



NASPGHAN
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Why Do We Need Dietary Therapy in Crohn's Disease in an Era of Biologics? Part 1

Program Director: Robert N. Baldassano, MD
Colman Professor of Pediatrics, Children's Hospital of Philadelphia

Why Do We Need Nutrition Therapies for IBD?
Dr. Lindsey Albenberg, Children's Hospital of Philadelphia

Targets for Dietary Intervention: Development of the Crohn's Disease Exclusion Diet
Dr. Arie Levine, Wolfson Medical Center, Israel

NNI Nestlé
Nutrition
Institute



Learning Objectives:

Part 1


✓ Recognize the importance of dietary therapy as a part of the therapeutic arsenal in Crohn's disease management

✓ Gain a deeper understanding of the role of diet in the pathogenesis of Crohn's disease

Part 2

Describe the principles of a novel dietary approach to the induction of remission of Crohn's disease

Describe clinical data on a novel exclusion diet for induction of remission of Crohn's disease.



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Why Do We Need Dietary Therapies for IBD?

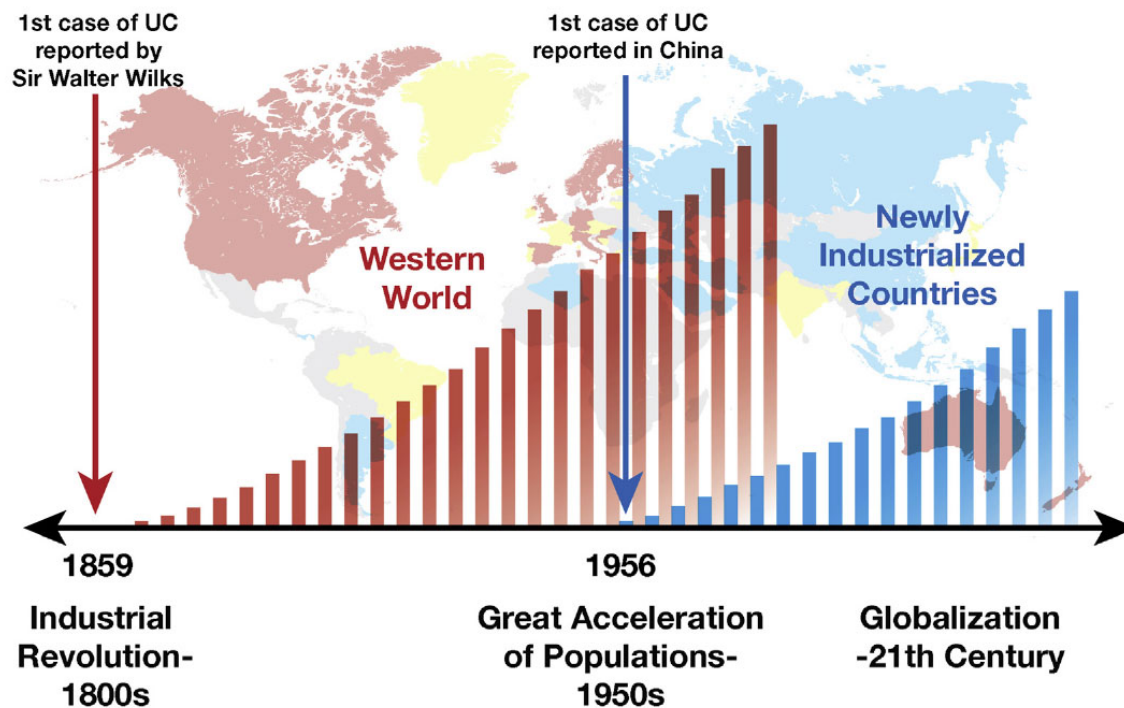
Lindsey Albenberg, DO

Center for Pediatric Inflammatory Bowel Disease

Assistant Professor of Pediatrics

Division of Gastroenterology, Hepatology, and Nutrition

The IBD epidemic



- Incidence of IBD rose steadily in the 20th century in the Western world
- IBD was relatively rare in developing nations
- Over the past few decades, newly industrialized countries have documented the emergence of IBD

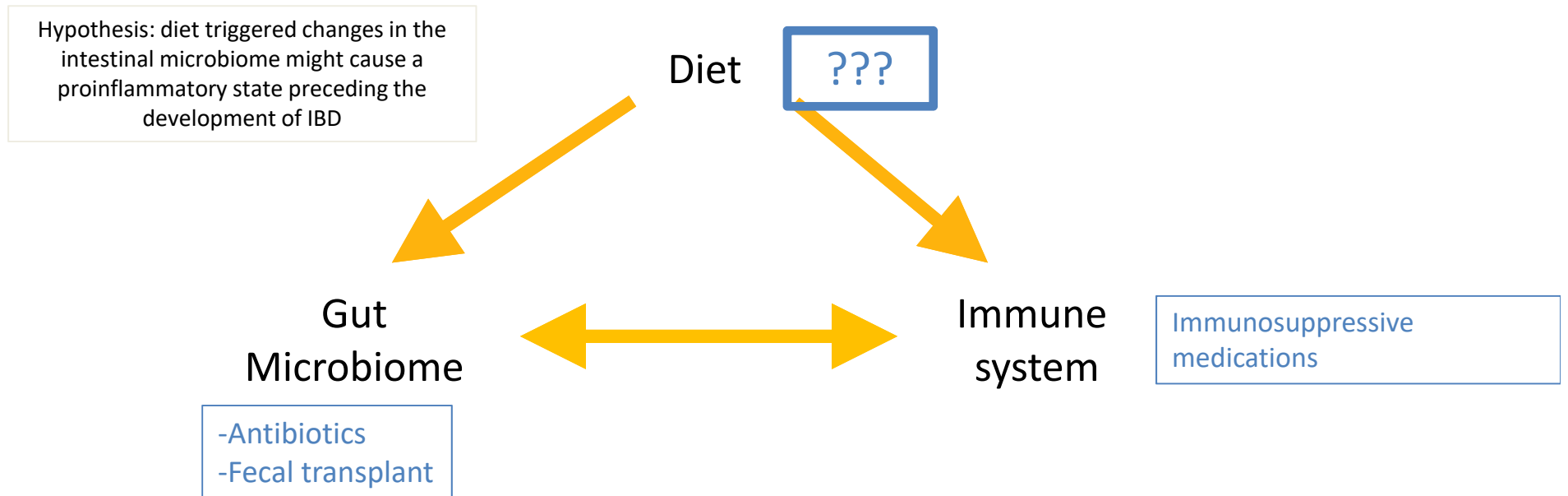
Global Burden of IBD: Prediction in 2025

- IBD is a global disease
- ~5 million affected worldwide
- Prevalence in the Western World 0.5%
- Rate in the rise of incidence is steep in

newly industrialized countries and in adolescents in industrialized countries

- The number of patients with IBD in newly industrialized countries might approximate that in the Western world by 2025 owing to rising prevalence and rapidly growing populations

Targets in IBD Pathogenesis



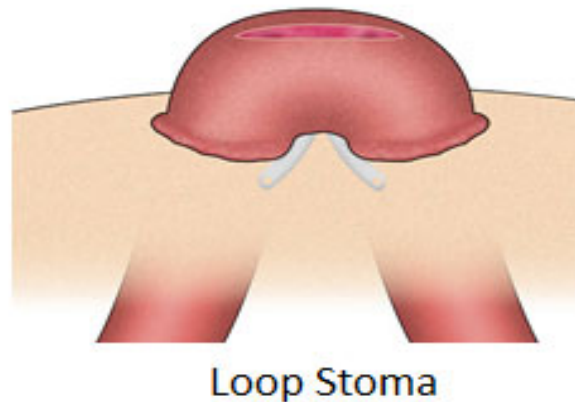
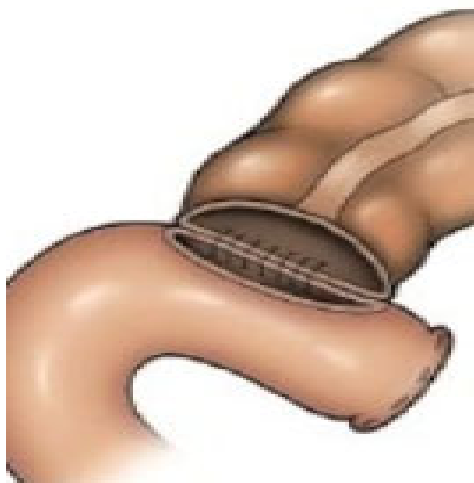
Why Do We Need Dietary Therapies for IBD?

