The Role for Pre & Probiotics in Chronic Gut Disorders

(in the Asia-Pacific Region)

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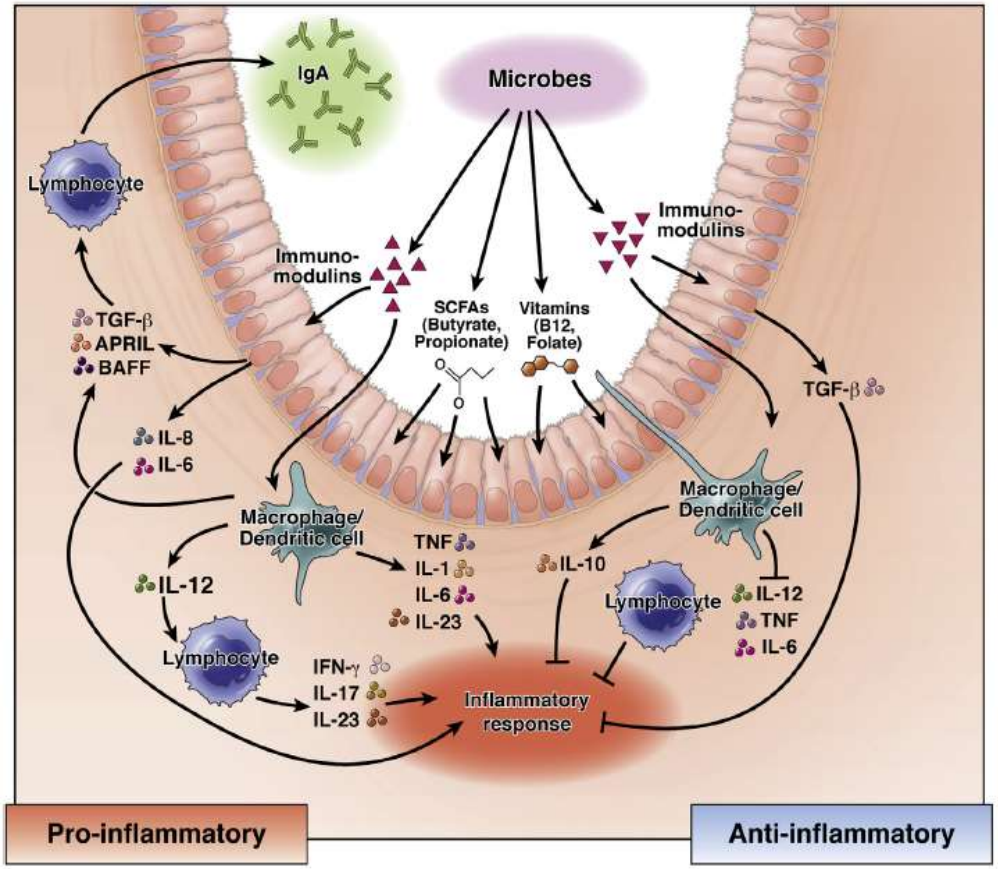
Scope

1. **Microbial Influence in GI disease**
2. **Changing the "bug-scape"**
    1. Probiotics & Prebiotics
    2. Antibiotics
    3. Fecal Microbial Transplantation
3. **The evidence for microbial manipulation**
    1. Diar
    2. IBS
    3. IBD
    4. Liver Disease

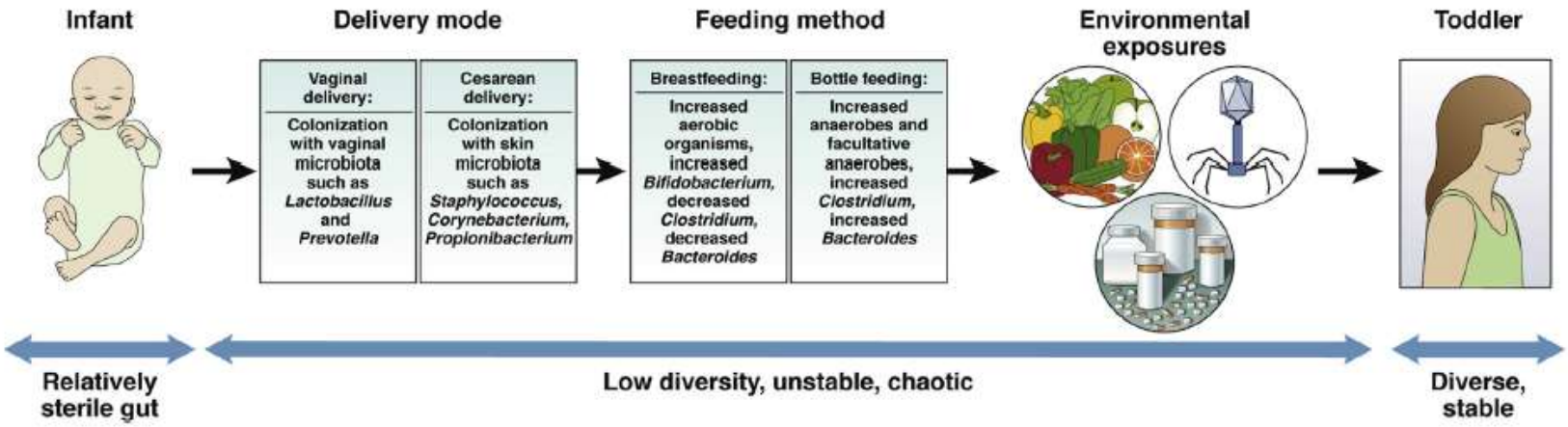

apollo
endosurgery

The Microbial Balance



Hollister et al. Compositional and functional features of GI Microbiome and effects of health. Gastro 2014

Our Microflora Evolves



Stomach and duodenum

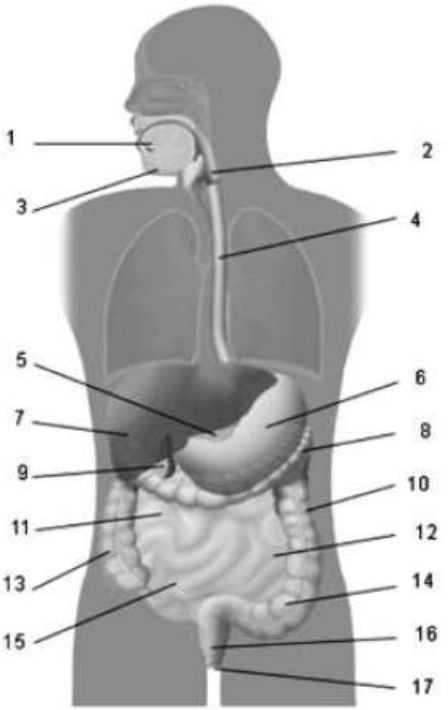
- Harbor very low numbers of microorganisms: $< 10^3$ bacterial cells/g of contents
- Mainly lactobacilli and streptococci
- Acid, bile, and pancreatic secretions suppress most ingested microbes
- Phasic propulsive motor activity impedes stable colonization of the lumen

Jejunum and ileum

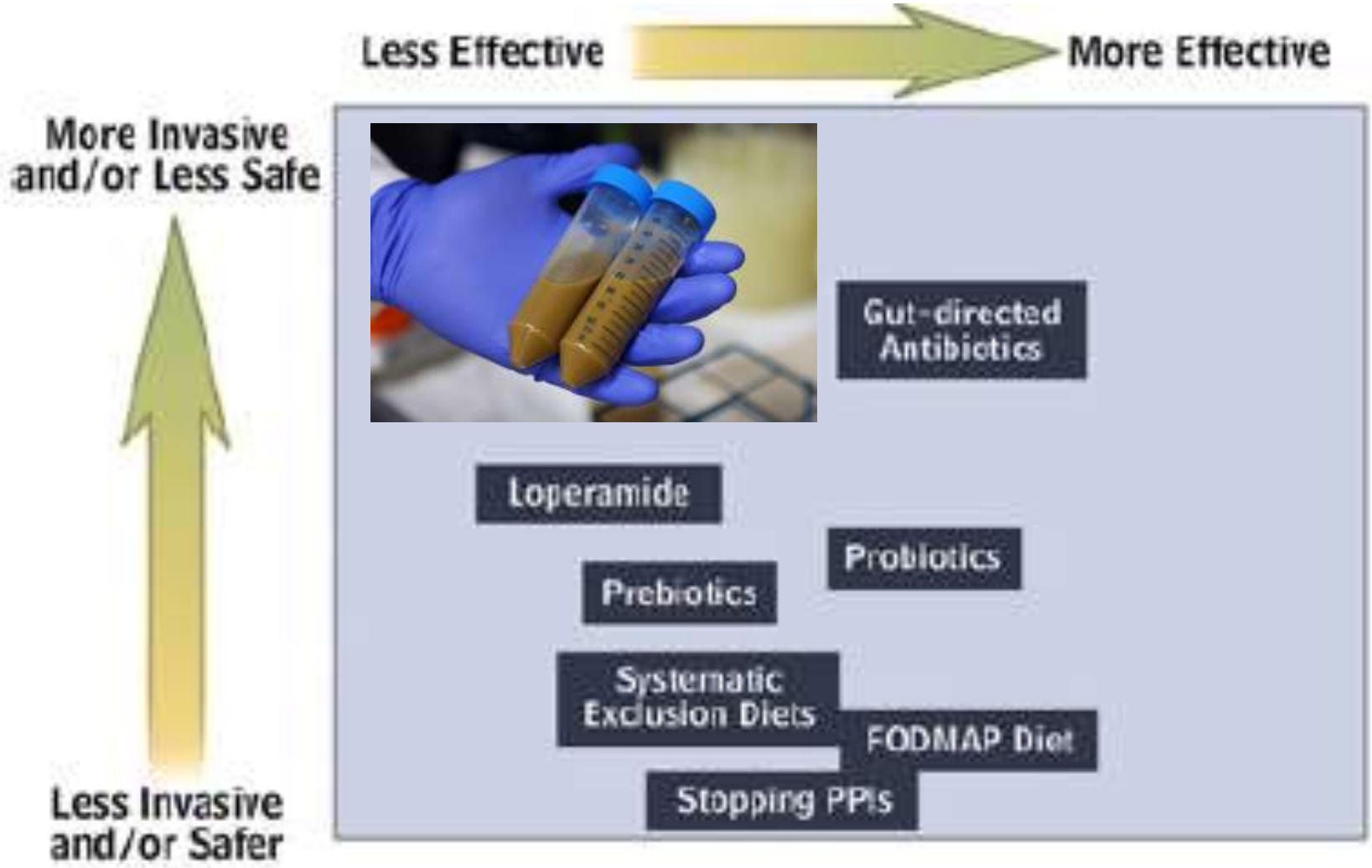
- No. bacteria progressively increase from approximately 10^4 cells in the jejunum to 10^7 cells/g of contents in the distal ileum

Large intestine

- Heavily populated by anaerobes: 10^{12} cells/g of luminal contents



WGO Probiotic & Prebiotic Guidelines 2011. J Clin Gastroenterol 2012


Less Effective
More Effective
More Invasive and/or Less Safe
Less Invasive and/or Safer
Gut-directed Antibiotics
Loperamide
Probiotics
Prebiotics
Systematic Exclusion Diets
FODMAP Diet
Stopping PPIs

Faecal Microbiota Transplantation (FMT)
The new kid on the block?

- Animals

- Ancient Medicine

1. "Yellow-Dragon Soup" CHINA
   - Tong-Jin Dynasty 4th Century
   - Ming Dynasty 16th Century
2. Modern Medicine

EISEMAN B, SILEN W, BASCOM GS, KAUVAR AJ.

Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery. 1958 Nov;44(5):854-9. PubMed PMID: 13592638.

REANIMATE

Don't pooh-pooh faeces transplant treatment

Method can potentially be used to treat common ailments but has yet to catch on

By LINETTE LAI

A FAECES transplant may smell – and sound like an odd cure, but it can potentially be used to treat common ailments such as irritable bowel syndrome if it catches on.

Two patients at the National University Hospital (NUH) have already found welcome relief: Healthy bacteria from a donor's faecal matter were used to help restore their digestive systems to full health earlier this year.

Patients who typically require this treatment are those who have been put on strong antibiotics, which kill all but the most resistant bacteria. But the surviving bacteria can cause problems, from frequent diarrhoea to ruptured intestines, and even death.

NUH sees 20 to 30 cases of such gut infections every month. Only about two-thirds of patients respond to conventional treatment methods, and even then, the problem may recur.

While the faecal procedure is common overseas, NUH doctors say it has not caught on here due to the "yuck factor". For, of course, the first step is to collect stool from donors – which is more complex than it sounds.

Donors must pass a health screening and this is "as strict as that for the usual organ transplants", said Dr Calvin Koh, a registrar at NUH's gastroenterology and hepatology division. Then, the collected matter is processed to extract the "good bacteria"

First local 'poop transplants'

NUH treats chronic gut infections with stool transplants

SINGAPORE – Faecal matter and cures are not words usually associated with each other. But doctors here have found a murky way to treat those with chronic gut infections by pumping microorganisms found in faeces from a healthy donor into a patient.

Earlier this year, doctors performed Singapore's first faecal microbiota transplant (FMT) under the REANIMATE programme and successfully treated two elderly female patients who were chronic sufferers of Clostridium difficile (C.diff) infection.

There has been a significant increase in antibiotic-associated C.diff infection, which was the result of widespread and sometimes indiscriminate use of antibiotics, said doctors from National University Hospital (NUH) at a press conference yesterday.

About 20 to 30 per cent of patients who suffer from C.diff infection no longer respond to conventional antibiotic treatments and recurrence rates are as high as 15 to 25 per cent.

Antibiotics can kill off the majority of bacteria in the gut, leaving resistant ones behind to multiply. One of which is C.diff, a bacterium that releases toxins that damage the intestinal lining. It can cause increased fluid production, inflamed gut lining and even tears in the intestine, which can lead to severe diarrhoea, abdominal pain or even death in severe cases.

"We started looking at other treatments, like possible new drugs. But in terms of antibiotic development, we are not discovering new antibiotics at the rate that we are requiring it. Thus, the other method of treatment would be stool transplant," said Dr Nicholas Chew, consultant and clinical director at NUH's Division of Infectious Diseases.

Under the FMT treatment, good microorganisms extracted from a healthy donor's stool sample are transplanted into a patient's gut with an endoscope through gastroscopy or colonoscopy. These microorganisms multiply in the recipient's colon and help to restore the gut's ecosystem.

Stool donors are stringently screened and tests are conducted to evaluate suitability. NUH is not looking to expand its existing pool of donors at the moment, but patients who wish to have their friends or family members become donors can visit the hospital and be screened.

Dr Chew also quoted "a steady increase in C.diff cases in hospitals over the recent two or three years", with about 20 to 30 patients treated for C.diff monthly. While C.diff infection can affect patients of any age group, it tends to be more severe in the elderly and the very ill as they frequently consume antibiotics to combat various illnesses.

Contrary to what one might assume, FMT is not a new-found medical procedure. For many years, it was a popular treatment method in the United States, Europe and Australia, and can even be traced back to ancient Chinese history. In the New England Journal of Medicine last year, an evidence-based study showed patients who had undergone FMT for C.diff infections had a success rate of 80 to 92 per cent. TAN SHI WEI

粪便移植技术 为患者重建健康肠道

医疗人员从身体健康的自愿捐献者收集粪便后，先在实验室进行处理，只保留肠便内健康的微生物群，然后拿到零下80摄氏度的冰柜冷冻，待需要移植时才解冻。

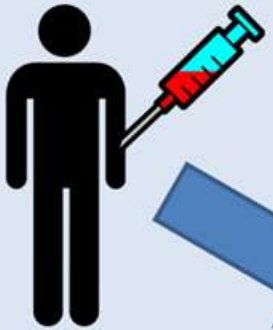
国大医院 研发粪便移植技术 为患者重建好肠道

国大医生成功掌握粪便移植技术，为患者的肠道重建健康的微生物菌群，解决由细

Faecal Microbiota Transplantation in a Nutshell

Donor Screening

The donor undergoes a stringent screening process to ensure the donor is free from infections and safe for transplant.

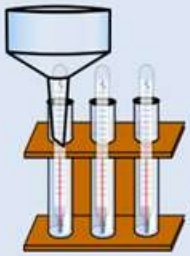


Sample Collection

The donor provides samples of his/her faeces and sends it to the hospital.

