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Nutritional Therapies for IBD

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Disclaimers

• Scientific advisor for Azora Therapeutics



Outline

- Does the Diet Matter?
- Bidirectional Relationship
- Enteral Nutrition
- Solid Food Diets
- Dietary Supplements



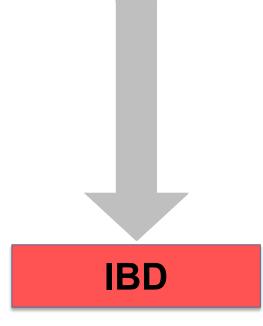
This presentation will broadly touch on major themes and is not intended to be comprehensive
 Image: Wikipedia
 A lot of research is still needed



Does the Diet Matter?

Genetics

- Over 200 risk genes
- 22% of IBD patients have family members with IBD
- 27% CD in identical twin of CD patient
- 15% UC in identical twin of UC patient



Environment

- Tobacco
- Pollution
- Medications
- Infections
- Microorganisms
- Oral contraceptives
- Dietary intake



Does the Diet Matter?

Japanese Survey

- Surveys of up to 68,000 Japanese (1966-1985)
- 242 CD patients had ↑ animal protein, ↑ omega-6, ↓ omega-3

European Prospective Investigation into Cancer

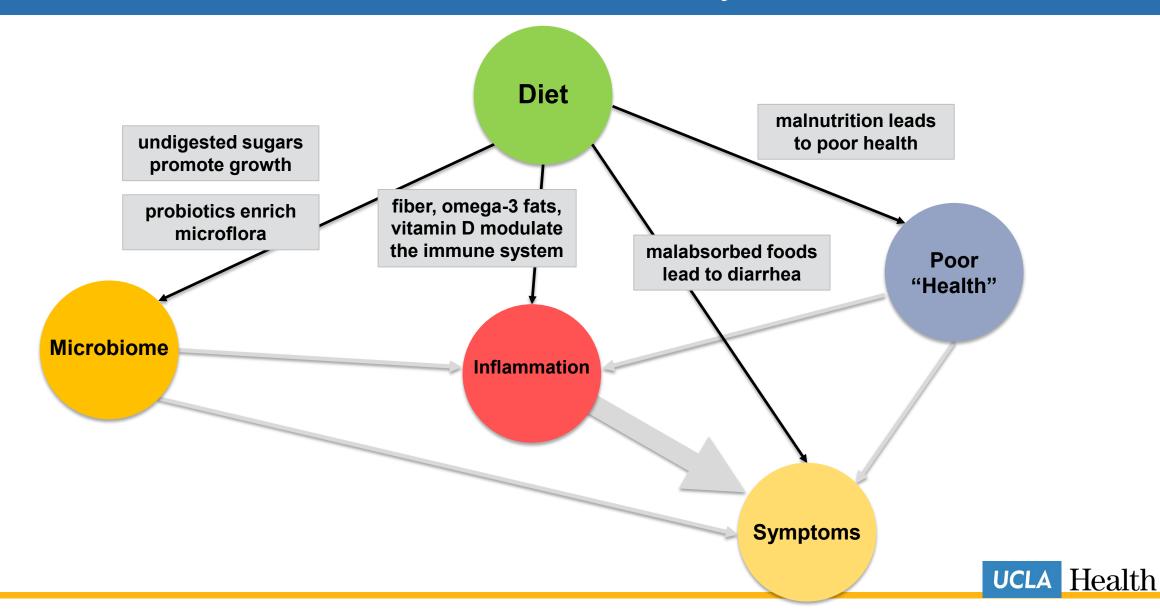
- Surveys of 203,193 Europeans (1991-1998)
- 126 UC patients had ↑ omega-6