- Science tells us that something in the lumen of the gut is driving inflammation
- Our patients want to know what they should eat and the information on the internet is not consistent and not evidence based
 - Our patients are already changing their diets
- Even our best therapies are not effective in all patients and they are associated with risks

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Crohn's Disease Surgery: An Experimental Model



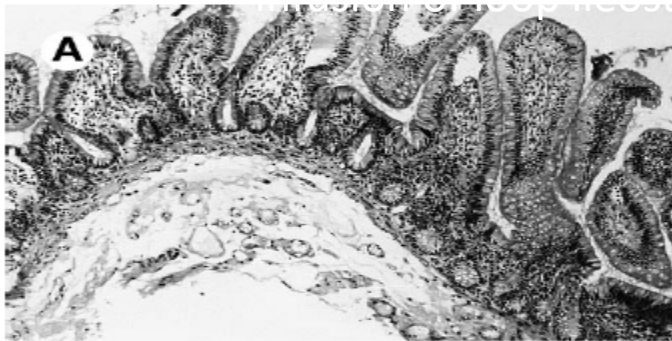
- We have known for 20 years that diversion of the fecal stream is a treatment for some patients with CD

D'Haens GR, et al. *Gastroenterology*. 1998;114(2):262-267.

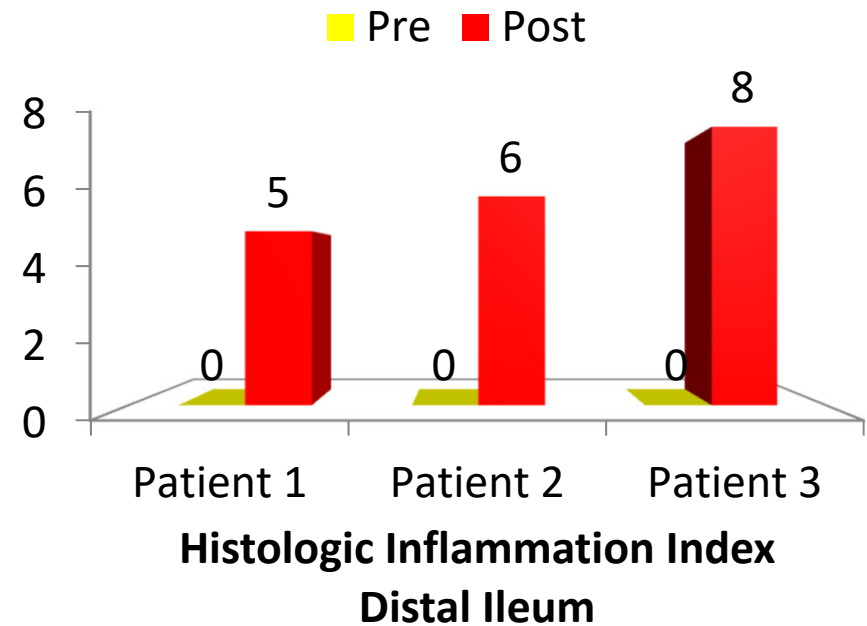
Fecal Diversion Heals Ileal Mucosa

Exposure to Ileal Contents Lead to Inflammation

Prior to
infusion of
ileal
contents



Following
infusion of
ileal
contents



The Effect of Early-Life Environmental Exposures on Disease Phenotype and Clinical Course of Crohn's Disease in Children

Livia Lindoso, MD¹, Kajari Mondal, PhD¹, Suresh Venkateswaran, PhD¹, Hari K. Somineni, MS¹, Cortney Ballengee, MD¹, Thomas D. Walters, MD², Anne Griffiths, MD², Joshua D. Noe, MD³, Wallace Crandall, MD⁴, Scott Snapper, MD, PhD⁵, Shervin Rabizadeh, MD⁶, Joel R. Rosh, MD⁷, Neal LeLeiko, MD, PhD⁸, Stephen Guthery, MD⁹, David Mack, MD¹⁰, Richard Kellermayer, MD, PhD¹¹, Ajay S. Gulati, MD¹², Marian D. Pfefferkorn, MD¹³, Dedrick E. Moulton, MD¹⁴, David Keljo, MD, PhD¹⁵, Stanley Cohen, MD¹⁶, Maria Oliva-Hemker, MD¹⁷, Melvin B. Heyman, MD¹⁸, Anthony Otley, MD¹⁹, Susan S. Baker, MD, PhD²⁰, Jonathan S. Evans, MD²¹, Barbara S. Kirschner, MD²², Ashish S. Patel, MD²³, David Ziring, MD⁶, Michael C. Stephens, MD²⁴, Robert Baldassano, MD²⁵, Marla C. Dubinsky, MD²⁶, James Markowitz, MD²⁷, Lee A. Denson, MD²⁸, Jeffrey Hyams, MD²⁹, Subra Kugathasan, MD^{1,16} and Ashwin N. Ananthakrishnan, MD, MPH³⁰

Breastfeeding	OR (95% CI)
Strictures of penetrating complications	0.65 (0.44 – 0.96)

Lindoso L. Am J Gastroenterol 2018
<https://doi.org/10.1038/s41395-018-0239-9>

Diet is Associated with New Onset IBD

- High dietary intakes of total fats, PUFAs, omega-6 and meat were associated with an increased risk of CD and UC
- High fiber and fruit intakes were associated with decreased CD risk
- High vegetable intake was associated with decreased UC risk.

Hou JK et al. American Journal of Gastro 2011;106:563-73.

High School Diet and Risk of Crohn's disease

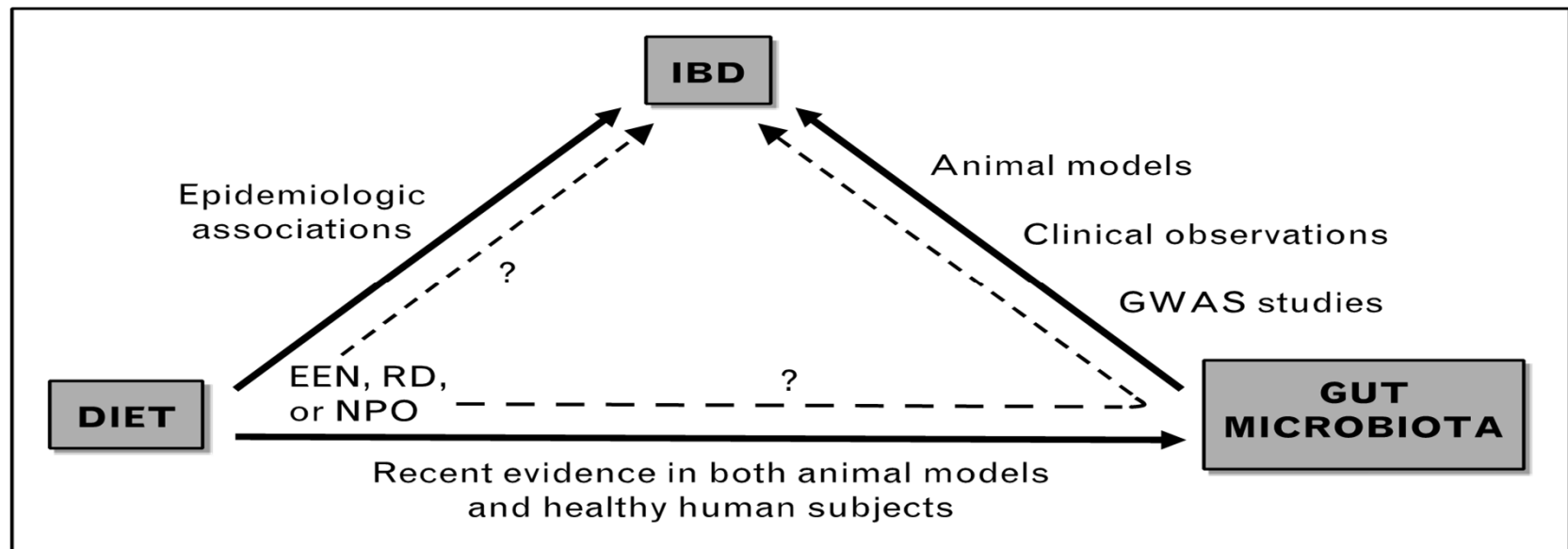
Risk of IBD may also be modified by intake in early childhood and adolescence

