Microbiome manipulation as therapeutics

-2020 Annual Refresher Course for Family Physicians-

Marty Teltscher, MDCM, FRCPC

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Disclosure

- Consulting market research for REBYOTA, Rebiotix/Scherring

Objectives

(1) Define terms such as microbiome, microbiota, probiotics, prebiotics, and postbiotics

(2) Describe the utility and functioning of probiotics and assess the difficulty in studying their efficacy

(3) Explain the process and proposed mechanism-of-action of the fecal microbiota transplantation (FMT)

Caveat…

MAJOR ARTICLE

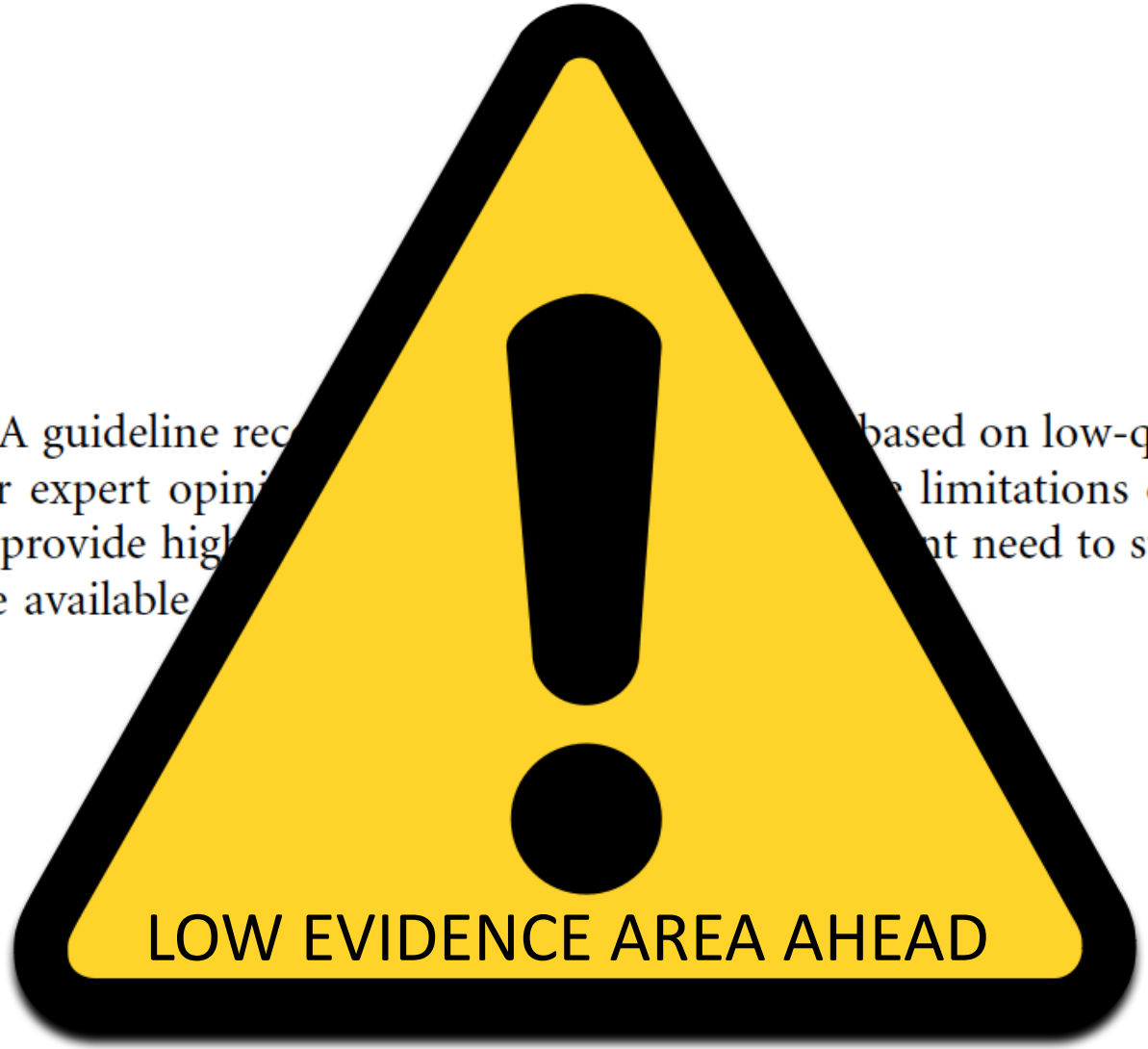
Quality and Strength of Evidence of the Infectious Diseases Society of America Clinical Practice Guidelines

Abdur Rahman Khan,[1] Sobia Khan, Valerie Zimmerman, Larry M. Baddour,[3] and Imad M. Tleyjeh[1,2,3,4]

[1]Division of Infectious Diseases, Department of Medicine, and [2]Research Centre, King Fahd Medical City, Riyadh, Saudi Arabia; and [3]Division of Infectious Diseases, Department of Medicine, and [4]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

CID 2010; 51: 1147-1156

Conclusions. The IDSA guideline rec…based on low-quality evidence derived from nonrandomized studies or expert opini… limitations of current clinical infectious diseases research that can provide high…nt need to support high-quality research to strengthen the evidence available…



