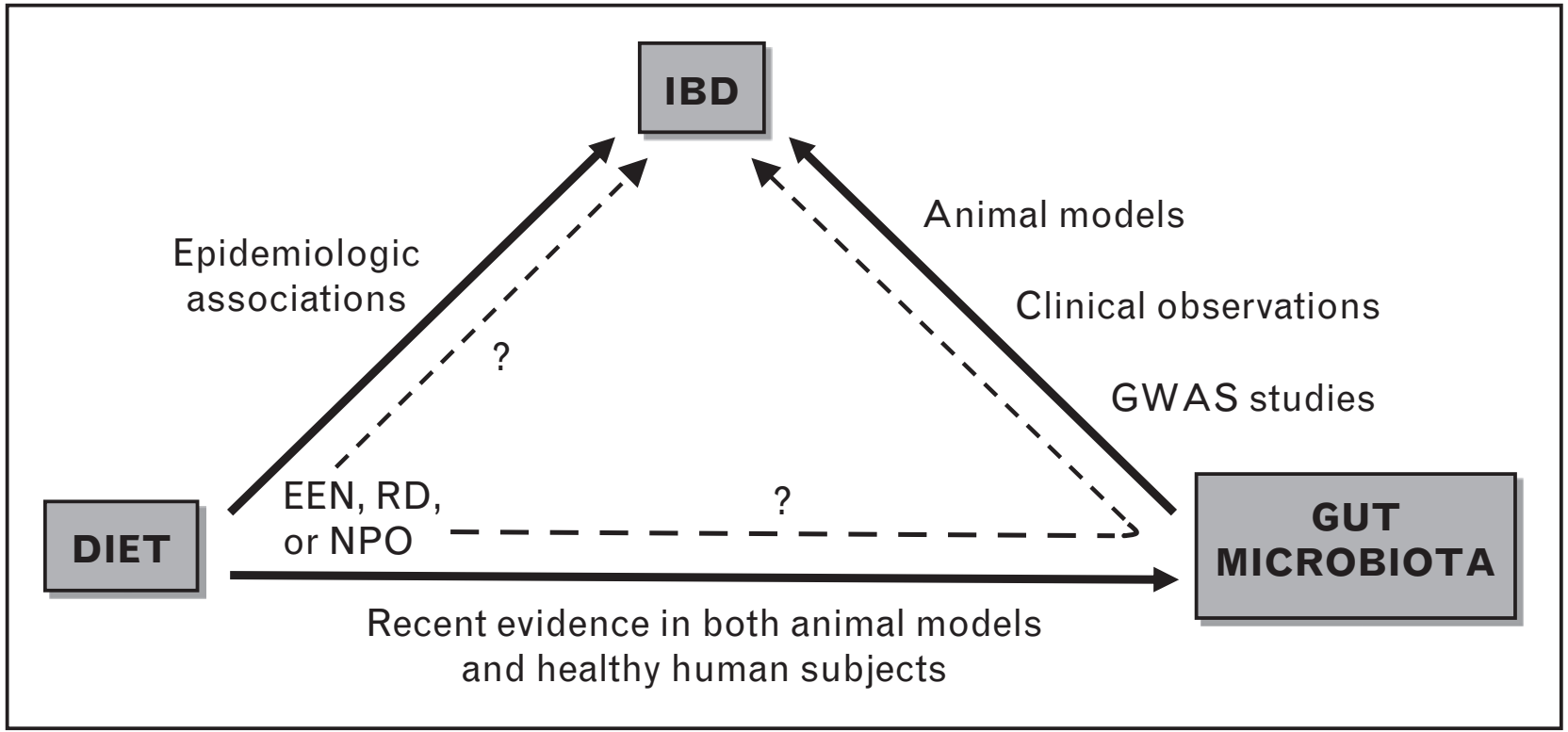
Wenhan Zhu[1*], Maria G. Winter[1*], Mariana X. Byndloss[2], Luisella Spiga[1], Breck A. Duerkop[3], Elizabeth R. Hughes[1], Lisa Büttner[1], Everton de Lima Romão[2], Cassie L. Behrendt[3], Christopher A. Lopez[2], Luis Sifuentes-Dominguez[4], Kayci Huff-Hardy[5], R. Paul Wilson[6†], Caroline C. Gillis[1], Çagla Tükel[6], Andrew Y. Koh[1,4], Ezra Burstein[5], Lora V. Hooper[3,7], Andreas J. Bäumler[2] & Sebastian E. Winter[1]

Humans

Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

Is There a Relationship Between Diet, the Gut Microbiota and IBD?