Food group	Adjusted HR Q5 vs. Q1	Adjusted p(trend)
Fiber	0.48 (0.22 – 1.05)	0.047
Animal Fat	1.38 (0.58 – 3.32)	0.08
Heme-Iron	1.81 (0.87 – 3.77)	0.058
Fish	0.45 (0.20 – 0.98)	0.027
Vegetables	0.44 (0.20 – 0.96)	0.097

What Can We Learn From Epidemiologic Data?

- What and when you eat potentially influences your risk of developing IBD
- Earlier exposure may be more important than dietary changes later in life for purpose of prevention of disease

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



Something “Bad” in the Diet and the Gut Microbiome?

LETTER

doi:10.1038/nature14232

Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome

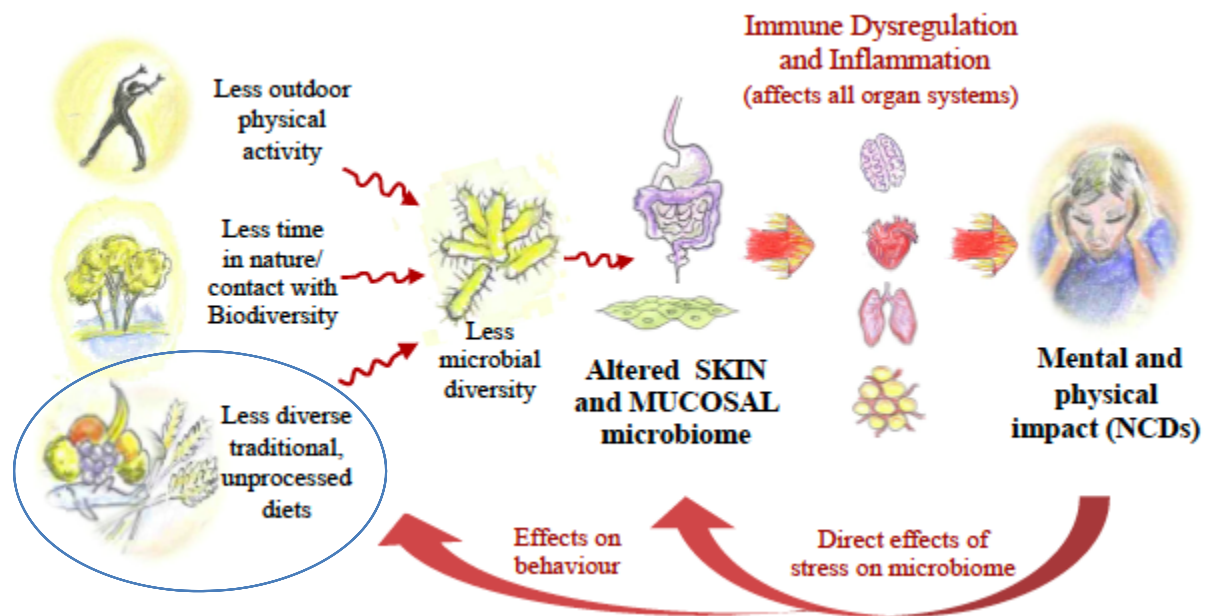
Benoit Chassaing¹, Omry Koren², Julia K. Goodrich¹, Angela C. Poole¹, Shanthi Srinivasan¹, Ruth E. Ley³ & Andrew T. Gewirtz¹

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem^{2*}, David Zeevi^{2*}, Gili Zilberman-Schapira^{1*}, Christoph A. Thaiss¹, Ori Maza¹, David Israeli¹, Niv Zmora^{1,2,3,4,5,6}, Shlomit Gilad⁷, Adina Weinberger², Yael Kuperman⁸, Alon Harmelin⁹, Ilana Kolodkin-Gal¹⁰, Hagit Shapero¹, Zohar Halperin¹⁰, Eran Segal² & Eran Elinav¹



Renz et al. J Allergy Clin Immunol. 2017.

Why Do We Need Dietary Therapies for IBD?

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Patient-reported foods that improve / worsen symptoms

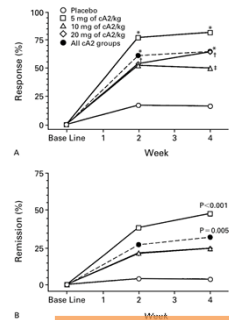
Food Items	CD (n=1121) (B, W)	UC (n=597) (B, W)	CD-O (n=405) (B, W)	UC-P (n=206) (B, W)
Improved Symptoms				
Yogurt	108, 7*	54, 3*	26, 0*	19, 0*
Rice	59, 3*	30, 3*	20, 3†	16, 0*
Bananas	NR	NR	NR	14, 0*
Worsened Symptoms				
Non-Leafy Vegetables	28, 221*	29, 81*	7, 90*	3, 36*
Spicy Foods	1, 145*	3, 79*	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.* 2013. 19

Why Do We Need Dietary Therapies for IBD?

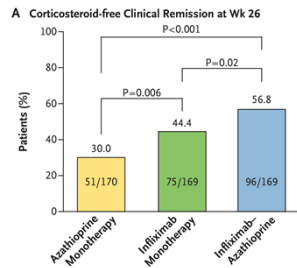
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- Even our best therapies are not effective in all patients and they are associated with risks
 - Patients with IBD diagnosed in childhood have years of disease and exposures

Biologic and small molecule therapies in the last 2 decades

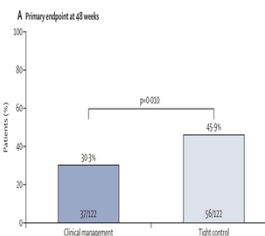


Infliximab

Targan et al, NEJM 1997

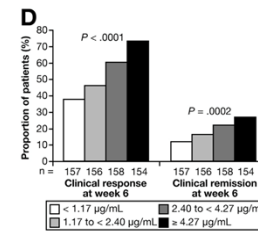


SONIC
Colombel et al, NEJM 2010



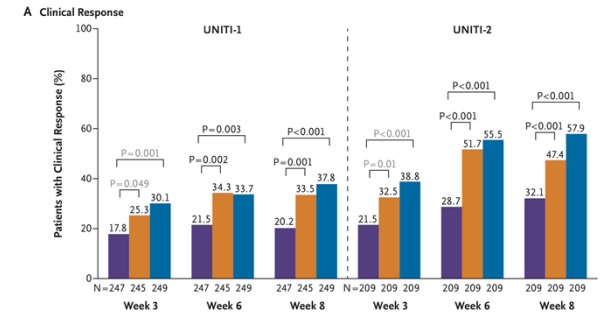
Adalimumab

CALM
Colombel et al, Lancet 2018



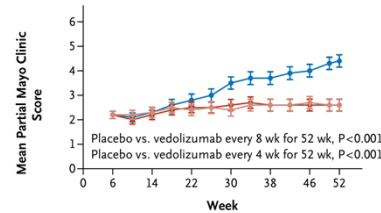
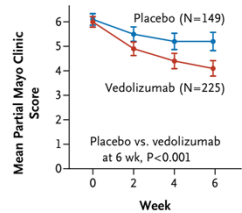
Golimumab