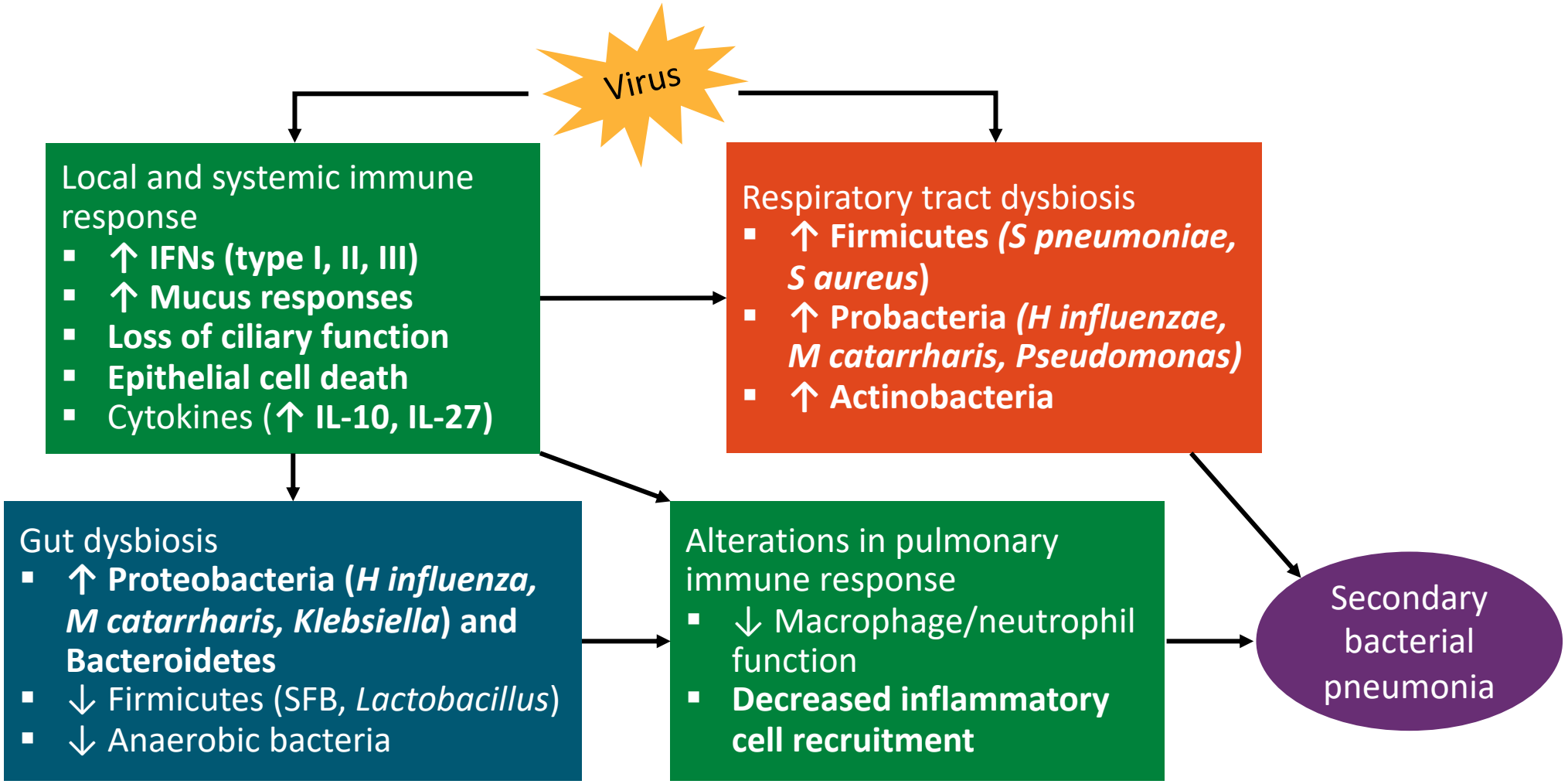
Key definitions

Microbiome The collection of all genomes of microbes in an ecosystem

Microbiota The microbes that collectively inhabit a given organism

Lynch and Perderen. *NEJM* 2016; 375:2369-79
WHO expert panel report 2001
Roberfroid. *J Nutr* 2007; 137:830S-837S

A Proposed Model for Viral-Induced Susceptibility to Secondary Bacterial Pneumonia



Hanada. Front Immunol. 2018;9:2640.

Slide credit: clinicaloptions.com

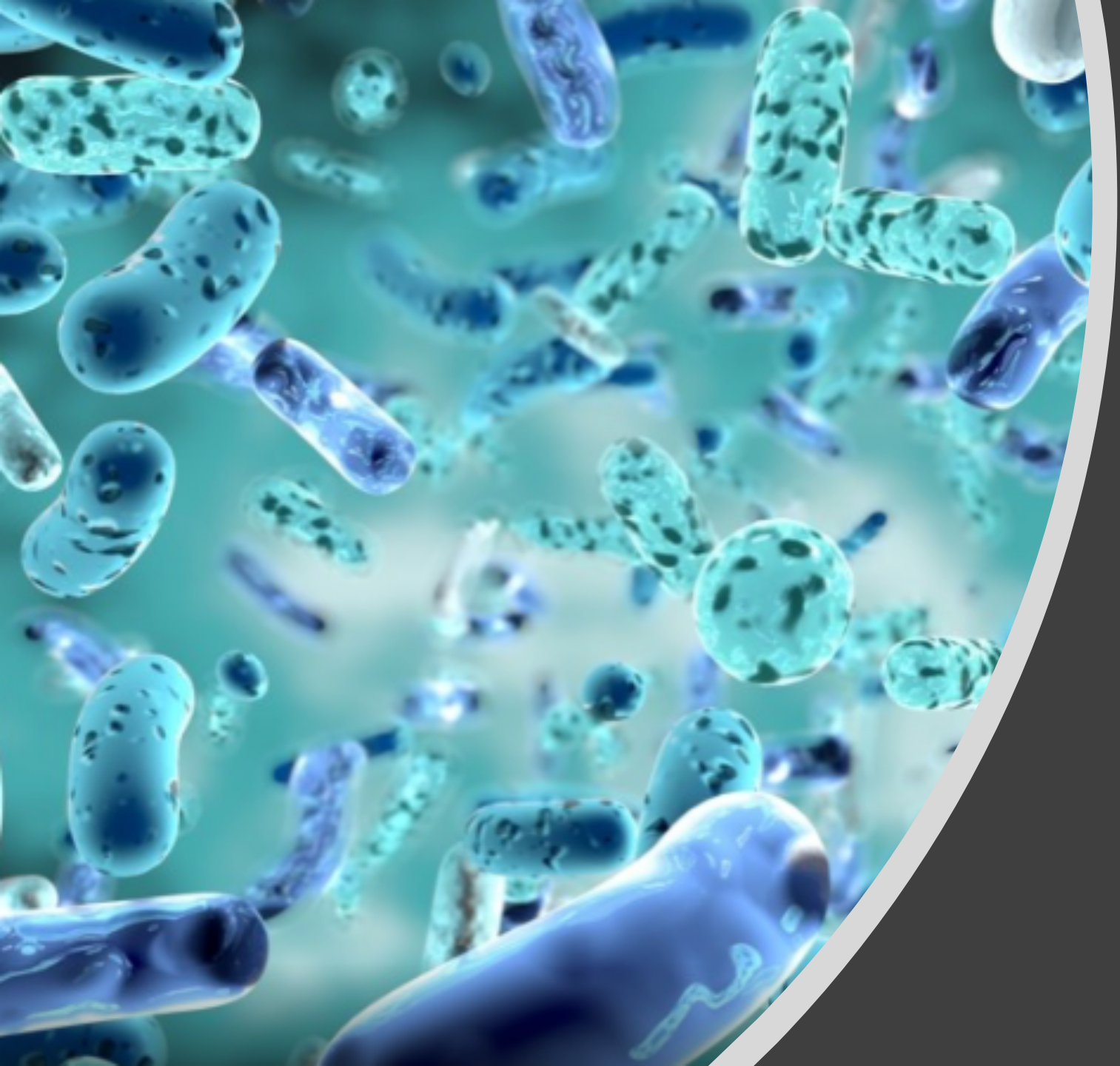
Key definitions

Probiotic	Live microbes that confer health benefits when administered in adequate amounts in the host
Prebiotic	selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health
Postbiotic	Substances released by or produced through the metabolic activity of the microorganisms which exert a beneficial effect on the host directly or indirectly
Synbiotic	Combination of probiotic + prebiotic in a complimentary or synergistic fashion to produce a health benefit

