CONVEGNO
MICROBIOTA:
Updates tra patologie
e terapia nutrizionale

Microbiota e trapianto fecale

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Università Cattolica del Sacro Cuore

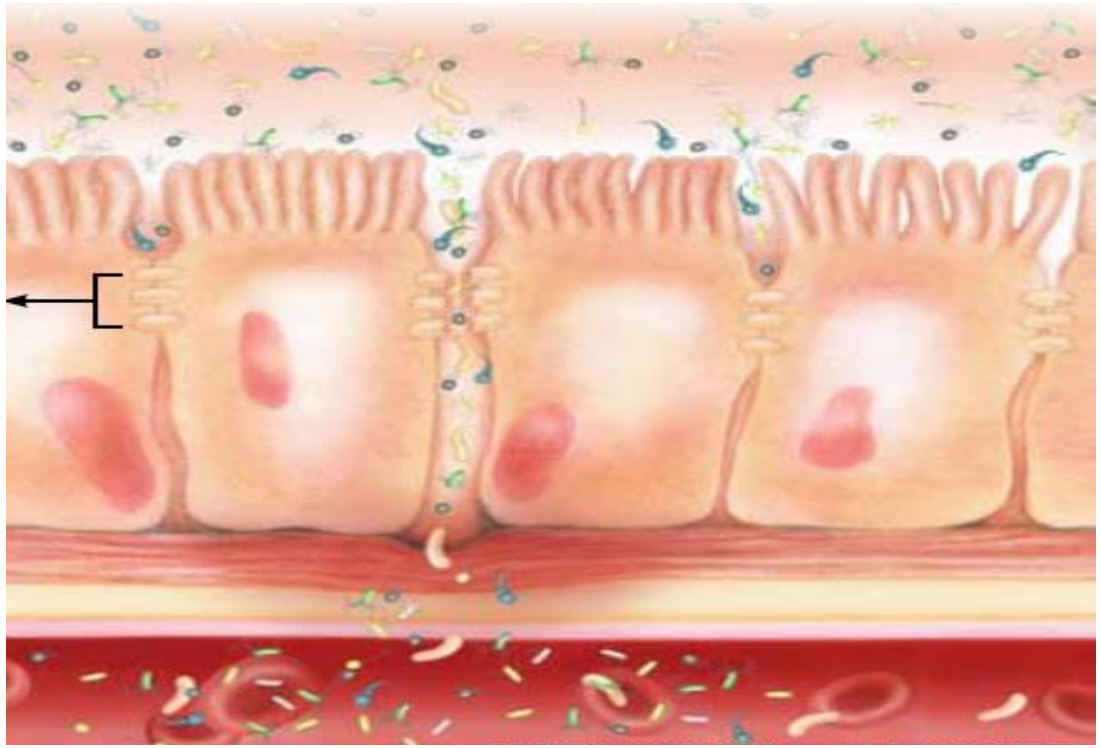
GUT Microbiota has many components

Virus/phages **Bacteria** Protozoa Helminth

Archea **Micro-eukaryotes** **Yeast** Parasite

Mucosal Barrier

Epithelial barrier



Acquired and Innate immunity

Endocrine system

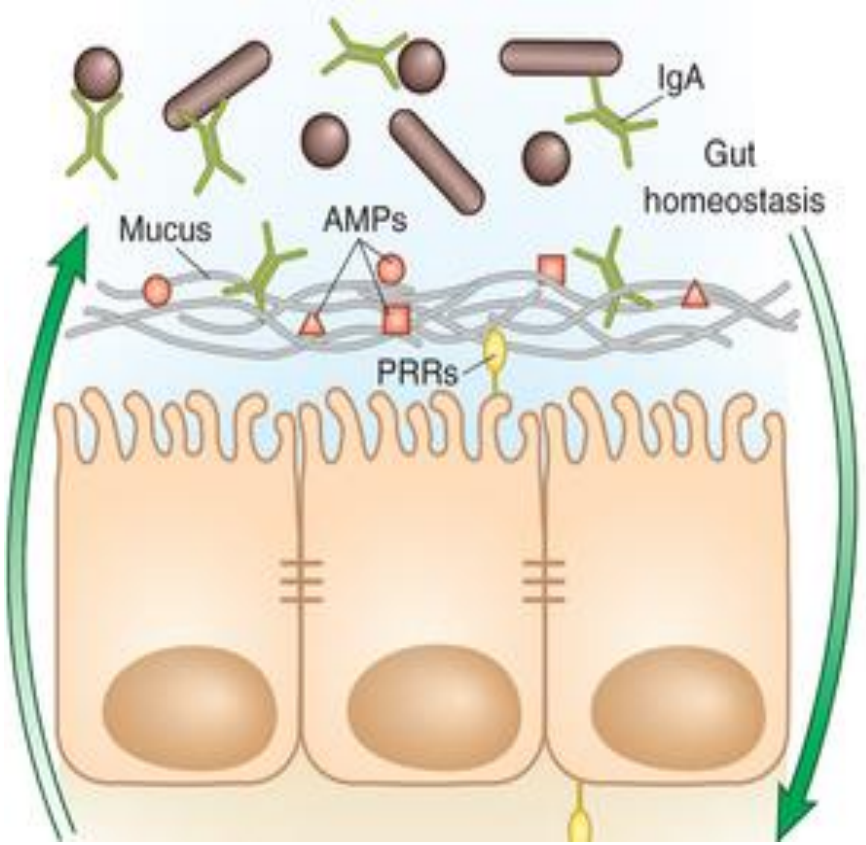
Vascular and lymphatic systems

Neuroenteric system

Digestive enzymes

FUNCTIONS OF GUT MICROBIOTA ON HOST HEALTH

- Immunocompetence/Tolerance
- Barrier effect
- Synthesis
- Metabolism
- Drug metabolism
- Behavior conditioning




THE ANATOMO-MICROBIOLOGICAL GUT BARRIER
BIOTIC SURFACE

How to define
a
HEALTY GUT MICROBIOTA?

What is EUBIOSIS?

EU= good; BIOS= life

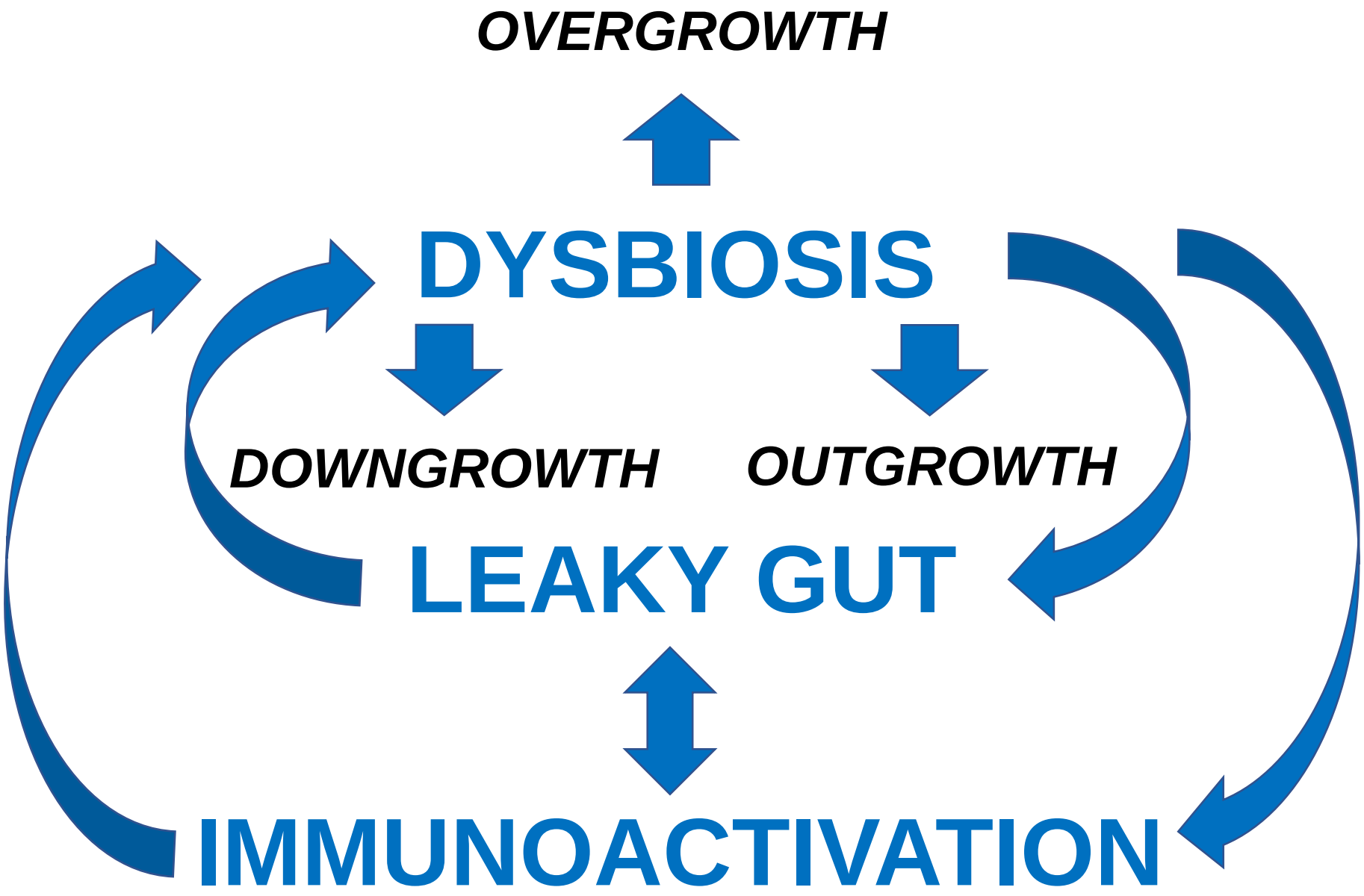
Eubiosis is the healthy relationship among commensal bacteria of the gut

COMPOSITION

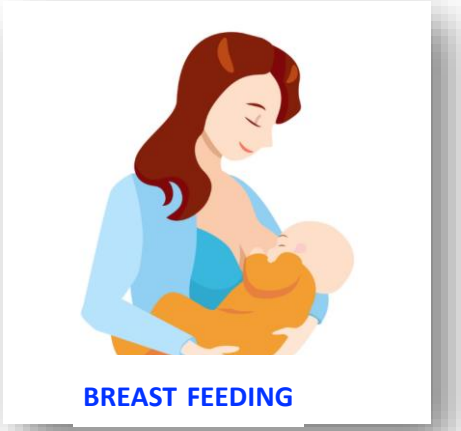
- ★ Diversity
- ★ Richness
- ★ Relative Abundance

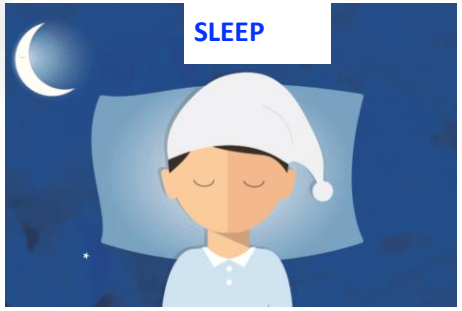
FUNCTION

★**Microbiota's effect on host health**


OVERGROWTH
DYSBIOSIS
DOWNGROWTH
OUTGROWTH
LEAKY GUT
IMMUNOACTIVATION

Microbiota influencers





How to modulate gut microbiota?