PURSUIT
Sandborn et al, Gastro 2014



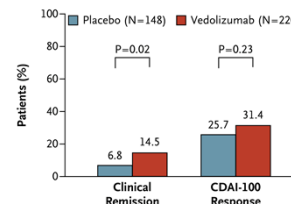
Ustekinumab

UNITI
Feagan et al, NEJM 2016

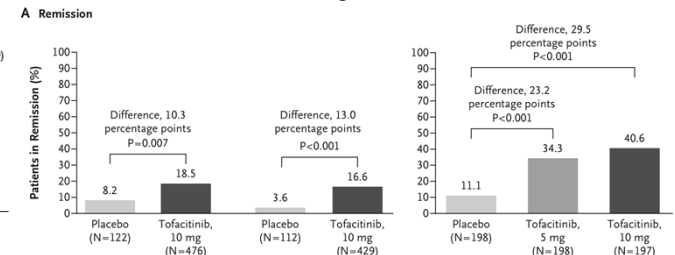


Vedolizumab

GEMINI
Feagan et al, NEJM 2013



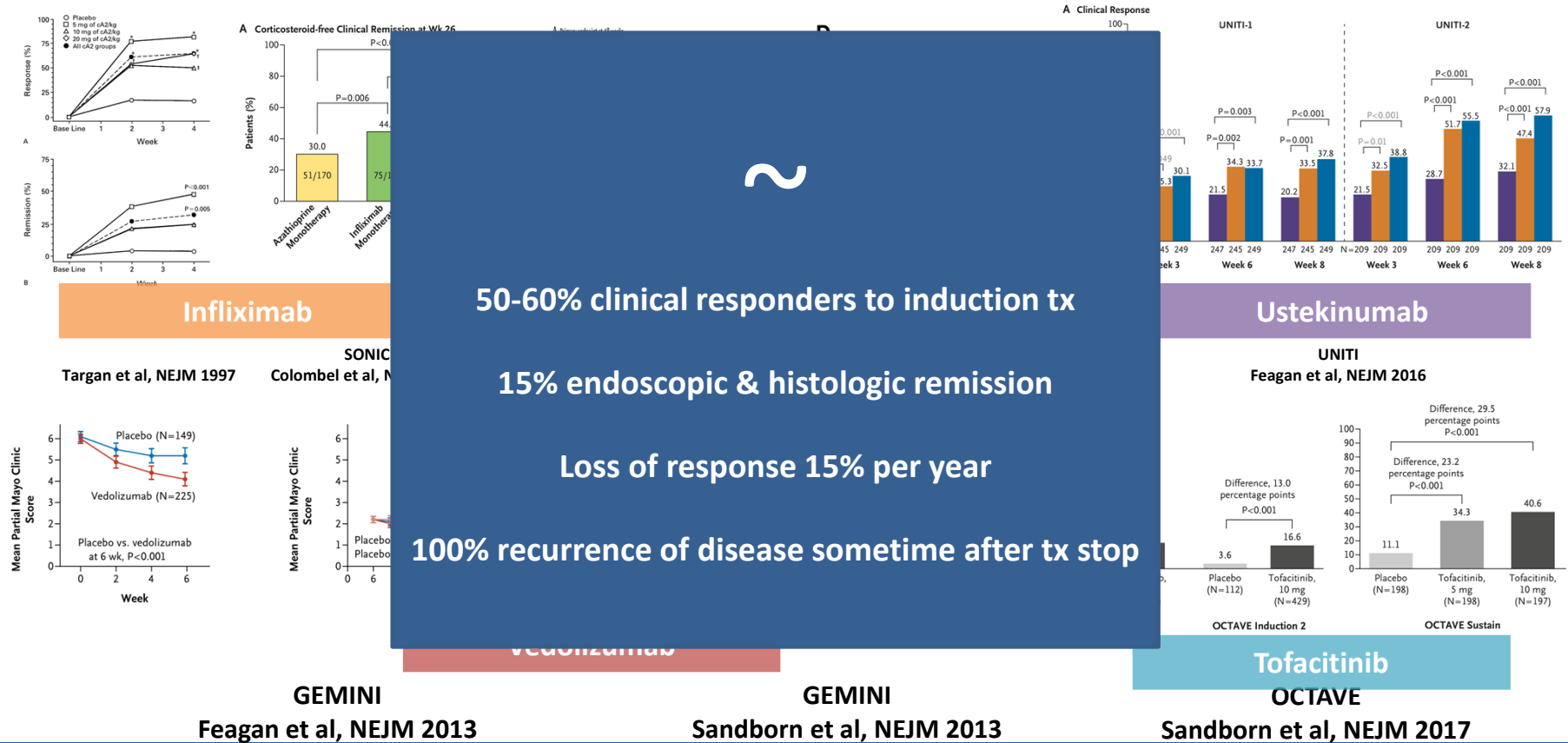
GEMINI
Sandborn et al, NEJM 2013



Tofacitinib

OCTAVE
Sandborn et al, NEJM 2017

Biologic and small molecule therapies in the last 2 decades

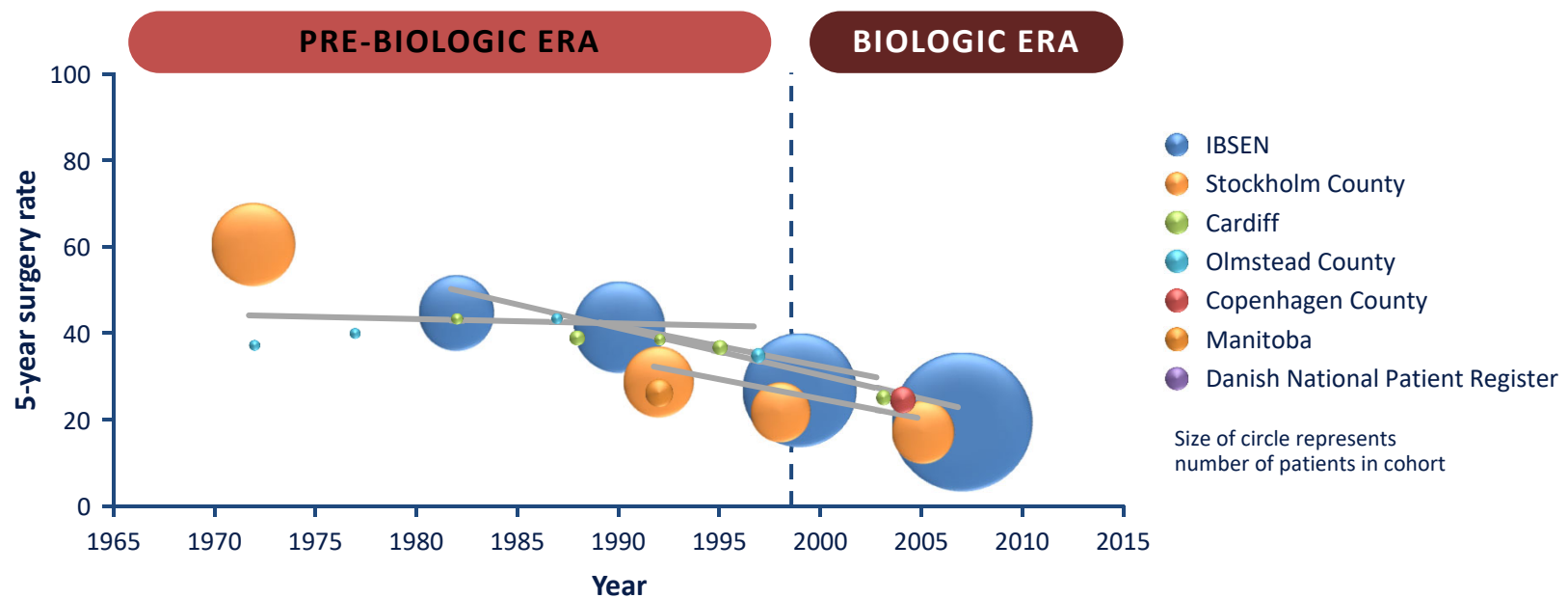


Biologic Remission Rates – Pediatric IBD

Trial name	N	Trial design	Drug	Results
REACH (CD)	112	RCT	Infliximab 5 mg/kg maintenance (8 weeks vs. 12 weeks) after open label induction	PCDAI ≤ 10 Week 8: 55.8% Week 12: 23.5%
Imagine1 (CD)	192 (188 prior exposure to IFX)	RCT	Adalimumab maintenance High dose (40mg/20mg for bw ≥ 40 kg or < 40 kg, n=93) versus Low dose (20mg/10mg for bw ≥ 40 kg or < 40 kg, n=95)	PCDAI ≤ 10 High dose: 39% (26 wks) 33% (52 wks) Low dose: 28% (26 wks) 23% (52 wks)
T72 study group (UC)	60	RCT	Infliximab 5 mg/kg Clinical response at week 8. Comparison of interval maintenance (8 vs 12 weeks) Responders (45/60, 73.3%) randomized at week 8 (open label induction)	Mayo score ≤ 2 with no individual subscore > 1 and PUCAI < 10 8 weeks : 38.1% 12 weeks : 18.2%

Reduction in surgical rates in Crohn's disease in the biologic era

Surgical trends in CD population-based studies



Can treating to target further decrease the number of surgeries?

Safety concerns...

Table 3. Absolute Risk of Cancer in Patients With IBD, and Adjusted Ratio of Cancer in Patients With IBD Exposed to Thiopurines and/or Anti-TNF Agents, Compared With Patients Not Exposed to Immunosuppressive Drugs