Sample Processing

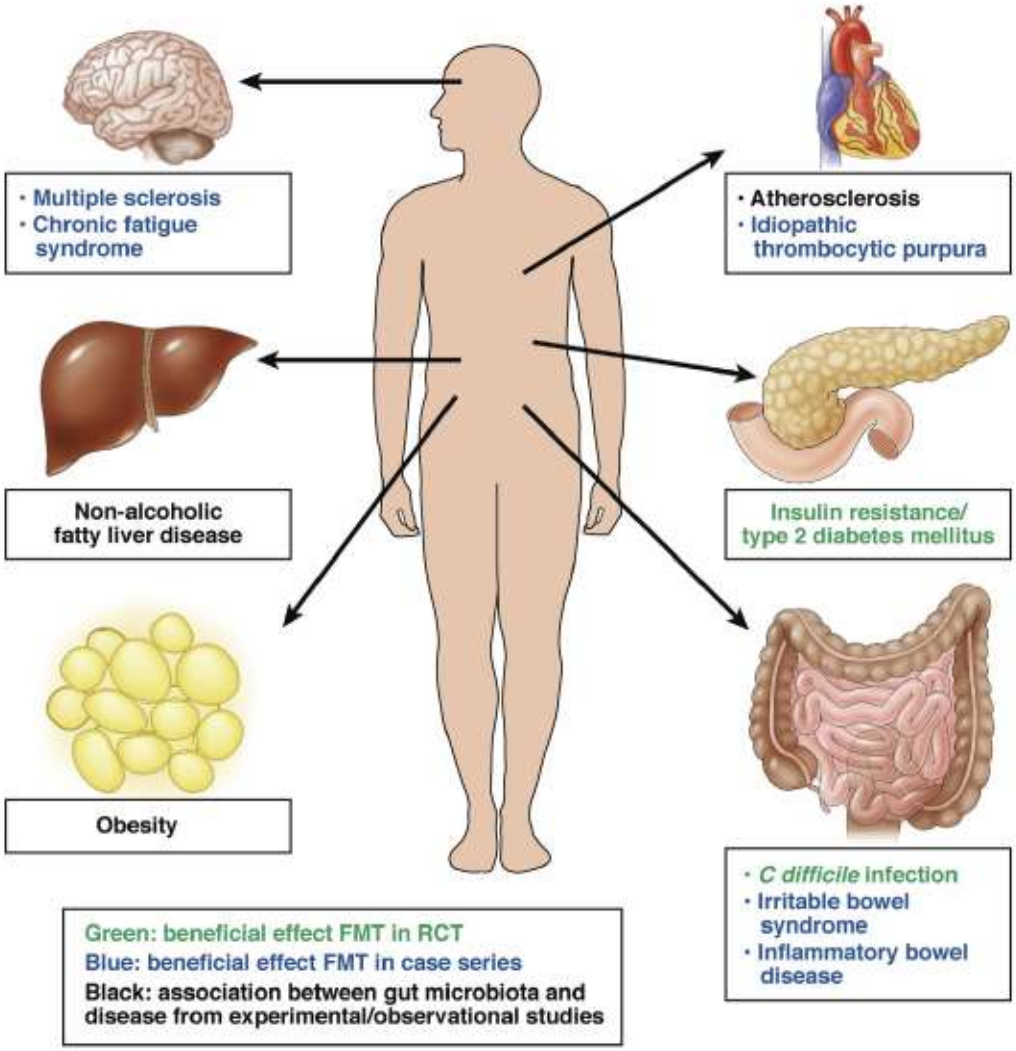
The sample is then processed in the lab where the team will remove some solid matters and mix the stool with sterile saline solution to make it liquid.



Transplant into the Recipient-Patient

The liquefied stool is transplanted into the gastrointestinal tract of the recipient-patient with an endoscope, by means of a gastroscopy or colonoscopy. Patient remains sedated throughout the procedure.

Potential Utility of FMT



Smits LP. Therapeutic potential of FMT. Gastro 2013

Regime Change…

"Cure-all"

The race for indications...

POOP is free…

Anyone can do it!

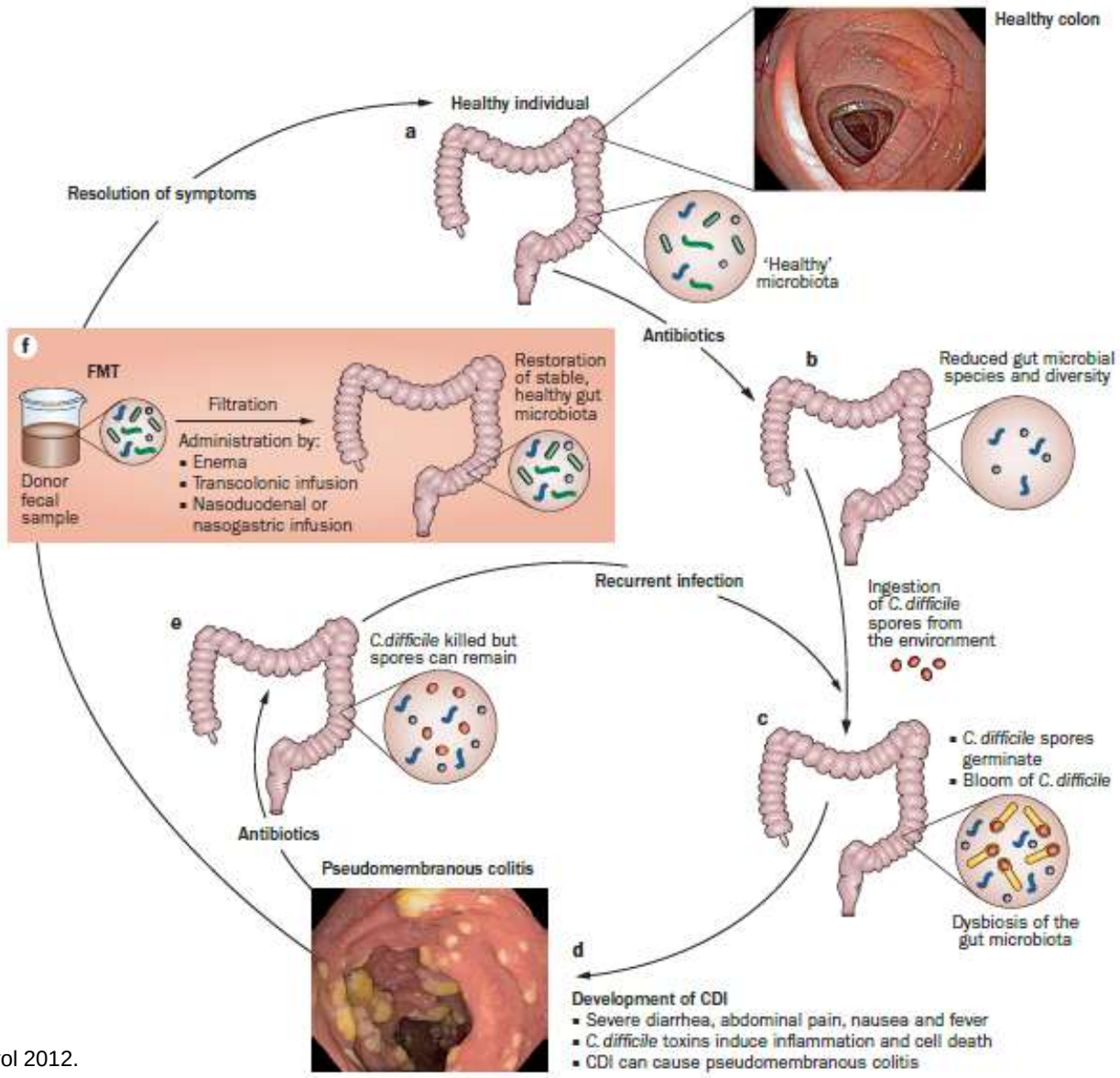
Long-term Effects

Metabonomic

Chronic Gut conditions amenable to microbiota manipulation

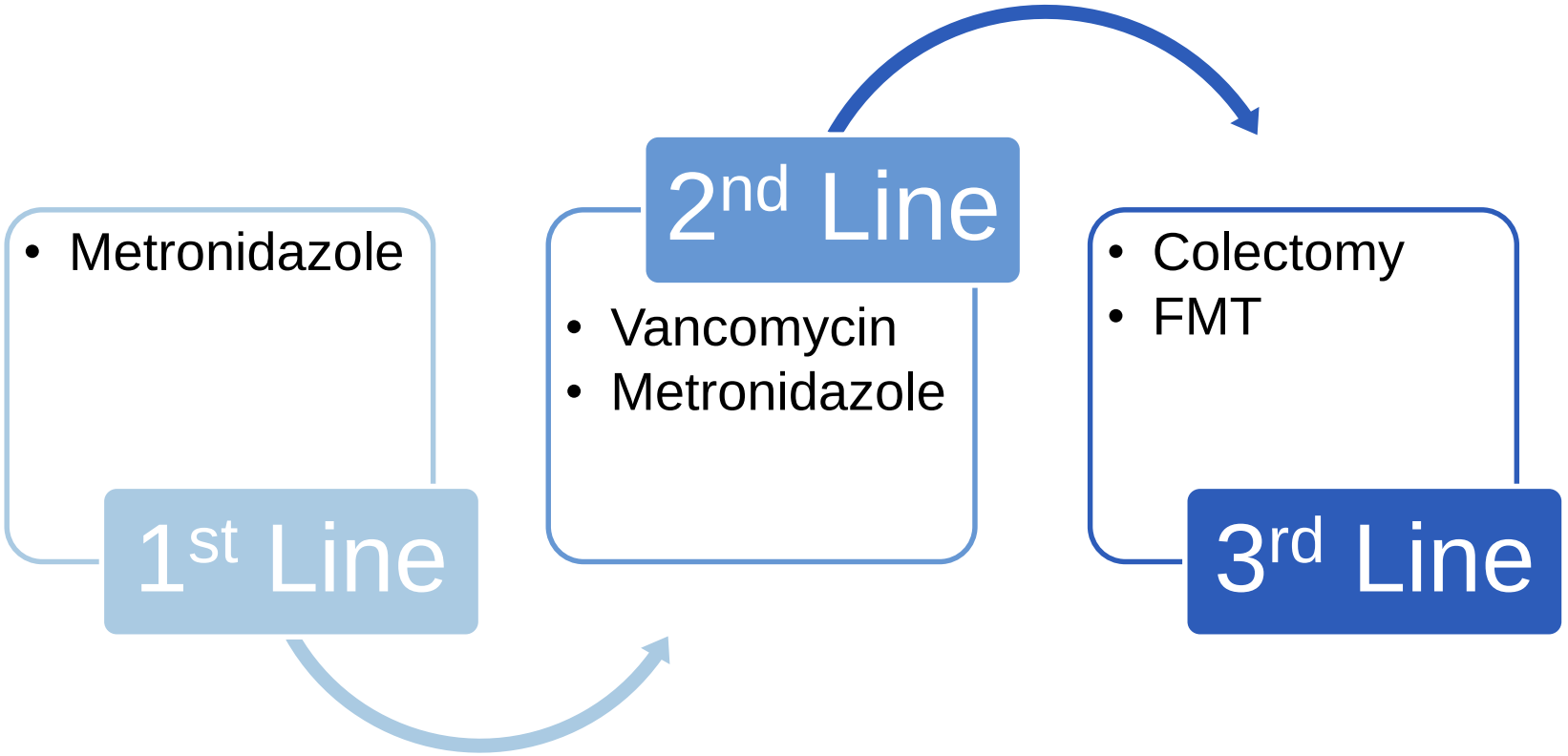
- Diarrhea
  - Gastroenteritis
  - C Difficile
  - Antibiotic Associated
- Colitis
  - Crohn's Disease
  - Ulcerative Colitis
  - Radiation Colitis
  - NEC
- Functional
  - IBS
- Hepatology
  - Hepatic encephalopathy
  - Fatty Liver
- Others
  - Colorectal Cancer
  - H Pylori

Clostridia Difficile Colitis



Brody TJ, Khoruts A.
FMT and emerging applications.
Nat Rev Gastroenterol 2012.

C. Difficile Treatment

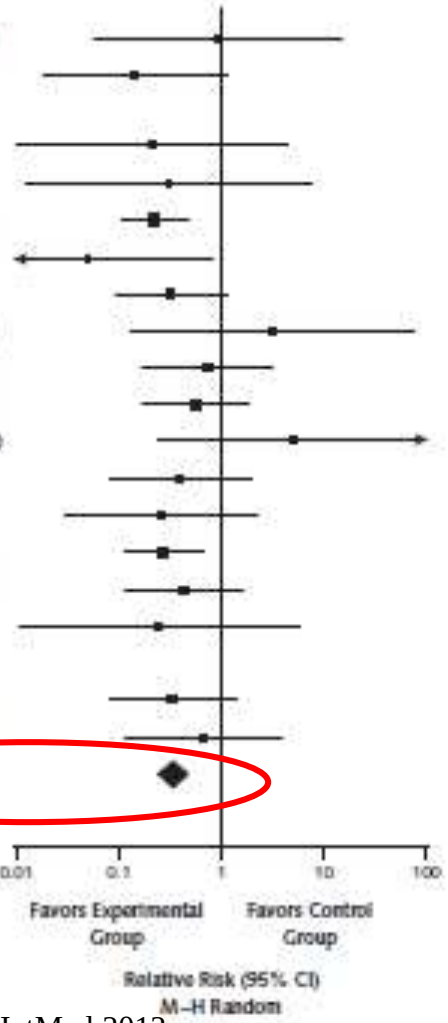


Probiotics to prevent *C Difficle*

Study, Year (Reference)	Experimental Group, *n* Events	Experimental Group, *n* Total	Control Group, *n* Events	Control Group, *n* Total	Weight, %	Relative Risk (95% CI) M–H Random
Arvola et al, 1999 (32)	1	61	1	58	1.7	0.95 (0.06–14.85)
Beausoleil et al, 2007 (33)	1	44	7	45	3.0	0.15 (0.02–1.14)
Bravo et al, 2008 (34)	0	41	0	45	–	Not estimable
Can et al, 2006 (35)	0	73	2	78	1.4	0.21 (0.01–4.37)
Duman et al, 2005 (36)	0	196	1	180	1.2	0.31 (0.01–7.47)
Gao et al, 2010 (37)	9	171	20	84	23.0	0.22 (0.11–0.46)
Hickson et al, 2007 (38)	0	56	9	53	1.6	0.05 (0.00–0.84)
Kotowska et al, 2005 (39)	3	119	10	127	7.9	0.32 (0.09–1.14)
Lönnermark et al, 2010 (40)	1	80	0	83	1.3	3.11 (0.13–75.26)
McFarland et al, 1995 (41)	3	97	4	96	5.9	0.74 (0.17–3.23)
Miller et al, 2008 (47)	4	95	7	94	8.9	0.57 (0.17–1.87)
Miller et al, 2008 (47)*	2	157	0	159	1.4	5.06 (0.25–104.63)
Plummer et al, 2004 (42)	2	69	5	69	4.9	0.40 (0.08–1.99)
Psaradellis et al, 2010 (48)	1	216	4	221	2.7	0.26 (0.03–2.27)
Rafiq et al, 2007 (49)	5	45	22	55	16.1	0.28 (0.11–0.67)
Ruszczynski et al, 2008 (43)	3	120	7	120	7.2	0.43 (0.11–1.62)
Safdar et al, 2008 (44)	0	23	1	17	1.3	0.25 (0.01–5.79)
Sellinger et al, 2011 (50)	0	62	0	62	–	Not estimable
Surawicz et al, 1989 (45)	3	116	5	64	6.5	0.33 (0.08–1.34)
Thomas et al, 2001 (46)	2	133	3	134	4.0	0.67 (0.11–3.96)
Total (95% CI)		1974		1844	100.0	0.34 (0.24–0.49)
Total events, *n*	40		108			

Heterogeneity: $\tau^2 = 0.00$; chi-square = 12.09; $P = 0.79$; $I^2 = 0\%$

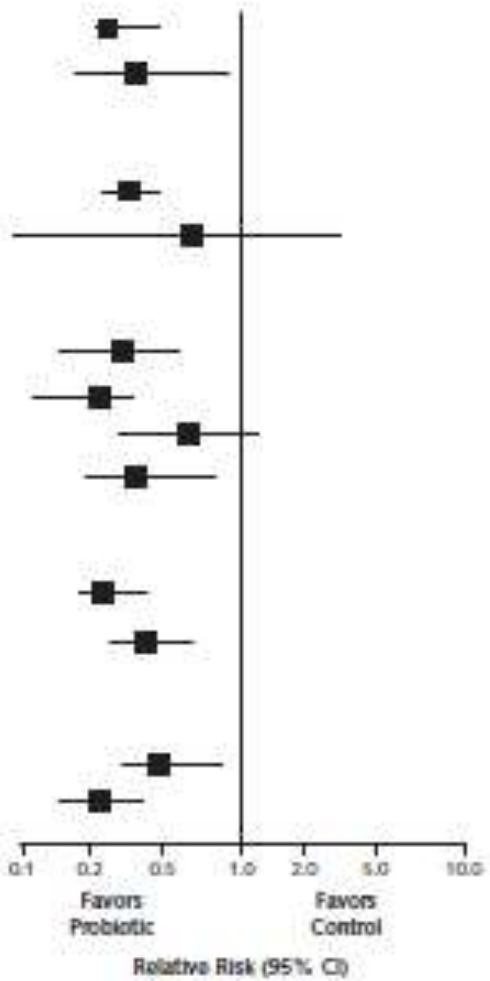
Test for overall effect: $Z = 5.87$; $P < 0.001$



Probiotics for the prevention of CD Diarrhea – Meta-anlysis & Sys Review: Annals IntMed 2012

Are there factors that affect outcome?

