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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



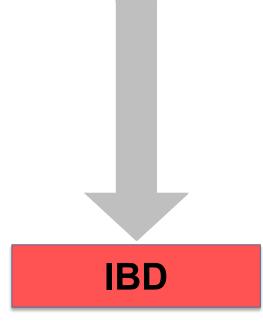
This presentation will broadly touch on major themes and is not intended to be comprehensive
 Image: Wikipedia
 A lot of research is still needed



# 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

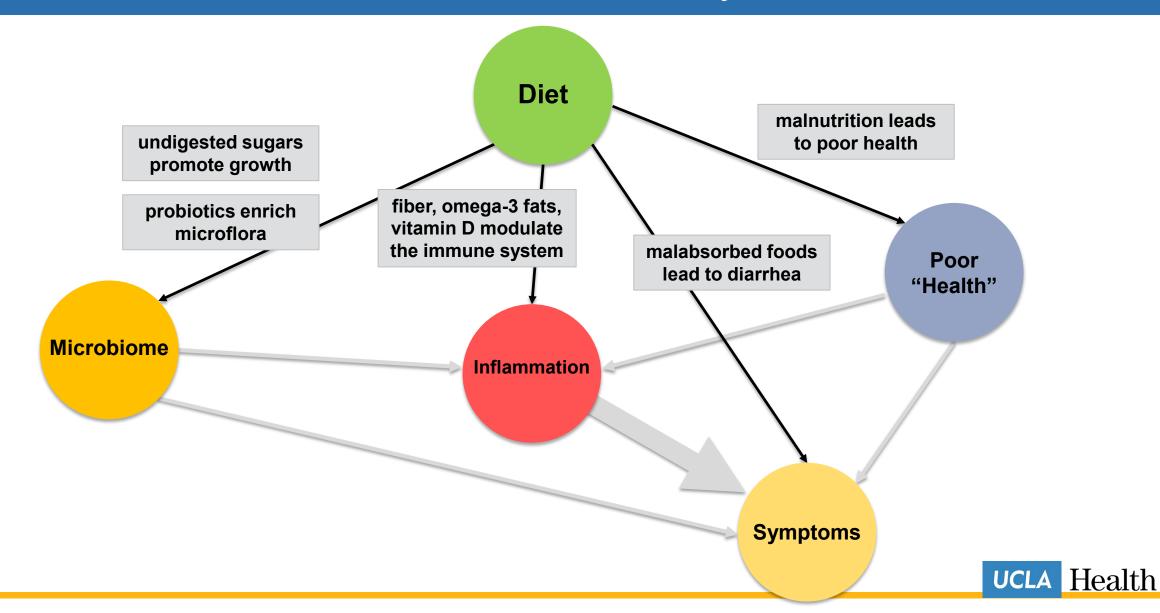
- Surveys of 203,193 Europeans (1991-1998)
- 126 UC patients had ↑ omega-6

### • Nurses' Health Study

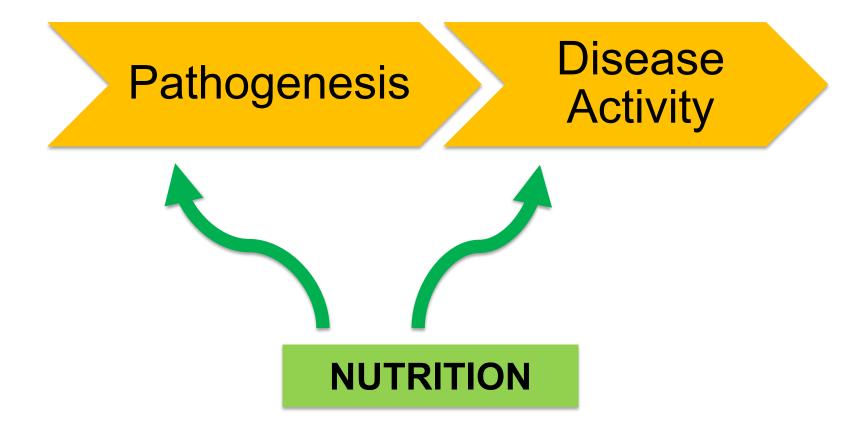
- Surveys of up to 170,000 women
- $\bullet$  Fiber was associated with  $\downarrow$  risk of CD but not UC
- $\bullet$  Vitamin D was associated with  $\downarrow$  risk of CD but not UC