	Incidence rate (cases per 1000 person-years) in total IBD population	Adjusted RR (95% CI), HR (95% CI), or OR (95% CI) in patients with IBD exposed to immunosuppressive therapy versus those not exposed to immunosuppressive therapy		
		Thiopurines alone	Anti-TNF agents alone	Thiopurines in combination with anti-TNF agents
All cancers, excluding nonmelanocytic skin cancers	7.3 ^a	RR, 1.4 (1.2–1.7) ^b	RR, 1.1 (0.9–1.4) ^a	ND
Hematologic malignancies				
All	0.5 ^a	ND	RR, 0.9 (0.4–1.9) ^a	ND
Lymphoma ^b	0.3 ^c	HR, 2.6 (2.0–3.4) ^c	HR, 2.4 (1.6–3.6) ^c	HR, 6.1 (1.3–4.2) ^c
Skin cancers				
Nonmelanocytic Skin cancer	9.1 ^d	OR, 1.9 (1.7–2.1) ^d	OR, 1.1 (0.9–1.4) ^d	ND
Melanoma	0.4 ^a	OR, 1.1 (0.7–1.7) ^d	OR, 1.9 (1.1–3.3) ^d	ND
Urinary tract cancer ^e	0.3 ^a	HR, 2.8 (1.0–7.7) ^e	RR, 1.6 (0.6–4.2) ^a	ND

Safety concerns...

Table 3. Absolute
Thiopurine

All cancers, excluding
nonmelanocytic
skin cancers
Hematologic malignancies
All
Lymphoma^b
Skin cancers
Nonmelanocytic
Melanoma
Urinary tract cancers

- Patients with IBD exposed to thiopurines exhibit an increased risk of cancers.
 - Young patients, particularly males, are at risk of postmononucleosis lymphomas and hepatosplenic T-cell lymphomas.
- Patients with IBD exposed to thiopurines exhibit an increased risk of nonmelanocytic skin cancers
- Patients exposed to anti-TNF agents are at increased risk of melanoma.
- Whether patients treated with anti-TNF agents alone exhibit an excess risk of lymphoma remains controversial.

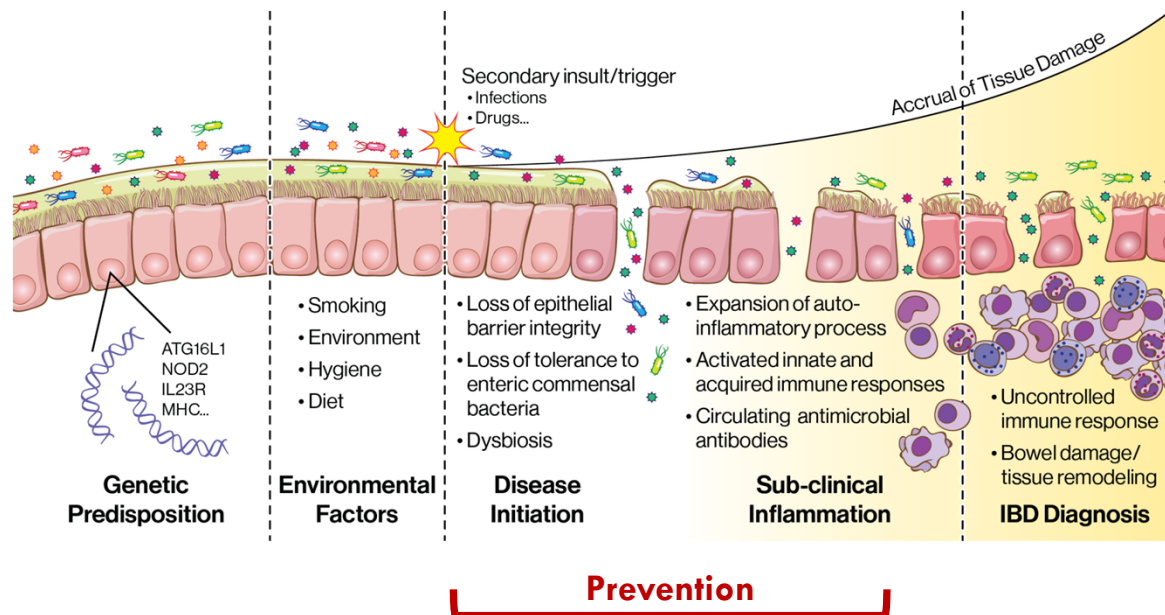
to

patients
us those

combination
agents

.2)^c

Intervening during the pre-clinical phase : road to prevention



Why do we need nutrition therapy in IBD?