Subgroup	Events/Patients, n/n		Relative Risk (95% CI)	P Value for Test of Interaction
	Probiotic Group (n = 1974)	Control Group (n = 1844)		
Age				
Adults	33/1674	90/1539	0.22 (0.23–0.49)	
Children	7/300	18/305	0.40 (0.17–0.96)	0.69
Probiotic dosage				
>10 billion CFU/d	36/1775	98/1634	0.34 (0.23–0.49)	
≤10 billion CFU/d	4/199	10/210	0.61 (0.08–4.60)	0.57
Species				
Other (mixed) species	8/335	37/339	0.30 (0.15–0.61)	
L. acidophilus + L. casei	11/431	31/350	0.21 (0.11–0.42)	0.34
L. rhamnosus	12/566	18/565	0.63 (0.30–1.33)	0.15
S. boulardii	9/642	22/590	0.39 (0.19–0.82)	0.84
Risk of bias				
Low	17/695	52/613	0.27 (0.16–0.46)	
High or unclear	23/1279	56/1231	0.42 (0.26–0.68)	0.24
Species				
Single	21/1208	40/1155	0.50 (0.29–0.84)	
Multiple	19/766	68/689	0.25 (0.15–0.41)	0.06



Probiotics for the prevention of CD Diarrhea – Meta-anlysis & Sys Review: Annals IntMed 2012

Table 1 | FMT treatment in CDI

Study	Indication	Patients (*n*)	Mode of administration	Outcome
Eiseman *et al.*[19] (1958)	Severe PMC	4	Fecal enema	Dramatic resolution of PMC in all patients (100%)
Cutolo *et al.*[62] (1959)	PMC	1	Cantor tube, then fecal enema	Resolution
Fenton *et al.*[63] (1974)	PMC	1	Fecal enema	Symptom resolution within 24 h; sigmoidoscopy at 4 days revealed normal mucosa
Bowden *et al.*[64] (1981)	PMC	16	Fecal enema ($n=15$); enteric tube ($n=1$)	Rapid and dramatic response in 13 of 20 (65%) patients. 3 of 20 (15%) patients died; no evidence of PMC on autopsy in 2 of those patients, the third patient was found to have small-bowel PMC
Schwan *et al.*[65] (1984)	Recurrent CDI	1	Fecal enema	Prompt and complete normalization of bowel function
Tvede & Rask-Madsen[16]	Recurrent CDI	6	Fecal enema	Prompt *C. difficile* eradication and symptom resolution,

The NEW ENGLAND JOURNAL of MEDICINE

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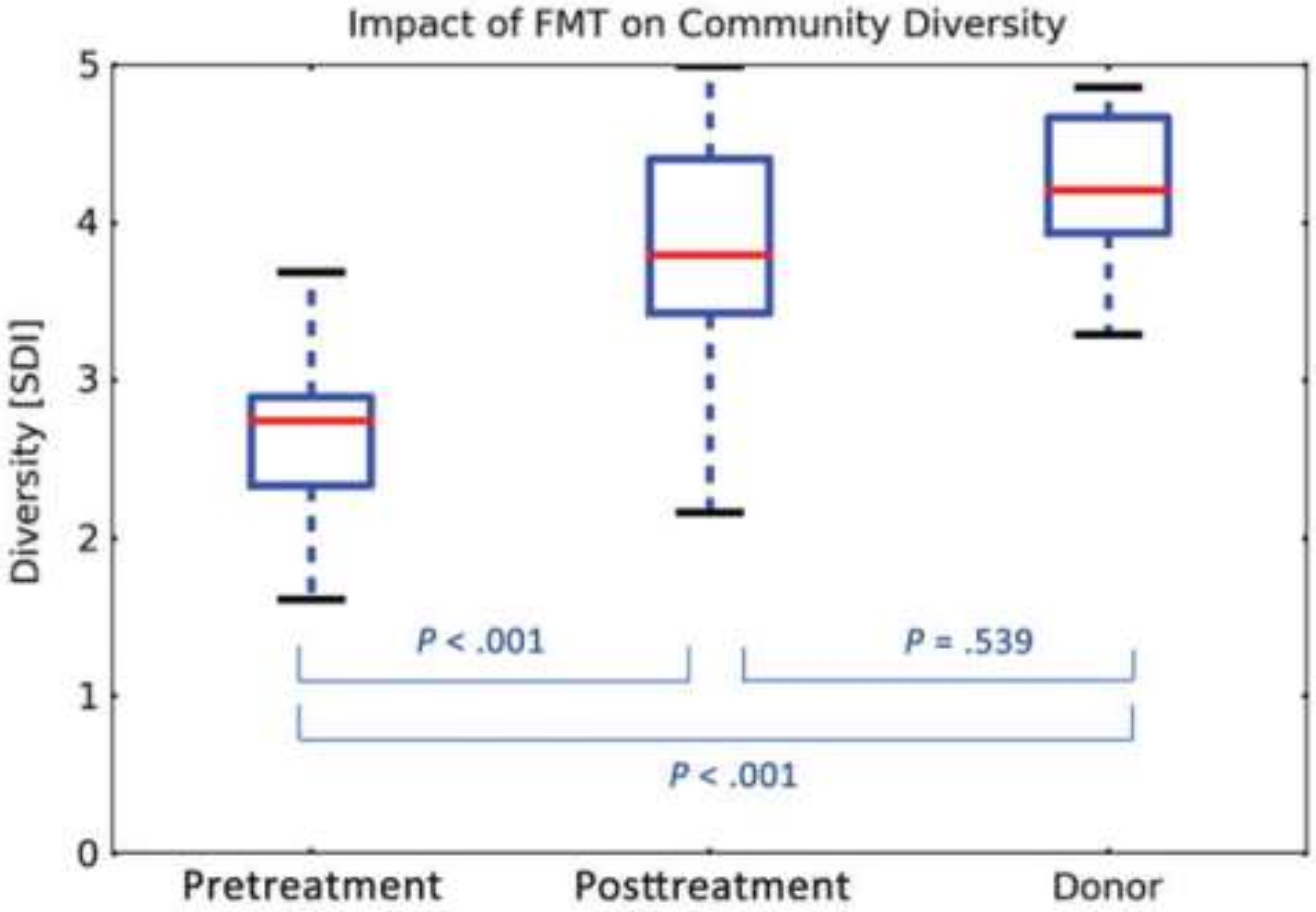
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

		027 strain)		
Khoruts *et al.*[33] (2010)	Recurrent CDAD	1	Colonoscope	*C. difficile* eradication, confirmed via negative culture; remained negative at 6-month follow-up
Yoon & Brandt[76] (2010)	Recurrent CDAD PMC	12 (2 with classic PMC on colonoscopy)	Colonoscope	All patients (100%) exhibited durable clinical response
Rohlke *et al.*[28] (2010)	Recurrent CDI	19	Colonoscope	18 of 19 (94.7%) patients clinically asymptomatic between 6 months and 5 years post-FMT
Silverman *et al.*[77] (2010)	Chronic recurrent CDI	7	Low-volume fecal enema	All (100%) patients clinically asymptomatic
Garborg *et al.*[78] (2010)	Recurrent CDAD	40	Colonoscope ($n=2$); duodenal instillation ($n=38$)	Eradication of *C. difficile* in 33 of 40 (82.5%) patients
Russell *et al.*[79] (2010)	Recurrent CDI	1	Nasogastric tube	Resolution of diarrhea within 36 h; repeat *C. difficile* toxin assay negative
Kelly *et al.*[80] (2010)	Chronic, recurrent CDI	12	Colonoscope	All (100%) patients exhibited clinical response
Mellow *et al.*[81] (2010)	Recurrent and refractory CDI	13	Colonoscope	12 of 13 (92.3%) patients were *C. difficile* toxin negative, coinciding with rapid resolution of diarrhea

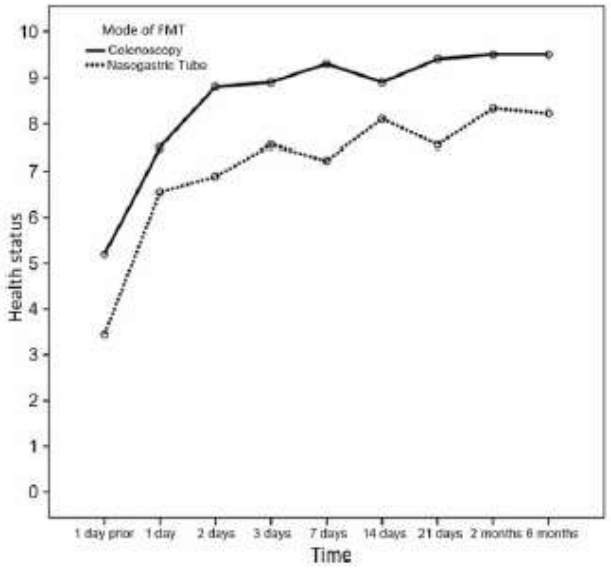
Brody TJ, Khoruts A.
FMT and emerging applications.
Nat Rev Gastroenterol 2012.

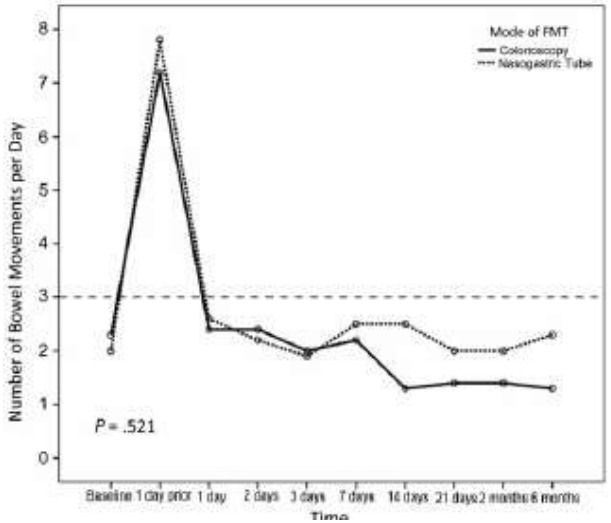
Why is FMT so successful in C. Difficile

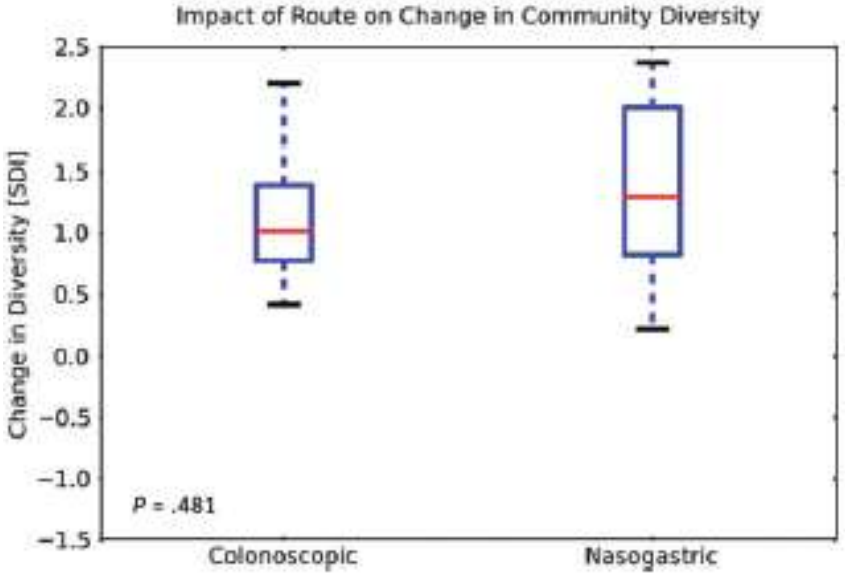


Youngster I et al. FMT for replapsing C Diff Infection. Clin Infec Dis 2014

“Top-down or Bottom-up?”
The Best Route for Stool Delivery







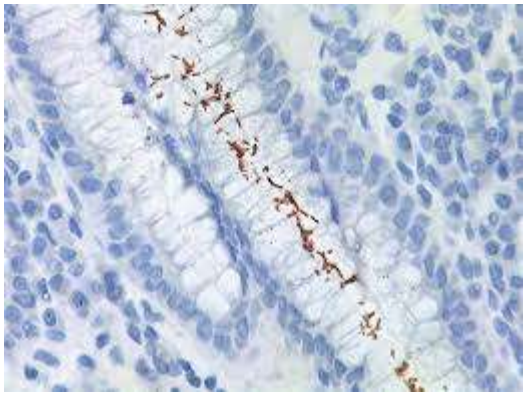
Youngster I et al. FMT for replapsing C Diff Infection. Clin Infec Dis 2014

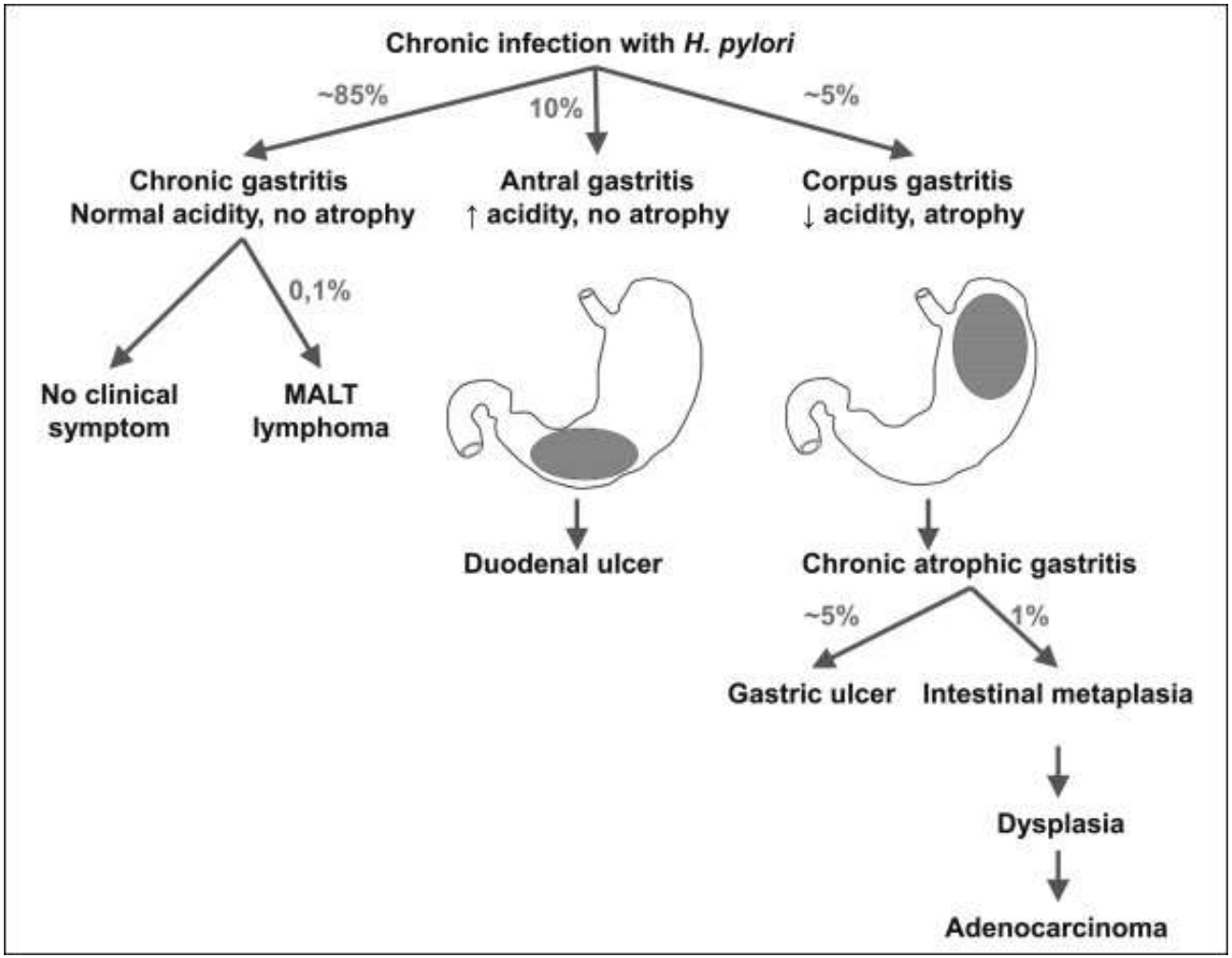
Whose Poop to use?