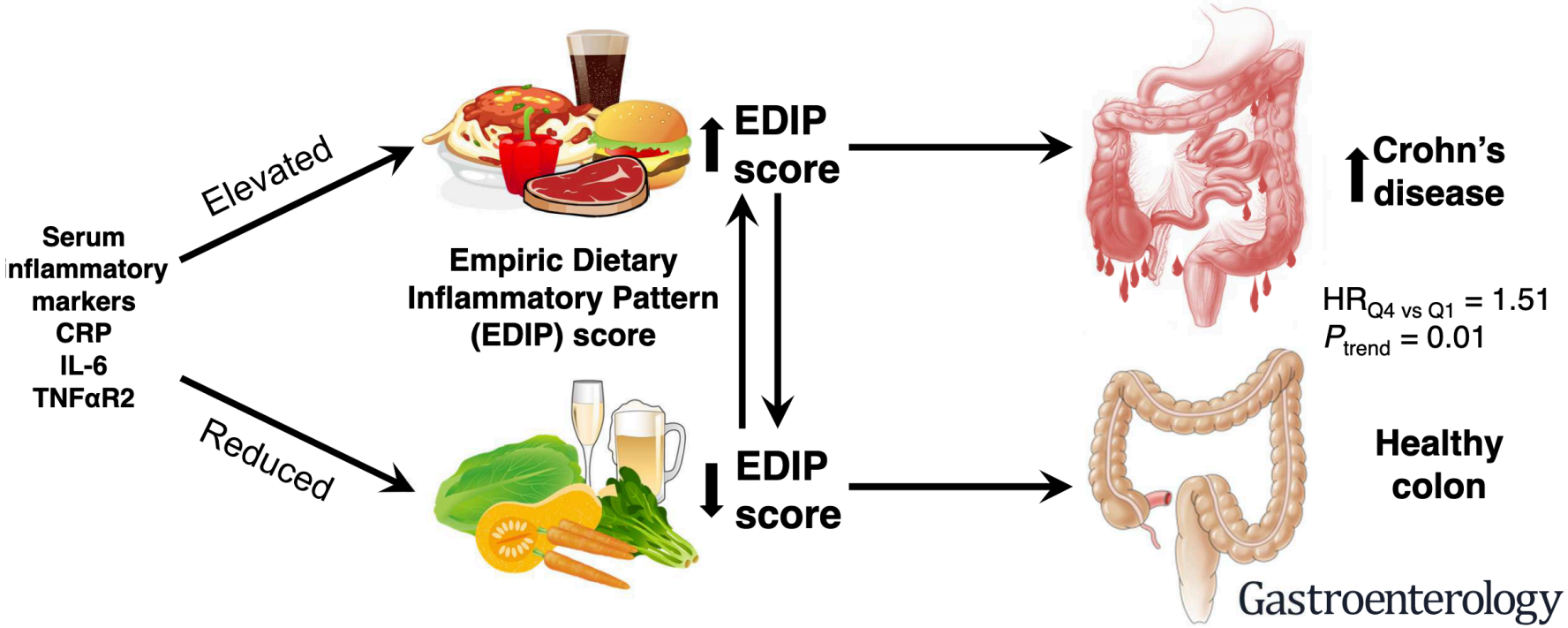
Albenberg et al. *Current Opinion Gastro*. 2012.

Patient-reported foods that improve / worsen symptoms

Food Items	CD (n=1121) (B, W)	UC (n=597) (B, W)	CD-O (n=405) (B, W)	UC-P (n=206) (B, W)
Improved Symptoms				
Yogurt	108, 7*	54, 3*	26, 0*	19, 0*
Rice	59, 3*	30, 3*	20, 3†	16, 0*
Bananas	NR	NR	NR	14, 0*
Worsened Symptoms				
Non-Leafy Vegetables	28, 221*	29, 81*	7, 90*	3, 36*
Spicy Foods	1, 145*	3, 79*	0, 46*	0, 33*
Fruit	50, 136*	40, 63	22, 51†	15, 24
Nuts	3, 120*	1, 33*	0, 52*	0, 21*
Leafy Vegetables	6, 115*	2, 50*	2, 29*	1, 14†
Fried Foods	0, 105*	0, 53*	0, 22*	0, 11†
Milk	6, 105*	0, 49*	5, 28*	2, 14†
Red Meat	6, 103*	7, 47*	2, 24*	NR
Soda	11, 99*	0, 46*	0, 33*	0, 28*
Popcorn	2, 97*	NR	0, 27*	0, 18*
Dairy	3, 94*	1, 56*	NR	0, 12†
Alcohol	0, 90*	0, 54*	NR	0, 23*
High Fiber	19, 87*	19, 35†	7, 46*	NR
Corn	0, 77*	0, 31*	0, 29*	NR
Fatty Foods	0, 62*	NR	NR	NR
Seeds	NR	NR	0, 22*	NR
Coffee	NR	4, 37*	NR	NR
Beans	NR	5, 30*	NR	NR

P values from the sign test. Bonferroni method p<0.00039 (i.e., 0.05/127) identified with an asterisk (*). Cohen AB *Dig. Dis. Sci.* 2012.

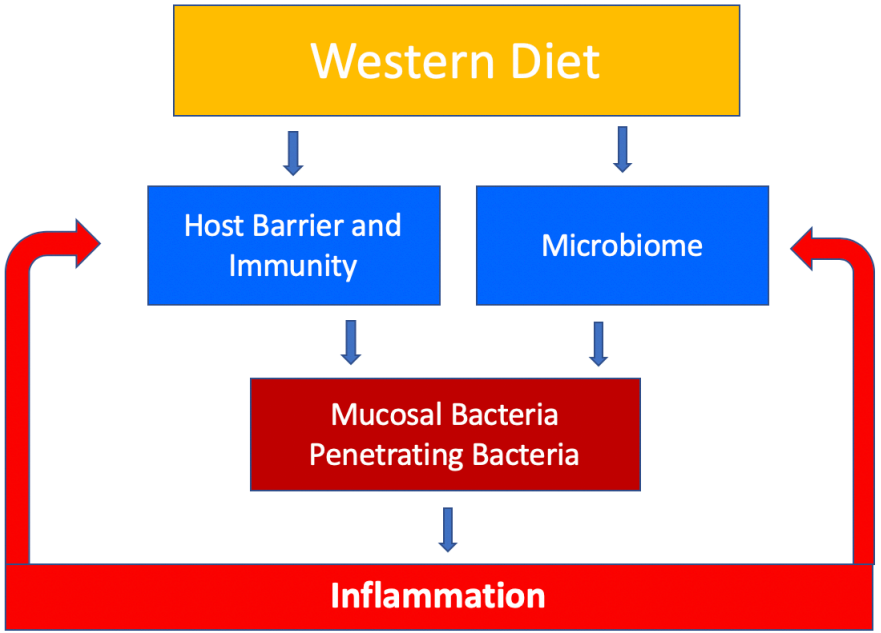
Dietary Inflammatory Potential



Lo et al. *Gastroenterology.* May 2020.