How to modulate microbiota modulation in the clinical practice?

Diet & nutritional support

- Caloric amount, minerals, vitamins
- Diet composition

Removal of predisposing conditions

- Treat diabetes, endocrine, other motility disorders..
- Surgery or prokinetics when indicated

Therapeutic interventions

- Antibiotics
- Prebiotics, probiotics, symbiotics, eubiotics
- Fecal Microbiota Transplantation

Modulation

Reset

Reconstitution

How to modulate microbiota modulation in the clinical practice?

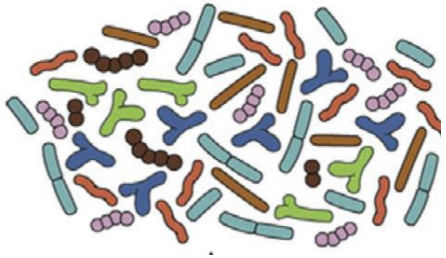
Therapeutic interventions

- Antibiotics
- Prebiotics, probiotics, symbiotics, eubiotics
- Fecal Microbiota Transplantation

Reconstitution

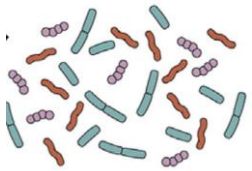
Rationale of microbiota modulation

Microbiota Sano



Dieta e Stile di vita
Farmaci
Malattie sistemiche
Eventi stressanti

Disbiosi
(Perdita della simbiosi)



Quantità

Qualità

Malattie

- GI infezioni

- Disordini metabolici

- IBD

- IBS

- Encefalopatia epatica

Trapianto di microbiota

Individuo sano

FMT – Definition

Intestinal microbiota transplantation (FMT) involves the transfer of gut microbiota from a healthy donor with a view to introducing or re-establishing a stable microbial community in the gut of the recipient

FMT is also known as

- ✓ faecal bacteriotherapy
- ✓ faecal transplantation
- ✓ faecal microbiota reconstitution
- ✓ human probiotic infusion
- ✓ infusion of donor feces

DONOR SCREENING

Starting questionnaire
To rule out:
- Risk factors for **infect. dis**
- **Drugs** that impair microbiota
- **Diseases** that impair microbiota

Blood & Stool Exams
To exclude transmittable diseases

Questionnaire before donation
To exclude issues risen during screening

INFUSATE PREPARATION

Fresh Material
- To be used **within 6 hours** after defecation
- Manufacturing should be as brief as possible
- **At least 30 g** of faeces should be used
- Feces should be suspended in **saline** with a blender or manual effort & sieved to avoid clogging

Frozen Material
- **At least 30 g of feces** and **150 mL of saline** to be used
- Before freezing, add **glycerol up to 10%**
- Suspensions should be labelled, traceable, stored at **–80°C**
- **Thaw at 37°C** and **infuse within 6 hours** from thawing

FECAL DELIVERY

Bridging atb pre-treatment
Usually vanco 3 days before FMT

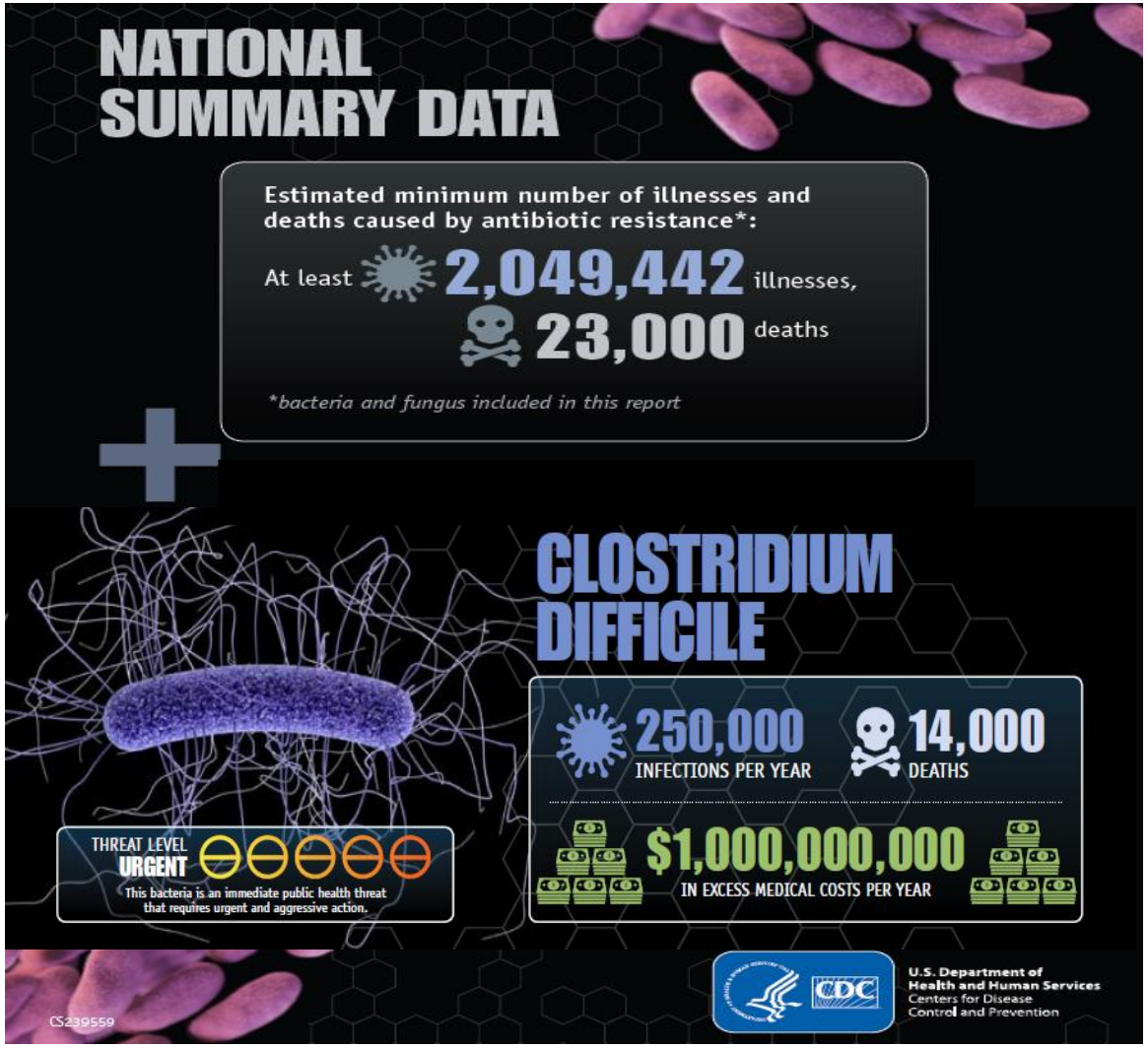
Bowel preparation
- To reduce bowels
- To remove patient's feces