- **Because it makes sense !**
- **Medications have limited efficacy**
- **Medications are not a cure !**
- **Safety concerns**
- **Children with IBD have a lifetime of treatment ahead of them**



Targets For Dietary Intervention: Development of the Crohns Disease Exclusion Diet

Arie Levine MD

Wolfson Medical Center

Holon

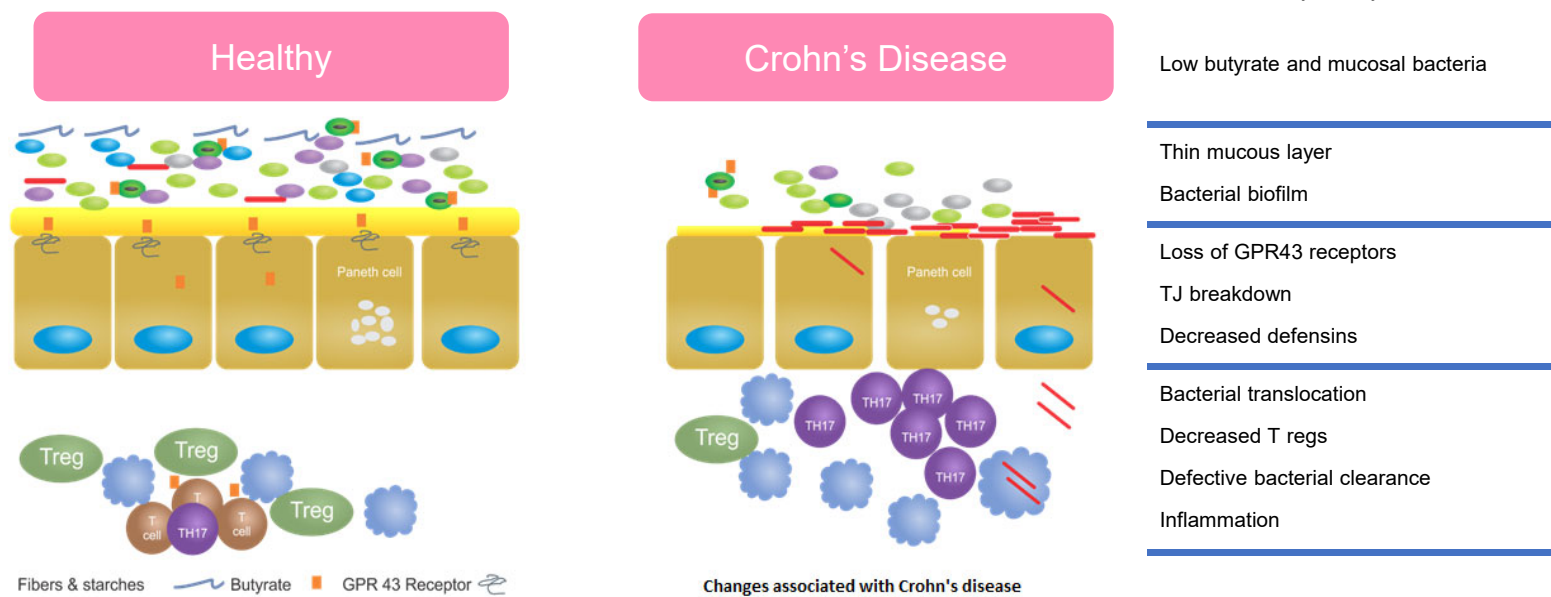
Tel Aviv University

Israel

Disclosures COI last 3 years

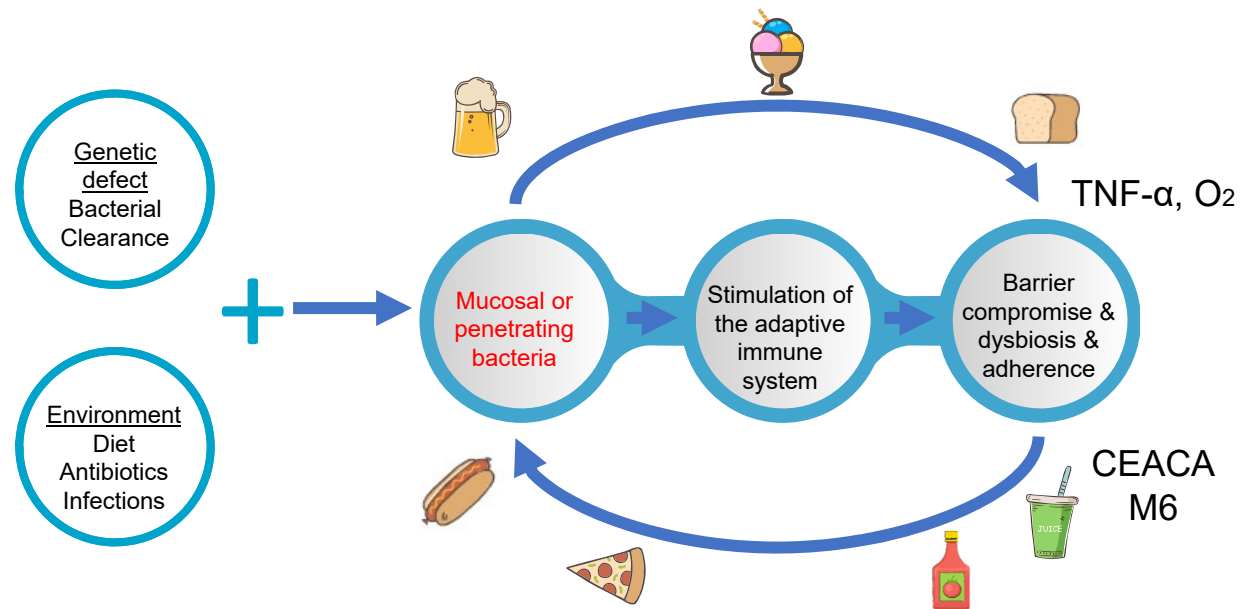
- Grants, Speaker fees, consulting , DSMB and advisory boards , :
- Nestlé Health Science (Grants, consulting , IP)
- Abbvie
- Celgene
- Takeda
- Ferring