Something “Bad” in Diet and the Microbiome?

Nutrient	Effect on permeability	Proposed mechanisms
SCFAs	↓	↑ATP, Treg regulation, cytokine production, HIF-1 regulation, relocation of ZO-1& occludin
Vitamin D	↓	Regulation of innate& adaptive immunity, ↑Ezrin, altered villous morphology
Vitamin A	↓	↑ Mucus and defensin production, ↑TLRs
Zinc	↓	↓Phosphorylated occludin & claudin-1, ↑claudin-2
Anthocyanins	↓	↑ GLP-2 and MUC-2
Cysteine	↓	↑ GSH
Methionine	↓	↑Occludin, ZO-1 and claudin-3
Glutamine	↓	↑ATP, ↑ERK1/2 and JNK, growth factors EGF, TGF and IGF-1 pathways
Tryptophan	↓	AHR and PXR pathways
Arginine	↓	NOS pathway
Gluten	↑	Binding to CXCR3
Glucose	↑	Altering AJ proteins
Fructose	↑	↓ATP
Bile acids	↑	TGR5 and FXR pathways
Fat	↑	Change the microbiota composition
Ethanol	↑	Direct damage to epithelia, altering TJ proteins
Emulsifiers	↑	Change the microbiota composition



Courtesy of Arie Levine

Khoshbin and Camilleri. *Am J Physiol Gastrointest Liver Physiol.* September 2020.

Dietary Approaches for Treating IBD

- Exclusive Enteral Nutrition (EEN)
- Whole Food Therapeutic Diets:
  - Specific carbohydrate diet (SCD)
  - Crohn's disease exclusion diet
  - Semi-vegetarian diet
  - CD-TREAT
  - "Anti-inflammatory" diet

Defined Formula Diets for CD: Children

WILEY AP&T Alimentary Pharmacology & Therapeutics

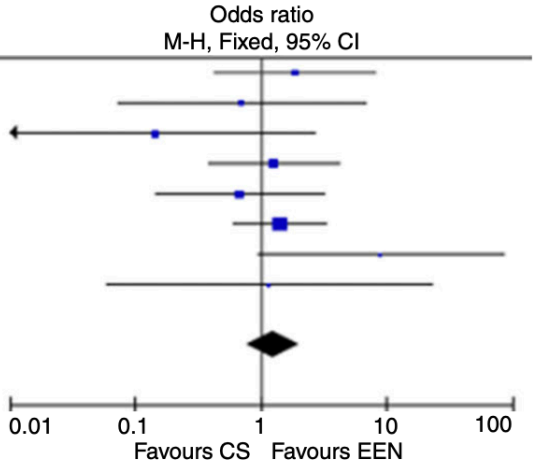
Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease

A. Swaminath[1] | A. Feathers[1] | A. N. Ananthakrishnan[2] | L. Falzon[3] | S. Li Ferry[4]

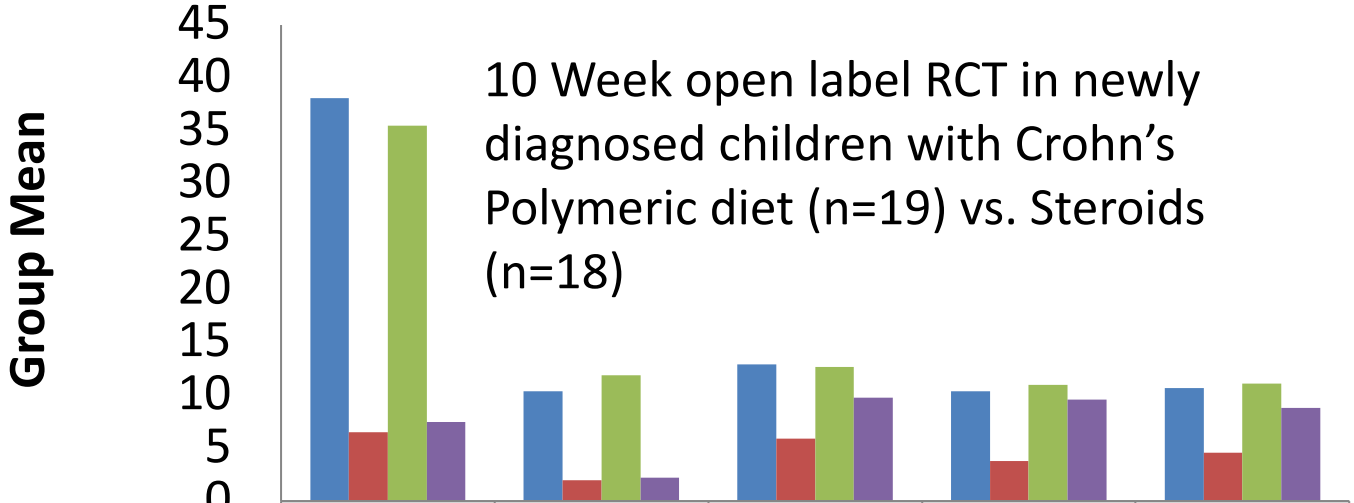
Study or Subgroup	EEN Events	EEN Total	CS Events	CS Total	Weight	Odds ratio M-H, Fixed, 95% CI
Borrelli 2006	15	19	12	18	9.1%	1.88 [0.43, 8.20]
Canani 2006	32	37	9	10	6.7%	0.71 [0.07, 6.89]
Hojsak 2014	48	57	17	17	15.4%	0.15 [0.01, 2.64]
Kierkas 2013	11	24	8	20	16.7%	1.27 [0.38, 4.22]
Lambert 2013	26	31	23	26	14.2%	0.68 [0.15, 3.16]
Levine 2014	31	40	77	109	32.8%	1.43 [0.61, 3.35]
Luo 2015	9	10	9	18	2.3%	9.00 [0.94, 86.52]
Sanderson 1987	7	8	6	7	2.8%	1.17 [0.06, 22.94]
Total (95% CI)		226		225	100.0%	1.26 [0.77, 2.05]
Total events	179		161			