## How Does Diet Affect Disease Activity?

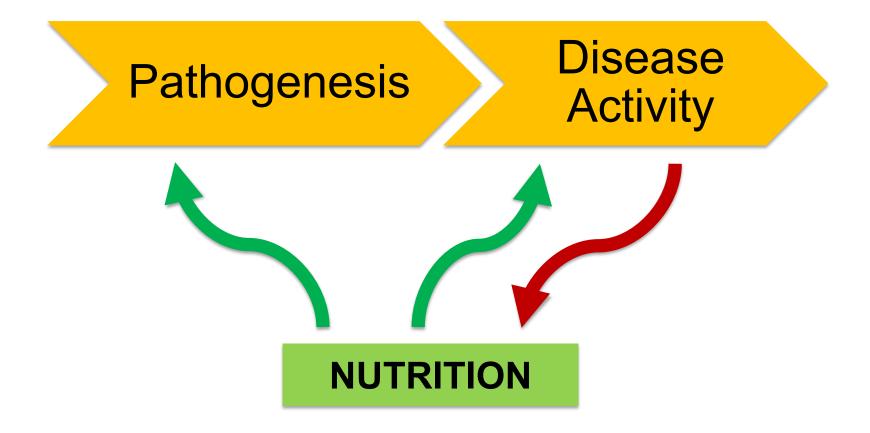


## Bidirectional Relationship of Nutrition and IBD





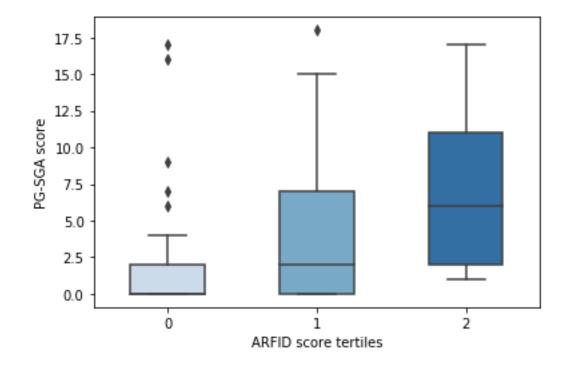
## Bidirectional Relationship of Nutrition and IBD





## 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



# What are Dietary Strategies for IBD?

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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**