• Nurses' Health Study

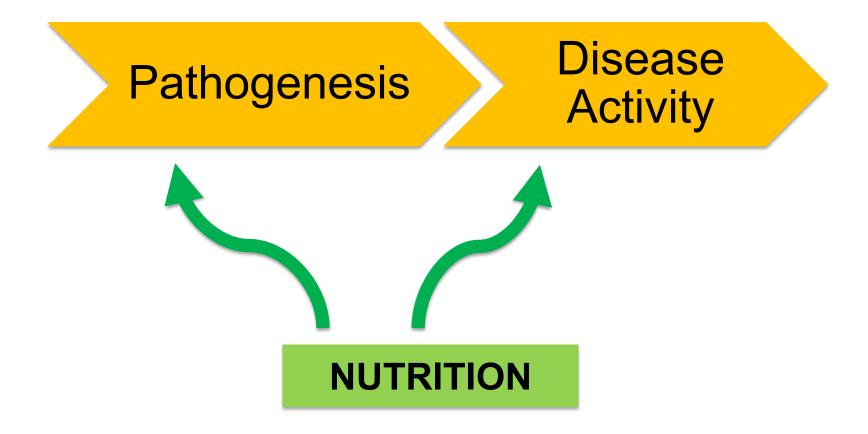
- Surveys of up to 170,000 women
- \bullet Fiber was associated with \downarrow risk of CD but not UC
- \bullet Vitamin D was associated with \downarrow risk of CD but not UC



How Does Diet Affect Disease Activity?

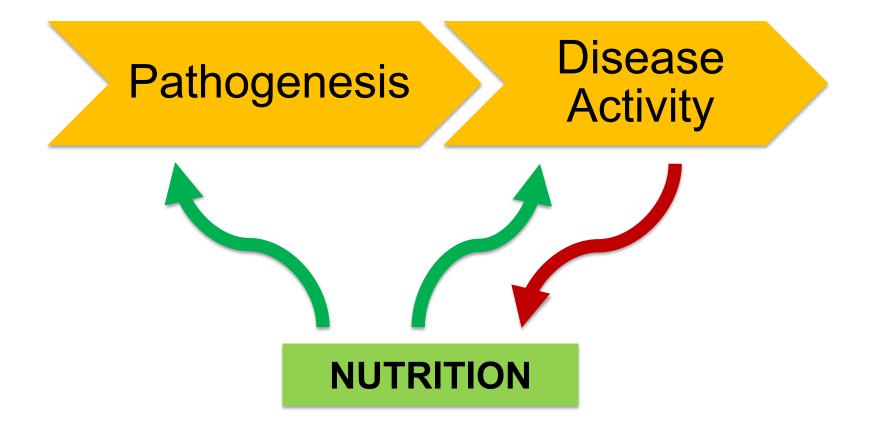


Bidirectional Relationship of Nutrition and IBD





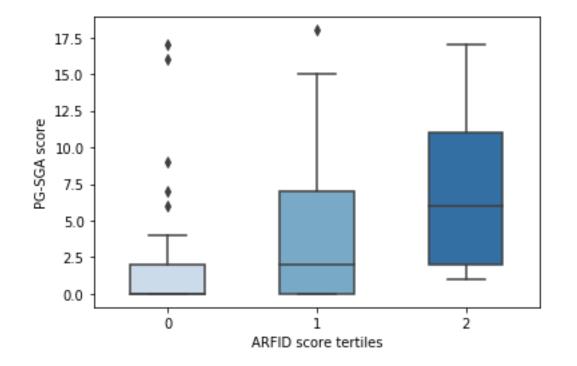
Bidirectional Relationship of Nutrition and IBD





High Risk of Restrictive Eating Behaviors

- 58% had characteristics of restrictive eating
- Most commonly reported symptoms influencing intake: pain (14%), diarrhea (12%), fatigue (12%)
- Restrictive eating patterns associated with malnutrition





What are Dietary Strategies for IBD?

Established Evidence

Enteral nutrition

Emerging Evidence

- Solid food diets
- Probiotics

Extrapolated Evidence

- Omega-3 fatty acids
- Fiber



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Enteral Nutrition

 Specialized liquid formulae that are either delivered orally or through a feeding tube

Premise

- Provides a supplementary source of calories
- Reduces intake of "pro-inflammatory" substances
- Preserves integrity of bowel
- Modulates gut immune system



Crohn's Disease

- Effective for induction and maintenance of remission in CD
- Can be used as monotherapy when corticosteroids not possible (Grade A evidence)