Heterogeneity: $Chi^2 = 6.27$, df = 7 ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: Z = 0.91 ($P = 0.37$)



Defined Formula Diets for CD



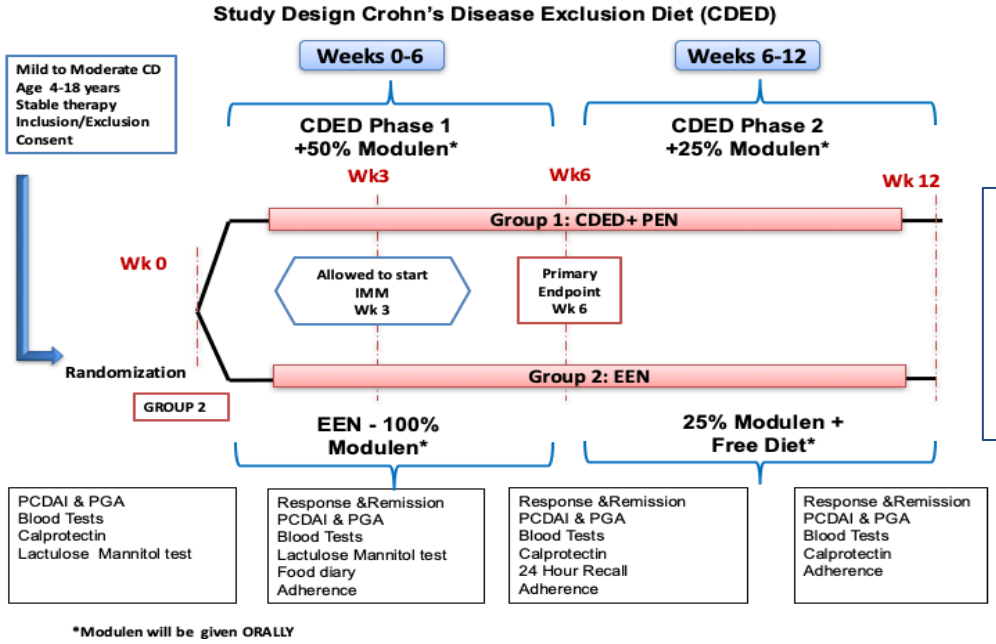
* P<0.05 for Pre vs Post

	PCDAI	CRP	CDEIS	Histol - Ileum	Histol - Colon
Polymeric diet - Pre	38.1	10.4	12.9	10.4	10.7
Polymeric diet - Post	6.53*	2*	5.9*	3.8*	4.6*
Corticosteroids - Pre	35.5	11.9	12.7	11	11.1
Corticosteroids - Post	7.5*	2.2*	9.8	9.6	8.8

Borrelli O. *CGH* 2006;4:744-53

CDED Trial - RCT comparing CDED+PEN to EEN followed by PEN

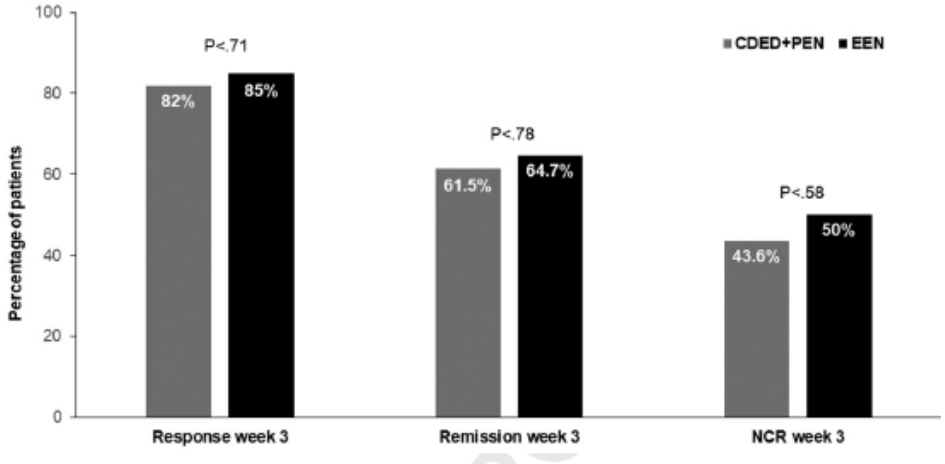
78 patients mild to moderate CD , mean age 14.2±2.7 years



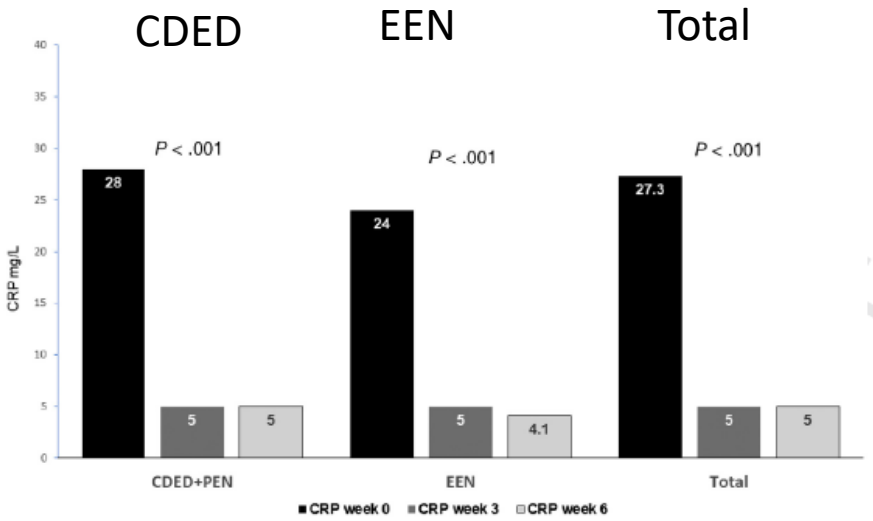
*Primary outcome = tolerance

Rapid Response to Dietary Therapy

Response, Remission, normal
CRP at week 3



CRP at weeks 0, 3, 6



Sigall Boneh *et al*., Clin Gastro and Hepatology 2020;46:546-56.