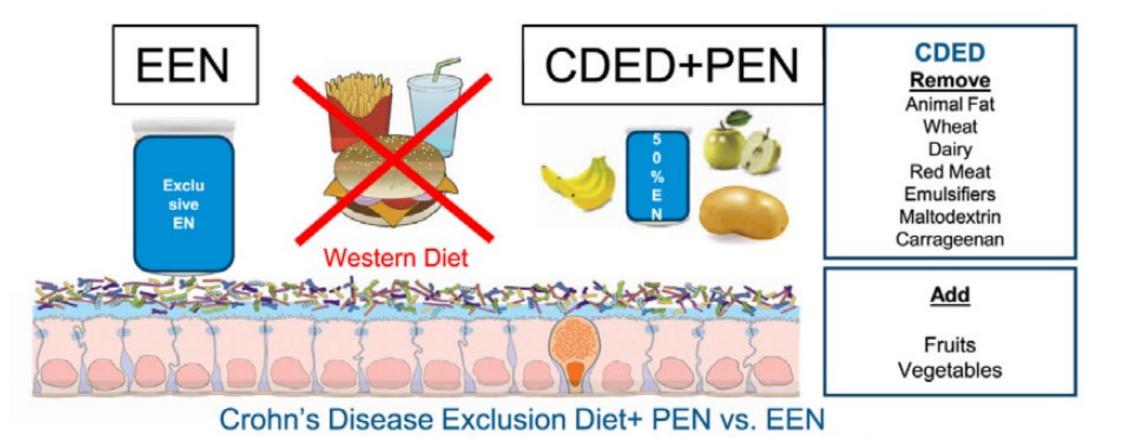
• No clear benefit

## But ...

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

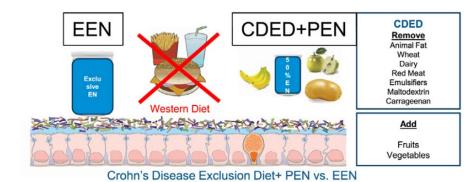


## What about *Partial* Enteral Nutrition?



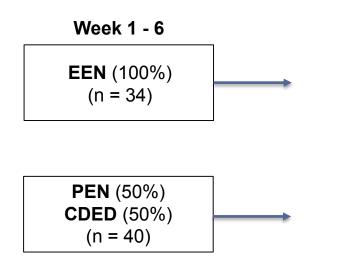
UCLA Health

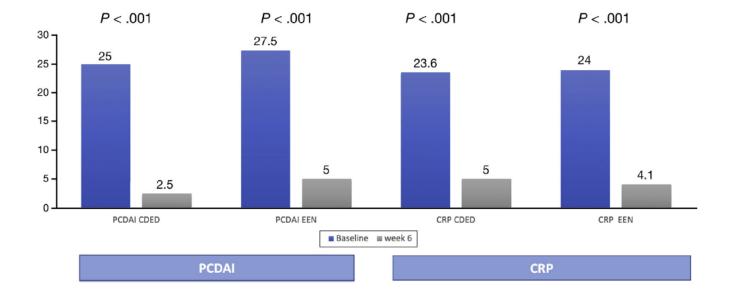
## What about *Partial* Enteral Nutrition?