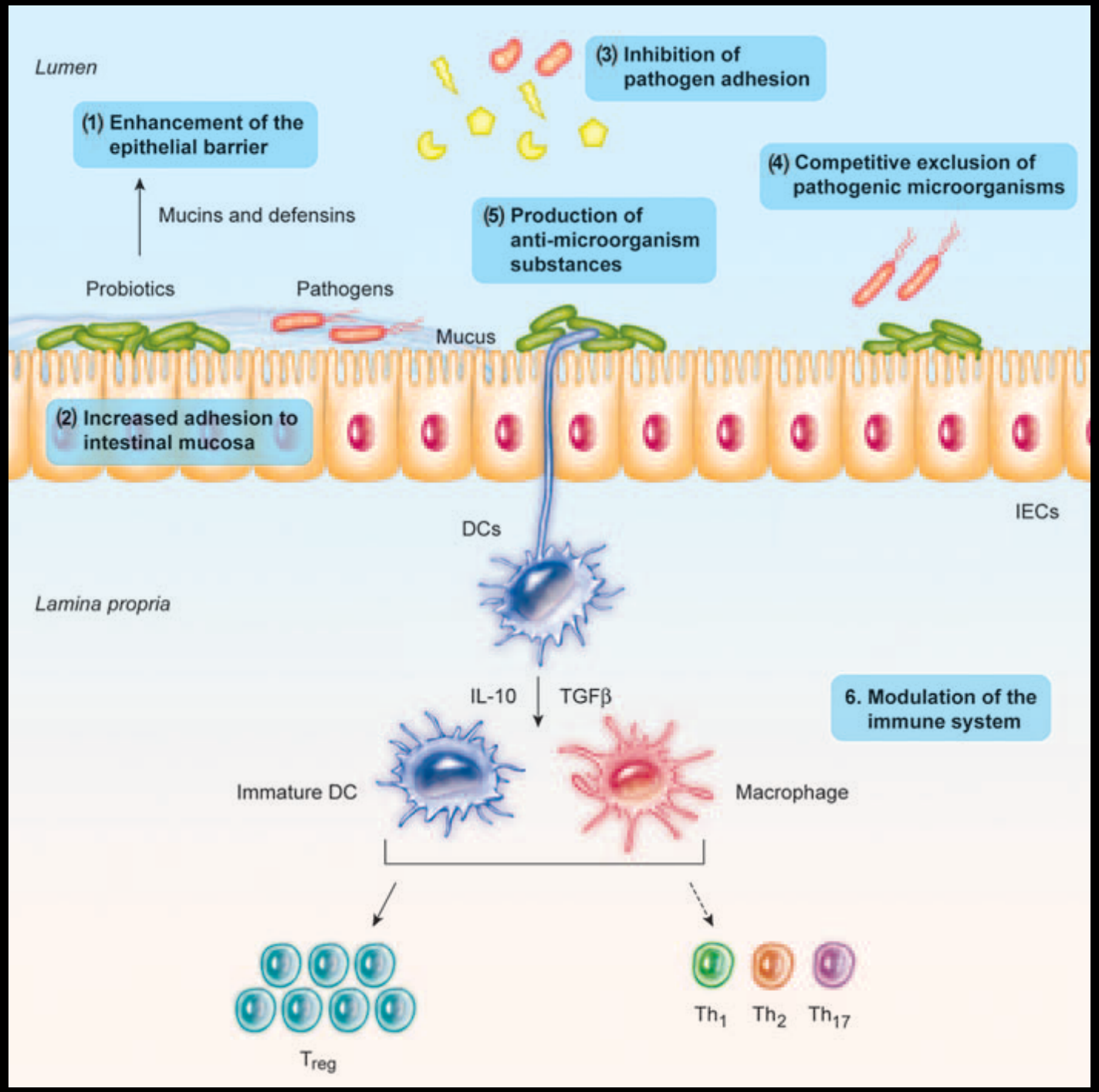
Lynch and Perderen. *NEJM* 2016; 375:2369-79

WHO expert panel report 2001

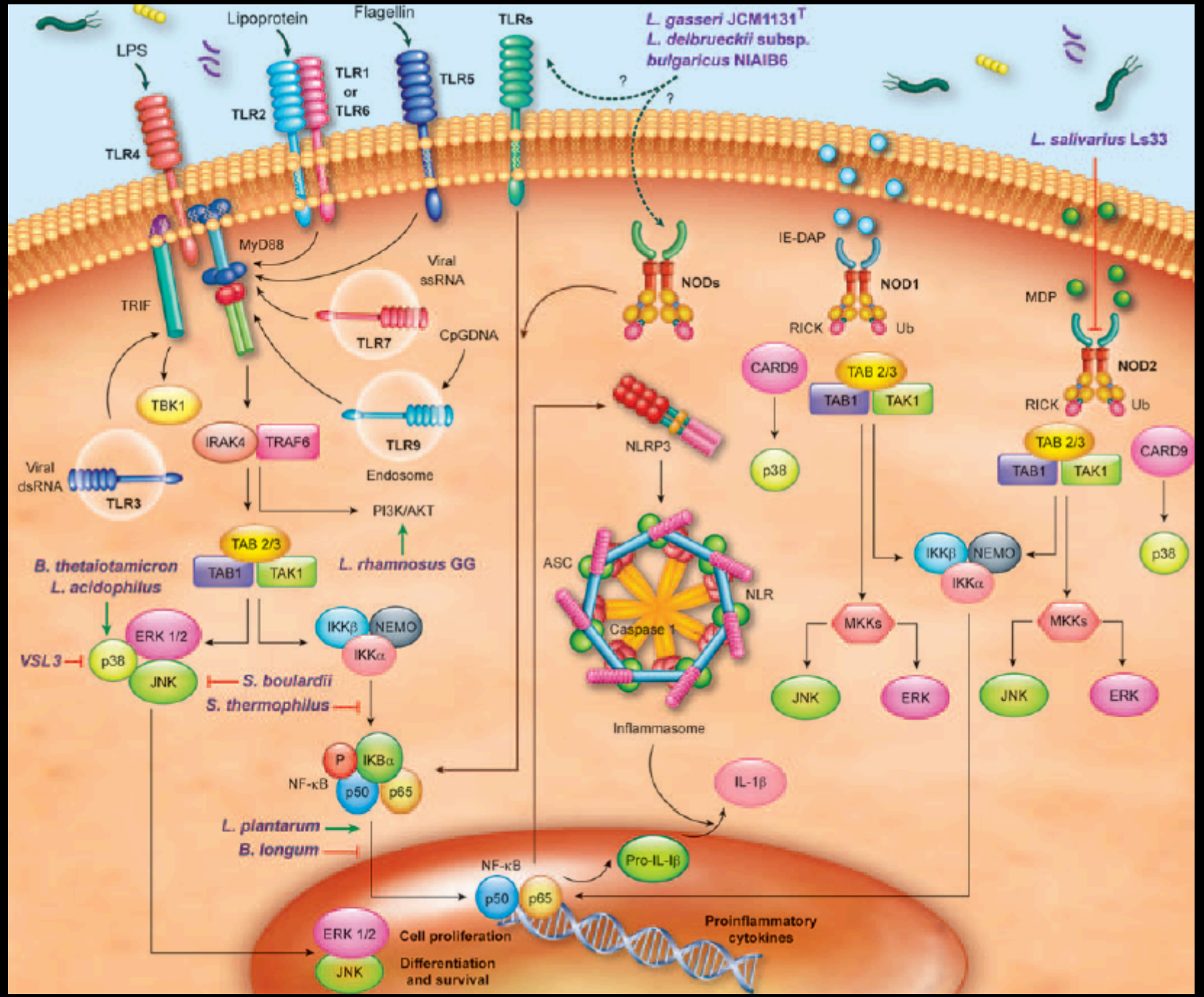
Roberfroid. *J Nutr* 2007; 137:830S-837S