Ulcerative Colitis

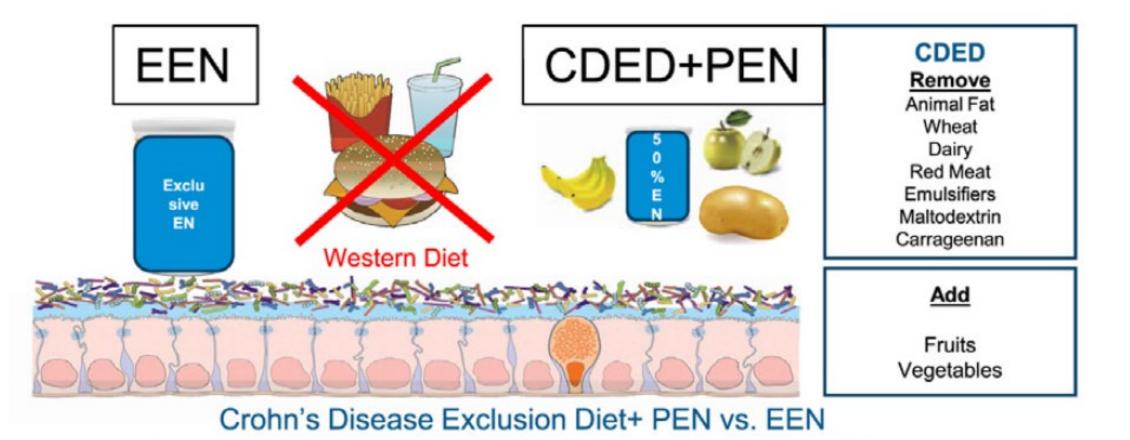
• No clear benefit

But ...

• Adherence is very challenging due to discomfort, distaste, social reasons, insurance coverage, etc.

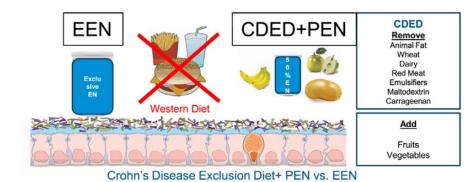


What about *Partial* Enteral Nutrition?



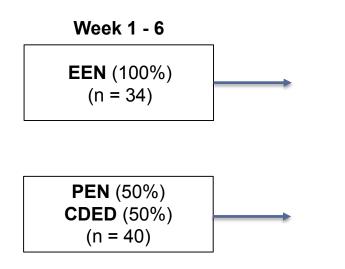
UCLA Health

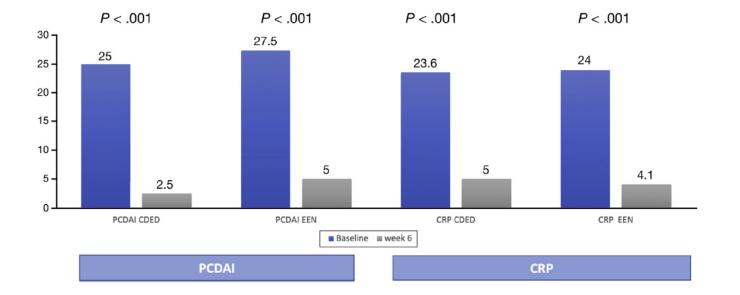
What about *Partial* Enteral Nutrition?



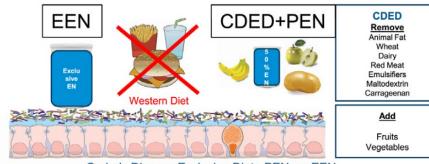
Findings

PEN and EEN improved symptoms and CRP

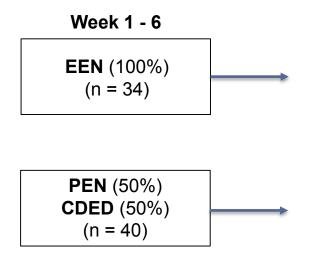




What about *Partial* Enteral Nutrition?