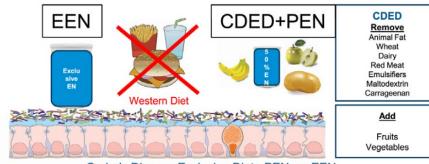
### Findings

PEN and EEN improved symptoms and CRP

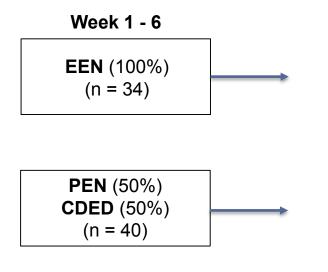




## What about *Partial* Enteral Nutrition?

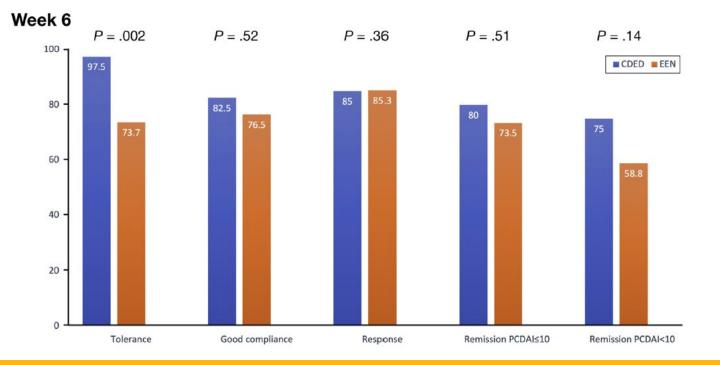


Crohn's Disease Exclusion Diet+ PEN vs. EEN



### 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**

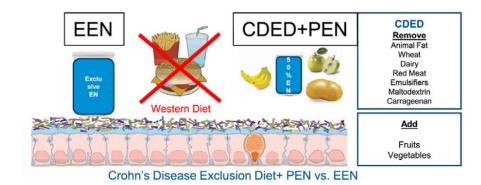
- Solid food diets
- Probiotics

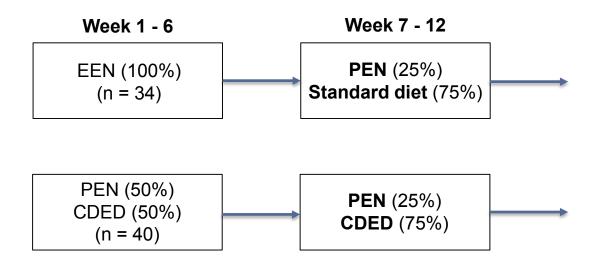
**Extrapolated Evidence** 

- Omega-3 fatty acids
- Fiber



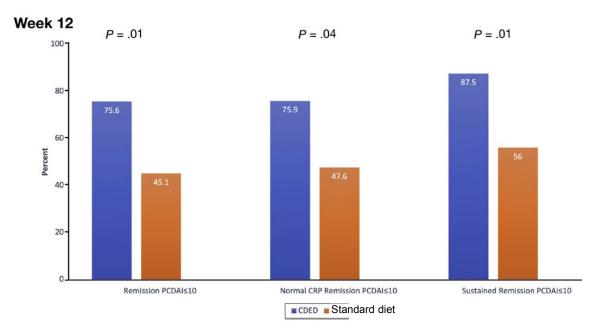
# What about *Solid Food* Diets?





### 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

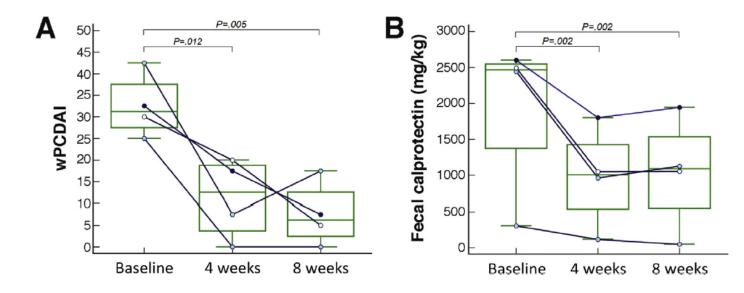
Soft drinks, fruit juices, sweetened beverages, alcoholic beverages, coffee

Candies, chocolate, cakes, cookies, and gum



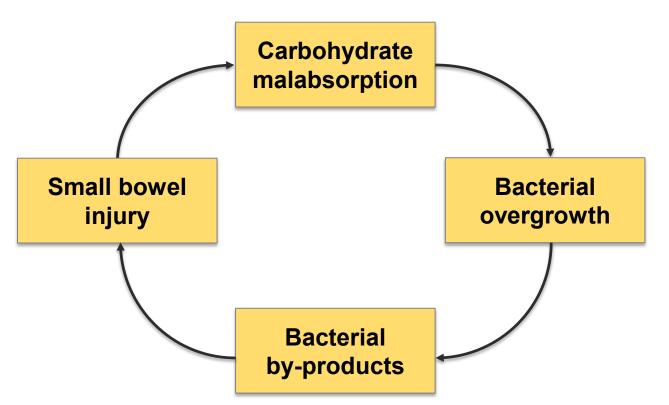
## **CD-TREAT Diet**

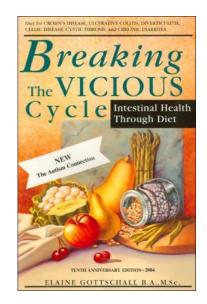
- Aim to develop solid food diet that recapitulates the microbiome changes from using exclusive enteral nutrition
- Diet components still proprietary
- Tested on 5 children with mild-to-moderate CD





- 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,<br>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)<br>Bean sprouts, fava beans, garbanzo beans, soy<br>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

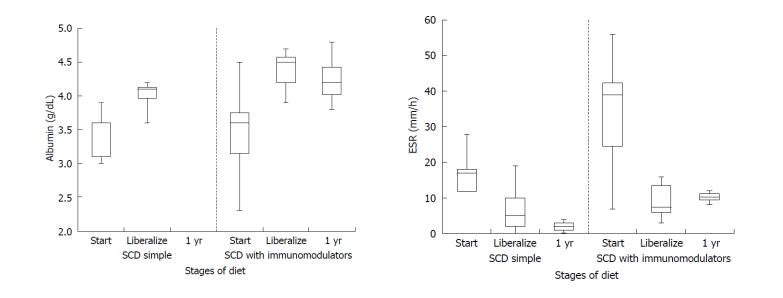
### Children's Healthcare of Atlanta (2014)