Routes of delivery
- NJT/NDT
- Capsules
- Colonoscopy
- Enema

Cammarota, Ianiro et al – Gut – 2017

C. difficile infection

The new infectious burden

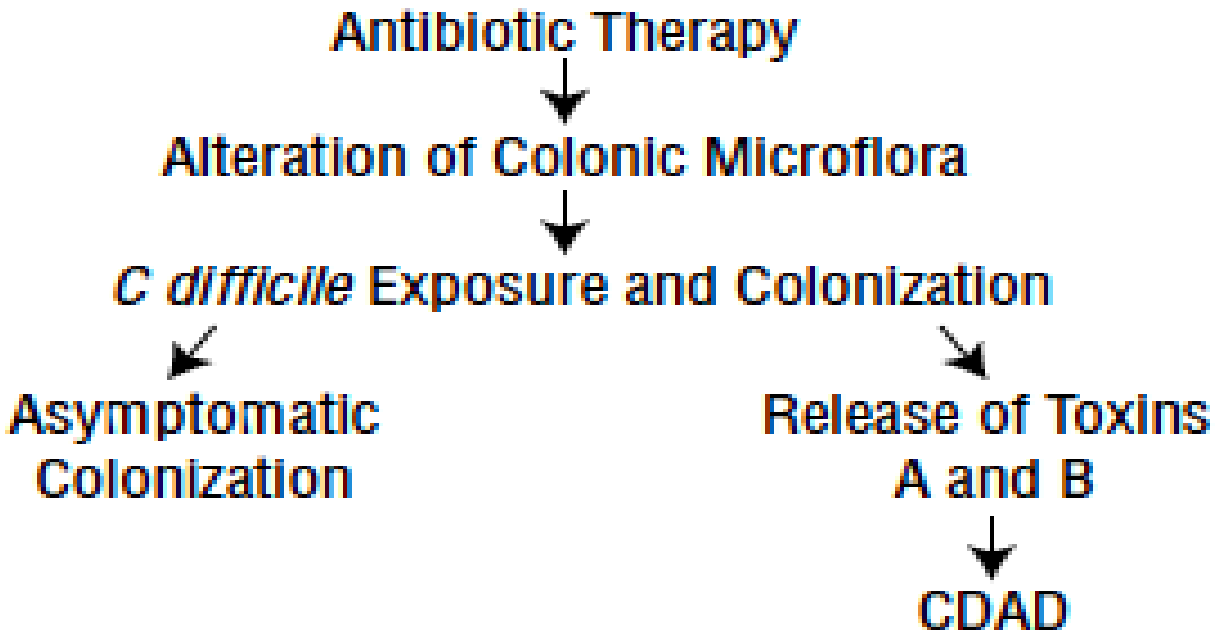


MAIN RISK FACTORS

- ★ Antibiotics
- ★ PPIs
- ★ Elderly

Lessa et al., N Engl J Med 2015

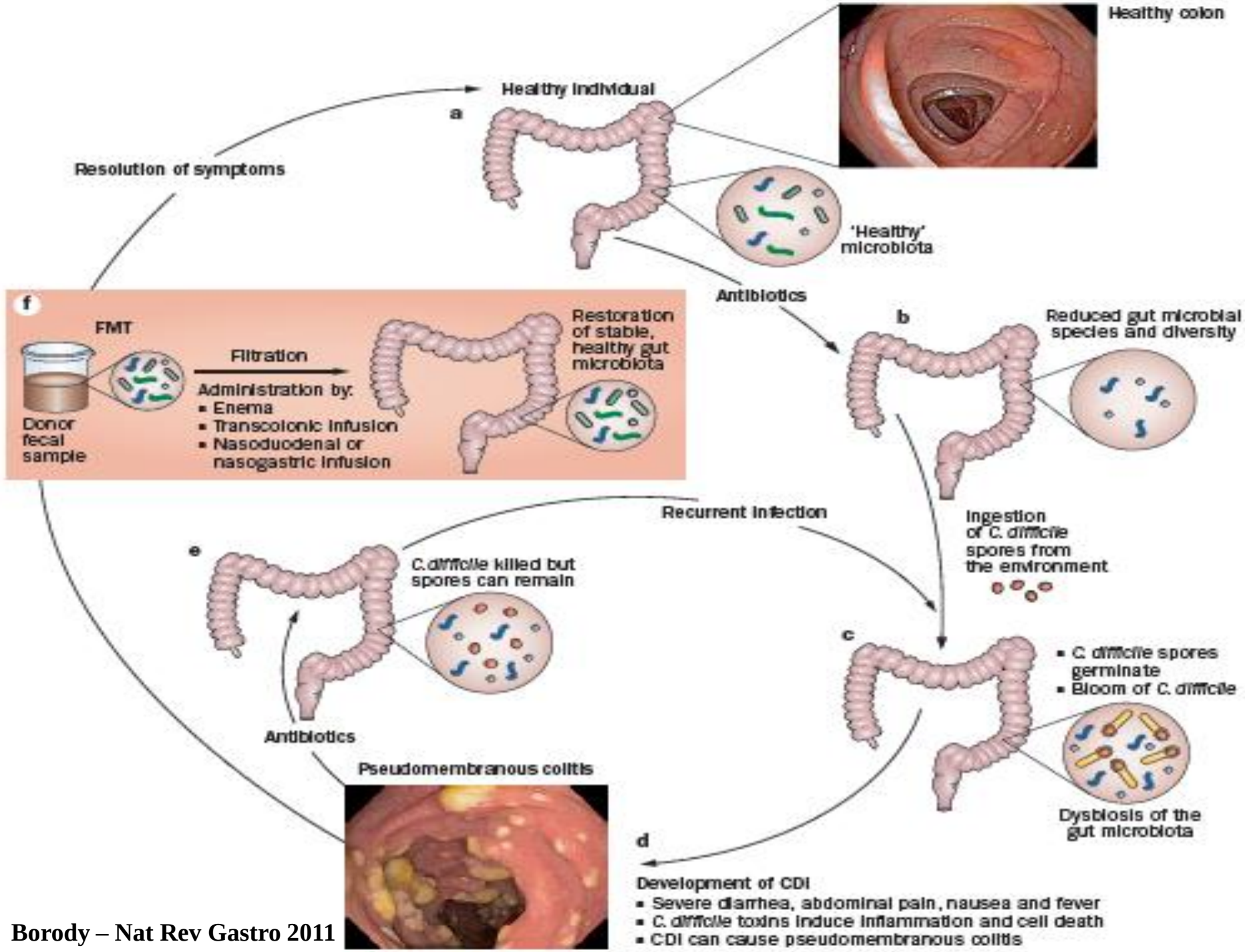
Pathogenesis of CDAD



Antibiotics predisposing to CDI

Frequently	Infrequently	Rarely
Ampicillin and amoxicillin	Tetracyclines	Parenteral aminoglycosides
Cephalosporins	Sulfonamides	Bacitracin
Clindamycin	Erythromycin	Metronidazole
	Chloramphenicol	Vancomycin
	Trimethoprim	
	Quinolones	

Hurley BW – Arch Intern Med 2002



Borody – Nat Rev Gastro 2011

FMT for recurrent CDI: practical guidelines

- **USA**
  - **Recurrent or relapsing CDI**
    - ≥3 episodes of mild/moderate CDI w/ failure of 6- to 8-w tapered vanco
    - ≥2 episodes of severe CDI w/ hospitalization & significant morbidity.
  - **Moderate CDI** not responding to 7d vanco
  - **Severe-fulminant CDI** not responding to vanco after 48h
- **Canada**
  - FMT is effective in CDI and is a viable option in patients who experience a **relapse after two courses of antibiotics**
- **France**
  - **Multiply recurrent CDI** after failure of standard vanco or fidaxo treatment
- **Austria**
  - **Recurrent CDI**
  - **Severe CDI** (suggested as an alternative to colectomy, if standard therapy fails)

Bakken et al – Clin Gastro Hep 2011; Kump et al – Z Gastroenterol 2014; Moayyedi et al – Can J Gastro 2014; Sokol et al – DLD 2015

FMT for recurrent CDI: Evidence-based consensus report

European Consensus Conference on FMT in Clinical Practice

FMT for recurrent *Clostridium difficile* infection

Statement: FMT is recommended as a highly effective and safe treatment option for both mild and severe rCDI. Its implementation in clinical practice is recommended

Quality of evidence: high **Strength of recommendation:** strong

FMT for the first episode of *Clostridium difficile* infection

Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI. Additional studies are needed to determine if FMT could have an advantage over antibiotics for this indication

Quality of evidence: low **Strength of recommendation:** weak

FMT for refractory *Clostridium difficile* infection

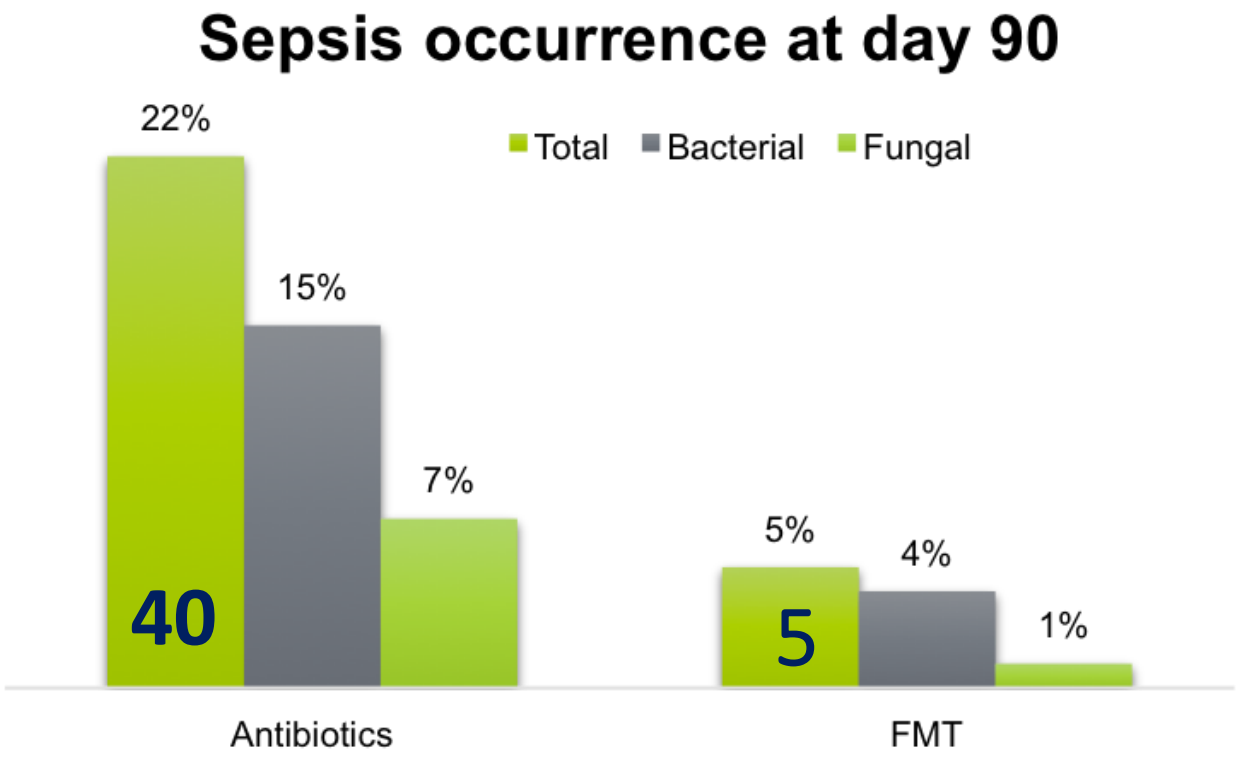
Statement: FMT can be considered as a treatment option for refractory CDI

Quality of evidence: high **Strength of recommendation:** strong

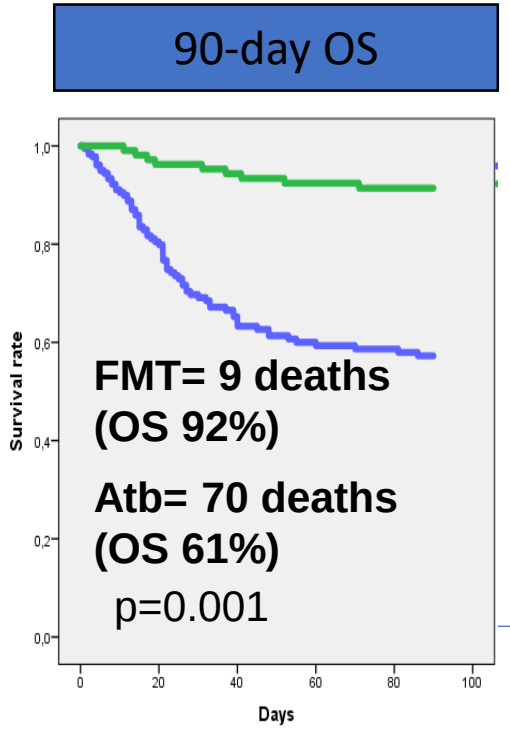
Cammarota, Ianiro et al – Gut – 2017, 2019