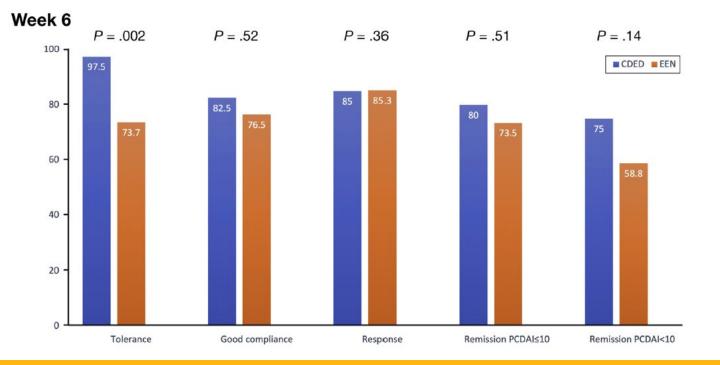


Crohn's Disease Exclusion Diet+ PEN vs. EEN



Findings

- PEN was more tolerable than EEN
- PEN ~ EEN for achieving 6-week response and remission



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

What are Dietary Strategies for IBD?

Established Evidence

Enteral nutrition

Emerging Evidence

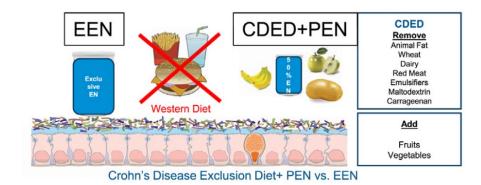
- Solid food diets
- Probiotics

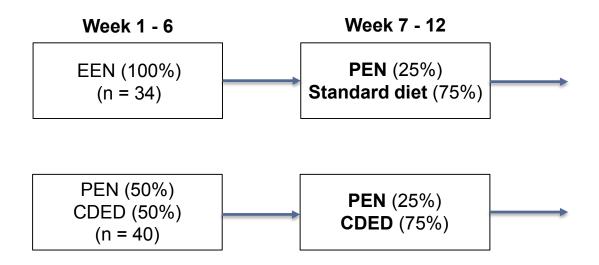
Extrapolated Evidence

- Omega-3 fatty acids
- Fiber



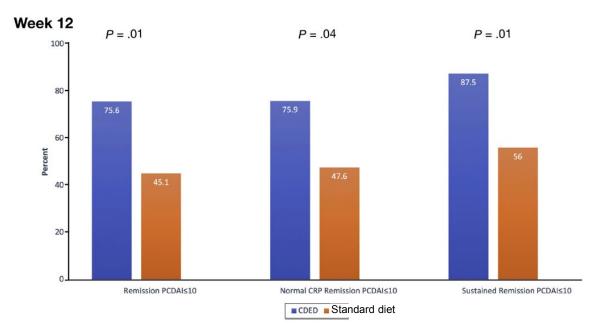
What about *Solid Food* Diets?





Findings

• CDED was superior to standard diet for sustained remission





CD Exclusion Diet

"Forbidden Foods"

Dairy products, margarine

Wheat, breakfast cereals, breads and baked goods, yeast for baking

Gluten products, soy products, potato or corn flour

Processed or smoked meats and fish

Sauces, salad dressings, syrups and jams

Canned products, dried fruits

Packaged snacks

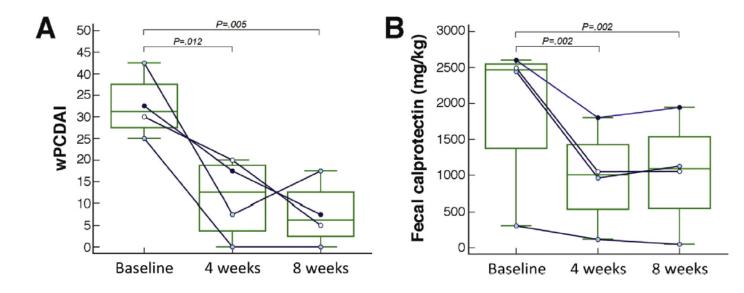
Soft drinks, fruit juices, sweetened beverages, alcoholic beverages, coffee