CHOP "Partial" EN Protocol

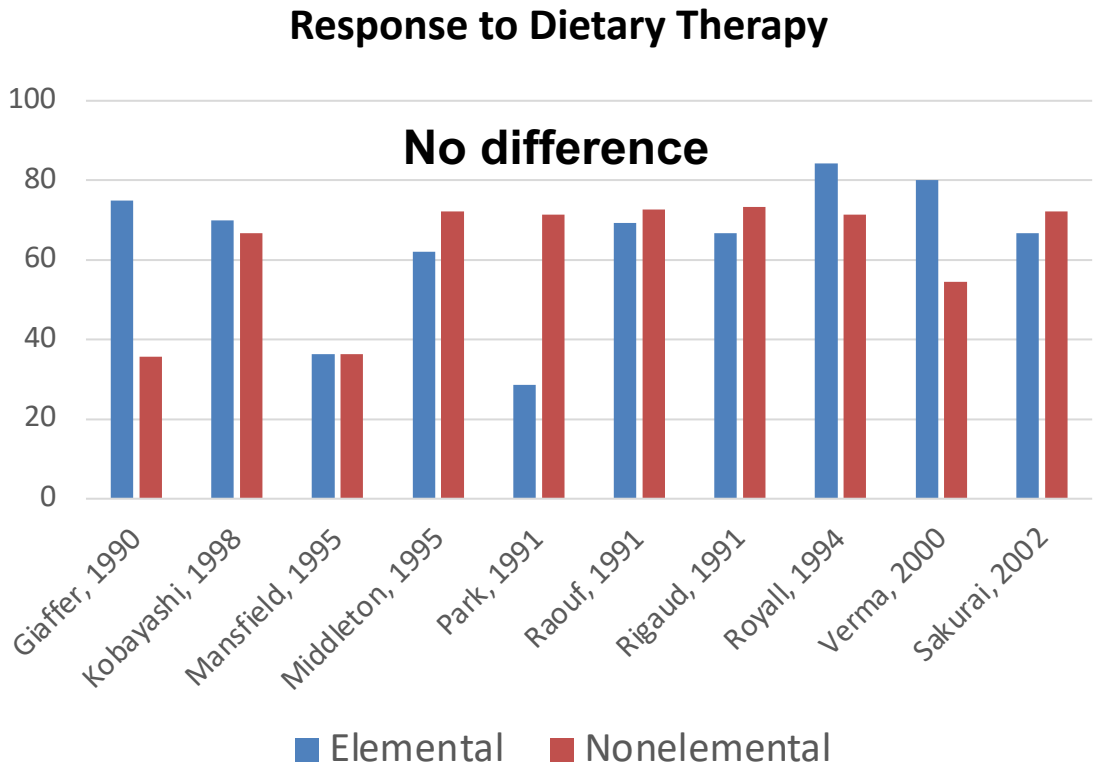
- **CHOP protocol**
- 8-12 weeks
- 80-90% of estimated needs from formula
- 10-20% food
  - Pediatric anti-inflammatory diet pyramid
- NG tube/oral/combo

- WHO's REE multiplied by activity factor
  - REE x 1.5 for no malnutrition
  - REE x 1.7-1.8 if moderately malnourished or more than 2 hours/day high intensity physical activity

REE	Males	Females
0-3	60.9W - 54	61.0W - 51
3-10	22.7W + 495	22.5W + 499
10-18	17.5W + 651	12.2W + 746
18-30	15.3W + 679	14.7W + 496

Gupta K et al. Inflamm Bowel Dis. 2013

Elemental vs. Nonelemental



Adapted from Zachos M. Cochrane Review 2007

Pediatric Anti-Inflammatory Diet Pyramid

H. McClafferty, MD FAAP

Where should we place EEN?

- Most common placement of EEN observed in the literature: alternative to corticosteroid as a bridge to thiopurine
- Scarce data evaluating combination of EEN with other therapies (1 study with anti-TNF)
- Bridge to PEN for maintenance?
- Bridge to exclusion diets?
- Bridge to anti-TNF (delayed insurance approval, allow immunization catch-up in unimmunized, patients with intra-abdominal abscess)

Exclusive Enteral Nutrition: Pros and Cons

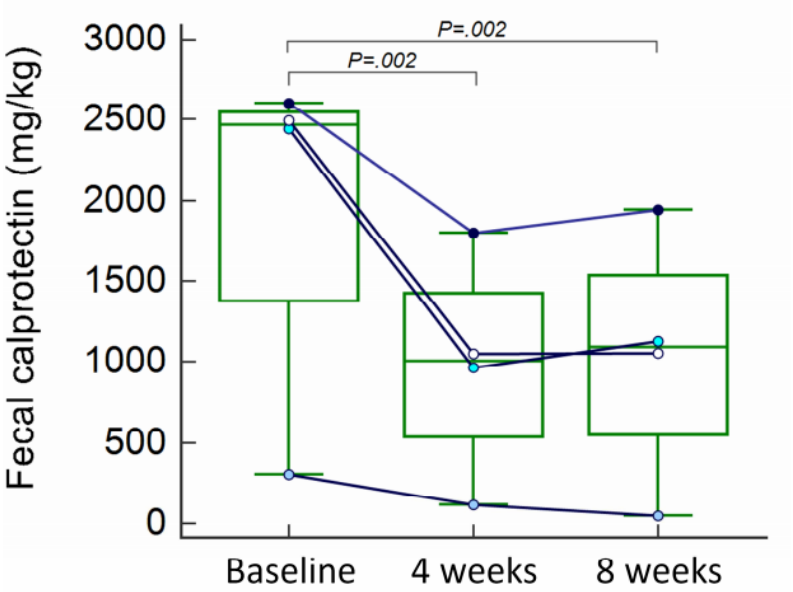
+ At least as effective as steroids
+ Associated mucosal healing
+ Works quickly
+ Improves nutritional status
+ Improves bone health
+ No side effects

- Demands resources, education, & dedication
- Limited long-term benefit
- Exit strategy?