- 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





# What are Dietary Strategies for IBD?

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**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]   |                                 |
| <ul> <li>No known benefit</li> </ul> | 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 <sup>2</sup> = 0.5 | 7. df = 1 ( | P = 0.4 | 5); I <sup>2</sup> = 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    |                       |                                |      |                     |
| <ol> <li>Brithelmert, Sharrachinary Laboration</li> </ol> |                      |                |           |         |                       |                                |      |                     |
| 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 <sup>2</sup> = | 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 <sup>2</sup> | = 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   |     |
|---|-------------------------------|------------------|---------|----------|---------|--------------|---------------------------|-------|----------|-----------|---------|-----|
| 2.2.1 E coli       Fruis 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)       107         Total events       74       76       111, df = 2 (P = 0.57); l² = 0%       127       12       60       15.8%       0.79 (0.41-1.50)       2006         Zocco 2006       20       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       12         Heterogeneity: Not applicable       127       60       15.8%       0.79 (0.41-1.50)       2006       12         Total events       20       127       12       60       15.8%       0.79 (0.41-1.50)       2009         Subtotal (95% CI)       14       15       7.2%       0.29 (0.10-0.83)       2009       0.29 (0.10-0.83)       2009       10.01       10.01       10  | Study or Subaroup             |                  |         |          |         | Weight       |                           | 2.2   |          |           |         | ĩ   |
| 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% $0.99 (0.79-1.24)$ $0.99 (0.79-1.24)$ Total events       74       76         Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 1.11$ , $df = 2$ ( $P = 0.57$ ); $l^2 = 0\%$ $0.99 (0.79-1.24)$ Zocco 2006       20       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 $0.29 (0.10-0.83)$ 2009         Z.2.3 Multi-strain probiotic       12       60       15.8% $0.29 (0.10-0.83)$ 2009         Subtotal (95% CI)       14       15 $7.2\%$ $0.29 (0.10-0.83)$ 2009         Subtotal (95% CI)       14       15 $7.2\%$ $0.29 (0.10-0.83)$ 2009         Subtotal (95% CI)       14       15 $7.2\%$ $0.29 (0.10-0.83)$ 2009         Total events       3       11       14       15 $7.2\%$ $0.29 (0.10-0.83)$ <  |                               | Lients           | Total   |          | Total   | ireigitt     |                           | . cui |          |           |         | · · |
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| Subtotal (95% CI) 251 262 77.0% $0.99 (0.79-1.24)$<br>Total events 74 76<br>Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 1.11$ , df = 2 (P = 0.57); l <sup>2</sup> = 0%<br>Test for overall effect: Z = 0.11 (P = 0.92)<br>2.2.2 Lactobacillus<br>Zocco 2006 20 127 12 60 15.8% $0.79 (0.41-1.50)$ 2006<br>Subtotal (95% CI) 127 60 15.8% $0.79 (0.41-1.50)$<br>Total events 20 12<br>Heterogeneity: Not applicable<br>Test for overall effect: Z = 0.72 (P = 0.47)<br>2.2.3 Multi-strain probiotic<br>Miele 2009 3 14 11 15 7.2% $0.29 (0.10-0.83)$ 2009<br>Subtotal (95% CI) 14 15 7.2% $0.29 (0.10-0.83)$ 2009<br>Subtotal (95% CI) 14 15 7.2% $0.29 (0.10-0.83)$ 2009<br>Subtotal (95% CI) 14 15 7.2% $0.29 (0.10-0.83)$ 2009<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: Z = 2.30 (P = 0.02)<br>Total (95% CI) 392 337 100.0% $0.89 (0.66-1.21)$<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: Z = 0.73 (P = 0.47)   | Rembacken 1999                | 26               | 39      | 32       | 44      | 38.9%        |                           |       |          |           |         |     |
| Total events 74 76<br>Heterogeneity: $\tau^2 = 0.00$ ; $\chi^2 = 1.11$ , $df = 2$ ( $P = 0.57$ ); $l^2 = 0\%$<br>Test for overall effect: $Z = 0.11$ ( $P = 0.92$ )<br>2.2.2 Lactobacillus<br>Zocco 2006 20 127 12 60 15.8% 0.79 (0.41–1.50) 2006<br>Subtotal (95% CI) 127 60 15.8% 0.79 (0.41–1.50)<br>Total events 20 12<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )<br>2.2.3 Multi-strain probiotic<br>Miele 2009 3 14 11 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30$ ( $P = 0.02$ )<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , $df = 4$ ( $P = 0.19$ ); $l^2 = 35\%$<br>Test for overall effect: $Z = 0.73$ ( $P = 0.47$ )   | Kruis 2004                    | 40               | 162     | 38       | 165     | 30.0%        | 1.07 (0.73-1.58)          | 2004  |          | -         | -       |     |
| Heterogeneity: $t^2 = 0.00$ ; $\chi^2 = 1.11$ , $df = 2$ ( $P = 0.57$ ); $l^2 = 0\%$<br>Test for overall effect: $Z = 0.11$ ( $P = 0.92$ )<br>2.2.2 Lactobacillus<br>Zocco 2006 20 127 12 60 15.8% 0.79 (0.41–1.50) 2006<br>Subtotal (95% CI) 127 60 15.8% 0.79 (0.41–1.50)<br>Total events 20 12<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )<br>2.2.3 Multi-strain probiotic<br>Miele 2009 3 14 11 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30$ ( $P = 0.02$ )<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $t^2 = 0.04$ ; $\chi^2 = 6.15$ , $df = 4$ ( $P = 0.19$ ); $l^2 = 35\%$<br>Test for overall effect: $Z = 0.73$ ( $P = 0.47$ )   | Subtotal (95% CI)             |                  | 251     |          | 262     | 77.0%        | 0.99 (0.79-1.24)          |       |          |           |         |     |