Candies, chocolate, cakes, cookies, and gum



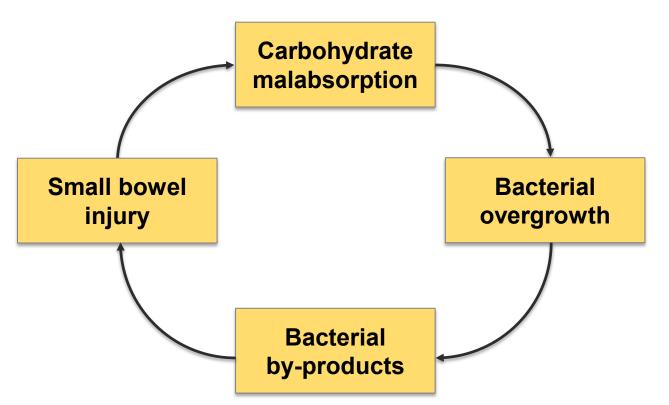
CD-TREAT Diet

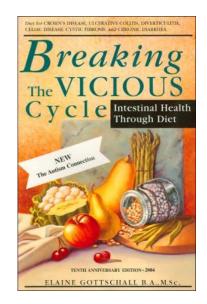
- Aim to develop solid food diet that recapitulates the microbiome changes from using exclusive enteral nutrition
- Diet components still proprietary
- Tested on 5 children with mild-to-moderate CD





- Originally developed to treat celiac disease
- Popularized by the book "Breaking the Vicious Cycle"
- Elimination of di-, oligo-, and polysaccharides







Allowed ("Legal food")	Not Allowed ("Illegal food")
All fresh meats, fish, shellfish	Packaged, deli, preserved meats
Most vegetables	Potatoes, corn, starchy vegetables. Tapioca starch, cornstarch
Most fruits	Canned fruits, Green bananas, plantains and young coconut
All fats and oils, including butter	
Cheeses (aged >30days)	Cream, ricotta, mozzarella, other soft un-aged cheeses
Lactose free yogurt	Milk, store- bought yogurt
Honey	All other sweeteners (cane sugar, artificial sweeteners, agave, maple syrups)
Legumes (soaked) (lentils &most beans)	Grains (wheat, rye, oats, rice, buckwheat, quinoa) Bean sprouts, fava beans, garbanzo beans, soy beans
Nuts : Almonds, pecans, hazelnuts, walnuts, cashews, chestnuts, peanuts, brazil nuts	Not candied, salted, flavored nuts
Drinks: weak tea/coffee, water, mineral water, club soda, dry wine, gin, scotch, bourbon, vodka	Instant coffee, fruit juices, milk, soda, sweet wines, flavored liqueurs, brandy, sherry, beer



Seattle Children's Hospital (2014)

- 7 CD patients had normalization of symptoms, albumin, and CRP by 3 months
- Stool inflammation markers significantly improved
- No concurrent medications

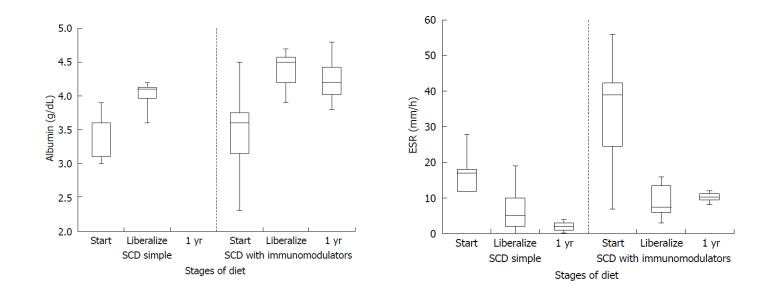
Children's Healthcare of Atlanta (2014)

- 6/9 CD patients had clinical remission by 3 months
- No changes to existing medications



Stanford Children's Hospital (2016)

- 11 CD pediatric patients
- Albumin, ESR, height, weight improved and remained stable
 - ... even after progressive liberalization of diet





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Emerging Evidence

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- Probiotics

Extrapolated Evidence

- Omega-3 fatty acids
- Fiber



Where Do We Stand with Probiotics?