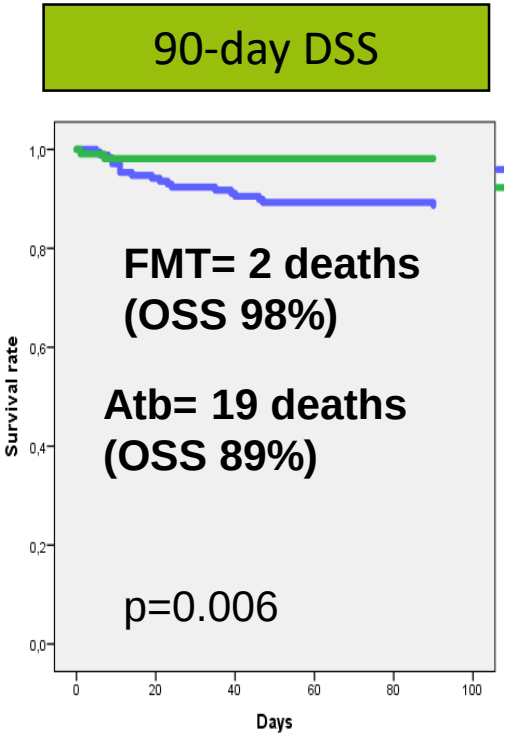
FMT decreases sepsis rates and increases survival in rCDI

Observational cohort, 290 hospitalized pts (181 atb, 109 FMT)



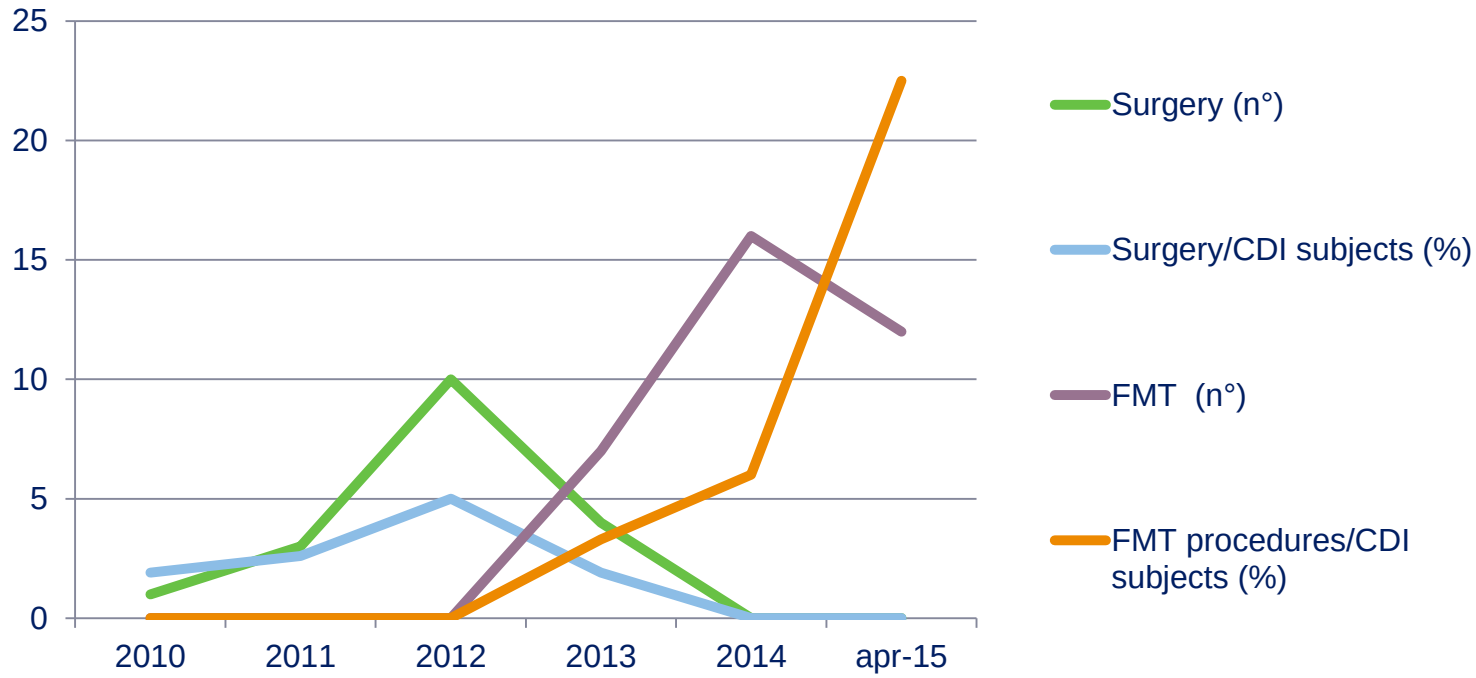
Hospitalization
29.7 d (Atb) vs 13.3 d (FMT) p<0.001





FMT cuts the need for C. difficile-related surgery

- Retrospective review of **901 pts with CDI**
- **No more surgery after the establishment of a FMT service**
- Relevant **decrease in CDI-related mortality** (surgical pts: 83%; FMT pts: 6%)



Cammarota, Ianiro et al – Ann Intern Med 2015

Sequential FMT in severe CDI

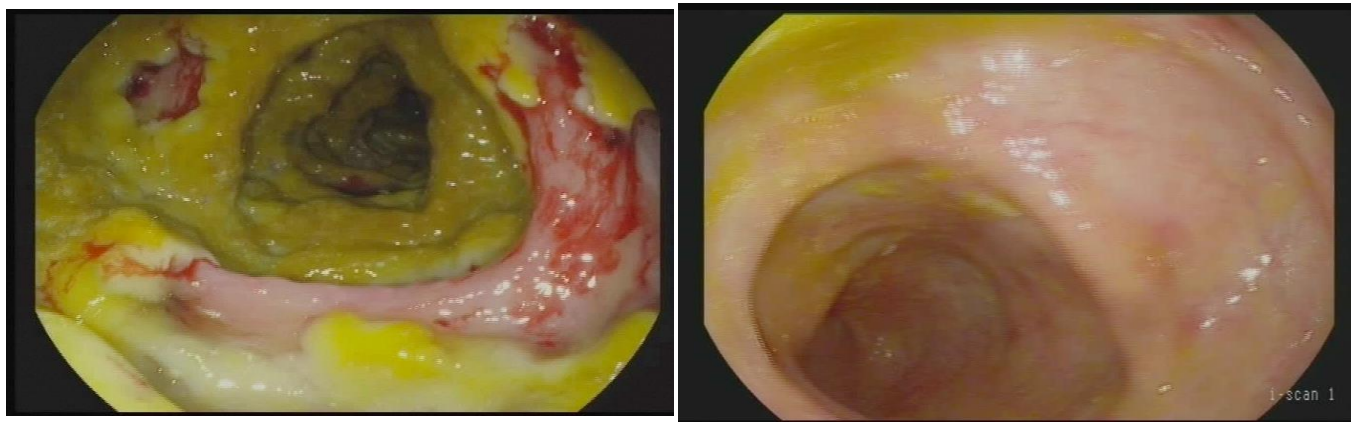
- **Severe CDI is a risk factor for recurrence after FMT**

- **Repeated faecal infusions improve CDI cure rates and are relevant for FMT success in severe CDI**

+30 % of success rate

Risk factor	Odds ratio (95% confidence interval)	*P* value
Severe or severe/complicated indication	5.95 (2.26–15.62)	<0.001

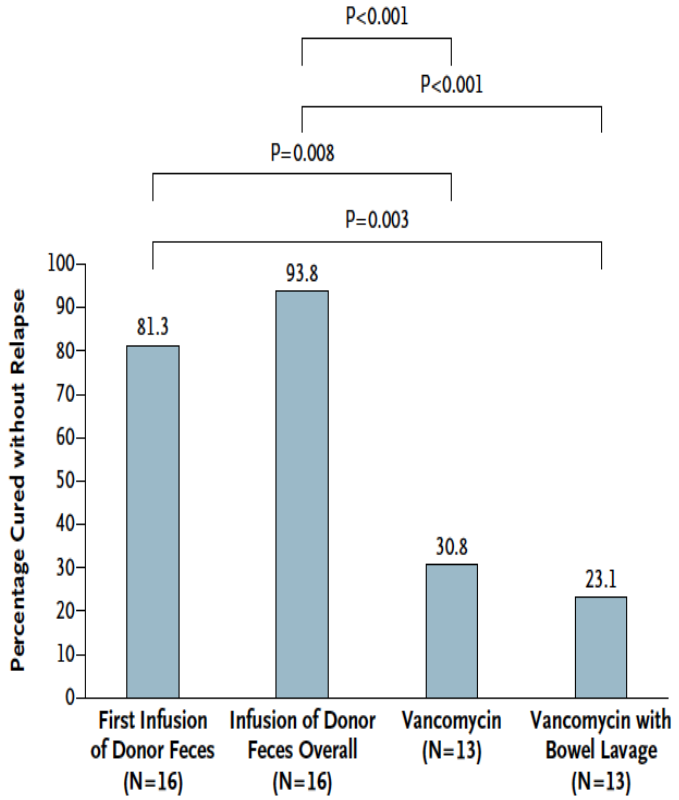
Risk factor	OR (95% CI)	P value
Severe CDI	24.66 (4.44-242.08)	0.001



Cammarota et al – AP&T 2015 ; Fischer et al – AP&T 2015; Fischer et al – Gut Microbes 2016 ; Ianiro et al – Clin Microbiol Infect 2017

FMT for recurrent CDI: RCTs

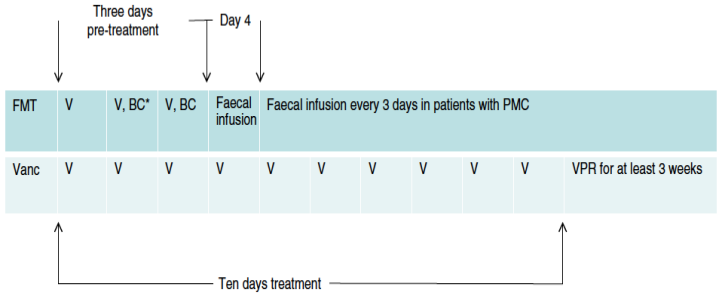
- Short vanco+FMT vs Short vanco+bowel prep vs Standard vanco
- Study stopped after an interim analysis
- Resolution of CDAD
  - FMT group (n=16): 81%1 FMT, **94% >1 FMT**
  - Vancomycin group (n=13): 31%
  - Bowel prep (n=13): 23%
- No significant adverse events

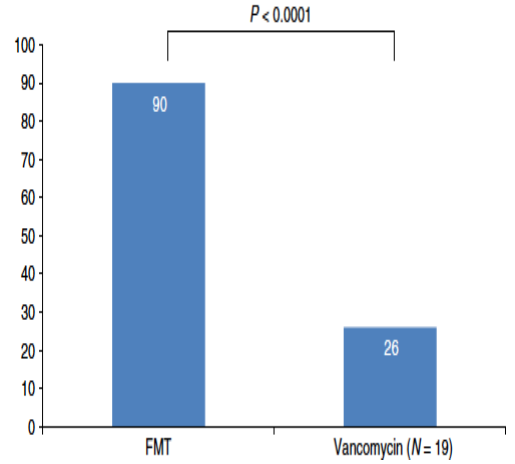


Van Nood et al – NEJM 2013

FMT for recurrent CDI: RCTs

- Short vanco+FMT vs Standard vanco
- Study stopped after interim analysis
- Resolution of CDAD
  - FMT group (n=20): **90%**
  - Vancomycin group (n=19): 26%
- **5/7 pts with severe disease (PMC): progressive disappearance of PMC and resolution of CDAD after multiple FMT**
- No significant adverse events