Probiotics



Ann Nutr Metab
2012; 61:160-174



Ann Nutr Metab
2012; 61:160-174

Probiotics

Pitfalls

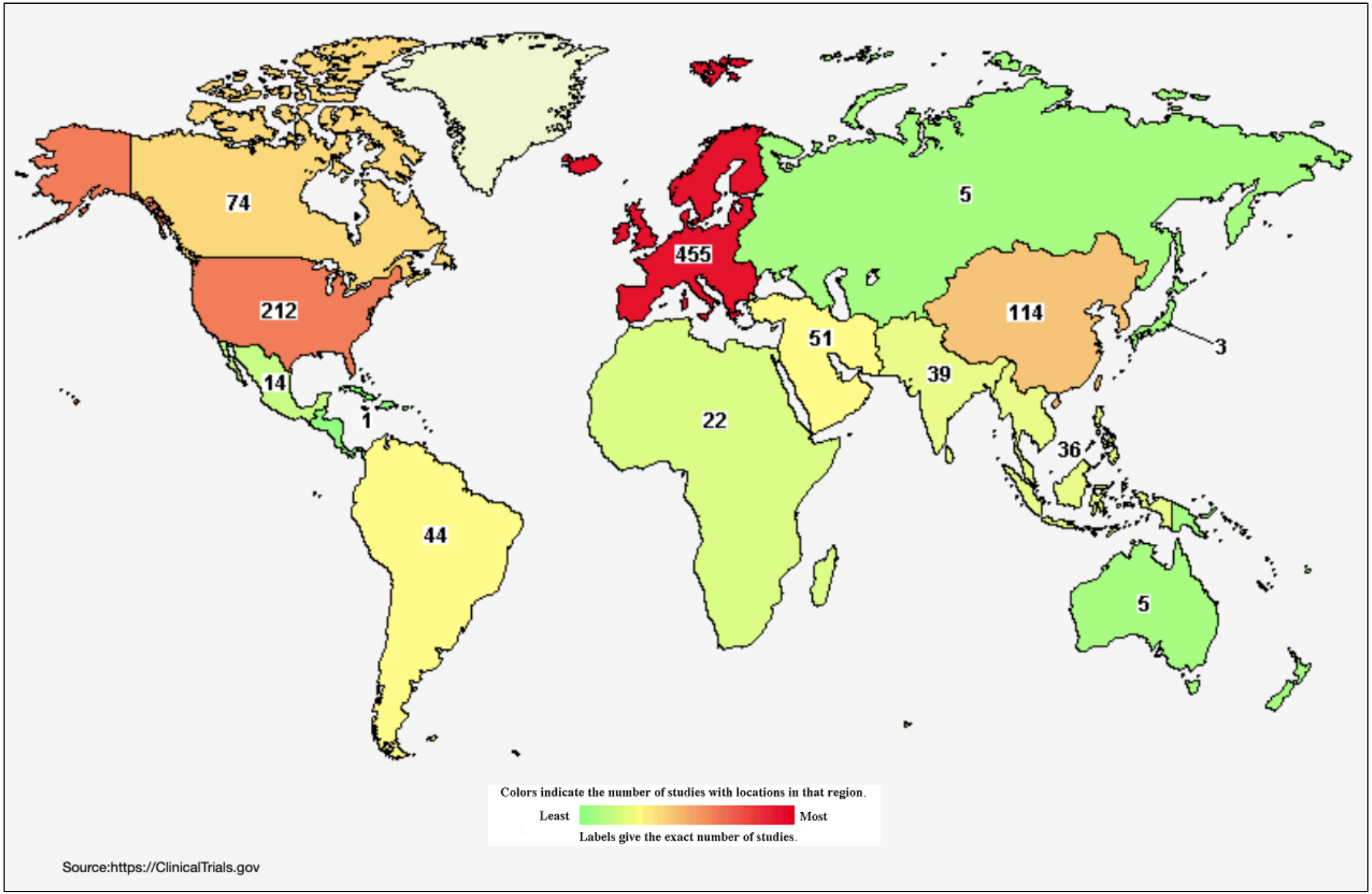
- Lack of consensus
- Lack of regulatory requirements, “dietary supplement”
- Which formulation? Which Strain? Which combination? For which condition?
- High dose vs Low dose? Lack of assurance of number of active cultures
- Cost and insurance coverage
- Toxicity and lack of reporting – bloodstream infections

Local Assessment of Probiotics

- MUHC Technology Assessment unit, 2005:

"There is very little evidence relating to the use of probiotics for either prevention or treatment of CDAD. Available evidence does not support the administration of probiotics with antibiotics to prevent the development of CDAD, and is inadequate to justify its introduction as a treatment for developed CDAD at the MUHC. The suggestive, but as yet inconclusive, evidence of benefit with probiotics in the treatment of AAD suggests direction for future studies."

"Recommendation: It is recommended that the MUHC does not adopt the use of probiotics for the prevention or treatment of CDAD at the present time. The literature should be re-evaluated as more evidence becomes available."


74
212
14
1
44
455
5
51
22
114
39
3
36
5
Colors indicate the number of studies with locations in that region.
Least
Most
Labels give the exact number of studies.
Source:https://ClinicalTrials.gov

Registered Studies on Probiotics

- C difficile infection (19)
- Colic (19)
- Abdominal pain (16)
- IBS (59), Digestive disorders (243)
- Colitis (41), Colonic diseases (89)
- Diarrhea (118)
- Liver disease (42)
- Colorectal neoplasm (16)
- Chronic periodontitis (16)
- Communicable diseases (243)
- Diabetes (43)
- Metabolic diseases (104)
- Body Weight and body weight changes (76)
- Anxiety disorders (18)
- Psychotic disorders (50)
- Depression (26)
- Behavioural Syndromes (27)
- Brain disease and CNS disease (54)
- Asthma (17) Respiratory disease (92)
- Hypersensitivity (71)
- Dermatitis and atopic dermatitis (55)
- Acquired immunodeficiency syndrome (22)
- Autoimmune disease (16)
- Bacterial infections (58)
- Birth Weight (15)

Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial

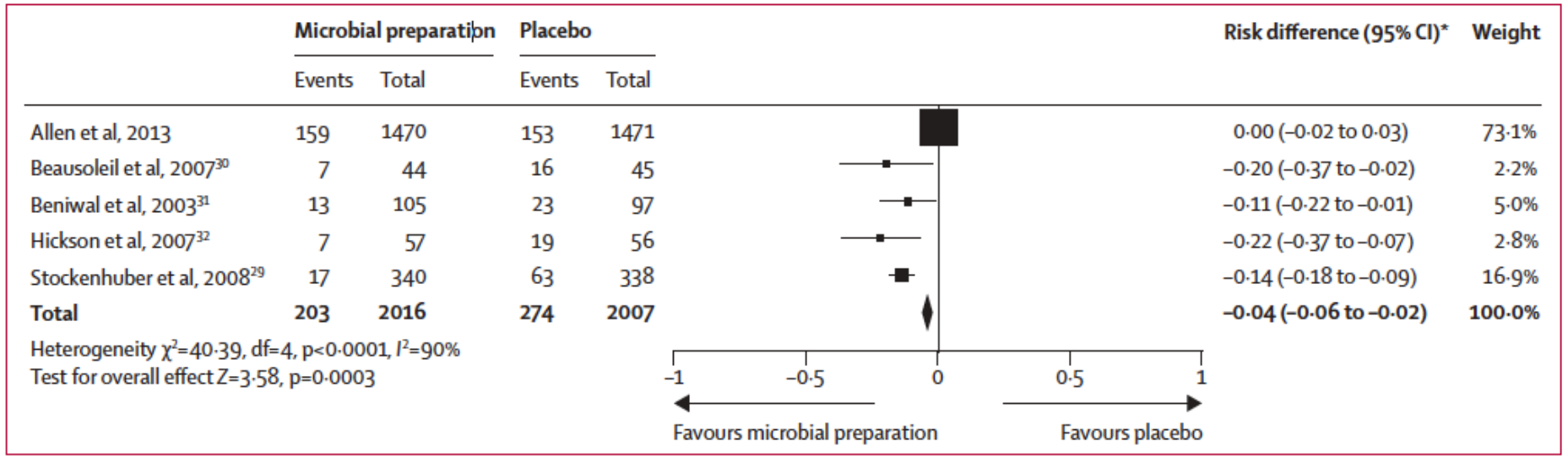
Stephen J Allen, Kathie Wareham, Duolao Wang, Caroline Bradley, Hayley Hutchings, Wyn Harris, Anjan Dhar, Helga Brown, Alwyn Foden, Michael B Gravenor, Dietrich Mack

Lancet 2013; 382: 1249-57

PLACIDE

- A look at AAD in inpatients over the age of 65 exposed to 1+ antibiotics
- UK 2013
- Multicenter, randomized, double blind, placebo controlled, efficacy trial
- 17420 patients screened, 2981 patients randomized
- Treatment was a multistrain preparation of lactobacilli and bifidobacterium – 6x10e10 CFU daily for 21 days

- Findings:
  - ADD (including CDD) RR 1.04 (0.84-1.28) p=0.71
  - CDD RR 0.71 (0.34-1.47) p=0.35
    - CDD occurred in 12 treatment subjects, and 17 placebo subjects



	Microbial preparation		Placebo		Risk difference (95% CI)*	Weight
	Events	Total	Events	Total		
Allen et al, 2013	159	1470	153	1471	0·00 (–0·02 to 0·03)	73·1%
Beausoleil et al, 2007[30]	7	44	16	45	–0·20 (–0·37 to –0·02)	2·2%
Beniwal et al, 2003[31]	13	105	23	97	–0·11 (–0·22 to –0·01)	5·0%
Hickson et al, 2007[32]	7	57	19	56	–0·22 (–0·37 to –0·07)	2·8%
Stockenhuber et al, 2008[29]	17	340	63	338	–0·14 (–0·18 to –0·09)	16·9%
Total	**203**	**2016**	**274**	**2007**	**–0·04 (–0·06 to –0·02)**	**100·0%**

Heterogeneity χ^2=40·39, df=4, p<0·0001, I^2=90%
Test for overall effect Z=3·58, p=0·0003

Figure 4: Meta-analysis of trials of lactobacilli or bifidobacteria, or both, in the prevention of antibiotic-associated diarrhoea in older inpatients
*From Mantel-Haenszel fixed effects analysis.

Gastroenterology 2020;159:708–738

AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders

Geoffrey A. Preidis,[1] Adam V. Weizman,[2] Purna C. Kashyap,[3] and Rebecca L. Morgan[4]

[1]Section of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; [2]Division of Gastroenterology, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [3]Enteric Neuroscience Program, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; and [4]Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Role of Probiotics – Management of GI disorders

- In **symptomatic adults with confirmed CDI**, should probiotics be used as part of the treatment regimen?
  - "The overall CoE across all critical outcomes for probiotics as part of the treatment of CDI infection was low"
- In adults and children receiving antibiotics therapy for any indication except CDI, **should probiotics be used to prevent CDAD**?
  - "The overall CoE across all critical outcomes for probiotics, based on the best available evidence [for various formulation] for the prevention of CDAD in adults and children was low"

Priedis GA, *et al*. "AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders." Gastroenterology 2020; 159:708-738

Role of Probiotics – Management of GI disorders

- In **adults and children with Crohn's disease**, should probiotics be used for induction or maintenance of remissions?
  - "The overall CoE across all critical outcomes for probiotics for the induction or maintenance of remission in children or adults with Crohn's disease was low"

- In **adults and children with ulcerative colitis**, should probiotics be used for induction of maintenance of remission?
  - "The overall CoE across all critical outcomes for probiotics for induction or maintenance of remission in children or adults with ulcerative colitis was low"

Priedis GA, *et al*. "AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders." Gastroenterology 2020; 159:708-738

Role of Probiotics – Management of GI disorders

- In **symptomatic children and adults with irritable bowel syndrome**, should probiotics be used to improve global response or abdominal pain severity?
  - "The overall CoE across all critical outcomes for probiotics for the treatment of children and adults with IBS was low"

- In **children with acute infectious gastroenteritis**, should probiotics be used to reduce the duration or severity of diarrhea?
  - "The overall CoE across all critical outcomes suggesting that probiotics **are not beneficial** for the treatment of children with acute gastroenteritis is Moderate on the evidence from studies conducted in the USA and Canada"

Priedis GA, *et al*. "AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders." Gastroenterology 2020; 159:708-738

Role of Probiotics – Management of GI disorders

- It’s not all bad news – potential utility:
  - Prevention of NEC and all cause mortality among preterm, low-birth weight infants (moderate/high CoE)
  - Prevention of CDAD (low CoE)
  - Prevention of pouchitis (very low CoE)

Priedis GA, *et al*. “AGA Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders.” Gastroenterology 2020; 159:708-738

Closer Look at Probiotics for CDI Prevention

Example Moderate CoE → Low CoE

- 2017 Cochrane review Goldenberg, JZ *et al*
  - 39 studies included
  - 9955 participants
  - Heterogeneous populations, disease spectrum and risk, antibiotic exposures
  - Probiotics reduced risk of CDAD RR 0.4 (0.32-0.52) Mod CoE
  - Secondary analysis by CDAD baseline risk

Baseline Risk	RR	CI	CoE
>5%	0.30	0.21-0.42	mod
3%-5%	0.53	0.16-1.77	mod
0%-2%	0.77	0.45-1.32	mod

- AGA Technical review
  - No further studies for inclusion after review
  - Studies: 2 only abstracts, 3 unpublished data
  - Only 2 studies with low risk of bias for all outcomes
  - Publication bias – lack of peer review for registered trials
  - Potential for benefit and harm, adverse effects
  - 5 trials with recruitment of subjects with >15% baseline risk
  - Subgroup analysis on various formulations might reduce the risk of CDAD v placebo (low CoE)

Fecal Microbiota Transplantation

Clinical Trials Registered at *ClinTrials.gov*

220 studies listed to query of “fecal microbiota transplant” (Nov 2018)