- Related Donor
  - Less “icky” factor
  - “I’m getting my wife’s stool… part of her now lives in me!”
  - Dysbiosis runs in families and a shared envioronment
- Unrelated Donor
  - 90-92% vs 70% success rate in CDI eradication (Hamilton et al)
- Fresh is Better?
  - 92% Fresh vs. 90% Frozen success rate
  - Ready-to-go poop

Hamilton MJ et al. Standardized frozen preparation FMT for treatment of C Difficile. Amer Journ Gastroenterol 2012

Helicobacter Pylori





Helicobacter Pylori

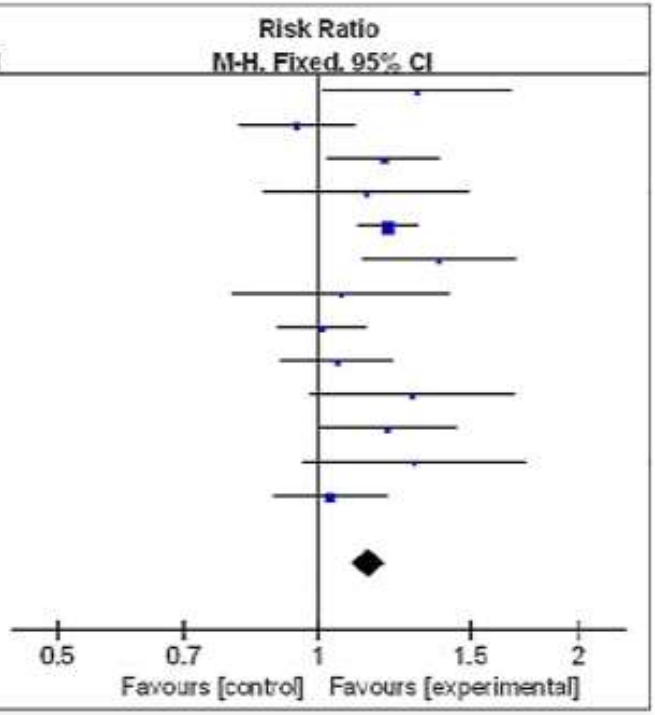
- Eradication
  - Rates vary widely but going down
  - Anything to boost eradication
  - Potential move back to single antibiotic regimen with PCABS
- Side-Effects
  - Maastricht VI
  - Triple Rx
  - Sequential Rx
  - Quadruple Rx

Eradication of H Pylori

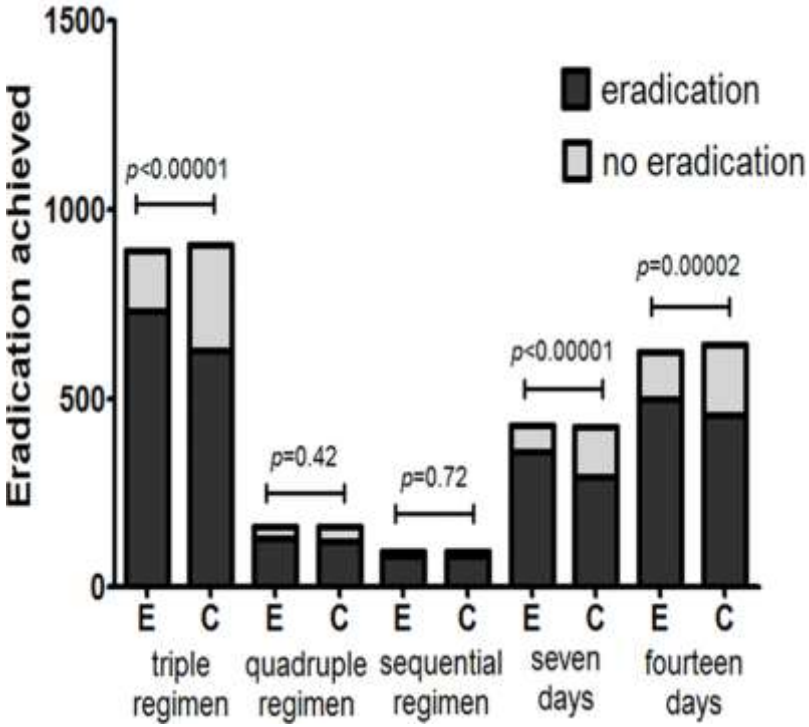
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmad K 2013	30	33	23	33	2.8%	1.30 [1.02, 1.67]
Ahmad S 2013	69	90	73	90	8.8%	0.95 [0.81, 1.10]
Deguchi R 2012	95	115	79	114	9.6%	1.19 [1.03, 1.38]
Francavilla R 2014	33	44	29	44	3.5%	1.14 [0.87, 1.49]
Hauser G 2015	291	333	230	317	28.6%	1.20 [1.11, 1.30]
Ling Y 2014	58	66	42	66	5.1%	1.38 [1.13, 1.69]
Lionetti E 2006	17	20	16	20	1.9%	1.06 [0.80, 1.41]
Manfredi M 2012	65	73	67	76	8.0%	1.01 [0.90, 1.13]
Navarro-Rodriguez 2013	49	55	44	52	5.5%	1.05 [0.91, 1.22]
Ojetti V 2012	36	45	28	45	3.4%	1.29 [0.98, 1.69]
Sheu BS 2006	59	69	49	69	5.9%	1.20 [1.01, 1.44]
Wang YH 2014	36	49	29	51	3.4%	1.29 [0.96, 1.73]
Yoon H 2011	104	151	124	186	13.5%	1.03 [0.89, 1.20]
Total (95% CI)		**1143**		**1163**	**100.0%**	**1.15 [1.10, 1.20]**
Total events	942		833			

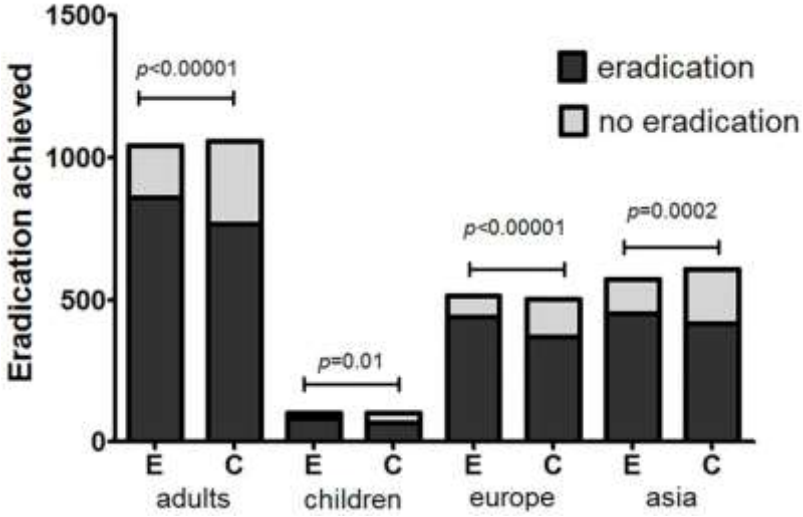
Heterogeneity: $Chi^2 = 21.95$, $df = 12$ ($P = 0.04$); $I^2 = 45\%$

Test for overall effect: $Z = 5.94$ ($P < 0.00001$)

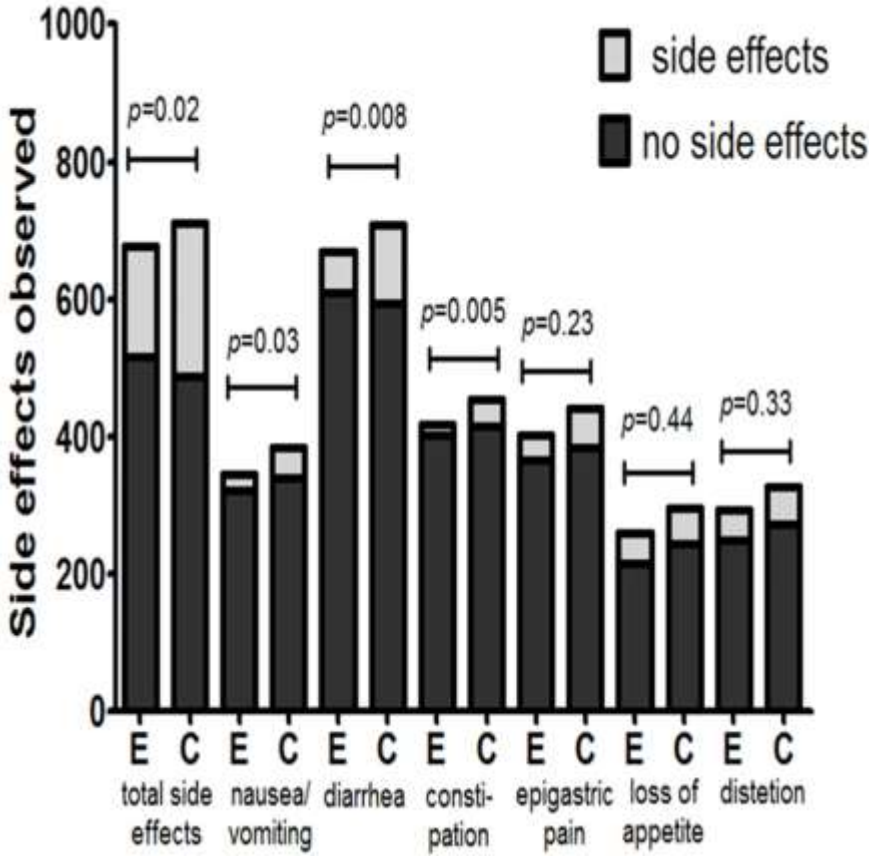


H Pylori Eradication





Reduction of Side Effects



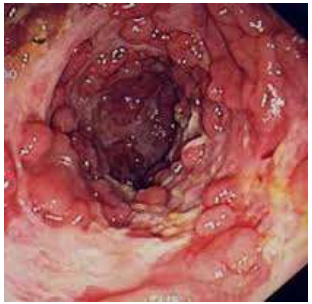
Is there a role for probiotics in H Pylori

- Works best in combination with antibiotic eradication regimens
- Meta-analysis of 14 RCTs
- OR 1.84 (95% CI 1.34-2.54) in favour of probiotics in HP eradication
- Reduced AAD, OR 0.44 (95% CI 0.30-0.66)

Inflammatory Bowel Disease

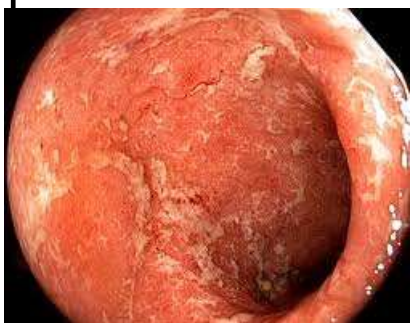
Crohn's Disease

- Colon
- Illeum & small bowel
- Granulomatous Disease
- Extra-intestinal Involvement
- Treatment:
  - Biologics
  - Immunosupressants



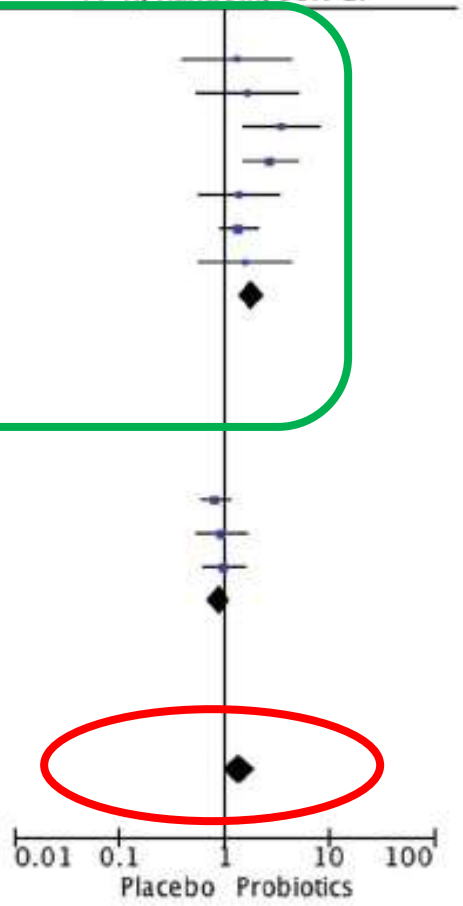
Ulcerative Colitis

- Colon
- Backwash ileitis
- Ulceration with crypt abcesses
- Treatment:
  - Aminosalicylates
  - Immunosuppressants
  - Microflora manipulation



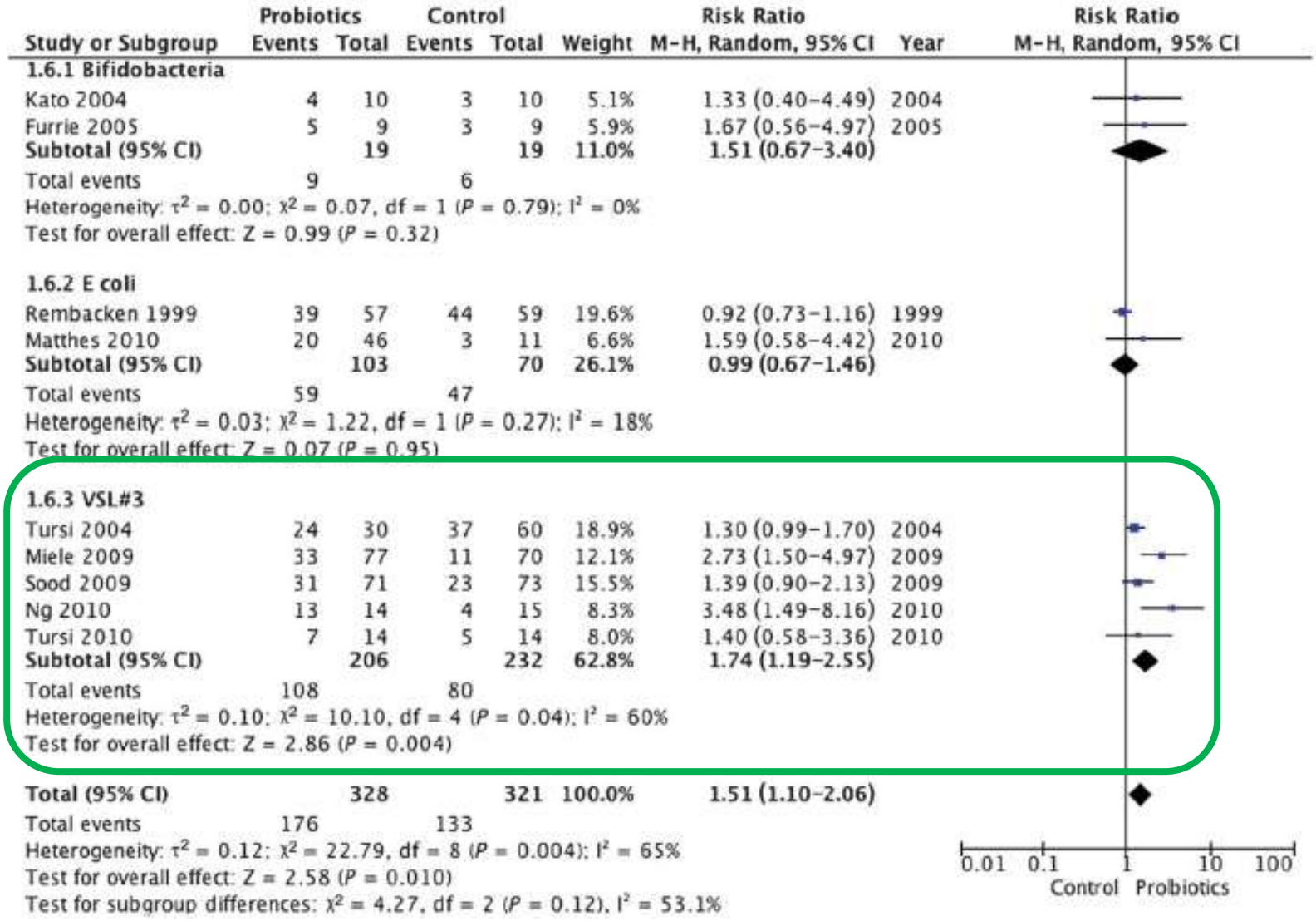
Can probiotics induce remission of IBD?