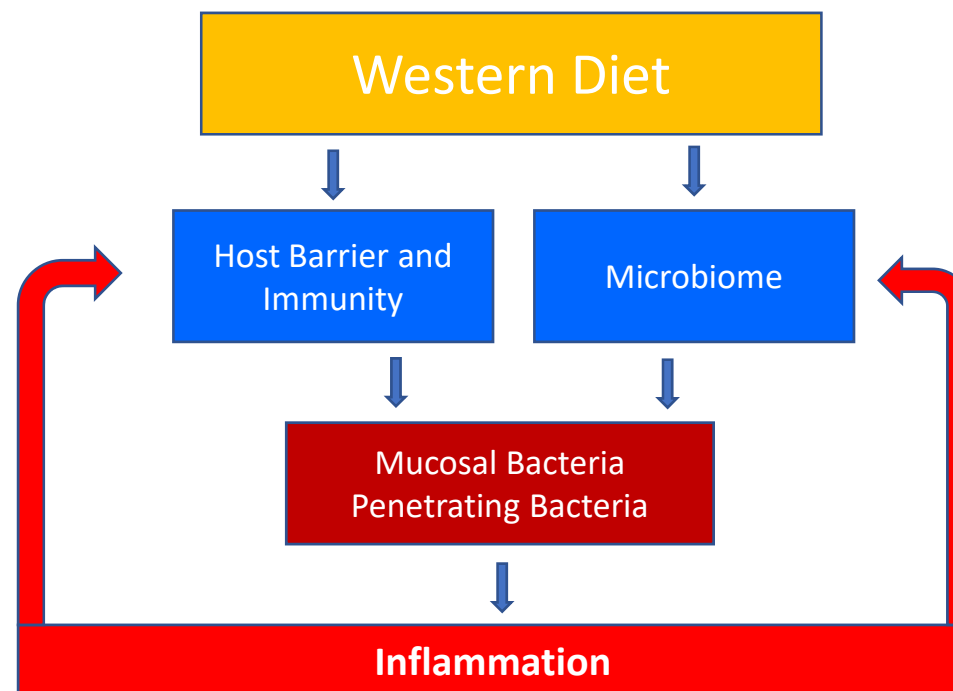
THE UPSTREAM EFFECTS OF MICROBIOTA AND ROLE IN INFLAMMATION



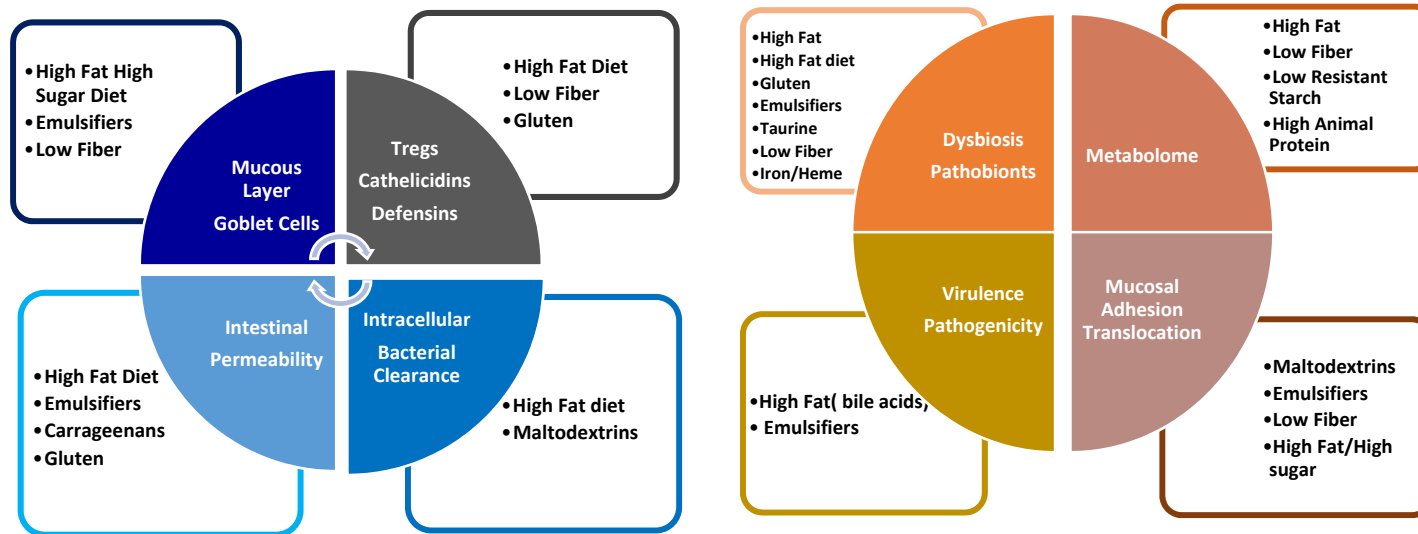
Levine, Sigall-Boneh, Wine. *Gut*. 2018.

INTERRUPTING THE BACTERIAL PENETRATION CYCLE





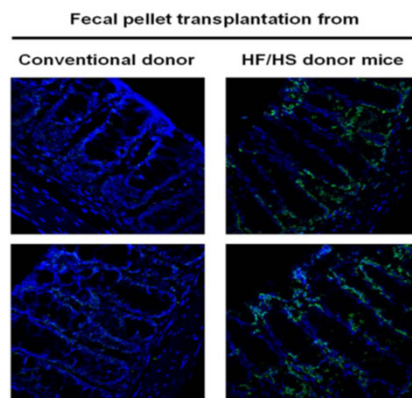
Diet Host and Microbiome



Levine, Sigall Boneh, Wine. Gut 2018

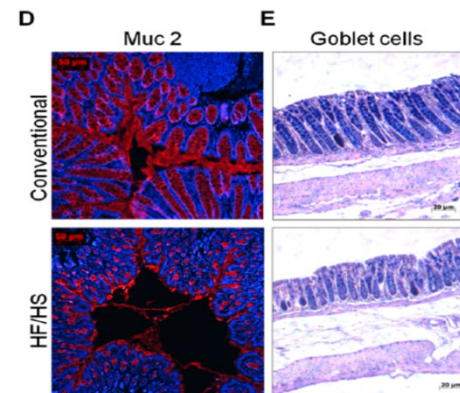
High Fat High Sugar Diet CEABAC 10 Model

Mucosal Proximity AIEC HF/HS



Agus et al. Nature
Science Reports 2016

Muc 2 and Mucous decreased HF/HS



Martinez Medina Gut
2013

IMPLICATIONS OF HIGH FAT-HIGH SUGAR OR HIGH FAT DIET

High Fat-High Sugar Diet

- Decreases mRNA level of *Muc2* gene in colonic mucosa¹
- Increases intestinal permeability¹
- Increases mucosal *A/EC* colonization²
- Increases mucosa-associated *E. coli*²

High Fat Diet

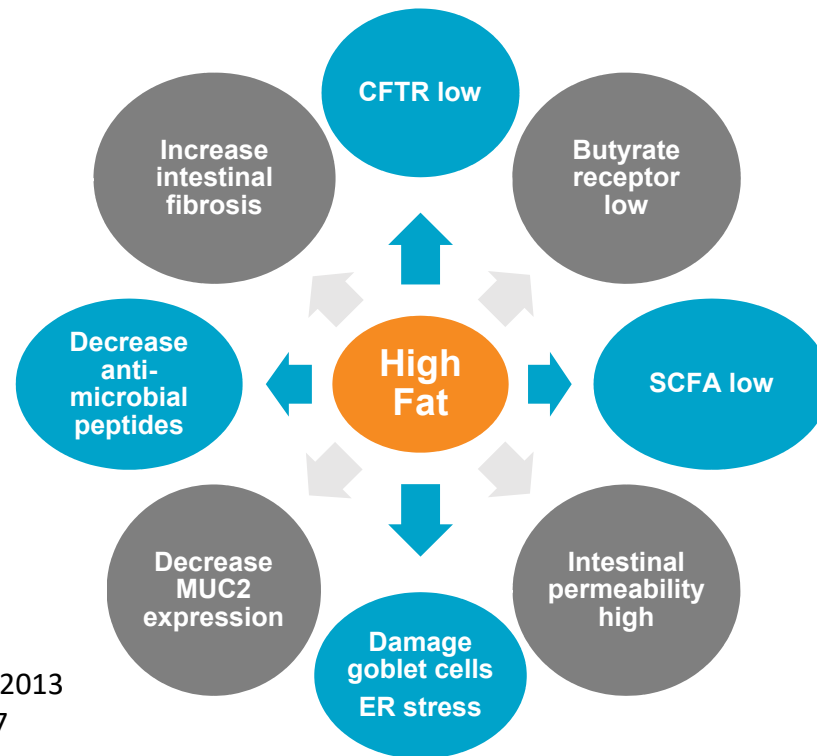
- Decreases accumulation of *Muc2* in goblet cells of ileum³
- Increases intestinal permeability¹
- Increases mucosal bacteria
Increase in *Proteobacteria* 3.5% to 17.5% in the cecal and fecal microbiota³

Martinez-Medina et al. Gut. 2014

Agus et al. Sci Rep. 2016

Tomas et al. PNAS. 2016

HIGH FAT DIET, HOST BARRIER AND IMMUNITY



Tomas et al. PNAS. 2016

Agus et al. Sci Rep. 2016

Chaissaing et al. Env Microbiology. 2013

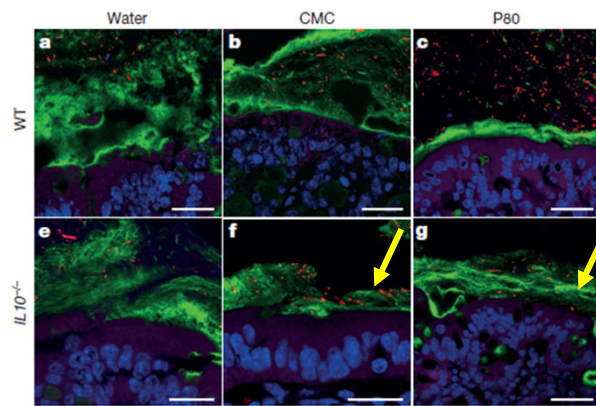
Guo et al. Mediators Inflamm. 2017

Gulhane et al. Sci Rep. 2018

ECCO 2018. <https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2018/item/op018-high-fat-diet-and-inflammation-drive-intestinal-fibrosis-enhancing-epithelial-x2013-mesenchymal-transition-through-the-activation-of-s1p3-signalling.html>.