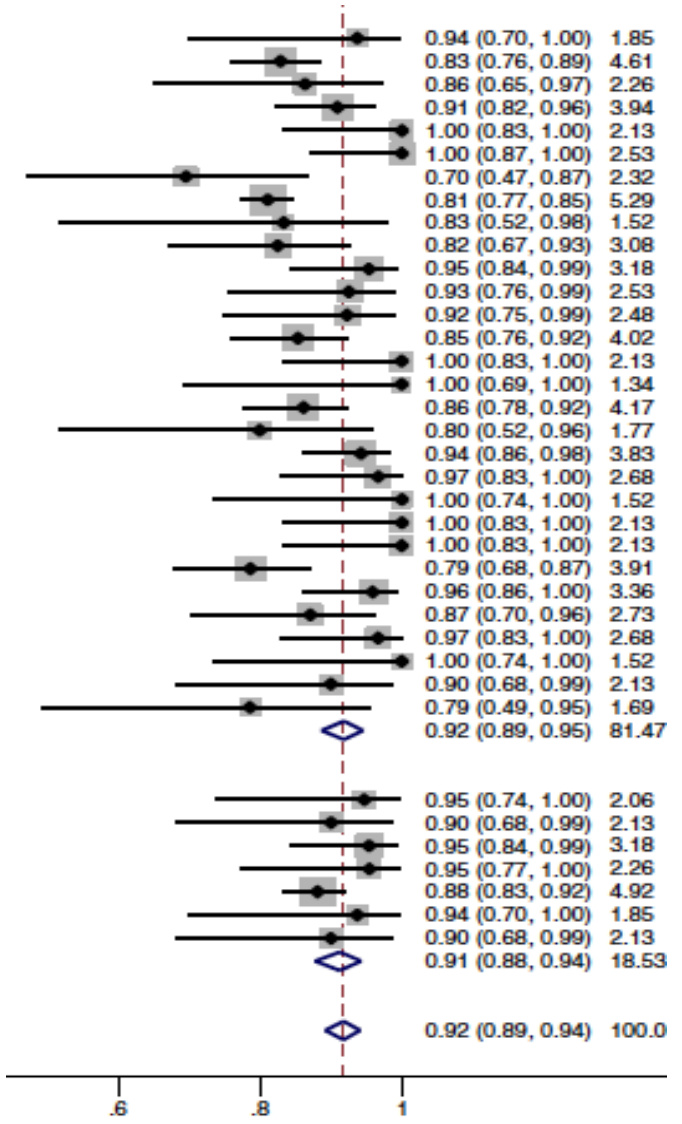




Cammarota et al – APT 2015

FMT for recurrent CDI: systematic reviews and metanalyses

- **37 studies** (7 RCTs, 30 case series)
- FMT **more effective than vancomycin** (**RR: 0.23** 95%CI 0.07- 0.80) in curing rCDI
- **Overall clinical resolution 92%** (95%CI 89%-94%)
- Significant **difference** between **lower GI** (95%; 95%CI 92%-97%) and **upper GI delivery** (88%; 95%CI 82%-94%), P=0.02
- **No difference** between **fresh and frozen** FMT (P=0.84)



Quraishi et al – AP&T 2017

- ★ Over the years, C. difficile infection has become a real economic and health-care burden

- ★ New weapons in our therapeutic armamentarium, as fidaxomycin or, especially, FMT, are improving the management of C. difficile infection

FMT

nuove prospettive e indicazioni

Proposed indications for FMT - 307 trials

Squamous cell cancer

Obesity

Metabolic syndrome

Diabetes Mellitus

Immune thrombocytopenia

Acute myeloid leukemia

Non alcoholic steatohepatitis

Hepatitis B infection

Kidney transplantation

Multiple Myeloma

Alcoholic hepatitis

HIV Infection

Liver transplantation

IgA Nephropathy

Amyotrofic Lateral Sclerosis

Pancreatitis

Malnutrition

Multiple Sclerosis

Ankylosing spondilitis

Melanoma

Pouchitis

Bipolar Disorder

Peanut allergy

Sjogren's syndrome

Anorexia nervosa

Chronic Fatigue Syndrome

Epilepsy

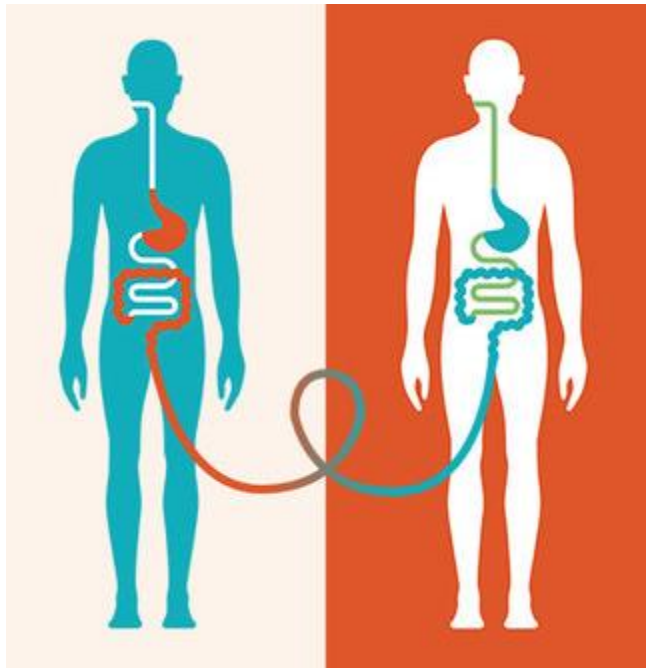
Reumatoid arthritis

Autism

Depression

Parkinsons's Disease

Urinary tract infection



Rosenbaum JT. Expert Review of Clinical Immunology 2019

Proposed indications for FMT *beyond C.difficile infection*

- Multidrug resistant infections
- Hepatic Encephalopathy
- Metabolic syndrome and obesity
- Cardiovascuolar Disease
- Cancer

Proposed indications for FMT *beyond C.difficile infection*

DECOLONIZATION USING ANTIMICROBIALS IS NOT CURRENTLY RECOMMENDED

- resistance increase
- "**rebound effect**" after discontinuation of decolonization regimens

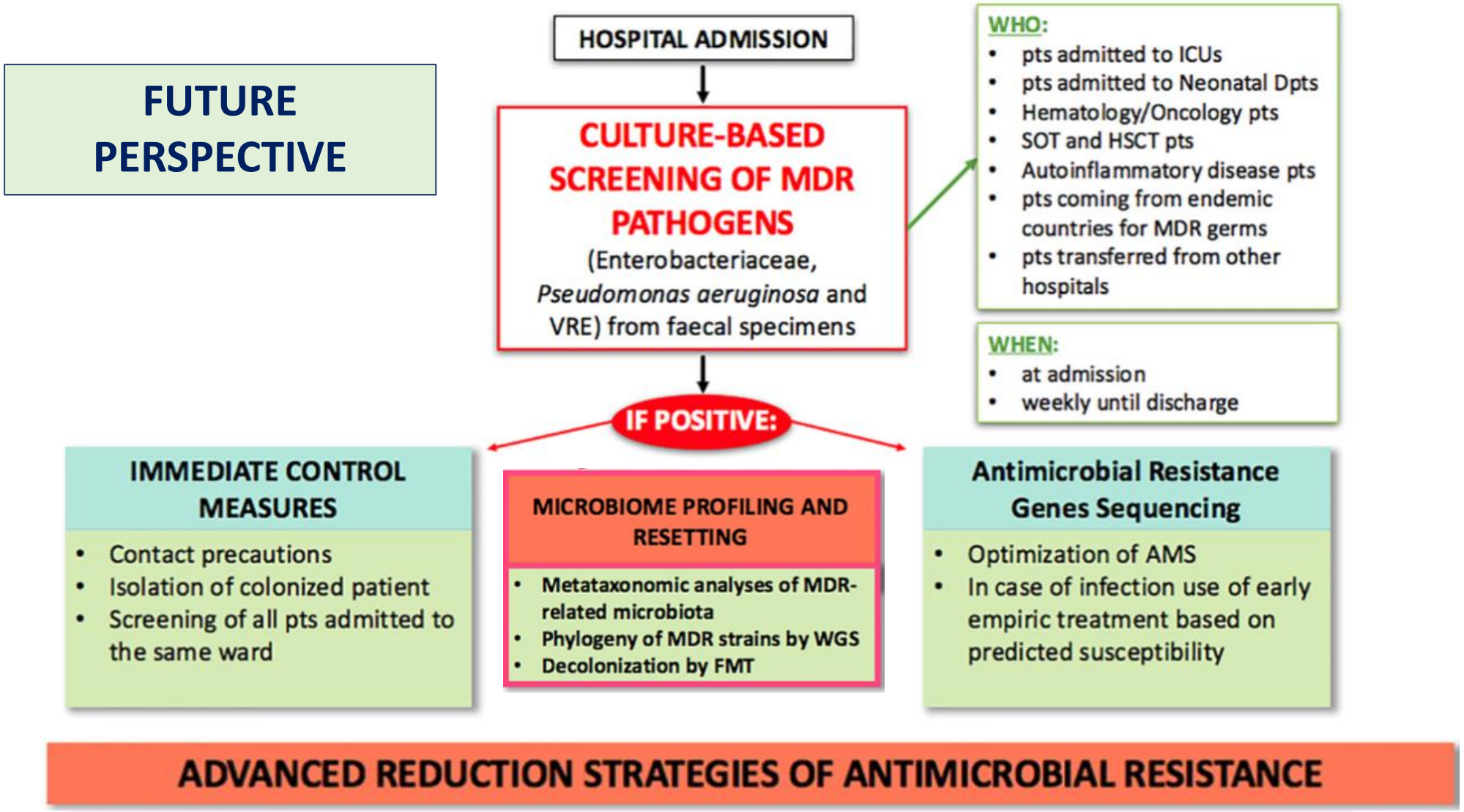
25,000 deaths/years associated with MDR infections in Europe

Acinetobacter
- *Staphylococcus aureus* (MRSA)
- vancomycin-resistant Enterococci (VRE)

ANTIBIOTIC RESISTANCE
- therapeutic failure
- relapses
- longer hospitalizations
- worse clinical outcomes

Gargiullo Frontiers in Microbiology 2019
Woodworth Open Forum Infectious Diseases 2019

