The Chinese University of Hong Kong, Faculty of Medicine,
Department of Microbiology
Joint Graduate Student Seminar

Fecal Microbiota Transplantation: How it's Done, How it Works, and What Challenges Does it Face

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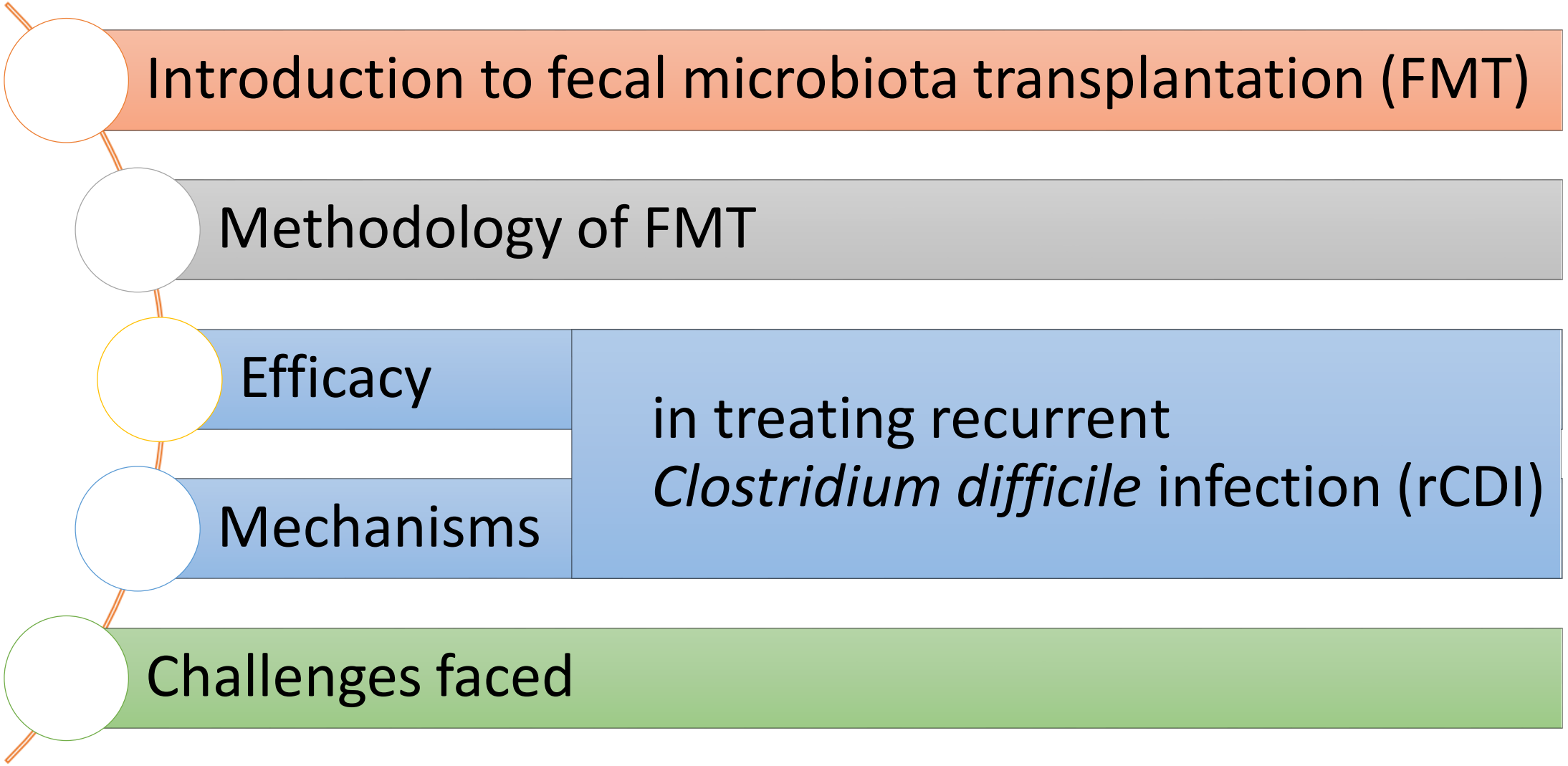
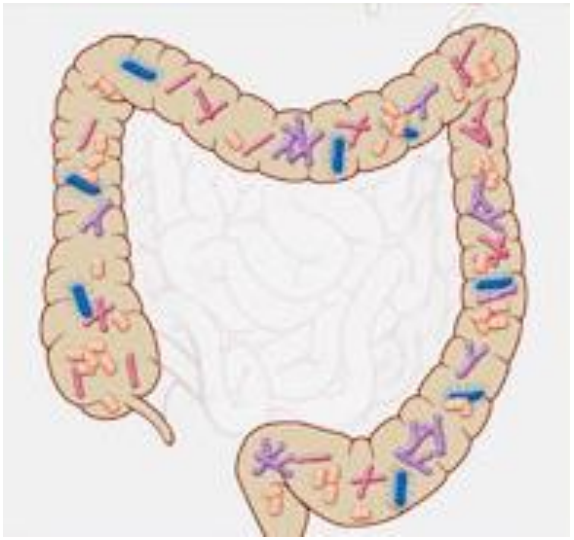
Presentation outline