Courtesy of Eytan Wine

CD-TREAT: Emulating EEN with food

- Hypothesis: Ordinary food diet based on composition of Modulen formula can achieve similar efficacy as EEN for treatment of Crohn's
- Diet:
  - Avoid gluten, lactose
  - Match macronutrients, vitamins, minerals, and fiber
  - Food delivered by catering company
- Results:
  - 28 Healthy adults: similar effects on microbiome and metabolome
  - 5 children with Crohn's: 4 improved, 1 discontinued because of symptom exacerbation



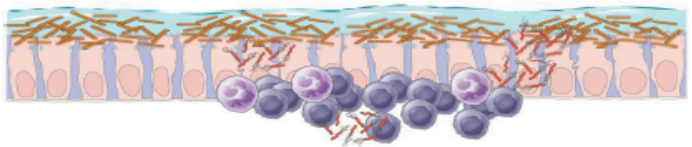
Svolos V. *Gastroenterology.* 2018.

Author	Study design	n	Summary
Two ongoing multicenter trials: 1) n-of-1 study of SCD and modified SCD (120 participants) 2) SCD vs. Mediterranean diet (194 participants)			
Suskind DL, J Clin Gastro (2018)	Prospective case series	13	Clinical + laboratory improvements; significant microbiome shifts
Braly K, J Ped Gastro Nut (2017)	Prospective diet eval	9	Nutrient intake comparable to 2012 NHANES reference group for protein, vitamins, minerals
Obih C, Nutrition (2016)	Retrospective case series	26	Improved clinical and laboratory parameters for Crohn's disease and UC
Suskind DL, Dig Dis Sci (2016)	Patient survey	417	Majority of respondents perceive clinical benefit to SCD
Burgis JC, World J Gastro (2016)	Retrospective case series	11	Improved labs, growth parameters
Kakodkar S, J Acad Nut Diet (2015)	Retrospective case series	50	SCD is effective for some adults with IBD; High quality of life reported
Suskind DL, JPGN (2014)	Retrospective case series	7	Improvement in clinical + lab parameters (Hct, CRP)
Cohen SA, JPGN (2014)	Prospective case series	16	Clinical and mucosal improvements seen

Crohn's Disease Exclusion Diet is Equally Effective but Better Tolerated than Exclusive Enteral Nutrition for Induction of Remission in Mild to Moderate Active Paediatric Crohn's Disease: A Prospective Randomized Controlled Trial

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

Western Diet



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

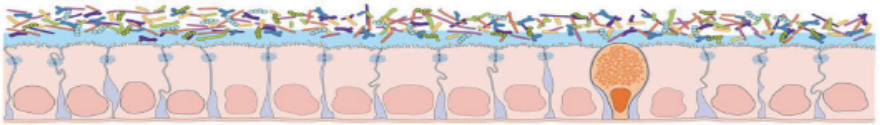
EEN

Western Diet

CDED+PEN

CDED
Remove
Animal Fat
Wheat
Dairy
Red Meat
Emulsifiers
Maltodextrin
Carrageenan

Add
Fruits
Vegetables

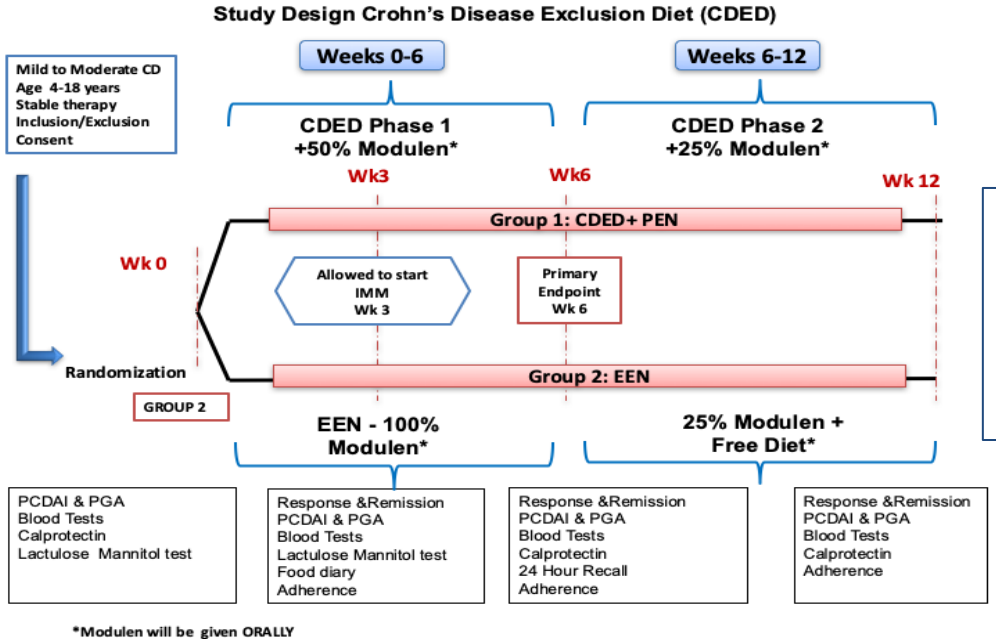


Crohn's Disease Exclusion Diet+ PEN vs. EEN
Primary endpoint: CDED+PEN is better tolerated than EEN
Secondary endpoints:
Both CDED+PEN and EEN are effective to achieve remission at week 6
CDED+PEN is superior to sustain remission and reduce inflammation at week 12
CDED+PEN: associated with reduction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

Levine *et al*. *Gastroenterology Aug 2019;157:440-50*.