- CDI
- Severe CDI
- Active Crohn’s
- vs Recurrent CD
- Ulcerative colitis
- NASH
- Liver failure
- Hepatic encephalopathy
- vs MDRO colonization in renal transplant
- vs recurrent pouchitis
- vs recurrent UTI

vs HBV

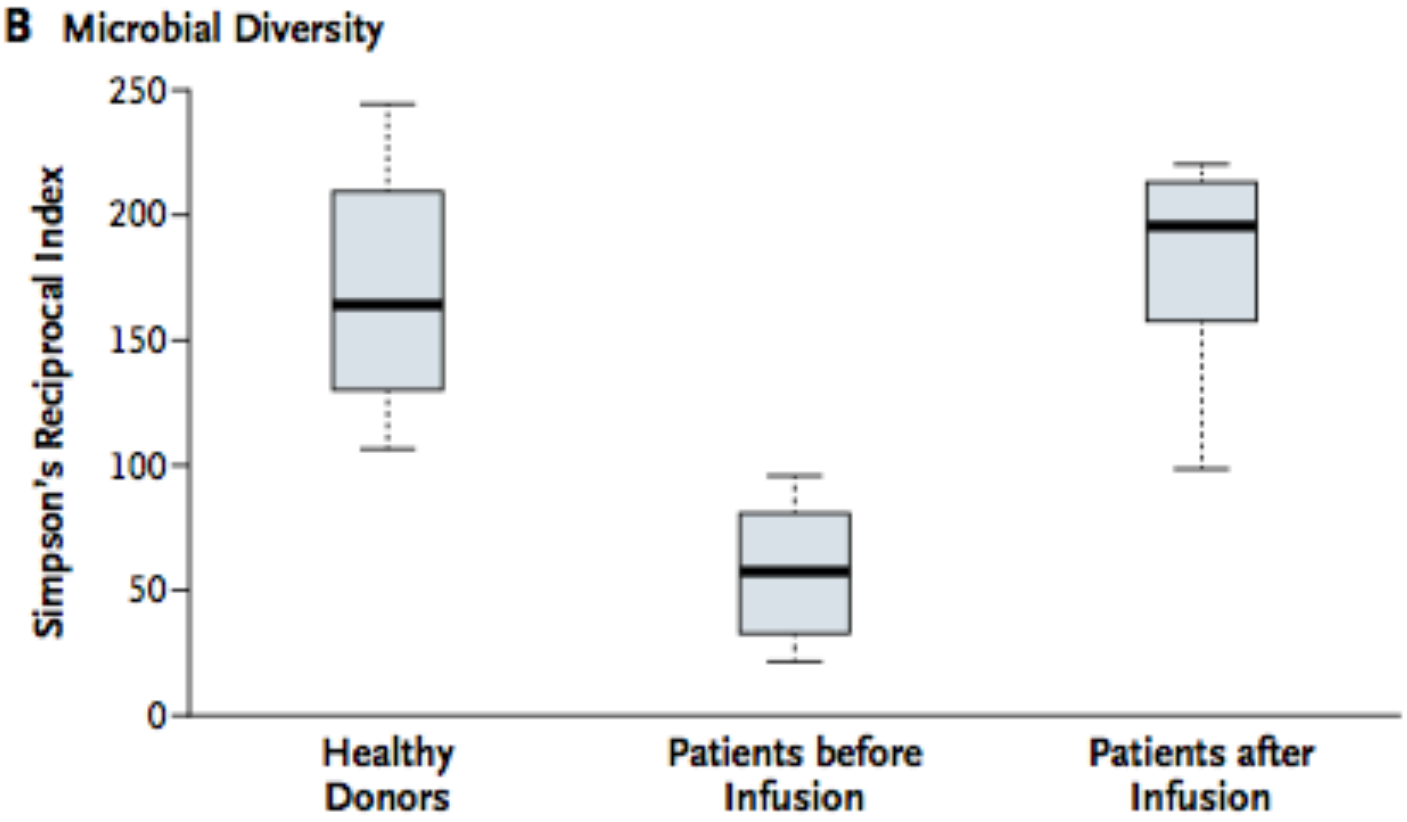
Depression

Bipolar disorder

- Melanoma (w/ , w/o pembrolizumab)
- Eradication of XDRO colonization
- Obesity and metabolism
- Insulin resistance
- Peanut allergy
- Body weight and glycemic control
- FMT for UTIs w/ MDRO
- Severe malnutrition
- Autism with GI disorders
- HIV associated disease
- In allo HSCT

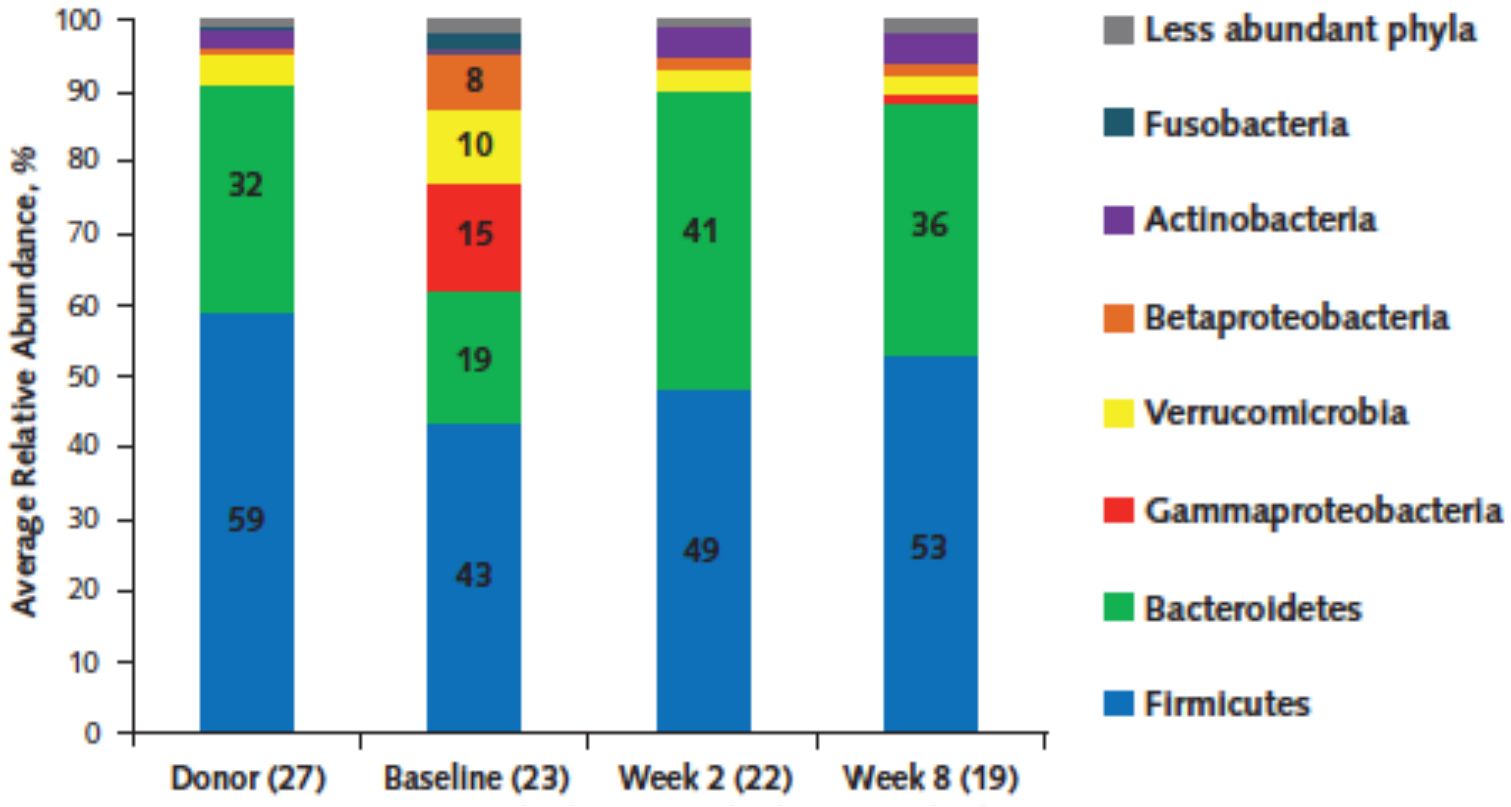
- Chronic functional constipation
- Severe acute pancreatitis
- Ankylosing spondylitis
- vs PSC
- vs IBS
- vs refractory IgA nephropathy
- vs chronic intestinal pseudo-obstruction
- MS
- Peripheral
- psoriatic arthritis
- Epilepsy