What's FMT?

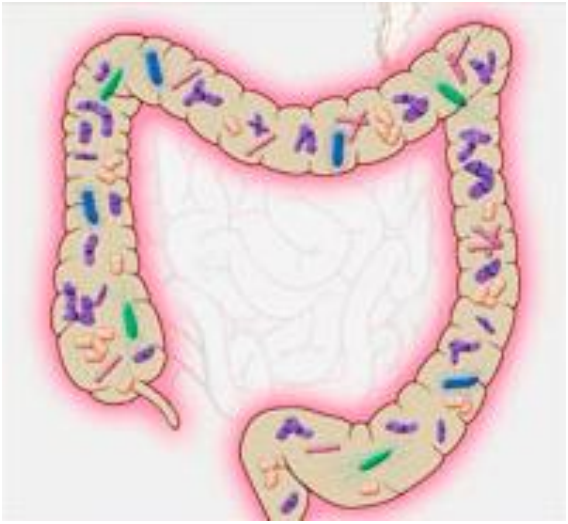
- Fecal Microbiota Transplantation



Healthy donor

Transplantation of gut microbiota

Through administration of fecal material



Patient

To cure the disease or improve the patient's conditions
By normalizing microbial diversity & community structure

History of FMT

1958: First case series of use of FMT

- Eiseman *et al.*, 1958
- Four patients with pseudomembranous enterocolitis (PMC)
- Fecal retention enemas → Prompt recovery in all patients

1983: First documented case of FMT for rCDI

- Schwan *et al.*, 1983
- 65-year-old woman with 5 episodes of CDI relapses
- Fecal enemas
  → Prompt and complete normalization of bowel function

History of FMT

- Since 2000: Booming of FMT practices

Driven by:

1. Increasing CDI incidence

- 6-25% of patients experienced recurrent CDI
- 60% of rCDI patients had multiply recurrent CDI (mrCDI)
- High rate of remission was achieved by FMT

(Cohen et al., 2010)