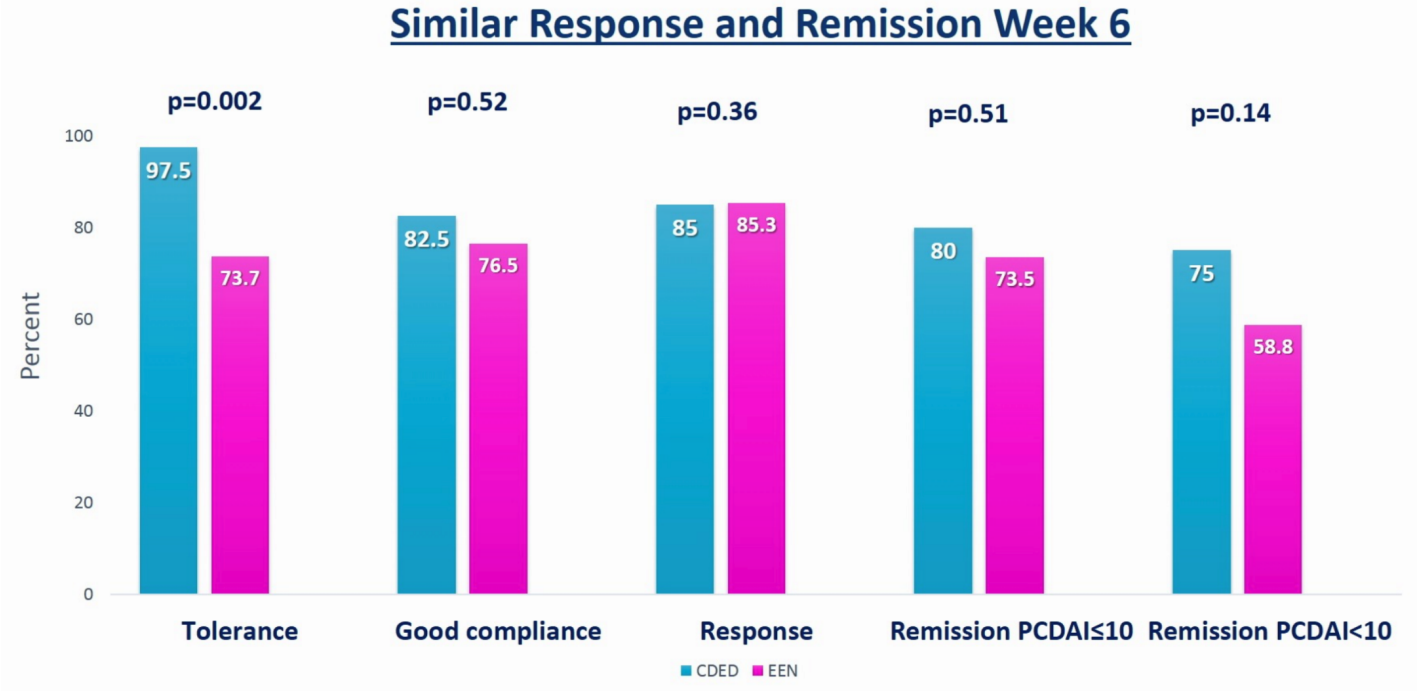
CDED Trial - RCT comparing CDED+PEN to EEN followed by PEN