Crohn's Disease		Probiotic			ol		Risk Ratio	Risk Ratio
CIVIII 5 DISCASE	Study or Subgroup	Events	lotal	Events	lota	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	Schultz 2004	4	5	5	6	71.6%	0.96 [0.55, 1.69]	
 No known benefit 	Steed 2010	8	19	5	16	28.4%	1.35 [0.55, 3.31]	
	Total (95% CI)		24		22	100.0%	1.06 [0.65, 1.71]	◆
	Total events	12		10				
	Heterogeneity: Tau²	= 0.00; Ch	i ² = 0.5	7. df = 1 (P = 0.4	5); I ² = 09	6	
	Test for overall effect							0.01 0.1 1 10 100
Ulcerative Colitis				-				Favors placebo Favors probiotic

Potential benefit from multi-strain probiotics in the induction and maintenance of remission

Pouchitis

Potential benefit from multi-strain probiotics



Probiotics for *Induction* of Remission

	Probio	tics	Cont	rol	Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	eight M-H, Random, 95% CI Year		M-H, Random, 95% Cl
1.6.1 Bifidobacteria								
Kato 2004	4	10	3	10	5.1%	1.33 (0.40-4.49)	2004	
Furrie 2005	5	9	3	9	5.9%	1.67 (0.56-4.97)	2005	
Subtotal (95% CI)		19		19	11.0%	1.51 (0.67-3.40)		🔶 📥
Total events	9		6					
Heterogeneity: $\tau^2 = 0$.	00; $\chi^2 =$	0.07, d	$f=1\ (P$	= 0.79); $I^2 = 0\%$			
Test for overall effect:	Z = 0.99	P = 0	.32)					
1.6.2 E coli								
Rembacken 1999	39	57	44	59	19.6%	0.92 (0.73-1.16)	1000	
Matthes 2010	20	46	3	11	6.6%	1.59(0.58-4.42)		
Subtotal (95% CI)	20	103	5	70	26.1%	0.99 (0.67-1.46)	2010	
Total events	59	200	47		2012/0	0.000 (0.011 2010)		
Heterogeneity: $\tau^2 = 0$.		1.22. d		= 0.27	$ ^{2} = 18^{\circ}$	*		
Test for overall effect:				0121				
 Brithelmert, Sharrachinary Laboration 								
1.6.3 Multi-strain p	robiotic							
Tursi 2004	24	30	37	60	18.9%	1.30 (0.99-1.70)	2004	•
Miele 2009	33	77	11	70	12.1%	2.73 (1.50-4.97)	2009	
Sood 2009	31	71	23	73	15.5%	1.39 (0.90-2.13)	2009	
Ng 2010	13	14	4	15	8.3%	3.48 (1.49-8.16)	2010	
Tursi 2010	7	14	5	14	8.0%	1.40 (0.58-3.36)	2010	
Subtotal (95% CI)		206		232	62.8%	1.74 (1.19–2.55)		♦
Total events	108		80					
Heterogeneity: $\tau^2 = 0$.				P = 0.0	4); $I^2 = 6$	0%		
Test for overall effect:	Z = 2.86	o(P = 0)	.004)					
Total (95% CI)		328		321	100.0%	1.51 (1.10-2.06)		◆
Total events	176		133					
Heterogeneity: $\tau^2 = 0$.	12; X ² =	22.79,	df = 8 (H	p = 0.0	$(04); I^2 =$	65%		0.01 0.1 1 10 100
Test for overall effect:	Control Probiotics							
Test for subgroup diff	erences:	$\chi^2 = 4.1$	27, df =	2 (P =	0.12), I ²	= 53.1%		control ribbiotics



Probiotics for *Maintenance* of Remission

Total Events Total Events Total Weight M-H, Random, 95% CI Year M-H, Random, 95% CI Year Xruis 1997 8 50 6 53 8.0% 1.41 (0.53–3.79) 1997 Rembacken 1999 26 39 32 44 38.9% 0.92 (0.69–1.22) 1999 Kruis 2004 40 162 38 165 30.0% 1.07 (0.73–1.58) 2004 Subtotal (95% CI) 251 262 77.0% 0.99 (0.79–1.24) 100 100 Total events 74 76 12 60 15.8% 0.79 (0.41–1.50) 2006 Subtotal (95% CI) 127 12 60 15.8% 0.79 (0.41–1.50) 2006 Subtotal (95% CI) 127 60 15.8% 0.79 (0.41–1.50) 2006 Subtotal (95% CI) 127 12 60 15.8% 0.79 (0.41–1.50) 2006 Total events 20 12 12 12 12 12 12 Meterogeneity: Not applicable 12 7.2% 0.29 (0.10–0.83) 2009 12 Total events	Α	Probio	tics	Cont	rol		Risk Ratio			Risk	Patio	
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					- 0.15	,, - 55/	×					1
					2(P =	0 07) 12	= 61 6%		P	robiotics	Control	