| Test for overall effect: $Z = 0.11 (P = 0.92)$ 2.2.2 Lactobacillus         Zocco 2006       20       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         Total events       20       12       12       12       12         Heterogeneity: Not applicable       12       12       12       12         Total events       20       12       12       12         Mile 2009       3       14       11       15       7.2%       0.29 (0.10–0.83)       2009         Subtotal (95% CI)       14       15       7.2%       0.29 (0.10–0.83)       2009       14         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total (95% CI)       392       337       100.0%       0.89 (0.66–1.21)       0.01       0.01       0.01   | Total events                  | 74               |         | 76       |         |              |                           |       |          | 1         |         |     |
| Test for overall effect: $Z = 0.11 (P = 0.92)$ 2.2.2 Lactobacillus         Zocco 2006       20       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         Total events       20       12       12       12       12         Heterogeneity: Not applicable       12       12       12       12         Total events       20       12       12       12         Mileiz 2009       3       14       11       15       7.2%       0.29 (0.10–0.83)       2009         Subtotal (95% CI)       14       15       7.2%       0.29 (0.10–0.83)       2009       14         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total events       3       11       14       15       7.2%       0.29 (0.10–0.83)       2009         Total (95% CI)       392       337       100.0%       0.89 (0.66–1.21)       0.01       0.01       0.01   | Heterogeneity: $\tau^2 = 0$ . | 00: $\chi^2 = 3$ | l.11. d | f = 2(P) | = 0.57) | $ l^2 = 0\%$ |                           |       |          |           |         |     |
| Zocco 2006       20       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         Total events       20       12       12       60       15.8% $0.79 (0.41-1.50)$ 2006         Total events       20       12       12       60       15.8% $0.79 (0.41-1.50)$ 2006         Total events       20       12       12       12       12       12         Heterogeneity: Not applicable       Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )       2.2.3       Multi-strain probiotic         Mile 2009       3       14       11       15       7.2% $0.29 (0.10-0.83)$ 2009         Subtotal (95% CI)       14       15       7.2% $0.29 (0.10-0.83)$ 2009         Subtotal (95% CI)       392       337       100.0% $0.89 (0.66-1.21)$ $0.01 0.1 1$ $0.01 0.1 1$ Total events       97       99       99       99 $0.01 0.1 1$ $10 1$ $0.01 0.1$ $10 1$ $0.01 0.1$ Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 ( $P = 0.19$ ); $I^2 = 35\%$   |                               |                  |         |          |         |              |                           |       |          |           |         |     |
| Zocco 2006       20       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         Total events       20       12       12       60       15.8% $0.79 (0.41-1.50)$ 2006         Total events       20       12       12       60       15.8% $0.79 (0.41-1.50)$ 2006         Total events       20       12       12       60       15.8% $0.79 (0.41-1.50)$ 2006         Z.2.3       Multi-strain probiotic       20   | 2.2.2 Lactobacillus           |                  |         |          |         |              |                           |       |          |           |         |     |
| Subtotal (95% CI) 127 60 15.8% 0.79 (0.41–1.50)<br>Total events 20 12<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )<br>2.2.3 Multi-strain probiotic<br>Miele 2009 3 14 11 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83) 2009<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30$ ( $P = 0.02$ )<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 ( $P = 0.19$ ); $I^2 = 35\%$<br>Test for overall effect: $Z = 0.73$ ( $P = 0.47$ )  |                               | 20               | 127     | 12       | 60      | 15.8%        | 0.79(0.41 - 1.50)         | 2006  |          |           | -       |     |
| Total events       20       12         Heterogeneity: Not applicable       12         Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )       0.29 ( $0.10-0.83$ )       2009         Subtotal (95% CI)       14       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Subtotal (95% CI)       14       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       3       11       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       3       11       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       3       11       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       3       11       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       3       11       15       7.2%       0.29 ( $0.10-0.83$ )       2009         Total events       97       99       99       99       99       90 </td <td></td> <td>20</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>2000</td> <td></td> <td>-</td> <td></td> <td></td> |                               | 20               |         |          |         |              |                           | 2000  |          | -         |         |     |