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.4.1 UC							
Kato 2004	4	10	3	10	5.6%	1.33 (0.40–4.49)	2004
Furrie 2005	5	9	3	9	6.4%	1.67 (0.56–4.97)	2005
Miele 2009	13	14	4	15	8.4%	3.48 (1.49–8.16)	2009
Sood 2009	33	77	11	70	11.3%	2.73 (1.50–4.97)	2009
Ng 2010	7	14	5	14	8.2%	1.40 (0.58–3.36)	2010
Tursi 2010	31	71	23	73	13.5%	1.39 (0.90–2.13)	2010
Matthes 2010	20	46	3	11	6.9%	1.59 (0.58–4.42)	2010
Subtotal (95% CI)		**241**		**202**	**60.3%**	**1.80 (1.36–2.39)**	
Total events	113		52				
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.26$, df = 6 ($P = 0.39$); $I^2 = 4\%$							
Test for overall effect: Z = 4.06 ($P < 0.0001$)							
1.4.2 CD							
Malchow 1997	12	16	11	12	14.7%	0.82 (0.59–1.14)	1997
Schultz 2004	4	5	5	6	11.7%	0.96 (0.55–1.69)	2004
Steed 2010	13	19	11	16	13.2%	1.00 (0.63–1.56)	2010
Subtotal (95% CI)		**40**		**34**	**39.7%**	**0.89 (0.70–1.13)**	
Total events	29		27				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.59$, df = 2 ($P = 0.74$); $I^2 = 0\%$							
Test for overall effect: Z = 0.94 ($P = 0.35$)							
Total (95% CI)		**281**		**236**	**100.0%**	**1.40 (0.99–1.98)**	
Total events	142		79				
Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 27.20$, df = 9 ($P = 0.001$); $I^2 = 67\%$							
Test for overall effect: Z = 1.89 ($P = 0.06$)							
Test for subgroup differences: $\chi^2 = 13.73$, df = 1 ($P = 0.0002$), $I^2 = 92.7\%$							



Effect of probiotics on UC,CD and pouchitis – Meta-analysis of RCTs: IBD 2014

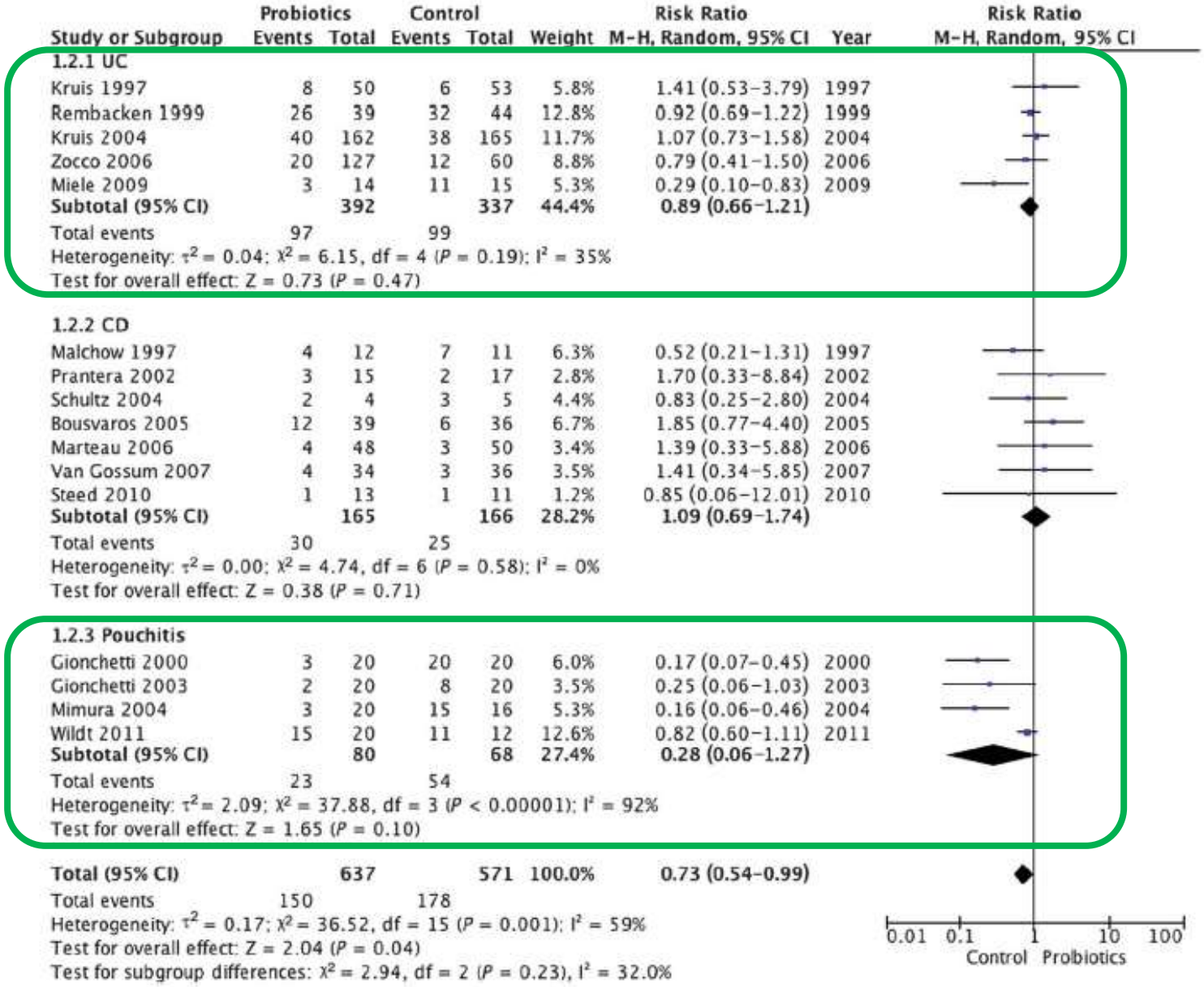
Which probiotic for inducing remission?



Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
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: $\tau^2 = 0.00$; $\chi^2 = 0.07$, df = 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)	1999
Matthes 2010	20	46	3	11	6.6%	1.59 (0.58–4.42)	2010
Subtotal (95% CI)		**103**		**70**	**26.1%**	**0.99 (0.67–1.46)**	
Total events	59		47				
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 1.22$, df = 1 ($P = 0.27$); $I^2 = 18\%$							
Test for overall effect: Z = 0.07 ($P = 0.95$)							
1.6.3 VSL#3							
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: $\tau^2 = 0.10$; $\chi^2 = 10.10$, df = 4 ($P = 0.04$); $I^2 = 60\%$							
Test for overall effect: Z = 2.86 ($P = 0.004$)							
Total (95% CI)		**328**		**321**	**100.0%**	**1.51 (1.10–2.06)**	
Total events	176		133				
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 22.79$, df = 8 ($P = 0.004$); $I^2 = 65\%$							
Test for overall effect: Z = 2.58 ($P = 0.010$)							
Test for subgroup differences: $\chi^2 = 4.27$, df = 2 ($P = 0.12$), $I^2 = 53.1\%$							

Effect of probiotics on UC,CD and pouchitis – Meta-analysis of RCTs: IBD 2014

Can probiotics maintain remission of IBD? (clinical relapse)



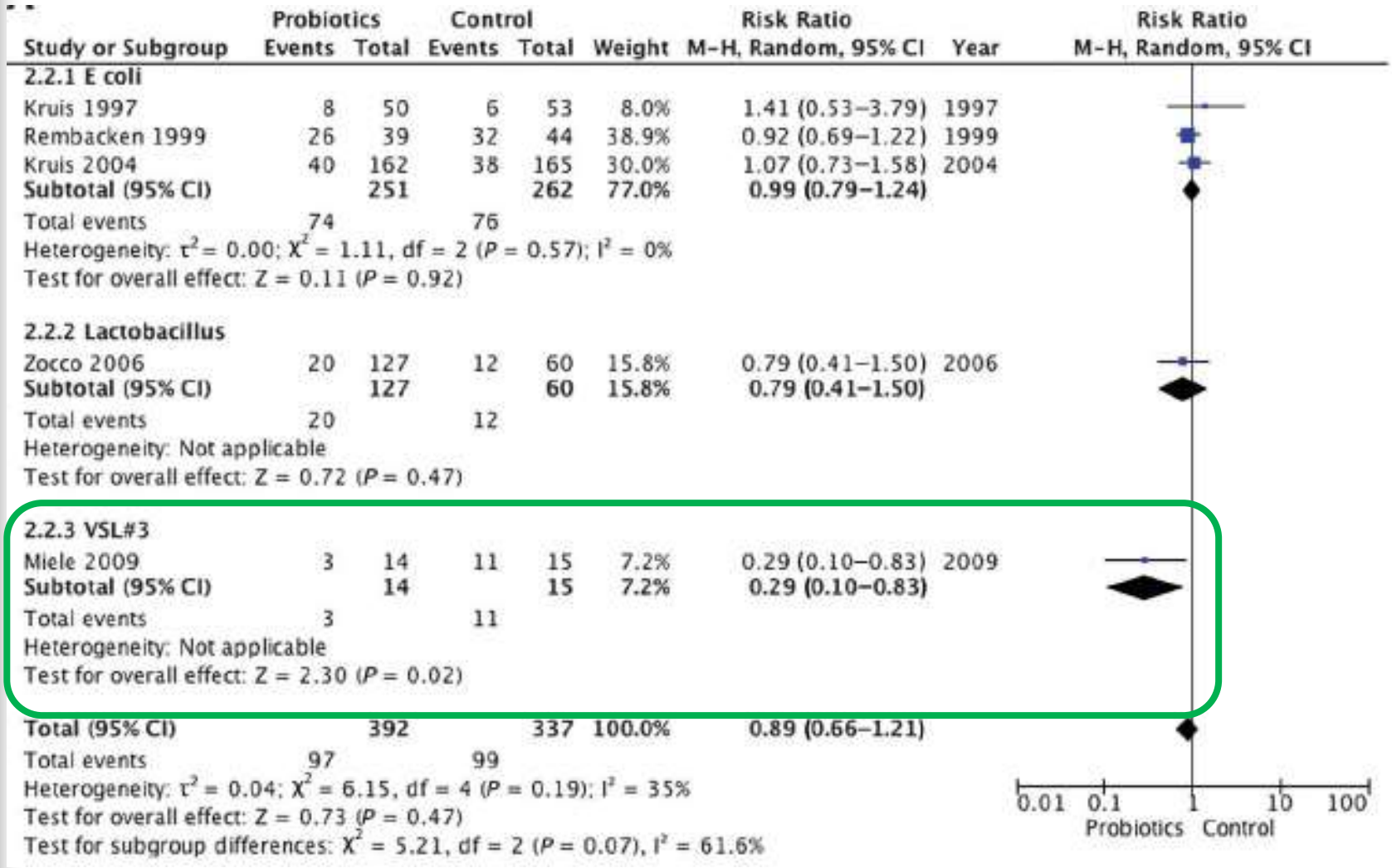
Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 UC							
Kruis 1997	8	50	6	53	5.8%	1.41 (0.53–3.79)	1997
Rembacken 1999	26	39	32	44	12.8%	0.92 (0.69–1.22)	1999
Kruis 2004	40	162	38	165	11.7%	1.07 (0.73–1.58)	2004
Zocco 2006	20	127	12	60	8.8%	0.79 (0.41–1.50)	2006
Miele 2009	3	14	11	15	5.3%	0.29 (0.10–0.83)	2009
Subtotal (95% CI)		**392**		**337**	**44.4%**	**0.89 (0.66–1.21)**	
Total events	97		99				
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 6.15$, df = 4 ($P = 0.19$); $I^2 = 35\%$							
Test for overall effect: $Z = 0.73$ ($P = 0.47$)							
1.2.2 CD							
Malchow 1997	4	12	7	11	6.3%	0.52 (0.21–1.31)	1997
Prantera 2002	3	15	2	17	2.8%	1.70 (0.33–8.84)	2002
Schultz 2004	2	4	3	5	4.4%	0.83 (0.25–2.80)	2004
Bousvaros 2005	12	39	6	36	6.7%	1.85 (0.77–4.40)	2005
Marteau 2006	4	48	3	50	3.4%	1.39 (0.33–5.88)	2006
Van Gossum 2007	4	34	3	36	3.5%	1.41 (0.34–5.85)	2007
Steed 2010	1	13	1	11	1.2%	0.85 (0.06–12.01)	2010
Subtotal (95% CI)		**165**		**166**	**28.2%**	**1.09 (0.69–1.74)**	
Total events	30		25				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.74$, df = 6 ($P = 0.58$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.38$ ($P = 0.71$)							
1.2.3 Pouchitis							
Gionchetti 2000	3	20	20	20	6.0%	0.17 (0.07–0.45)	2000
Gionchetti 2003	2	20	8	20	3.5%	0.25 (0.06–1.03)	2003
Mimura 2004	3	20	15	16	5.3%	0.16 (0.06–0.46)	2004
Wildt 2011	15	20	11	12	12.6%	0.82 (0.60–1.11)	2011
Subtotal (95% CI)		**80**		**68**	**27.4%**	**0.28 (0.06–1.27)**	
Total events	23		54				
Heterogeneity: $\tau^2 = 2.09$; $\chi^2 = 37.88$, df = 3 ($P < 0.00001$); $I^2 = 92\%$							
Test for overall effect: $Z = 1.65$ ($P = 0.10$)							
Total (95% CI)		**637**		**571**	**100.0%**	**0.73 (0.54–0.99)**	
Total events	150		178				
Heterogeneity: $\tau^2 = 0.17$; $\chi^2 = 36.52$, df = 15 ($P = 0.001$); $I^2 = 59\%$							
Test for overall effect: $Z = 2.04$ ($P = 0.04$)							
Test for subgroup differences: $\chi^2 = 2.94$, df = 2 ($P = 0.23$), $I^2 = 32.0\%$							

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Control Probiotics

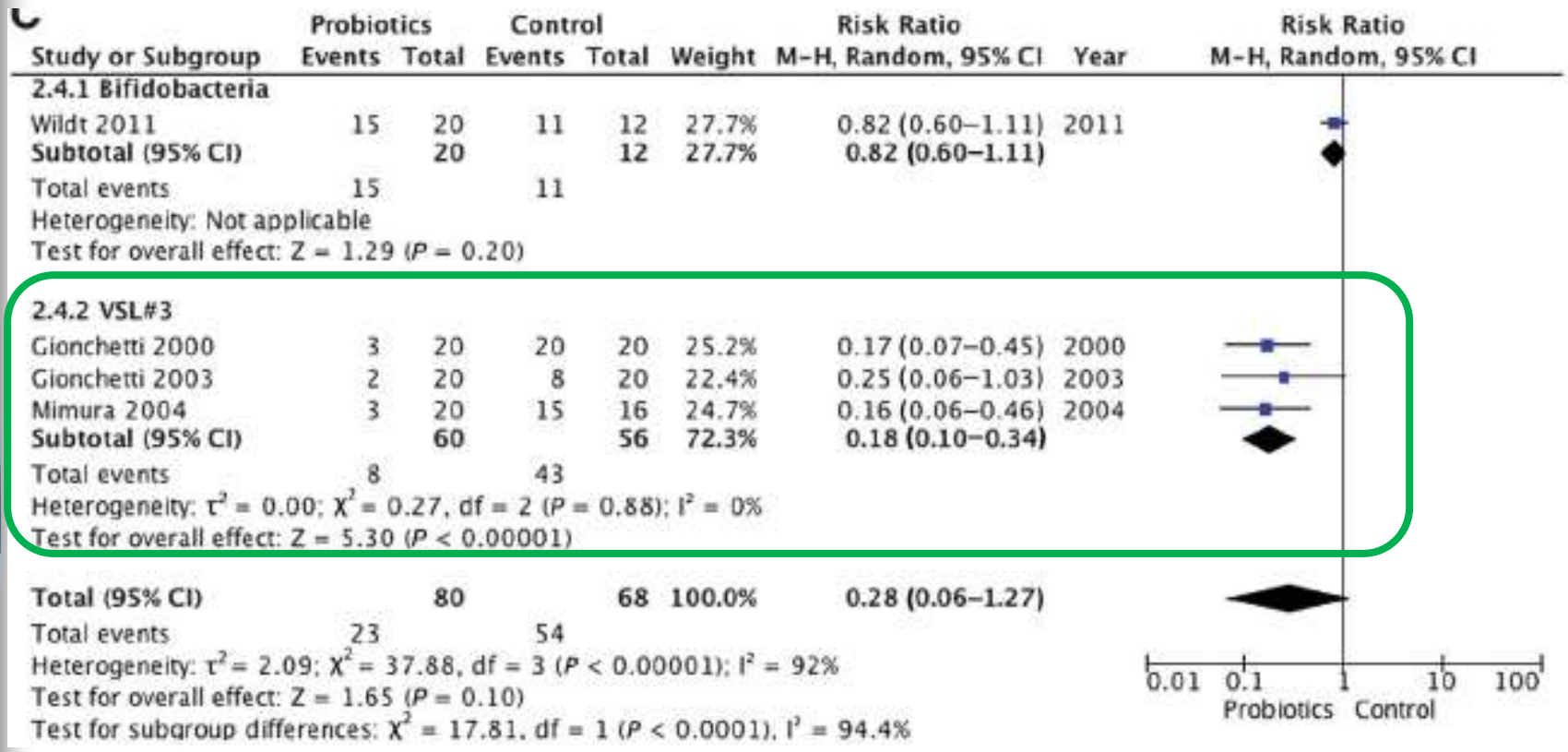
Which probiotic for maintaining remission in UC?



Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
2.2.1 E coli							
Kruis 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)**	
Total events	74		76				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.11$, df = 2 ($P = 0.57$); $I^2 = 0\%$							
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)**	
Total events	20		12				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.72 ($P = 0.47$)							
2.2.3 VSL#3							
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)**	
Total events	3		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.30 ($P = 0.02$)							
Total (95% CI)		**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 ($P = 0.19$); $I^2 = 35\%$							
Test for overall effect: Z = 0.73 ($P = 0.47$)							
Test for subgroup differences: $\chi^2 = 5.21$, df = 2 ($P = 0.07$), $I^2 = 61.6\%$							

Effect of probiotics on UC,CD and pouchitis – Meta-analysis of RCTs: IBD 2014

Which probiotic for maintaining remission of ***UC pouchitis***?