Proposed indications for FMT *beyond C.difficile infection*



Gargiullo Frontiers in Microbiology 2019
Woodworth Open Forum Infectious Diseases 2019

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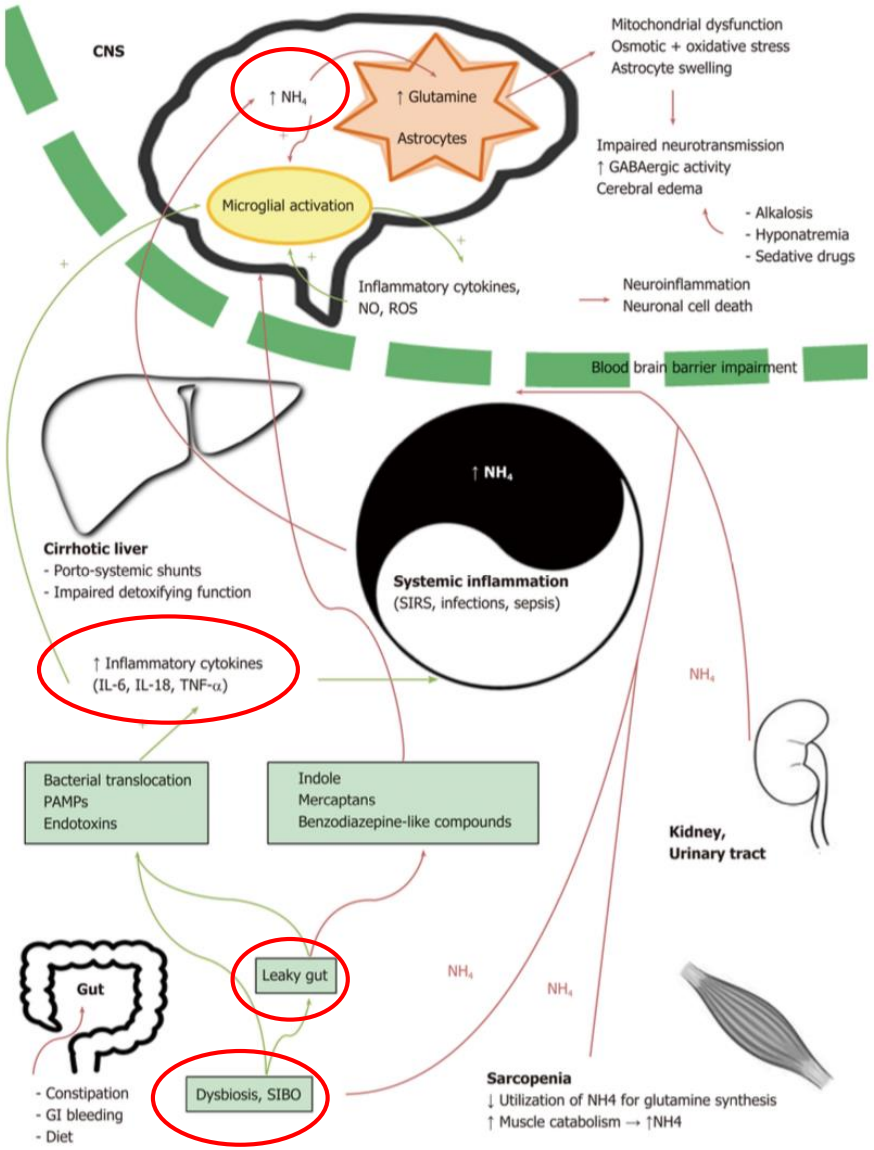
Proposed indications for FMT *beyond C.difficile infection*



Gut-liver-brain axis dysfunction → **Hepatic encephalopathy (HE)**

- intestinal hyperpermeability
- dysbiosis
- hyperammonemia
- inflammation

"GUT-CENTRIC" THERAPIES

FMT RESULTS

Long-term (12-15 months) safety and sustained improvement in clinical and cognitive function parameters with prevention of HE recurrence

Campion D. World Journal of Hepatology 2019
Bajaj JS Gastroenterology 2019

Proposed indications for FMT: Hepatic encephalopathy

HEPATOLOGY
JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

A Phase 1, Randomized, Placebo-Controlled Trial

20 Patients with cirrhosis with recurrent HE with MELD <17
15 FMT capsules versus placebo from a single donor enriched in Lachnospiraceae and Ruminococcaceae.

Endoscopies with duodenal and sigmoid biopsies, stool analysis, cognition, serum lipopolysaccharide-binding protein (LBP), and duodenal antimicrobial peptide (AMP) expression at baseline were used.
Clinical follow-up with standard of care maintenance was performed until 5 months. FMT-assigned patients underwent repeat endoscopies 4 weeks postenrollment.

6 pts in the placebo group required hospitalizations compared to 1 in FMT, which was deemed unrelated to FMT

oral FMT capsules are safe and well tolerated in patients with cirrhosis and recurrent HE

Bajaj JS Hepatology 2019

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- Multidrug resistant infections
- Hepatic Encephalopathy
- Metabolic syndrome and obesity
- Cancer

The New York Times

Seeking an Obesity Cure, Researchers Turn to the Gut Microbiome

The link between the gut and metabolic disease is a growing area of obesity research.

Published Sept. 10, 2019

Impact of Fecal Microbiota Transplantation on Obesity and Metabolic Syndrome

3 randomized placebo-controlled studies (76 patients with obesity and Metabolic Syndrome
body mass index = 34.8 4.1 kg/m2

Study	Vrieze et al. 2012 [40]	Koote et al. 2017 [41]	Smits et al. 2018 [42]
FMT Route	Nasoduodenal	Nasoduodenal	Nasoduodenal
Donor stool	Single unpooled FMT from different lean donors	Single unpooled FMT from different lean omnivorous donors	Single unpooled FMT from different vegan donors
Stool preparation	Fresh sample was immediately covered with sterile saline (500 mL, 0.9% NaCl), and stirred in blender (10 min) and filtered twice through metal sieve.	Fresh sample was immediately covered with sterile saline (500 mL, 0.9% NaCl), and stirred in blender (10 min) and filtered twice through metal	Fresh sample was immediately covered with sterile saline (500 mL, 0.9% NaCl), and stirred in blender (10 min) and filtered twice through metal sieve.
Stool Dose	Not reported	Not reported	Not reported
Time to FMT from stool donation	<6 h	<6 h	<6 h
FMT replicates	1	2	1
FMT infusion time	30 min	Not reported	30 min
Adverse event	N/A	No serious events	No serious events

N/A: not applicable, which indicated that the study did not report whether there were adverse events during the follow-up period.

Zhang Z. Nutrients 2019

Impact of Fecal Microbiota Transplantation on Obesity and Metabolic Syndrome

3 randomized placebo-controlled studies (76 patients with obesity and Metabolic Syndrome
body mass index = 34.8 4.1 kg/m2

- Two studies reported improved peripheral insulin sensitivity at 6 weeks in patients receiving donor FMT versus patients receiving the placebo control
- One study observed lower HbA1c levels in FMT patients at 6 weeks
- No di erences in fasting plasma glucose, hepatic insulin sensitivity, body mass index (BMI), or cholesterol markers were observed

Long-term clinical endpoints?

Zhang Z. Nutrients 2019

Proposed indications for FMT *beyond C.difficile infection*

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- Hepatic Encephalopathy
- Metabolic syndrome and obesity
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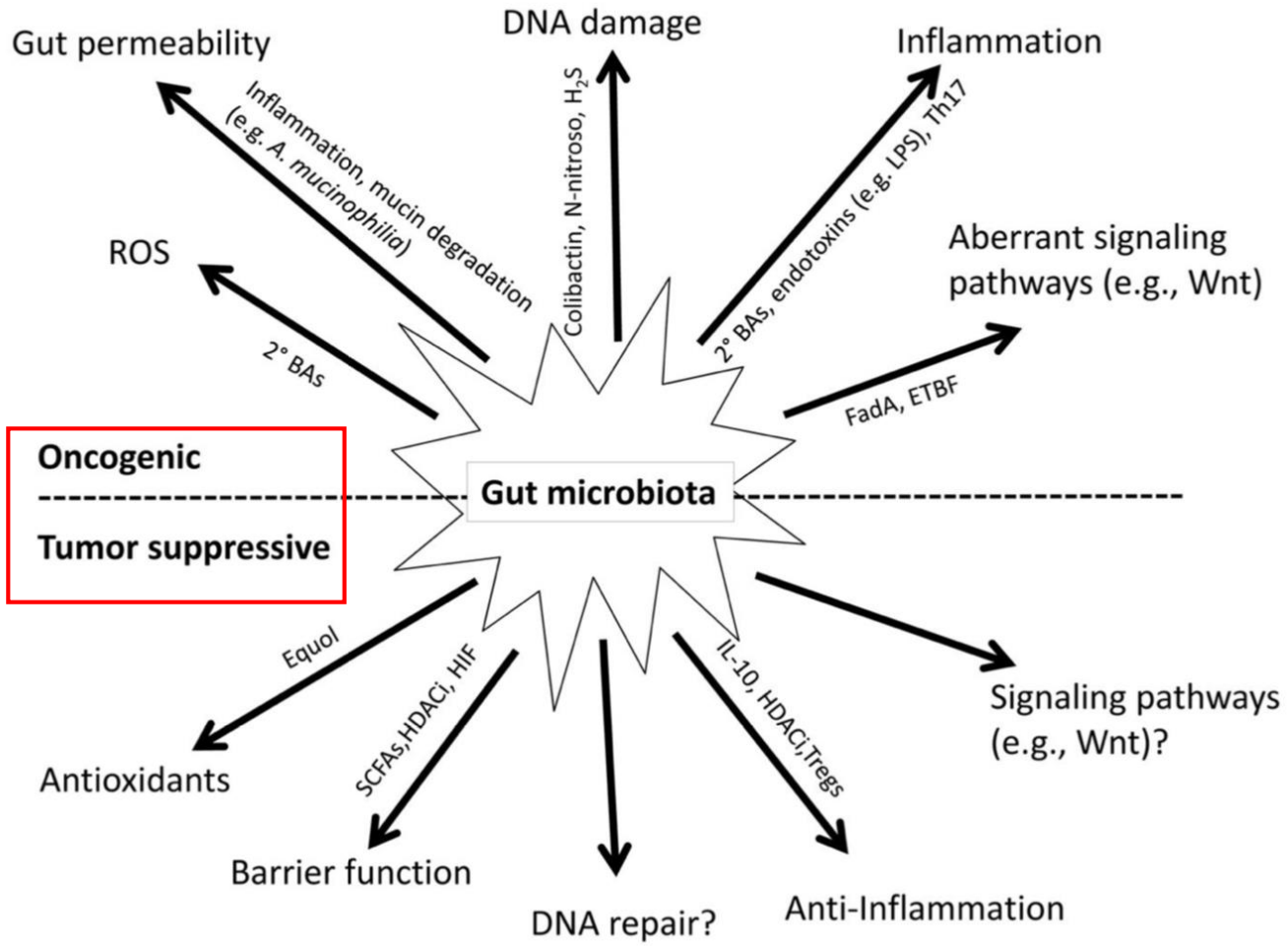
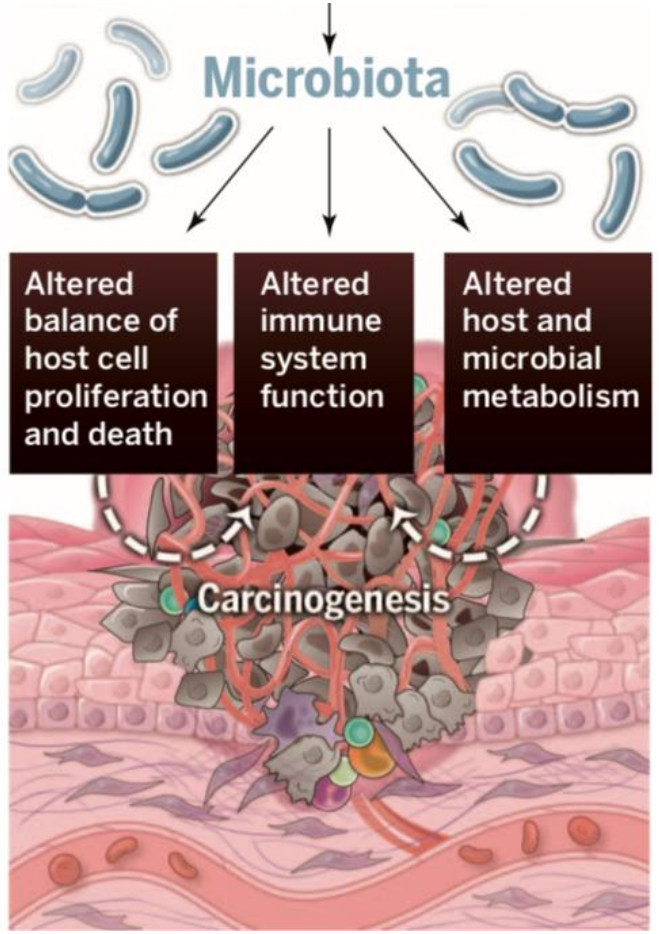
Proposed indications for FMT *beyond C.difficile infection*