| Heterogeneity: Not applicable<br>Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )<br>2.2.3 Multi-strain probiotic<br>Miele 2009 3 14 11 15 7.2% 0.29 (0.10-0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10-0.83) 2009<br>Subtotal (95% CI) 14 15 7.2% 0.29 (0.10-0.83) 2009<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30$ ( $P = 0.02$ )<br>Total (95% CI) 392 337 100.0% 0.89 (0.66-1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 ( $P = 0.19$ ); $I^2 = 35\%$<br>Test for overall effect: $Z = 0.73$ ( $P = 0.47$ )<br>Total events ( $P = 0.47$ )  | Total events                  | 20               |         | 12       |         |              |                           |       |          |           |         |     |
| Test for overall effect: $Z = 0.72$ ( $P = 0.47$ )         2.2.3 Multi-strain probiotic         Miele 2009       3       14       11       15       7.2%       0.29 (0.10-0.83)       2009         Subtotal (95% CI)       14       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       14       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       10       1       10       1         Heterogeneity: Not applicable       7       99       0.89 (0.66-1.21)       0.01       0.1       1       10       1         Total events       97       99       99       99       99       99       90   |                               | plicable         |         |          |         |              |                           |       |          |           |         |     |
| Miele 2009       3       14       11       15       7.2%       0.29 (0.10-0.83)       2009         Subtotal (95% Cl)       14       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       11       15       7.2%       0.29 (0.10-0.83)       2009         Total events       3       11       11       15       7.2%       0.29 (0.10-0.83)       2009         Total (95% Cl)       392       337       100.0%       0.89 (0.66-1.21)       0.01       0.1       1       10       1         Total events       97       99       99       99       90 <td></td> <td></td> <td>(P = 0)</td> <td>.47)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>   |                               |                  | (P = 0) | .47)     |         |              |                           |       |          |           |         |     |
| Subtotal (95% CI) 14 15 7.2% 0.29 (0.10–0.83)<br>Total events 3 11<br>Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30 (P = 0.02)$<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: $Z = 0.73 (P = 0.47)$   | 2.2.3 Multi-strain            | probiotic        | ;       |          |         |              |                           |       |          |           |         |     |
| Total events       3       11         Heterogeneity: Not applicable       11         Test for overall effect: Z = 2.30 (P = 0.02)       0.02         Total (95% Cl)       392       337 100.0%       0.89 (0.66–1.21)         Total events       97       99         Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l^2 = 35%       0.01       0.1       1       10       1         Test for overall effect: Z = 0.73 (P = 0.47)       99       90   | Miele 2009                    | 3                | 14      | 11       | 15      | 7.2%         | 0.29 (0.10-0.83)          | 2009  |          |           |         |     |
| Heterogeneity: Not applicable<br>Test for overall effect: $Z = 2.30 (P = 0.02)$<br>Total (95% Cl) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: $Z = 0.73 (P = 0.47)$   | Subtotal (95% CI)             |                  | 14      |          | 15      | 7.2%         | 0.29 (0.10-0.83)          |       |          |           |         |     |
| Test for overall effect: $Z = 2.30 (P = 0.02)$<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: $Z = 0.73 (P = 0.47)$  | Total events                  | 3                |         | 11       |         |              |                           |       |          |           |         |     |
| Test for overall effect: $Z = 2.30 (P = 0.02)$<br>Total (95% CI) 392 337 100.0% 0.89 (0.66–1.21)<br>Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: $Z = 0.73 (P = 0.47)$  | Heterogeneity: Not ap         | plicable         |         |          |         |              |                           |       |          |           |         |     |
| Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: Z = 0.73 (P = 0.47)  |                               |                  | (P = 0) | .02)     |         |              |                           |       |          |           |         |     |
| Total events 97 99<br>Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: Z = 0.73 (P = 0.47)  | Total (95% CI)                |                  | 392     |          | 337     | 100.0%       | 0.89 (0.66-1.21)          |       |          |           |         |     |
| Heterogeneity: $\tau^2 = 0.04$ ; $\chi^2 = 6.15$ , df = 4 (P = 0.19); l <sup>2</sup> = 35%<br>Test for overall effect: Z = 0.73 (P = 0.47)  | state and the second results  | 97               |         | 99       |         | 647 61 F MA  | Control Marchiel Children |       |          | ា         |         |     |
| Test for overall effect: $Z = 0.73$ ( $P = 0.47$ ) 0.01 0.1 1 10 1<br>Probability Control   |                               |                  | 6 1 5 d |          | = 0 19  | $1^2 = 359$  | 6                         |       | <b>—</b> | <u> </u>  |         |     |
|   |                               |                  |         |          | - 0.15  | ,, - 55/     | ×                         |       |          |           |         | 1   |
|   |                               |                  |         |          | 2(P =   | 0 07) 12     | = 61 6%                   |       | P        | robiotics | Control |     |