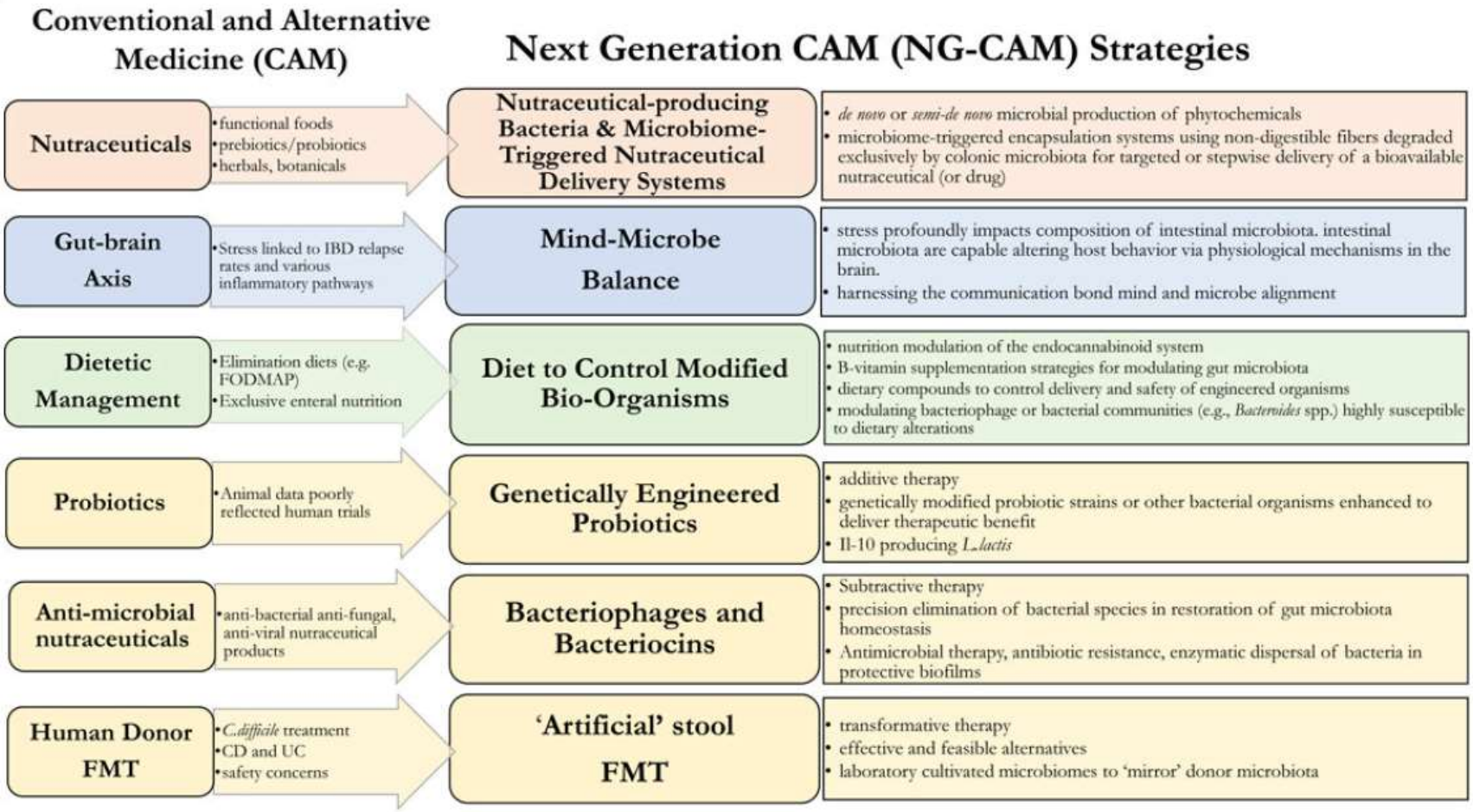
Effect of probiotics on UC,CD and pouchitis – Meta-analysis of RCTs: IBD 2014

Probiotics in IBD – What Works?

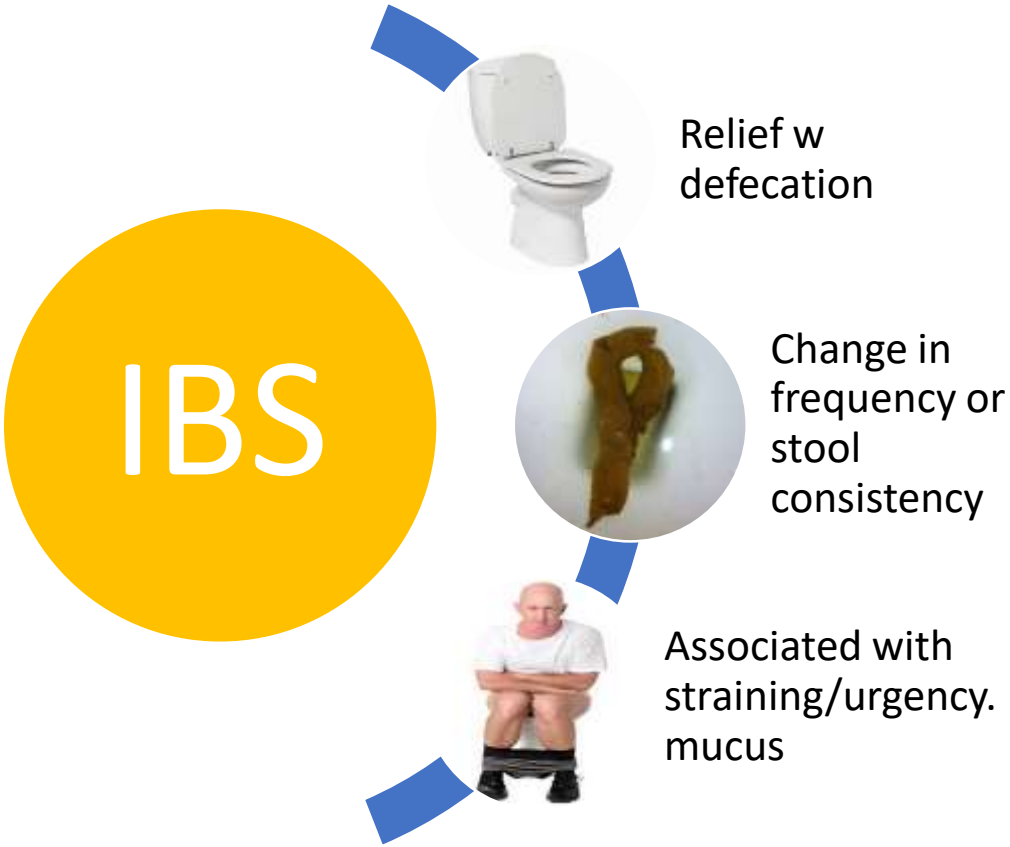
1. Ulcerative Colitis NOT Crohn's Dis.
2. Increase remission rates (RR=1.51)
3. Trend to preventing relapse (maintenance)
4. VSL#3
    1. Induction (RR=1.74)
    2. Maintenance – clinical relapse (RR=0.18)
    3. Pouchitis – most pronounced effect

Effect of probiotics on UC,CD and pouchitis – Meta-analysis of RCTs: IBD 2014

IBD and Microbiota CAM



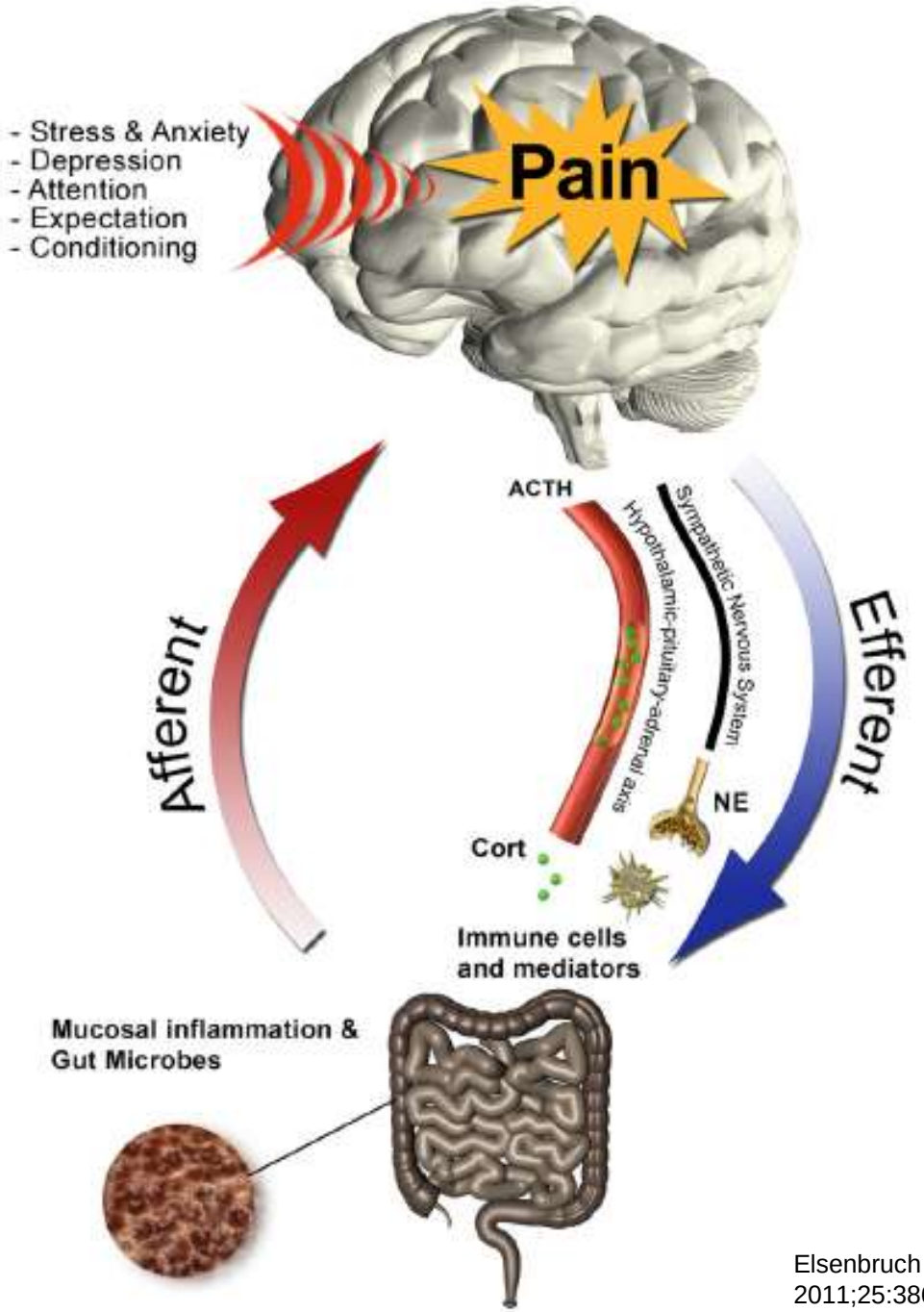
Irritable Bowel Syndrome



Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.



Elsenbruch S. Brain, Behavior & Immunity 2011;25:386-94

The case for a microbiota-IBS link

Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis

L-H Wang, X-C Fang, G-Z Pan

Gut 2004;53:1096–1101. doi: 10.1136/gut.2003.021154

INFLAMMATION AND MOTILITY

Increased rectal mucosal expression of interleukin 1β in recently acquired post-infectious irritable bowel syndrome

K-A Gwee, S M Collins, N W Read, A Rajnakova, Y Deng, J C Graham, M W McKendrick, S M Moochhala

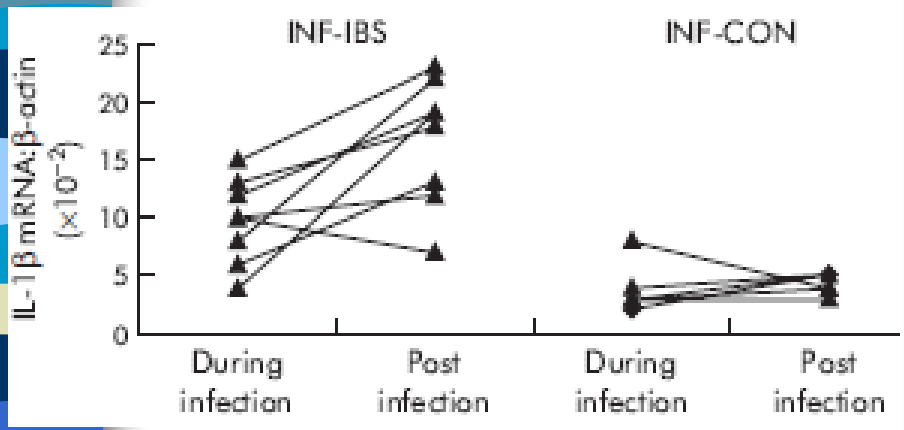


Table 1 Effect of duration of bacillary dysentery on the incidence of functional bowel disorders (FBD)

Duration (days)	n	FBD cases (%)	OR	95% CI
0–7	125	13 (10.40)	1.00	
8–14	104	30 (31.18)**	3.49	1.71–7.13
≥15	66	23 (34.85)**	4.61	2.14–9.91

Prolongation of the duration of BD over seven days significantly increased the incidence of FBD (**p<0.01).
FBD includes: IBS, n=24; functional diarrhoea, n=18; functional abdominal bloating, n=17; functional constipation, n=4; and unspecified functional bowel disorder, n=3.
OR, odds ratio; 95% CI, 95% confidence interval.

Do IBS pts have a different microbiome?

Study	Subject	Sample	Method	Patient group	Main finding	Country of study
Balsari *et al*[96]	IBS (n=20) Ctrls (n=20)	Faeces	Culture	IBS	↓ Coliform bacteria ↓ *Lactobacillus* spp. ↓ *Bifidobacterium* spp.	Italy
Si *et al*[98]	IBS (n=25) Ctrls (n=25)	Faeces	Culture	IBS	↓ Bifidobacterium ↑ Enterobacteriaceae ↓ *C perfringens*	China
Malinen *et al*[99]	IBS (n=27) Ctrls (n=22)	Faeces	qPCR	IBS IBS-D IBS-C	↓ *B catenulatum* ↓ *Cl coccoides* group ↓ *Lactobacillus* spp. ↑ *Veillonella* spp. ↑ *Lactobacillus* spp.	Finland
Mättö *et al*[100]	IBS (n=26) Ctrls (n=25)	Faeces	Culture PCR-DGGE	IBS	↑ Coliform bacteria ↑ Aerob to anaerob ratio ↓ Temporal stability	Finland
Maukonen *et al*[101]	IBS (n=24) Ctrls (n=16)	Faeces	PCR-DGGE Affinity capture	IBS IBS-C	↓ Temporal stability ↓ *Cl coccoides* group	Finland
Kassinen *et al*[102]	IBS (n=24) Ctrls (n=23)	Faeces	GC-profiling + sequencing of 16S rRNA genes qPCR	IBS	↓ *Collinsella aerofaciens* ↓ *Cl coclearium* ↓ *Coprococcus eutactus* Subgroup-diff (D, C, M)	Finland
Rajilić-Stojanović[103]	IBS (n=20) Ctrls (n=20)	Faeces	Microarray	IBS	Proteobacteria and specific Firmicutes↑ Other Firmicutes, Bacteroidetes and bifidobacteria ↓	Finland
Kerckhoffs *et al*[104]	IBS (n=41) Ctrls (n=26)	Faeces Duodenal mucosa	FISH qPCR	IBS	↓ *Bifidobacterium* spp. ↓ *B catenulatum*	The Netherlands
Krogius-Kurikka *et al*[105]	IBS-D (n=10) Ctrls (n=23)	Faeces	GC-profiling + sequencing of 16S rRNA genes	IBS-D	↑ Proteobacteria ↑ Firmicutes ↓ Actinobacteria ↓ Bacteroidetes	Finland
Lyra *et al*[106]	IBS (n=20) Ctrls (n=15)	Faeces	qPCR	IBS-D IBS-C IBS-A	↑ *R torques* 94% ↓ *Cl thermosuccinogenes* 85% ↑ *R bromii-like* ↓ *R torques* 93% ↑ *Cl thermosuccinogenes* 85%	Finland
Tana *et al*[107]	IBS (n=26) Ctrls (n=26)	Faeces	Culture qPCR	IBS	↑ *Veillonella* spp. ↑ *Lactobacillus* spp.	Japan
Codling *et al*[108]	IBS (n=41) Ctrls (n=33)	Faeces Colonic mucosa	PCR-DGGE	IBS	↑ Temporal stability No significant difference Faecal/mucosal	Ireland
Carroll *et al*[78]	IBS-D (n=10) Ctrls (n=10)	Faeces Colonic biopsies	Culture qPCR	IBS-D	↓ Aerobic bacteria *Lactobacillus* spp.	USA
Noor *et al*[109]	IBS (n=11) Ctrls (n=22) UC (n=13)	Faeces	PCR-DGGE + sequencing of 16S rRNA genes	IBS	↓ Bacterial species ↓ Biodiversity ↑ Biological variability of predominant bacteria	UK
Malinen *et al*[110]	IBS (n=44)	Faeces	qPCR		*R torques* 94% symptom severity Other phylotypes neg assoc.	Finland
Ponnusamy *et al*[111]	IBS (n=11) Ctrls (n=8)	Faeces	DGGE + qPCR of 16sRNA genes		↑ Diversity in Bacteroidetes & Lactobacilli ↑ Alanine & pyroglutamic acid & phenolic compounds	Korea
Rinttilä *et al*[112]	IBS (n=96) Ctrls (n=23)	Faeces	qPCR	IBS	*S aureus* (17%)	Finland
Saulnier *et al*[113]	IBS (n=22) Ctrls (n=22) (Children)	Faeces	16s Metagenomic sequencing and DNA microarray	IBS	↑ γ Proteobacteria Classified IBS subtypes using sets of discriminant bacterial species	USA
Rajilic-Stojanovic *et al*[114]	IBS (n=62) Ctrls (n=42)	Faeces	Phylogenetic 16S rRNA microarray and qPCR	IBS	↑ Proteobacteria and specific Firmicutes ↓ Other Firmicutes, Bacteroidetes and bifidobacteria	Finland

Simren et al. Intestinal Microflora in FBD: A Rome foundation Report. Gut 2014

TABLE 1. Important Randomized Controlled Trials Investigating Probiotics Vs. Placebo in IBS