MICROBIOTA AND CANCER BIOLOGY





Garrett Science 2015
Bhatt CA Cancer J Clin 2017

Proposed indications for FMT *beyond C.difficile infection*

MICROBIOTA AND GASTOINTESTINAL CANCER

Cancer Causes Control (2012) 23:399–404

Stomach

OPEN ACCESS

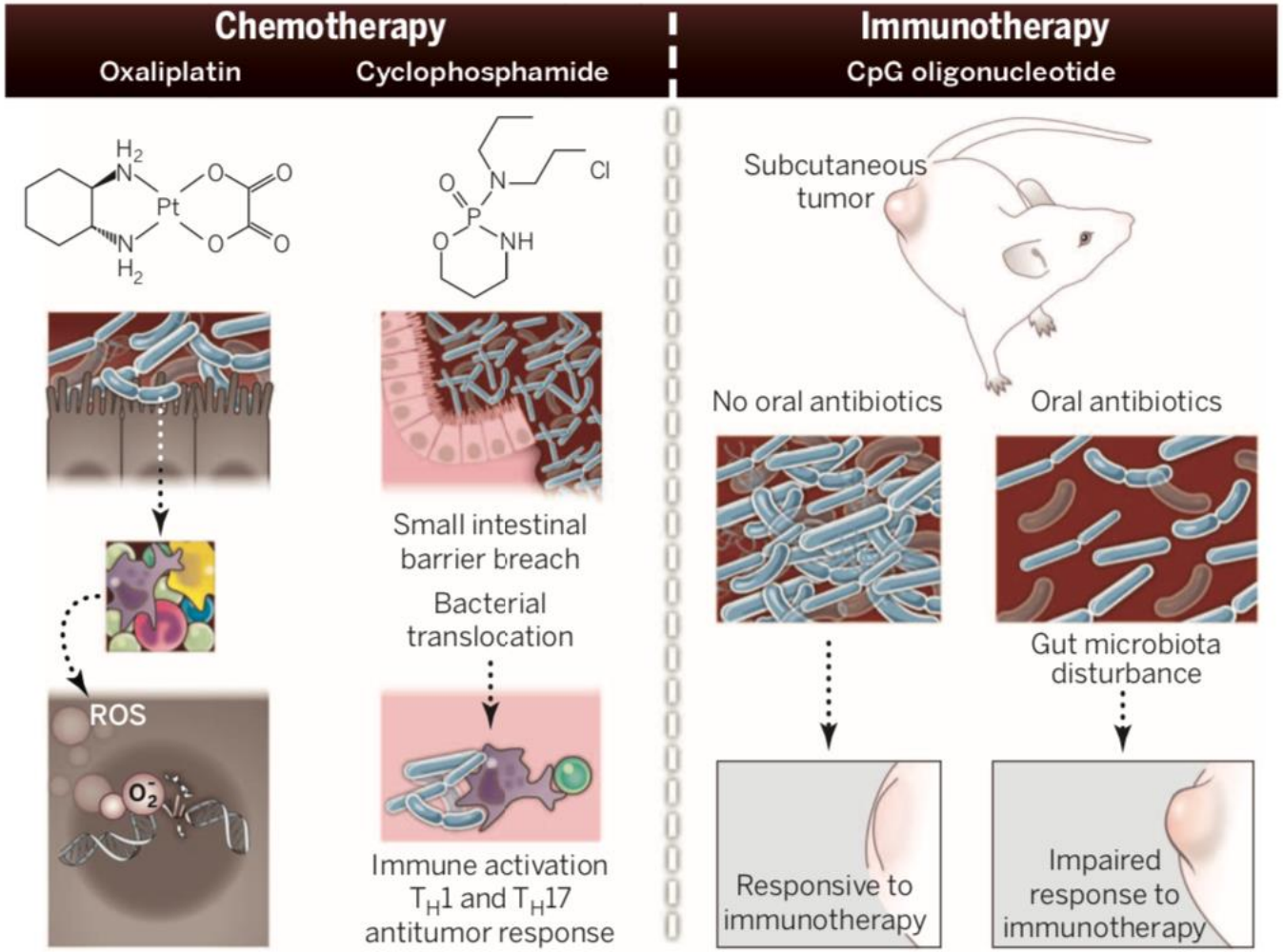
ORIGINAL ARTICLE

Mucosal microbiome dysbiosis in gastric carcinogenesis

Olabisi Oluwabukola Coker,[1] Zhenwei Dai,[1] Yongzhan Nie,[2] Guijun Zhao,[3] Lei Cao,[1] Geicho Nakatsu,[1] William KK Wu,[1] Sunny Hei Wong,[1] Zigui Chen,[4] Joseph J Y Sung,[1] Jun Yu[1]

Changting Meng [1,2,a], Chunmei Bai [2,b], Thomas D. Brown [3,c], Leroy E. Hood [1,3,d], Qiang Tian [1,4,*,e]

Microbiota and future modulation of chemotherapy



- *Intestinal barrier disruption can potentiate antitumor Th1 and Th17 responses*
- *Antibiotic demolition of gut micriobiota can compromise the efficacy of chemotherapy*