## Probiotics for Pouchitis

| С   | Probio   | tics     | Conti  | ol       |                        | <b>Risk Ratio</b>                    |      | 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<br>Subtotal (95% CI)   | 15       | 20<br>20 | 11     | 12<br>12 | 27.7%<br>27.7%         | 0.82 (0.60-1.11)<br>0.82 (0.60-1.11) | 2011 |                     | •                     |
| Total events<br>Heterogeneity: Not app  |          |          | 11     |          |                        |                                      |      |                     |                       |
| Test for overall effect:<br>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<br>Subtotal (95% CI)  | 3        | 20<br>60 | 15     | 16<br>56 | 24.7%<br>72.3%         |                                      | 2004 | •                   |                       |
| Total events  | 8        |          | 43     |          |                        |                                      |      |                     |                       |
| Heterogeneity: $\tau^2 = 0$ .<br>Test for overall effect:   |          |          |        | = 0.88)  | ); I <sup>2</sup> = 0% |                                      |      |                     |                       |
| Total (95% CI)  |          | 80       |        | 68       | 100.0%                 | 0.28 (0.06-1.27)                     |      |                     |                       |
| Total events<br>Heterogeneity: τ <sup>2</sup> = 2.<br>Test for overall effect:<br>Test for subgroup diffe | Z = 1.65 | (P = 0)  | .10)   |          |                        |                                      |      | 0.01 0.1<br>Probiot | 1 10 1<br>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<br>M-                  | Weight  | Risk Ratio<br>M-    |
|----------------------------------|---------------------------------------|--------------------------------|-----------------------------------|---------|---------------------|
|                                  | n/N                                   | n/N                            | H,Random,95%<br>Cl                |         | H,Random,95%<br>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 <sup>2</sup> = 12.01, df = 5 (f | P = 0.03); I <sup>2</sup> =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