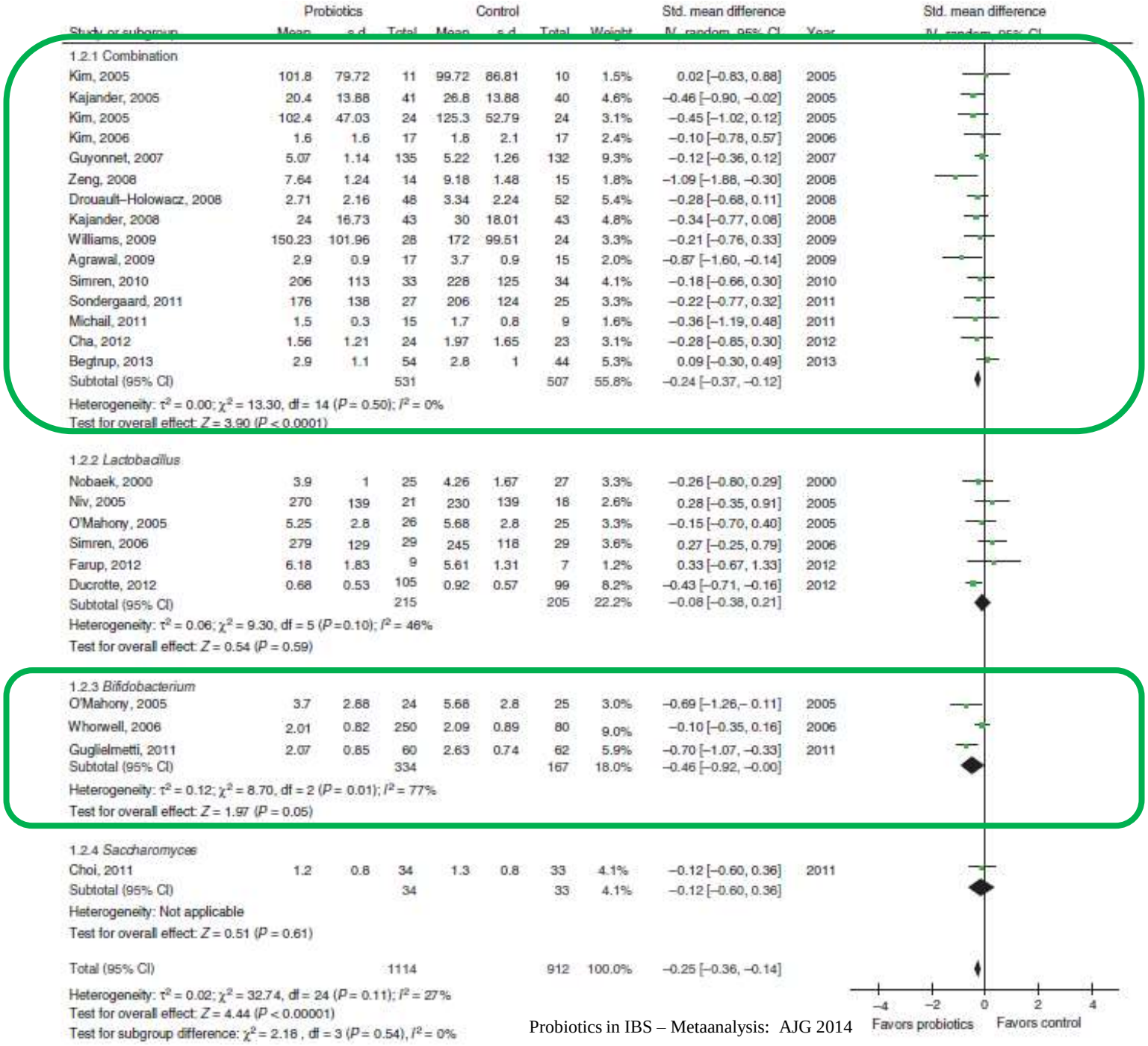
Probiotic Intervention	No. of Studies [Ref]	No. of Patients	Intervention Duration	Study Outcome	Recommendation†/‡
Single probiotics					
LGG	1.*Bausserman and Michail[22]	50	6 wk	No benefit over placebo	
	2.*Gawronska et al[23]	104	4 wk	Reduction in abdominal pain in IBS not in FAP or FD	B/C (in children)
	3.*Francavilla et al[24]	141	8 wk	Reduction in abdominal pain	
VSL#3	1. Kim et al[28]	25	8 wk	Reduction in bloating or symptoms No significant change in gut transit	
	2. Kim et al[29]	48	4/8 wk	Significant reduction in flatulence and slower transit	C
	3.*Guandalini et al[25]	59	6 wk	Improvement of IBS symptoms	C (in children)
B. infantis 35624	1. O'Mahony et al[18]	77	8 wk	Reduction in abdominal pain, bloating, bowel satisfaction, and composite score	B/C
B. infantis 35624	2. Whorwell et al[19]	362	4 wk	Improvement in IBS symptoms and IBS global assessment score for 1×10^8	
L. Plantarum (DSM 9843)	1. Nobaek et al[30]	60	4 wk	Reduction in flatulence	C
L. Plantarym 299V	1. Niedzielin et al[31]	40	4 wk	Resolution of pain	C
L. reuteri ATCC 55730	1. Niv et al[32]	54	6mo	No benefit over placebo	
B. animalis DN 173010	1. Guyonnet et al[33]	274	6 wk	No benefit over placebo. Subanalysis (n = 19) increase in stools frequency	C
Bacillus coagulans GBI-30, 6086	1. Dolin[34]	55	8 wk	Reduction in number of BM per day	C
Synbiotic					
Lactobacillus paracasei B21060 with prebiotics vs. prebiotics	1. Andriulli et al[35]	135	12 wk	No benefit of synbiotic over prebiotic. Significant reduction in BM, pain, IBS Score in D-IBS (n = 47)	C
Mixed probiotics					
LGG, *L. rhamnosus* LC705, *B. breve* Bb99	1. Kajanda et al[20]	103	6mo	Reduction in total symptom scores in intervention	
Propionibacterium freudenreichii spp shermanii JS	2. Kajanda et al[21]	86	5mo	Reduction in GSS	B/C
L. acidophilus SDC 2012 and 2013	1. Sinn et al[36]	40	2 wk	Reduction in abdominal pain	C
B. longum LA 101, *Lb. acidophilus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104	1. Drouault-Holowacz et al[37]	100	4 wk	No benefit over placebo. Some benefit in subgroup analysis	C
E. coli (DSM 17252) and *En. faecalis* (DSM 16440)	1. Enck et al[38] 2. Enck et al[39]	297	8 wk	Reduction in GSS by 50% Reanalysis of previous data	C
Lactobacillus acidophilus CUL60 (NCIMB 30157) and CUL21 (NCIMB 30156), *Bifidobacterium lactis* CUL34 (NCIMB 30172)	1. Williams et al[40]	52	8 wk	Significant reduction in Symptom severity score	C
L. paracasei, ssp. paracasei F19, *L. acidophilus* La5 and *B. lactis* Bb12	1. Simrén et al[41]	74	8 wk	No benefit over placebo	
L. acidophilus NCFM and *B. lactis* Bi-07	1. Ringel-Kulka et al[42]	60	8 wk	Significant reduction in bloating	C

*Study done in children.

†Recommendation is based on: A = strong, positive, well-conducted, controlled studies in the primary literature, not abstract form; B = some positive, controlled studies but presence of some negative studies or inadequate amount of work to establish the certainty; C = some positive studies but clearly inadequate amount of work to establish the certainty of "A" or "B."

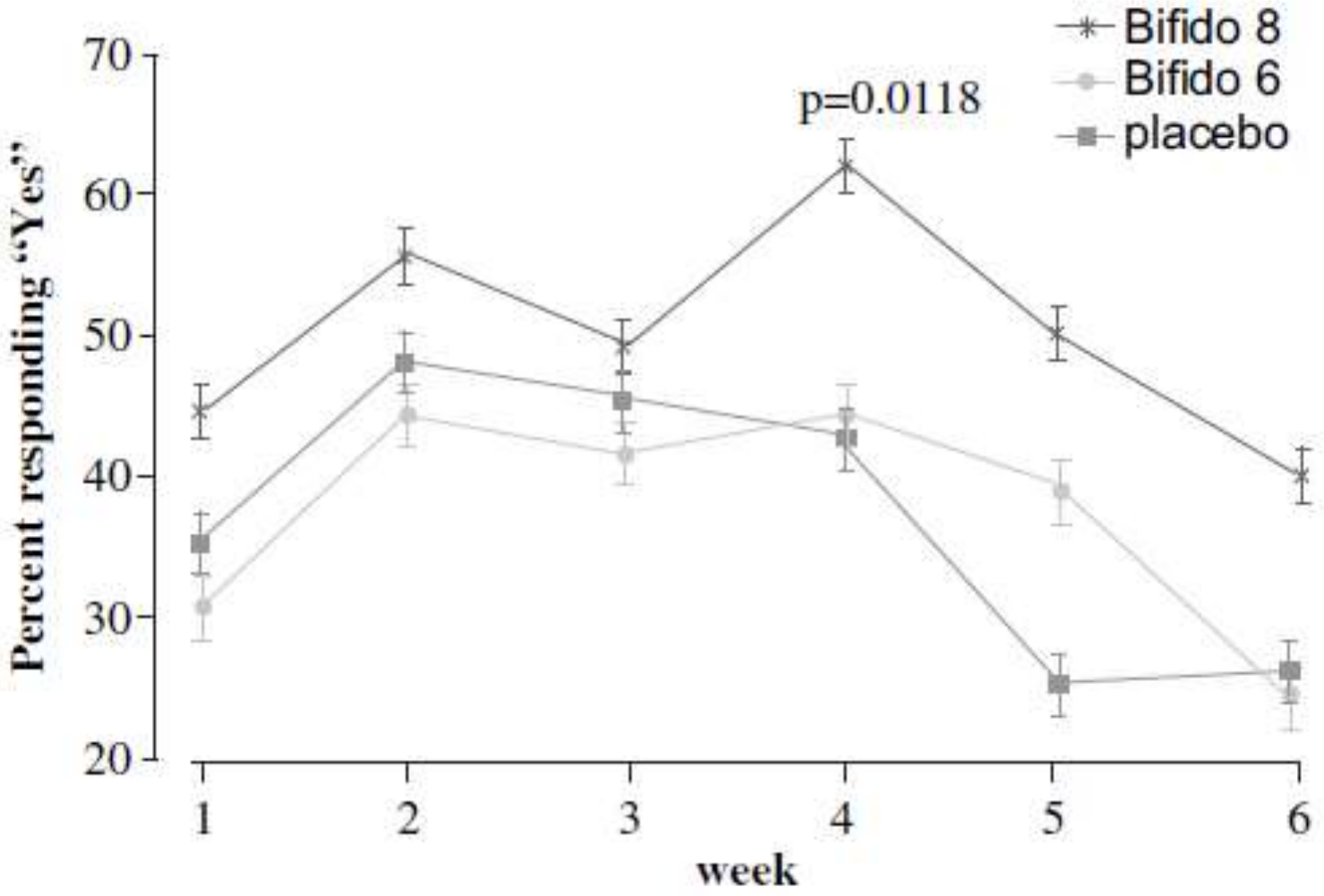
‡Recommendations relate to the specific strains that were tested and reported to be effective.

B indicates Bifidobacretium; BM, bowel movements; E, Escherichia; En, Enterococcus; FAP, functional abdominal pain; FD, functional dyspepsia; GSS, global symptom score; IBS, irritable bowel syndrome; L, Lactobacillus.



Probiotics in IBS – Metaanalysis: AJG 2014

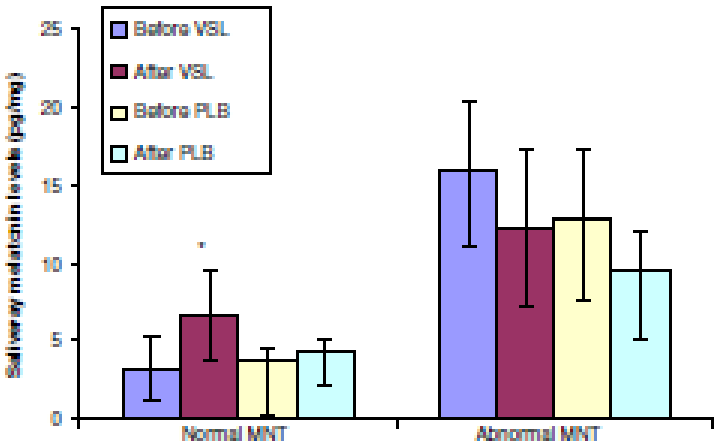
"Do you feel better?" with *B. Infantis*

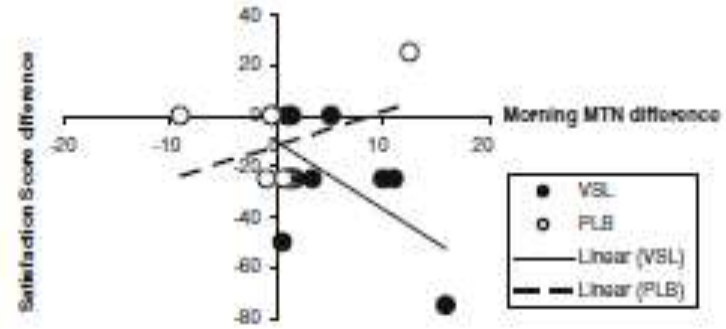


An alternative mechanism of action?

Melatonin Regulation as a Possible Mechanism for Probiotic (VSL#3) in Irritable Bowel Syndrome: A Randomized Double-Blinded Placebo Study

Reuben K. Wong · Cao Yang · Guang-Hui Song · Jennie Wong · Khek-Yu Ho





Melatonin Regulation as mechanism for VSL#3 : Dig Dis Sci 2015

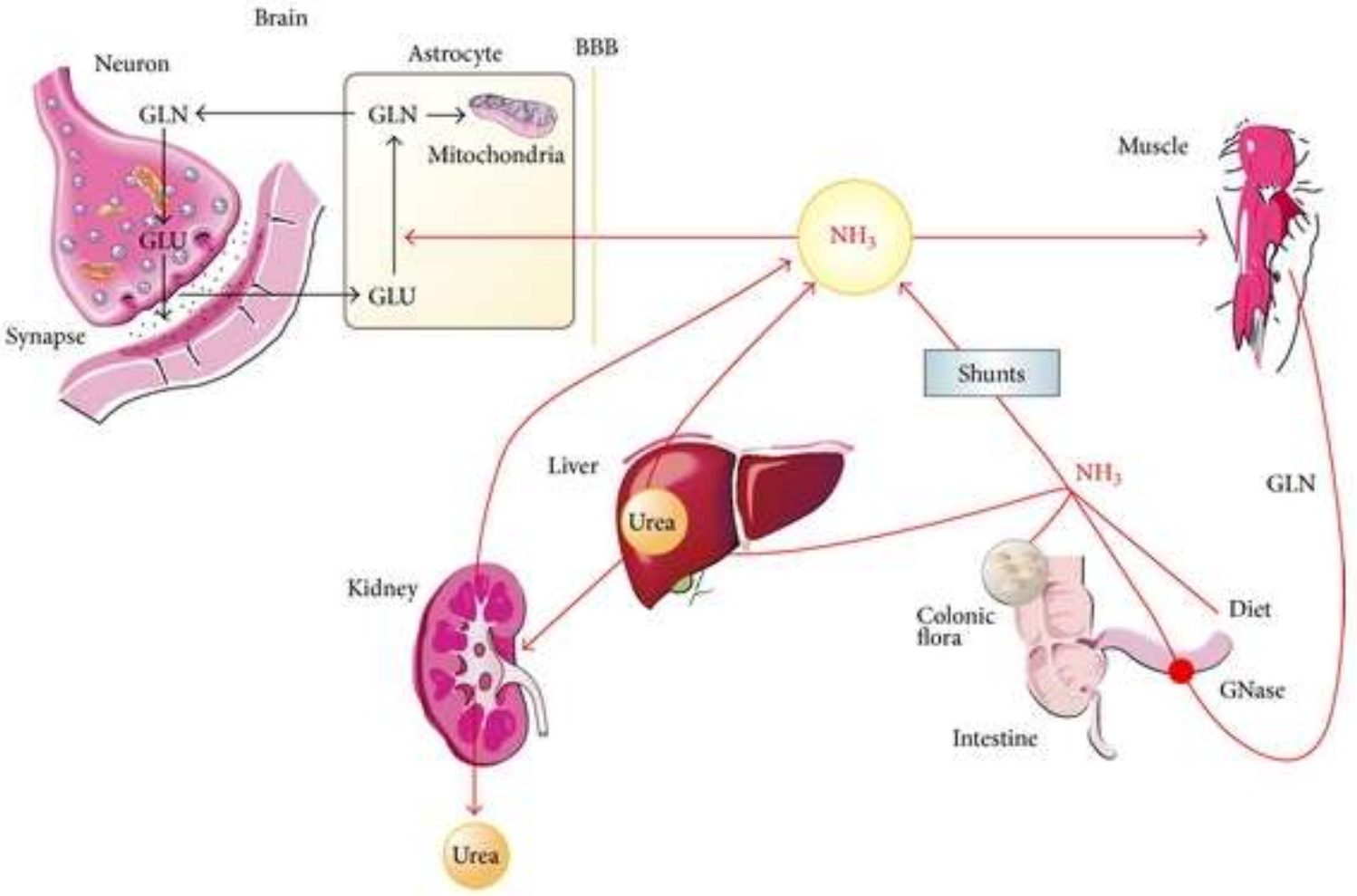
FMT in IBS (3 months)

Country	Author	Subjects	N	Outcome	Results %	P-value
Belgian	Holovert	IBS (NC)	64	AR	49 vs. 29	0.004
USA	Aroniatis	IBS-D	48	IBS-SSS	48 vs. 63	0.32
Danish	Halkjaer	IBS	52	IBS-SSS	-	-

1st RCT for FMT in IBS

- Significance is the 1st study of FMT for a Functional Disorder
- Norwegian study – 90 non-constipated
- RCT – Donor stool vs. Autologus Transplant
- Results (>75 pt improvement in the IBS-SSS)
  - 65 vs 43% (p=0.049) 6 mths
  - 56 vs 36% (p=0.075) 12 mths

Hepatic Encephalopathy



Balancing the Ammonia load

Predisposing to HE

- Porto-systemic shunt
- Poor hepatic function
- Constipation
- High protein load in diet
- GI bleed

Alleviating HE

- Diet modulation
- Laxatives (lactulose/PEG)
- Antibiotics (neomycin)

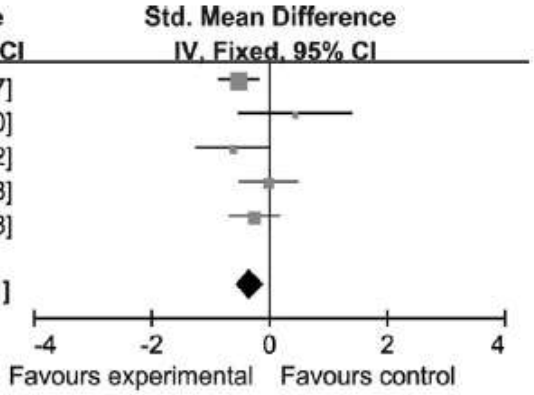
Alter intestinal protein metabolism…
Re-condition the Intestinal Microflora !