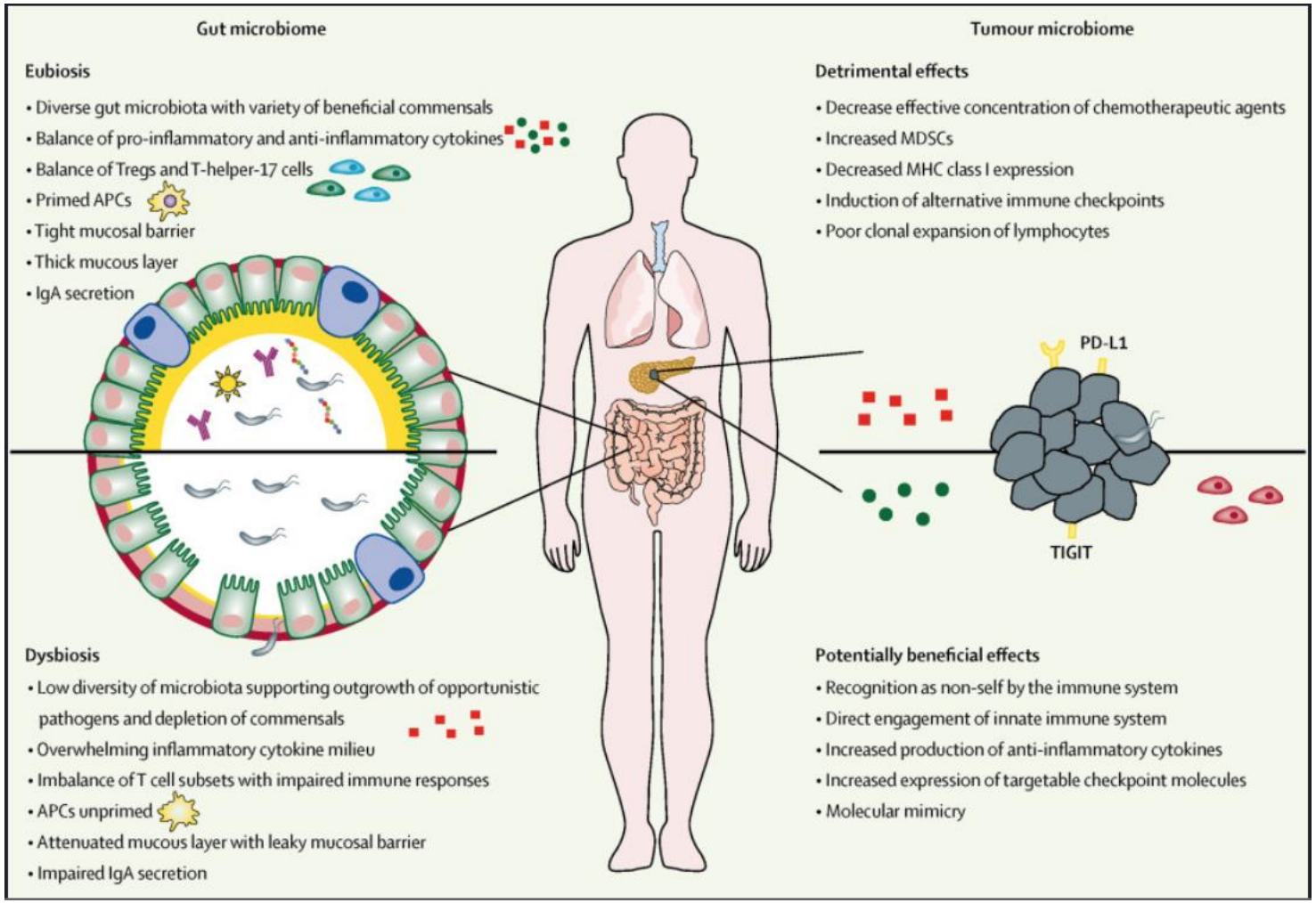
Garrett Science 2015

Modulating the microbiome to improve therapeutic response in cancer

- Jennifer L McQuade, 2019

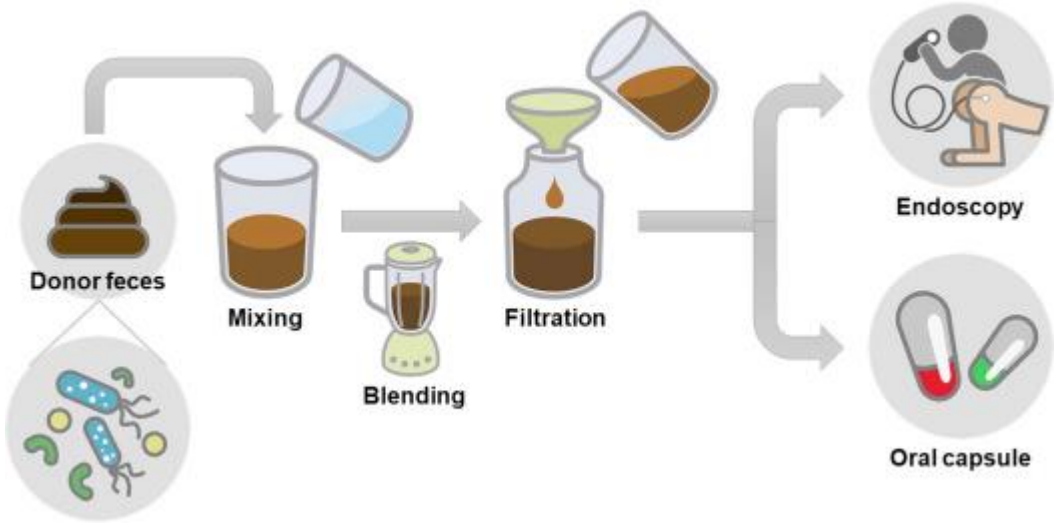
Predictors of response to cancer therapy focused on tumour-intrinsic features

→ host factors



MCQuade Lancet oncology 2019
Villeger Int J Mol Sciences 2019

FMT in future clinical practice: open issues



Which route of delivery?
Which formulation?
How many infusions?
Timing?
Which Bowel preparation?

Gundacker, Journal of hospital infections 2017

FMT in future clinical practice: open issues

Sweetening the pill

Table 3 Summary of studies of fecal microbiota transplantation delivered via oral capsules

Publication	# of patients	Amount of stool (g)	Capsule preparation	Duration of storage (days)	Capsules/ treatment	Overall cure rate %	Duration of follow up
Louie *et al* 2013 [88]	27	approx. 100	Fresh	Within hours	24-34	100	6 months
Youngster *et al* 2014 [90]	20	48	Frozen	30-252	30	90	6 months
Tian *et al* 2015[a] [59]	1	50	Lyophilized	Not reported	10	100	>14 days
Hirsch *et al* 2015 [51]	19	2.3	Frozen	49-63	6-22	89	90 days
Hecker *et al* 2016[b] [60]	20	40	Lyophilized	Not reported	20-40	95	204 days (31-408)
Youngster *et al* 2016 [50]	180	48	Frozen	Up to 180	30	93	Up to 6 months
Staley *et al* 2017[c] [54]	49	50	Lyophilized	Up to 365	2-27	87.8	Up to 12 months
Kao *et al* 2017[d] [27]	53	80-100	Frozen	Up to 60	40	96.2	At least 3 months

All studies used homologous stool from unrelated donors

Capsules are minimally invasive, convenient, and safe

Capsules are more esthetically pleasing

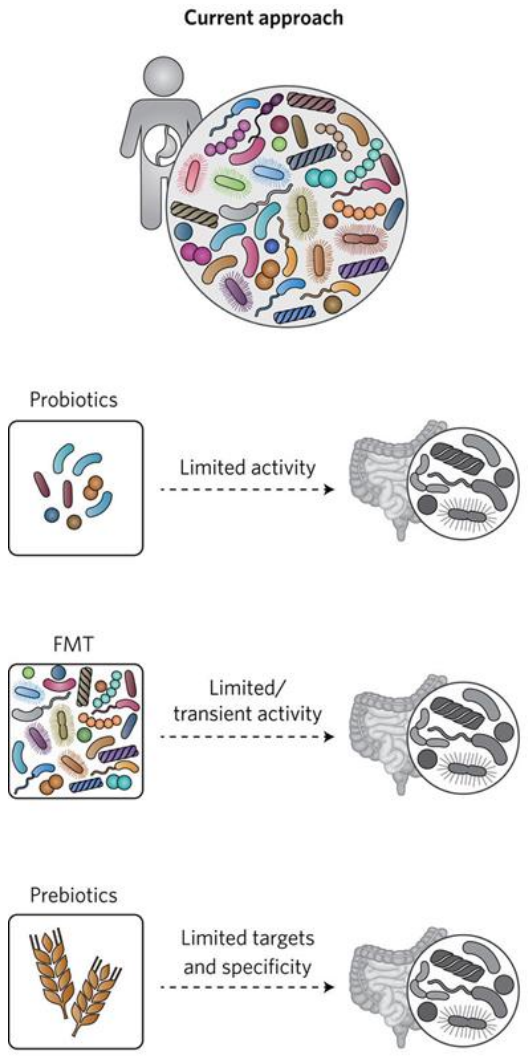
Which protocol of administration?

Ramai, Annals of Gastroenterology 2019

Gut microbiota in clinical practice: Challenges for 2019 and beyond

- Is there room for **precision medicine** in gut microbiota?
- Is there a role for a **microbiome clinic** in clinical practice?

Old microbiota modulation approach

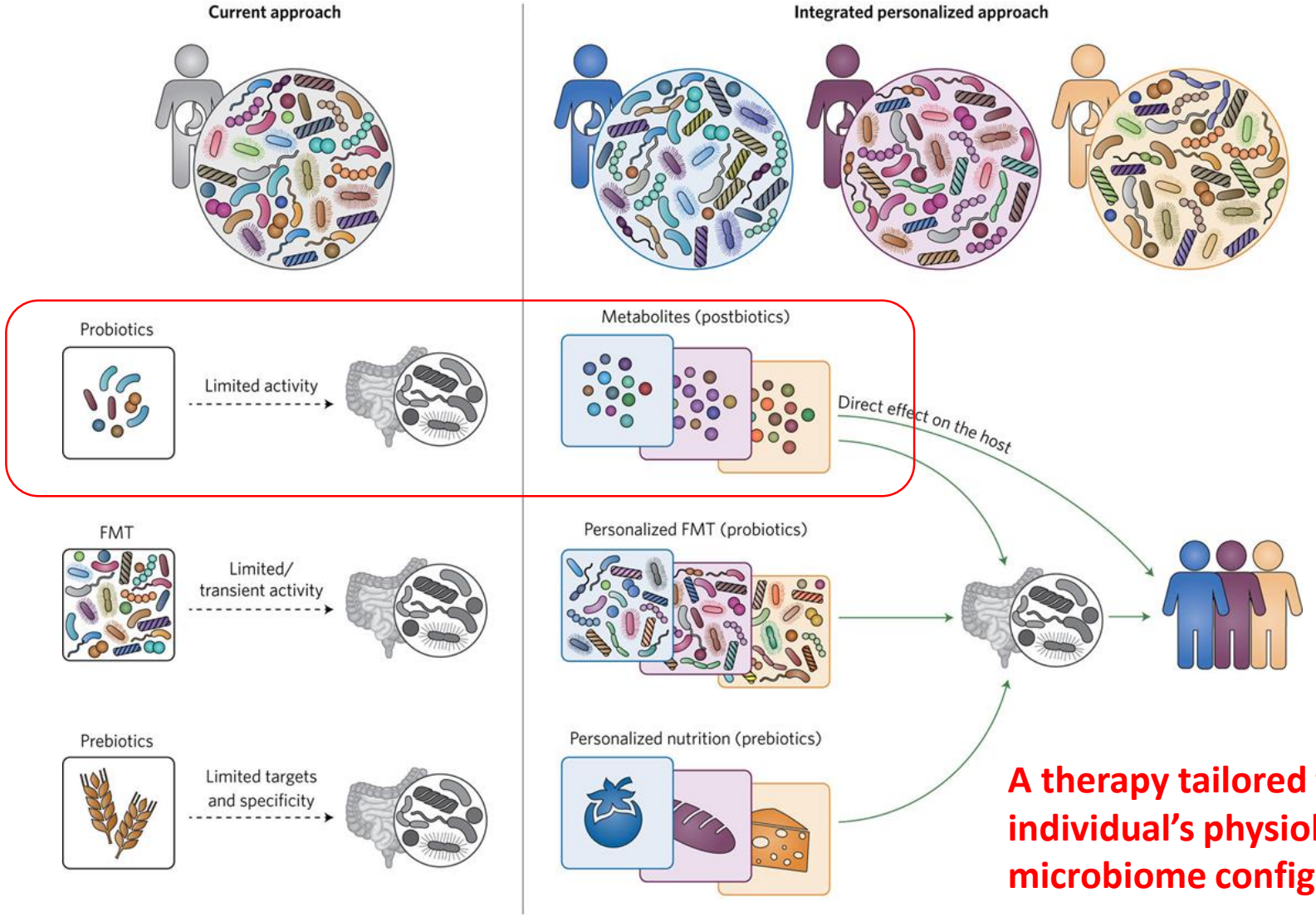


‘One approach fits all’

- Limited efficacy due to an inability of the exogenous bacteria to colonize a host that **harbours a discordant microbiome configuration**
- Many different composition
- Digestion of the bacterial components and amount of bacteria delivered to the colic tract
- Lack of specific targets for probiotics

Suez J Nature Microbiology 2017

A targeted and personalized approach



A therapy tailored to the individual's physiology and microbiome configuration

Suez J Nature Microbiology 2017

OPENBIOME – A nonprofit stool bank