2. Better understanding in gut microbiota

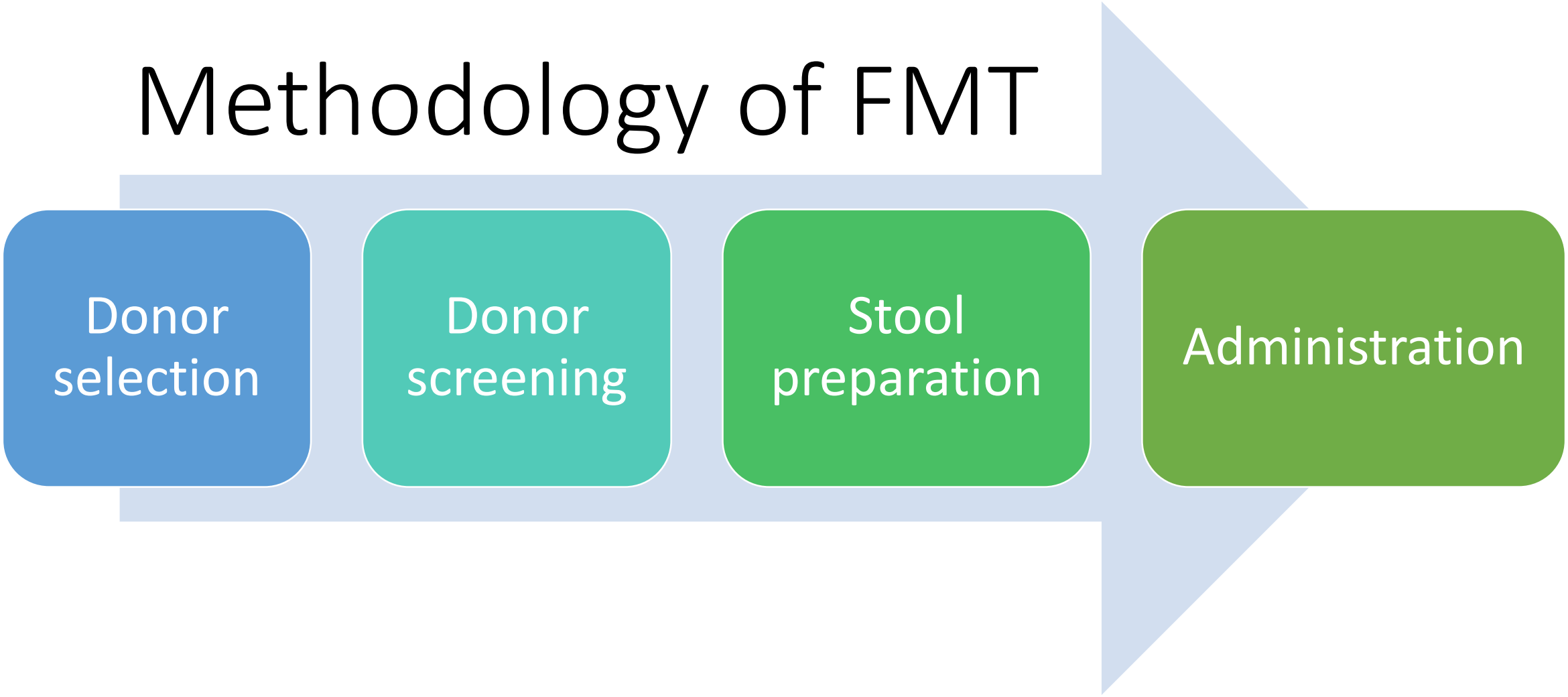
- Provided logical reasons for using FMT