Probiotics for Pouchitis

С	Probio	tics	Conti	ol		Risk Ratio		Ri	sk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Ra	ndom, 95% CI
2.4.1 Bifidobacteria									
Wildt 2011 Subtotal (95% CI)	15	20 20	11	12 12	27.7% 27.7%	0.82 (0.60-1.11) 0.82 (0.60-1.11)	2011		•
Total events Heterogeneity: Not app			11						
Test for overall effect: 2.4.2 Multi-strain p			.20)						
Gionchetti 2000	3	20	20	20	25.2%				-
Gionchetti 2003	2	20	8	20	22.4%	0.25 (0.06-1.03)	2003		-
Mimura 2004 Subtotal (95% CI)	3	20 60	15	16 56	24.7% 72.3%		2004	•	
Total events	8		43						
Heterogeneity: $\tau^2 = 0$. Test for overall effect:				= 0.88)); I ² = 0%				
Total (95% CI)		80		68	100.0%	0.28 (0.06-1.27)			
Total events Heterogeneity: τ ² = 2. Test for overall effect: Test for subgroup diffe	Z = 1.65	(P = 0)	.10)					0.01 0.1 Probiot	1 10 1 ics Control



Where Do We Stand with Probiotics?

Crohn's Disease

• No known benefit

Ulcerative Colitis

 Potential benefit from multi-strain probiotics in the induction and maintenance of remission

Pouchitis

Potential benefit from multi-strain probiotics



What are Dietary Strategies for IBD?

Established Evidence

Enteral nutrition

Emerging Evidence

- Solid food diets
- Probiotics

Extrapolated Evidence

- Omega-3 fatty acids
- Fiber



Omega-3 Fatty Acids

Crohns' Disease

• Induction: No trials

• Maintenance:

- Cochrane review of 1039 patients \rightarrow marginal benefit

Study or subgroup	Treatment	Control	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95% Cl
Belluzzi 1996	11/39	27/39		12.0 %	0.41 [0.24, 0.70]
Lorenz-Meyer 1996	40/70	36/65	+	21.4 %	1.03 [0.77, 1.39]
Belluzzi 1997	2/26	5/24	·	2.2 %	0.37 [0.08, 1.73]
Romano 2005	11/18	19/20		17.6 %	0.64 [0.44, 0.94]
Feagan 2008a	54/183	62/180	-	21.2 %	0.86 [0.63, 1.16]
Feagan 2008b	84/187	94/188	+	25.6 %	0.90 [0.73, 1.11]
Total (95% CI)	523	516	*	100.0 %	0.77 [0.61, 0.98]
Total events: 202 (Treatmer	nt), 243 (Control)				
Heterogeneity: $Tau^2 = 0.05$; Chi ² = 12.01, df = 5 (f	P = 0.03); I ² =58%			
Test for overall effect: $Z = 2$	2.16 (P = 0.031)				
Test for subgroup difference	es: Not applicable				
			0.1 0.2 0.5 1 2 5 10		
			Favours treatment Favours control		

Ulcerative Colitis

Induction

- Inconsistent results
- Largest study (86 patients) → no difference

Maintenance

 • 3 trials (138 patients) → no difference in 1-2 year relapse rates





• Fiber is non-digestible plant-based substance

• Premise

- Converted to short chain fatty acids (SCFA)
- SCFA serve as fuel for colonocytes
- SCFA enhances microbial diversity toward a favorable profile
- SCFA has anti-inflammatory properties

Current Evidence

- Inconsistent data with lack of high-quality studies
- Solid food diets with some data of benefit encourage use of **fiber** (fruits + vegetables)





Maintain good hydration

• Eat "healthy" balanced diet (plant-based diet? Mediterranean diet?)

- Sounds simple, but research up to 2019 supports this principle for IBD
- Current data suggest the benefit of exclusion (red meat? processed foods? refined carbohydrates? emulsifiers?) and inclusion (fruits and vegetables)
- Consider fiber (if not at risk of obstruction)
- Consider probiotics (UC)
- Much more research is needed!



Thank You