Do probiotics have an effect on ammonia?

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Agrawal 2012	75.2	20.9	64	85.2	16.7	65	39.0%	-0.53 [-0.88, -0.17]
Bajaj 2008	50	26	14	40	3	6	5.1%	0.43 [-0.54, 1.40]
Liu 2004	38.6	3.9	20	41.5	5.2	20	11.9%	-0.62 [-1.25, 0.02]
Sharma 2008	68.7	28.4	30	69.3	33.3	31	19.1%	-0.02 [-0.52, 0.48]
Zhao 2013	72.87	15.84	40	76.35	10.23	40	24.8%	-0.26 [-0.70, 0.18]
Total (95% CI)			**168**			**162**	**100.0%**	**-0.32 [-0.54, -0.11]**

Heterogeneity: Chi² = 5.94, df = 4 (P = 0.20); I² = 33%

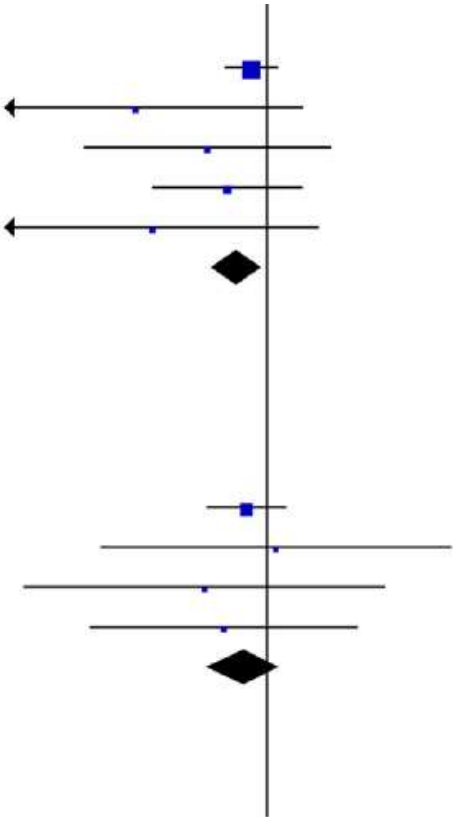
Test for overall effect: Z = 2.90 (P = 0.004)



Probiotics improve outcomes of HE – Updated Meta-analysis: Clin Res Gastro Hepatol 2015

Effects of Probiotics on reducing adverse outcomes in HE

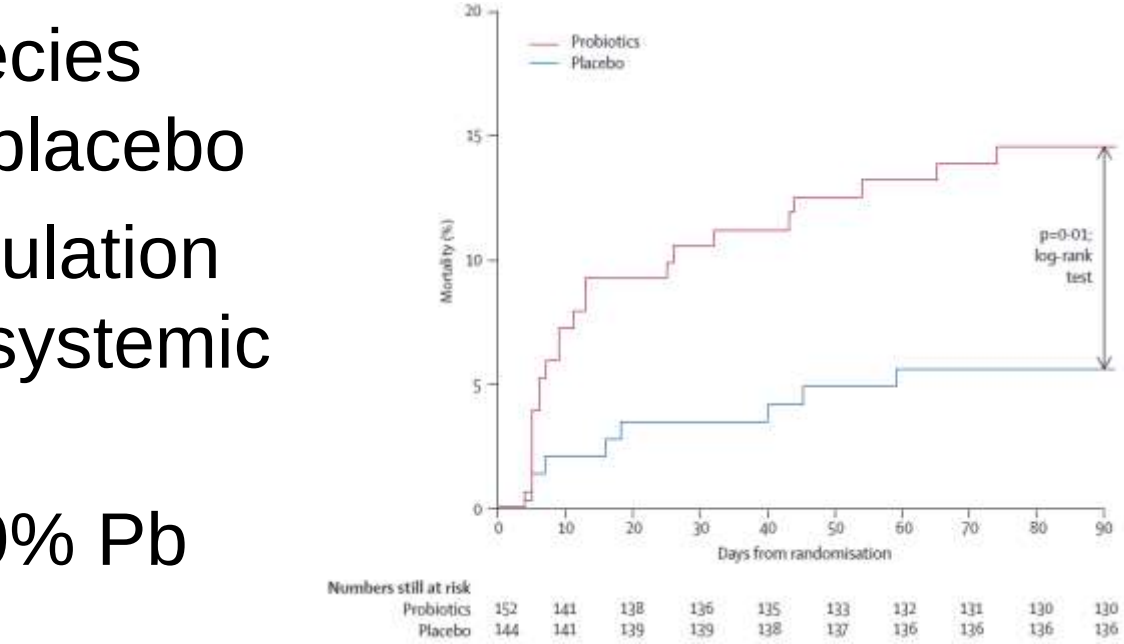
6.1.2 Severe adverse events						
Agrawal 2012	21	77	28	78	33.3%	0.76 [0.47, 1.22]
Bajaj 2008	0	17	2	8	4.0%	0.10 [0.01, 1.87]
Bajaj 2014	1	18	3	19	3.5%	0.35 [0.04, 3.08]
Mittal 2011	3	40	6	40	7.2%	0.50 [0.13, 1.86]
Sharma 2014	0	32	3	30	4.3%	0.13 [0.01, 2.49]
Subtotal (95% CI)		**184**		**175**	**52.4%**	**0.59 [0.39, 0.90]**
Total events	25		42			
Heterogeneity: Chi² = 3.75, df = 4 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
6.1.3 Mortality						
Agrawal 2012	11	77	16	78	19.1%	0.70 [0.35, 1.40]
Bajaj 2008	1	17	0	6	0.9%	1.17 [0.05, 25.37]
Mittal 2011	0	40	1	40	1.8%	0.33 [0.01, 7.95]
Sharma 2014	1	32	2	30	2.5%	0.47 [0.04, 4.91]
Subtotal (95% CI)		**166**		**154**	**24.2%**	**0.66 [0.35, 1.26]**
Total events	13		19			
Heterogeneity: Chi² = 0.41, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						



Probiotics improve outcomes of HE – Updated Meta-analysis: Clin Res Gastro Hepatol 2015

Are probiotics the universal panacea?

- Acute Pancreatitis
- 152 multispecies probiotic vs placebo
- Immunomodulation and reduce systemic sepsis
- Infections 30% Pb vs. 28% Pl
- 2.53 RR of death in Pb group



Probiotic Prophylaxis in predicted severe acute pancreatitis: Lancet 2008

Gut conditions amenable to microbiota manipulation

- Diarrhea
  - Gastroenteritis
  - C Difficile
  - Antibiotic Associated
- Colitis
  - Ulcerative Colitis
  - Radiation Colitis
  - NEC
- Functional
  - IBS
- Hepatology
  - Hepatic encephalopathy
- Others
  - H Pylori

The Role for Pre & Probiotics in Chronic Gut Disorders

(in the Asia-Pacific Region)

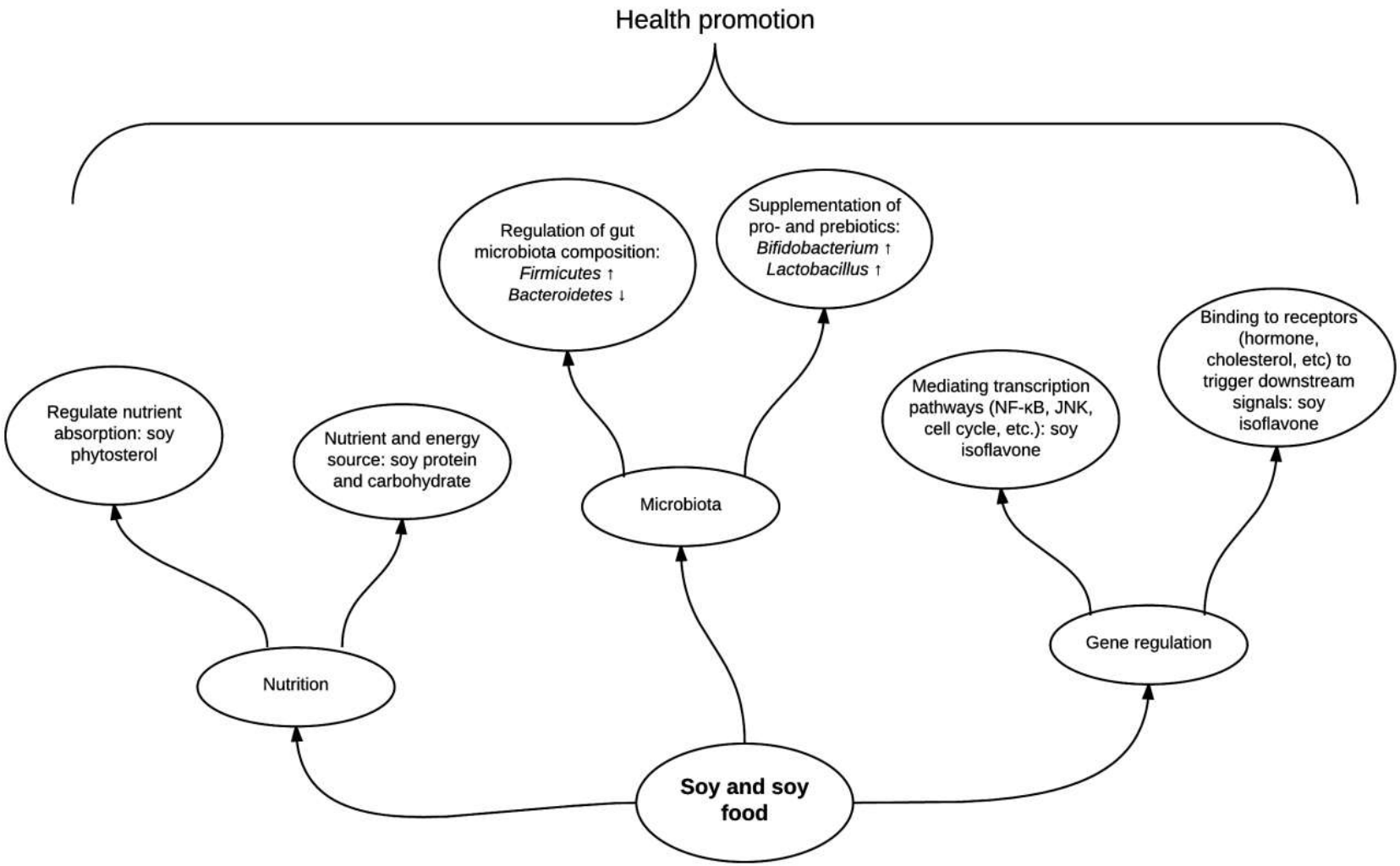
Reuben KM Wong

MBBS AGAF FRCP FAMS

Associate Professor

Gastroenterologist

Soy based foods



Where Are We?

- Role of Microbiota in Gut disorders is firmly established
- Clear that we can manipulate microbiota for benefit
- Different Ways of doing so…
  - Antibiotics
  - Probiotics
  - Regime Change (FMT)

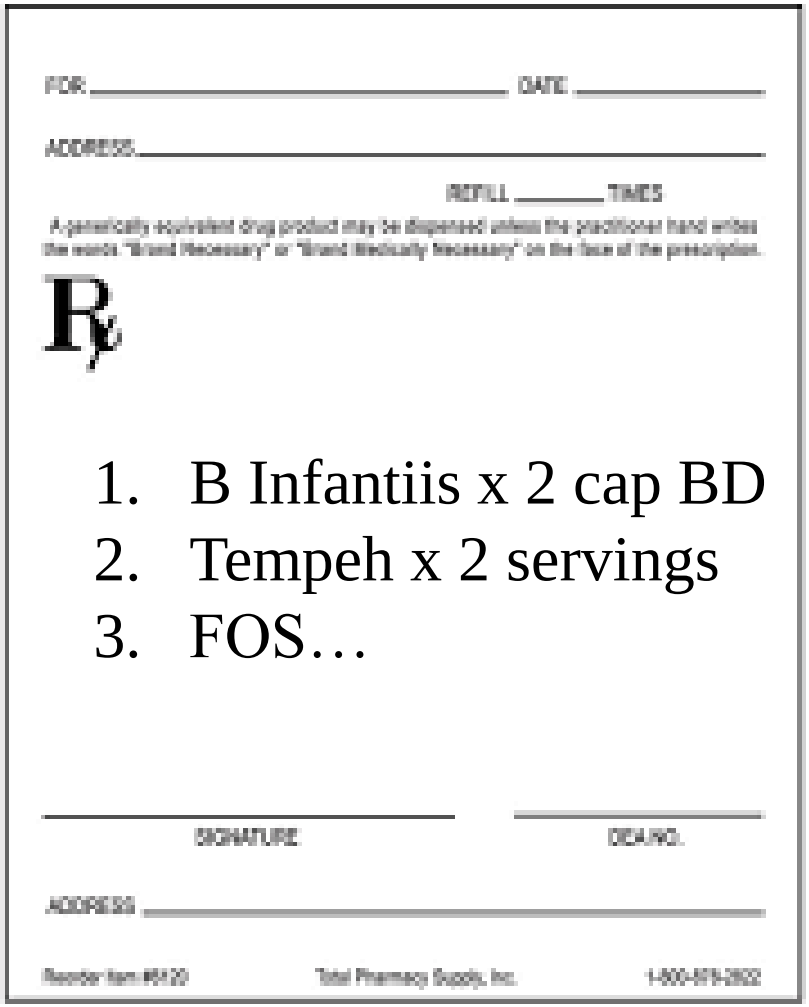
New Indications for Microbial Manipulation in chronic GID

- Distinct Microbial signature in BE (Yang et al. Gastro 2009)
- Progression to adenocarcinoma (Snider et al. DDW 2017)
  - Alpha diversity unchanged
  - Deceased Frimacutes and Increased Proteobacteria
  - Decreased Veillonella and Increased Streptomyces & Enterobacteria
- Oral Microbiome reflects Esophageal
- Chlorhexidine mouthwash alters flora

Ways to alter the microbiota

- Seed & Soil Hypothesis
  - Pro and Prebiotics synergistically
  - Consistent long-term dosing?
- FMT
  - Too blunt
  - Regime Change

Prescription



FOR: _____ DATE: _____

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A generically equivalent drug product may be dispensed unless the practitioner hand writes the words "Brand Necessary" or "Brand Medically Necessary" on the face of the prescription.

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1. B Infantiis x 2 cap BD
2. Tempeh x 2 servings
3. FOS…

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SIGNATURE DEA NO.

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Reorder Item #8120 Total Pharmacy Supply, Inc. 1-800-876-2802

Way Forwards

Yusof et al. Gut Pathog (2017) 9:75
https://doi.org/10.1186/s13099-017-0224-7

Gut Pathogens

RESEARCH Open Access

Exposure to environmental microbiota explains persistent abdominal pain and irritable bowel syndrome after a major flood

NurFadhilah Yusof[1†], Nurhazwani Hamid[1†], Zheng Feei Ma[1,2†], Rona Marie Lawenko[3], Wan Mohd Zahiruddin Wan Mohammad[1], Deirdre A. Collins[4], Min Tze Liong[5], Toshitaka Odamaki[6], Jinzhong Xiao[6] and Yeong Yeh Lee[1*]

- More Asian based studies
  - Local ways of manipulating flora
- Bring Bench to Bedside
  - Murine studies into humans
  - Practically test in humans
- Practical Guidance
  - Guidelines galore
  - No good international ones crafted by scientists with clinicians
  - ISAPP

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