78 patients mild to moderate CD , mean age 14.2±2.7 years



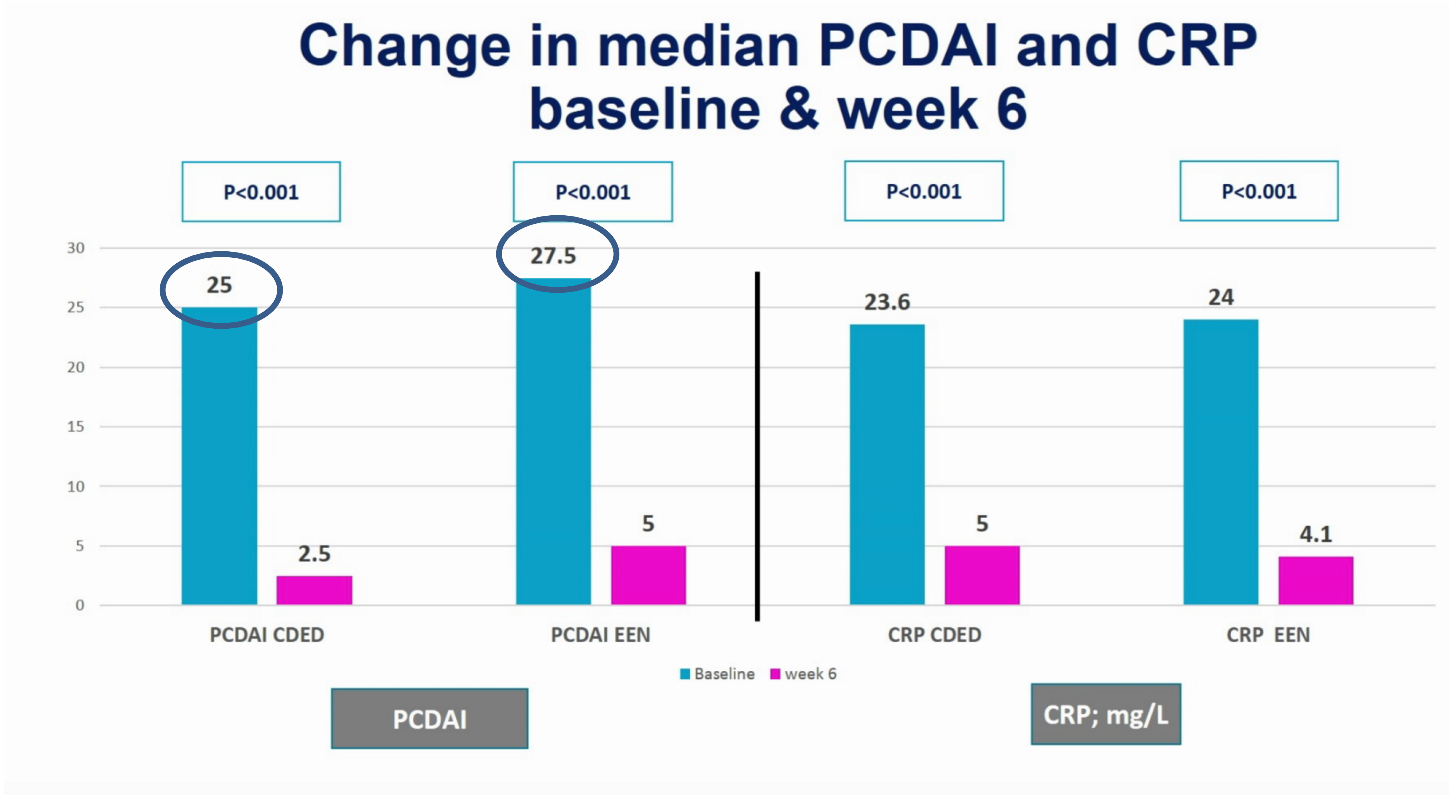
*Primary outcome = tolerance

Week 6: Comparison EEN vs CDED + PEN (50% calories from formula)



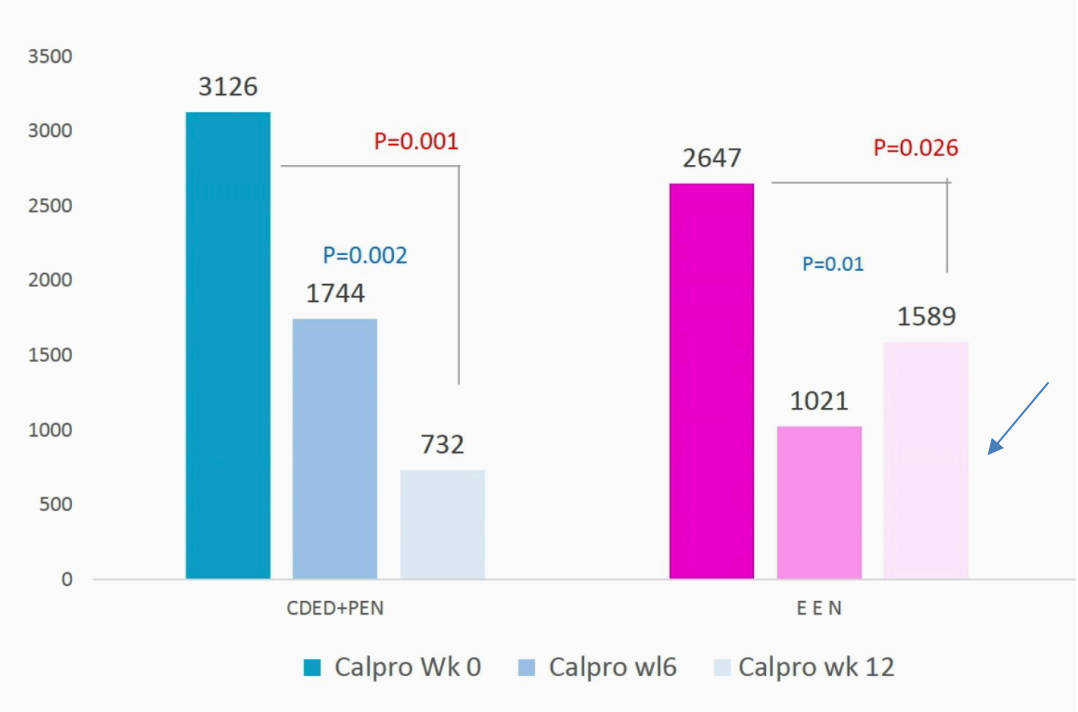
Levine A. Gastro. 2019.

Week 6 PCDAI and CRP



Levine A, Gastro. 2019.

Median FCP weeks 6 and 12



Rebound at week 12 in EEN group with transition to 25% formula, 75% free diet

Levine A, Gastro. 2019.

CDED RCT Conclusions

- Large (relatively)! And randomized, controlled!
- Not powered to be an efficacy trial but as good (? better) than EEN for induction of remission
- Mild disease cohort with short disease duration (<36 mos)
- No mucosal healing endpoint, but significant reduction in FCP
- Long term outcomes unknown
  - Will patients achieve mucosal healing with diet alone by 6 months?
  - Is the diet sustainable long term?
- Is the formula required? Which formula?

Conclusion

- Exclusive enteral nutrition (EEN) is effective therapy for Crohn's
- Restriction diets involving regular food have shown promise
- There are limitations to the clinical data for dietary therapy in IBD. *This should not necessarily be a deterrent.*
  - Shared decision making and following objective outcomes closely are critical
  - Consider dietary therapy "a drug"
    - I expect the same compliance with therapy and with monitoring and willingness to move on if therapy not working
    - ? Increased monitoring
- Further studies on dietary therapy needed, particularly those that address mechanism