→ Growing acceptance

- Association to other diseases

→ FMT applications other than rCDI

Methodology of FMT



Methodology of FMT—Donor Selection

Known donors

Patients' spouse, family members or friends

Pros: Better acceptance

Cons: Shared genetic / environmental risk factors

May conceal relevant infectious risk factors

Unrelated, rigorously screened healthy volunteers

Donations are processed and stored by stool banks

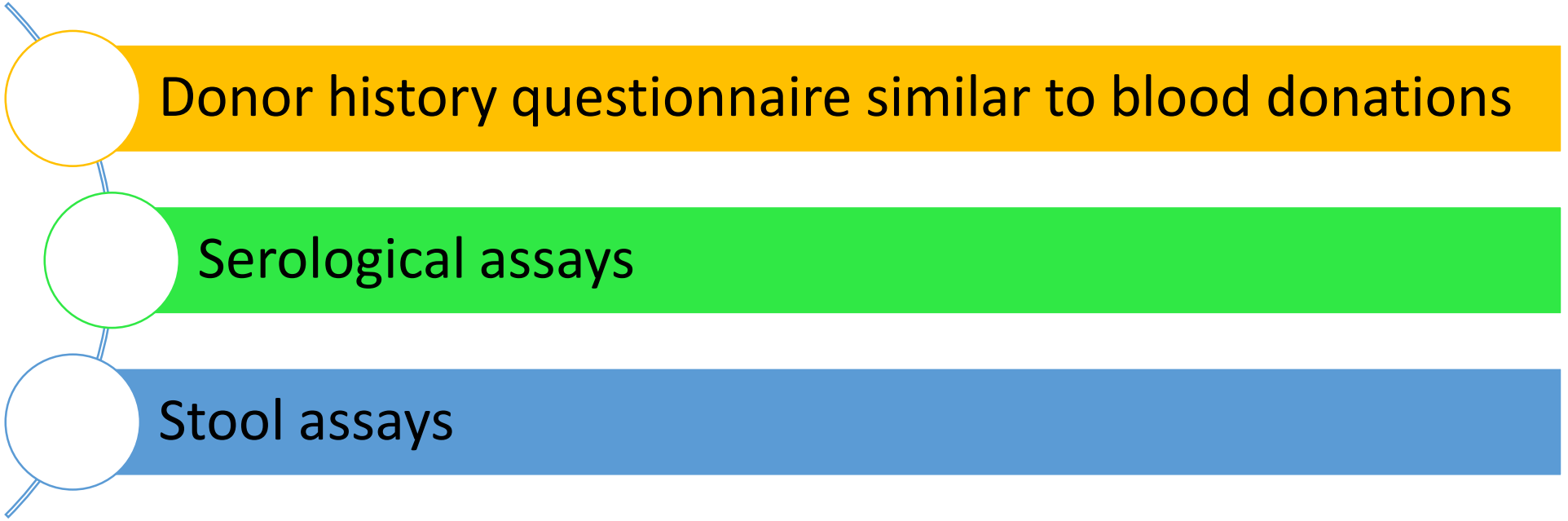
Pros: Do not share genetic / environmental risk factors