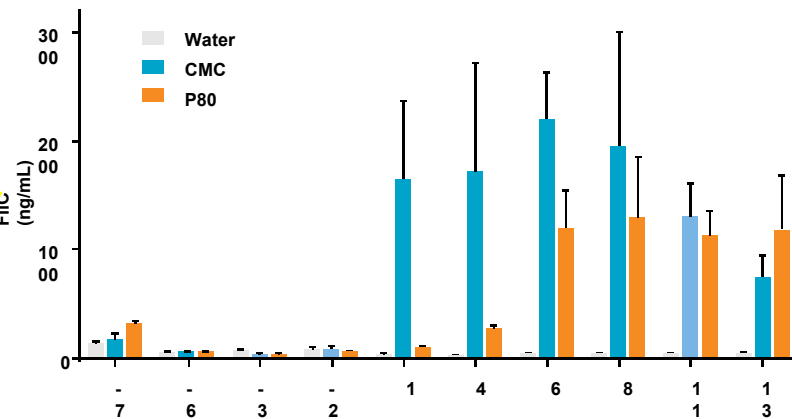
EMULSIFIERS ALTER MICROBIOTA COMPOSITION IN PRE-CLINICAL MODELS

Fig 1: Dietary emulsifiers alter microbiota



Adapted from Chassaing et al, 2017

Fig 2: Emulsifiers increase flagellin levels



Emulsifiers fed to mice resulted in microbiota encroachment into the mucus, altered microbiota composition, increased flagellin production and promoted bacterial translocation across mucosal surfaces

Chassaing et al. Nature. 2015.

Chassaing et al. Gut. 2017.

EFFECTS OF WHEAT IN THE DIET

Gluten

- Increases tight junction (TJ) breakdown via Zonulin
- Associated with development of ileitis in $\text{TNF}^{\Delta\text{ARE/WT}}$ Mice

α -Amylase/trypsin inhibitor (ATI)

- Increase inflammation

Wagner et al. Inflamm Bowel Dis 2013.

What to Add, What to Exclude

Host

Add

- Fiber

Reduce

- Animal Saturated Fat
- Emulsifiers
- Taurine rich protein
- Maltodextrins
- Gluten
- Carrageenan's
- Alcohol

Microbiome

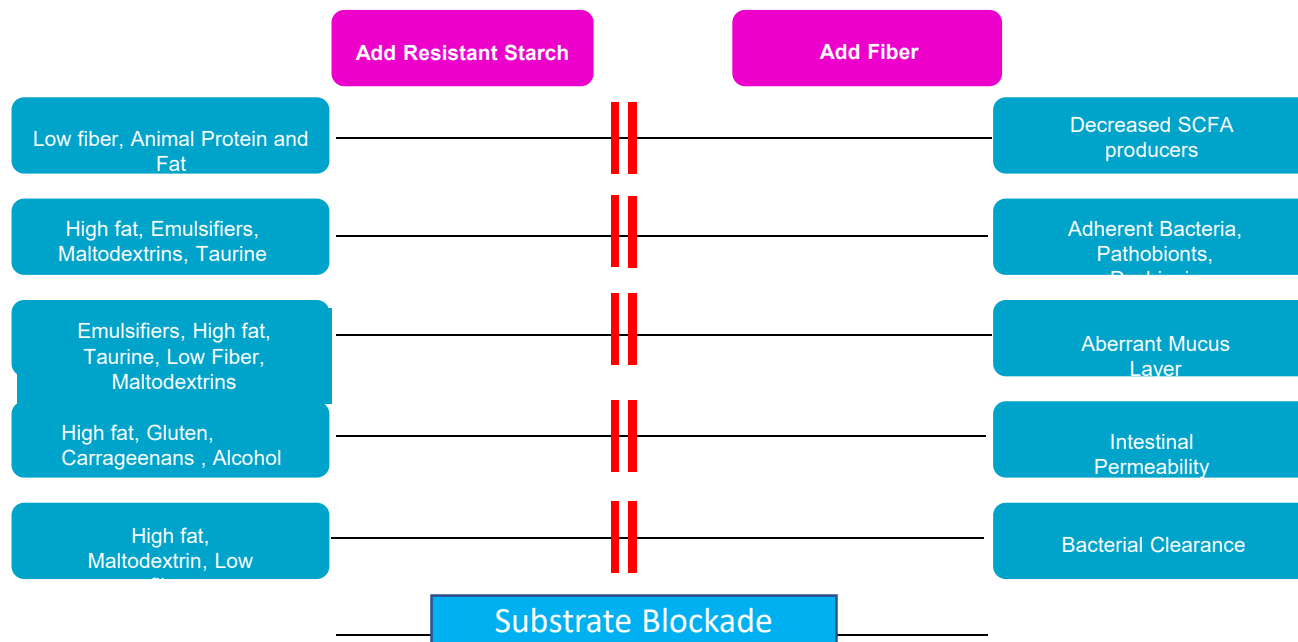
Add

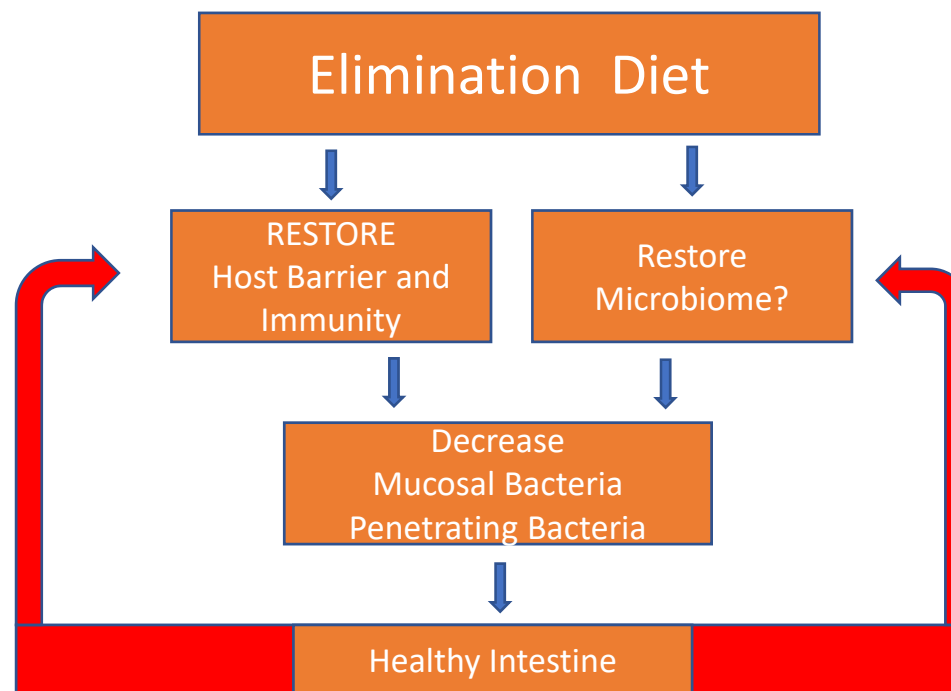
- Fiber (apple pectin, potato starch, RS)

Reduce

- Saturated +Dairy Fat
- Emulsifiers
- Taurine rich Protein
- Maltodextrins
- Heme, Iron
- Sulfites

SUBSTRATE DEPENDENT PATHWAYS for PATHOGENESIS IN CROHN'S DISEASE





Good in Theory, but Does it Work in Crohn's Disease?



Thank You

Nutrition-related resources and tools are available from Nestlé Nutrition Institute:

www.nestlenutrition-institute.org

Visit the MyCE site at

www.MyCEeducation.com

Offering CE to registered dietitians and registered nurses