Principle of FMT



Leffler DA and Lamont JT. *Clostridium difficile* Infection. NEJM 2015; 372(16): 1539-48

Principle of FMT



Kelly CR *et al.* Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection a randomized trial. Ann Intern Med 2016; 165:609-616

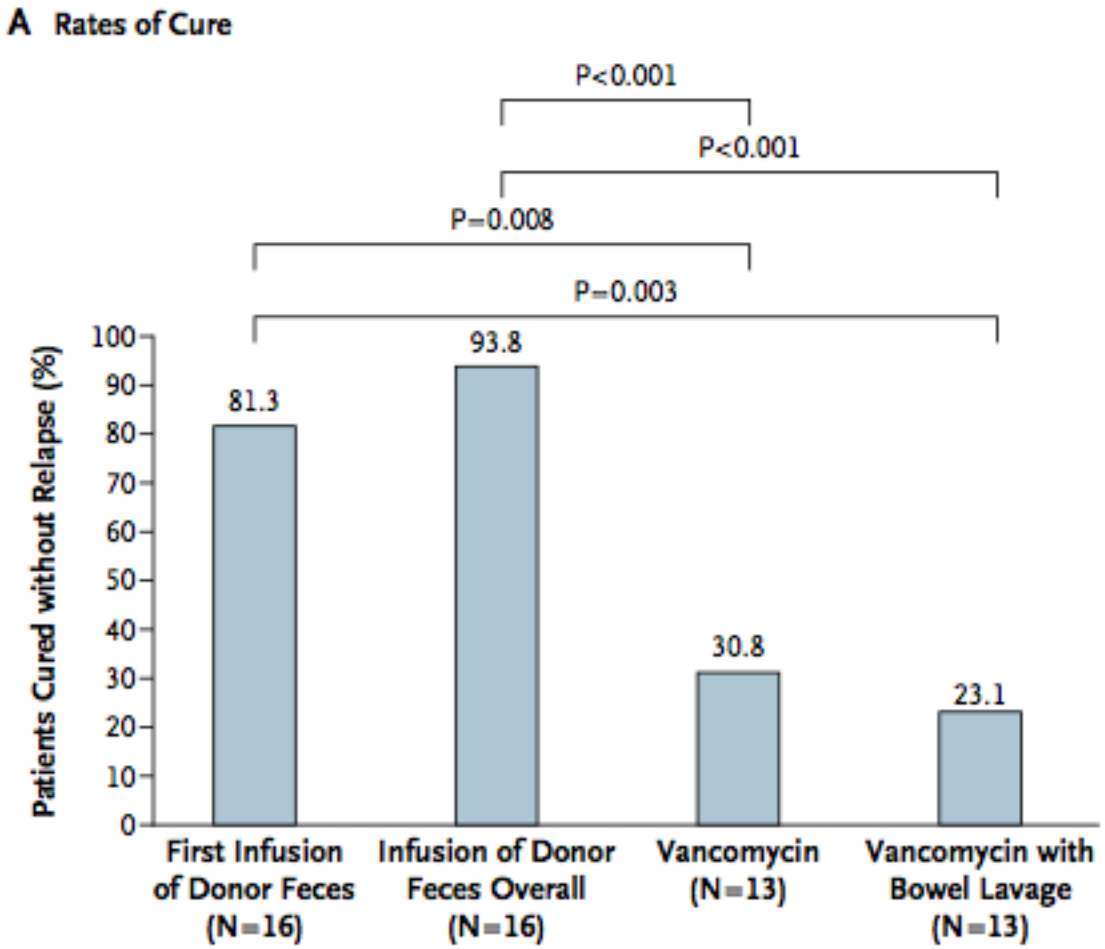
Principle of FMT

- Antibiotics diminish commensal organisms harbored in the colon
- rCDI correlated with reduced *Bacteroidetes* and *Firmicutes*
- In rCDI, short-chain fatty acids production, such as butyrate, is reduced as butyrate-producing microbial Families are diminished

⇓

FMT aims to restore these populations thereby reestablishing biodiversity, gut ecology, and metabolic function of the intestinal flora

FMT vs Oral Vancomycin for rCDI



Best route/anatomic site for FMT

- Method
  - **Nasogastric 93% response**
  - Colonoscopy 85% response (some sources this remains preferred)
  - Frozen donor fecal capsules 91% response (1 or 2 treatments)
- Best anatomic site
  - Infusion into stomach – 81% diarrhea resolution
  - Infusion into duodenum/jejunum – 86%
  - **Infusion into caecum/ascending colon – 93%**
  - Infusion into distal colon - 84%

Cammarota *et al.* Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection, a systematic review. 2014 48(8): 693-702

Draft – Not for Implementation

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies

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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

Health Canada Santé Canada

Guidance Document

Fecal Microbiota Therapy Used in the Treatment of *Clostridium difficile* Infection Not Responsive to Conventional Therapies

Safety Profile

- With proper donor screening and recipient selection and screening FMT is very safe.
  - Mild diarrhea, bloating and abdominal cramping resolving within hours-days
- Reported in clinical trial:
  - 1 case of Fournier's gangrene (not attributed to FMT)
- Case reports:
  - 3d s/p FMT abdo pain hypotension – pneumoperitoneum, toxic megacolon, polymicrobial bacteremia, death
  - Post FMT zoster (2 months post)
  - Recurrence of *E coli* bacteremia
  - Flare of quiescent UC
  - Norovirus gastroenteritis
- Procedural related harms
- **Potential for "black box" unidentified pathogen transfer**

Drekonja D *et al*. Fecal Microbiota Transplantation for *Clostridium difficile* Infection a systematic review. Ann Intern Med 2015; 162:630-638.

Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

June 13, 2019

Safety & Availability

Health Canada
Santé Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

Biologics and Genetic Therapies Directorate
100 Eglantine Driveway
Address Locator #0601C
Ottawa, Ontario K1A 0K9

July 17, 2019

Dr. Marty Teltscher
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CIUSSS-CO Montreal - Jewish General Hospital
3755 Cote ste Catherine / Division of infectious diseases, E0057
Montreal, QC H3T 1E2
Fax: 514-340-7546

Safety Notice: Fecal Microbiota Therapy (FMT)
for the Treatment of *C. difficile* Infections

Dear Dr. Marty Teltscher,

On June 13, 2019, the United States Food and Drug Administration issued a MedWatch Safety Communication regarding the risk of serious bacterial infections caused by multi-drug resistant organisms (MDROs), in the use of investigational fecal microbiota therapy (FMT) (see: https://www.fda.gov/safety/medwatch-safety-alerts-human-medical-products/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due)


RABAIS 50%
MØlangeur, rØcipient
verre, Black&Decker,
10 vit, 42oz, 350W
prix cour. 39.99
SOLDE 19.99
17.99
BIBLIOT,3TABL.CHE
34.99
BLACK&DECKER
10-Speed Blender
Mélangeur de 10 Vitesses


Starfrit
MARTY
TEITELBAUM
FOR
STOOL
TRANSPLANT
UNIT
MODE
ZERO
ON/OFF
Starfrit
Capacity | Capacité : 5 kg | 11 lb
GLASS TOP
PLATFORM
PLATE-FORME
EN VERRE
Plate-forme de pesée en verre
métrique / impériale
Arrêt automatique après deux minutes d'inactivité
Nécessite une pile au lithium (incluse)
Mesure aussi les volumes de lait et d'eau
Fonctions tare et remise à zéro
Capacité : 5 kg / 11 lb
Conversion automatique
Indicateurs de pile faible et de surcharge
Précision : 1 g / 0,1 oz
Starfrit


LAINE D'ACIER
LAINE D'ACIER
LAINE D'ACIER
ROLLAND
ENVIRO
COPY
8½" x 11"
5101

RAMA DESIGN
9 cm
8 cm
6 cm
$1.25
3
Assorted size FUNNELS
ENTONNOIRS de grandeurs assorties
SOURCE
140 g
MUKO
Lubricating Jelly
Gelée lubrifiante
7" Strainer
Tamis

Results

- 40 consults since July 2014
- 7 FMTs performed
  - All with resolved CDI at 28 days
  - 1 remains on vancomycin PO to this day due to dependency
- M:F = 15 : 25 (62% F)
- Average age 56.2 (19-86)

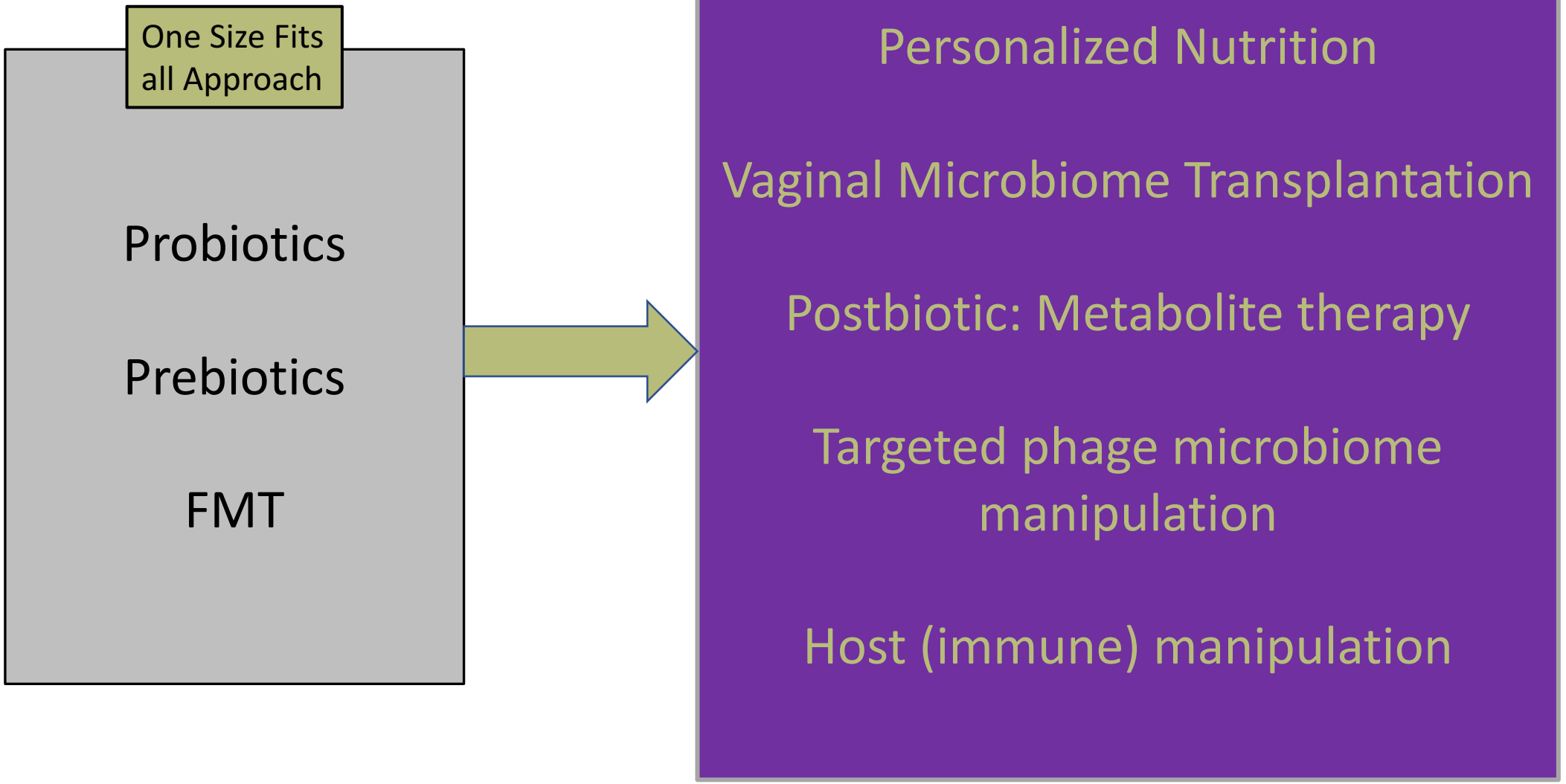
Referral Site	
JGH	23
MUHC	7
Outpatient clinics	4
Lakeshore	2
Pierre Boucher	2
Shawville	1
Hull	1

Results

	rCDI with FMT	rCDI no FMT
n	7	33
M:F	1 : 6	15 : 19
Mean age	62.4	54.8
Clinical resolution - 28d	7	? (low)*

Reason for not undergoing FMT protocol	*n*
Response to oral vancomycin and/or fidaxomicin	12
Did not satisfy inclusion/exclusion criteria/comorbidity	11
Donor issues (mismatch, unavailable, disqualified)	7
Apprehension about technique	3
***Almost all eventually resolved rCDI**	

The Future is Now



Elinav, E. IDWeek 2020 presentation.

Thank You!

Questions?

Discussion