Constant ready-to-use supply

Cons: Stool bank may not be available in the patients' region

Methodology of FMT—Donor Screening

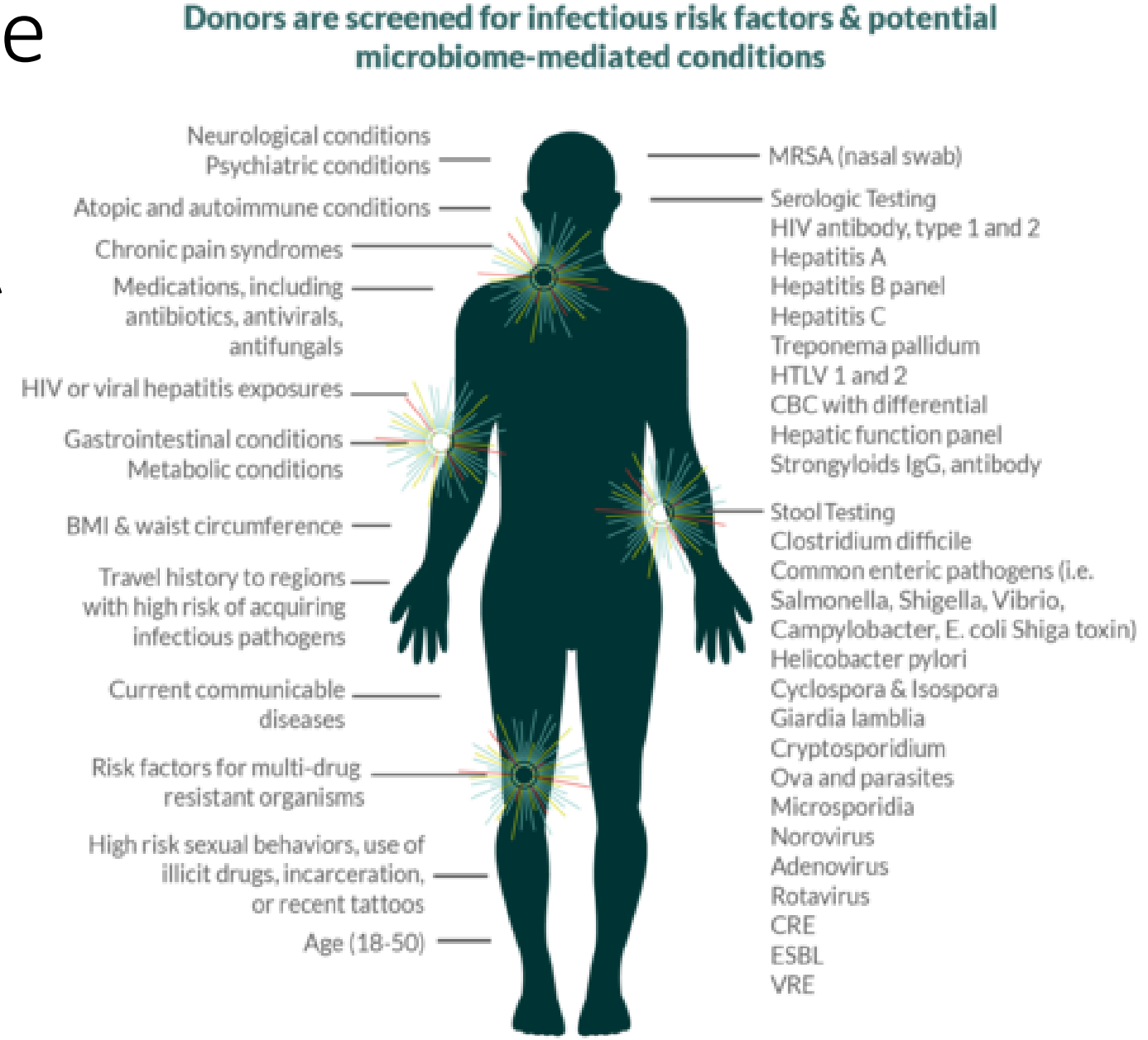
- General screening procedures:



- Screen for diseases or disorders
- Screen for risks of infection

Example of OpenBiome

- OpenBiome:
  First public stool bank in USA
- Donor Assessment:
  1. 200-question Clinical Evaluation with internal medicine specialist
  2. Serological assays
  3. Stool-based assays
- Only 3% of volunteers pass and become active donors



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Example of OpenBiome

- Donors donate stool 3 times a week for ≥ 60 days
- Their health conditions are monitored daily
- After the collection period, they are rescreened
- If passed, Stool from Day 1-38 can be released for clinical use
- Stool from Day 39 and on will be released after the 3rd screening

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Methodology of FMT—Stool preparation

- Stool Collection
  - Stool is collected in sterile containers
  - Delivered for processing within hours

An example of stool collection kit

Methodology of FMT—Stool preparation

- 30~50 g of fecal material are processed
- Homogenization
  - Manual effort
  - Blender

Household blender

Paddle blender

- Diluents
  - Tap water
  - Milk
  - Saline
  - Saline with glycerol

(Kelly et al., 2015)

https://images.kitchenaid.com/is/image/KitchenAid/KSB56POB?web_jpg&wid=290&hei=290
http://seward.co.uk/wp-content/uploads/2013/09/seward-stomacher.jpg

Methodology of FMT—Stool preparation

- Filtration
  - To remove particles
  - To prevent clogging in infusion tube
  - Can be done with gauze, coffee filter or strainer

- Processed sample can be
  - Directly administrated to patients
  - Frozen for later use

(Kelly et al., 2015)

https://yaleglobalhealthreview.files.wordpress.com/2016/12/fmtvials.jpg
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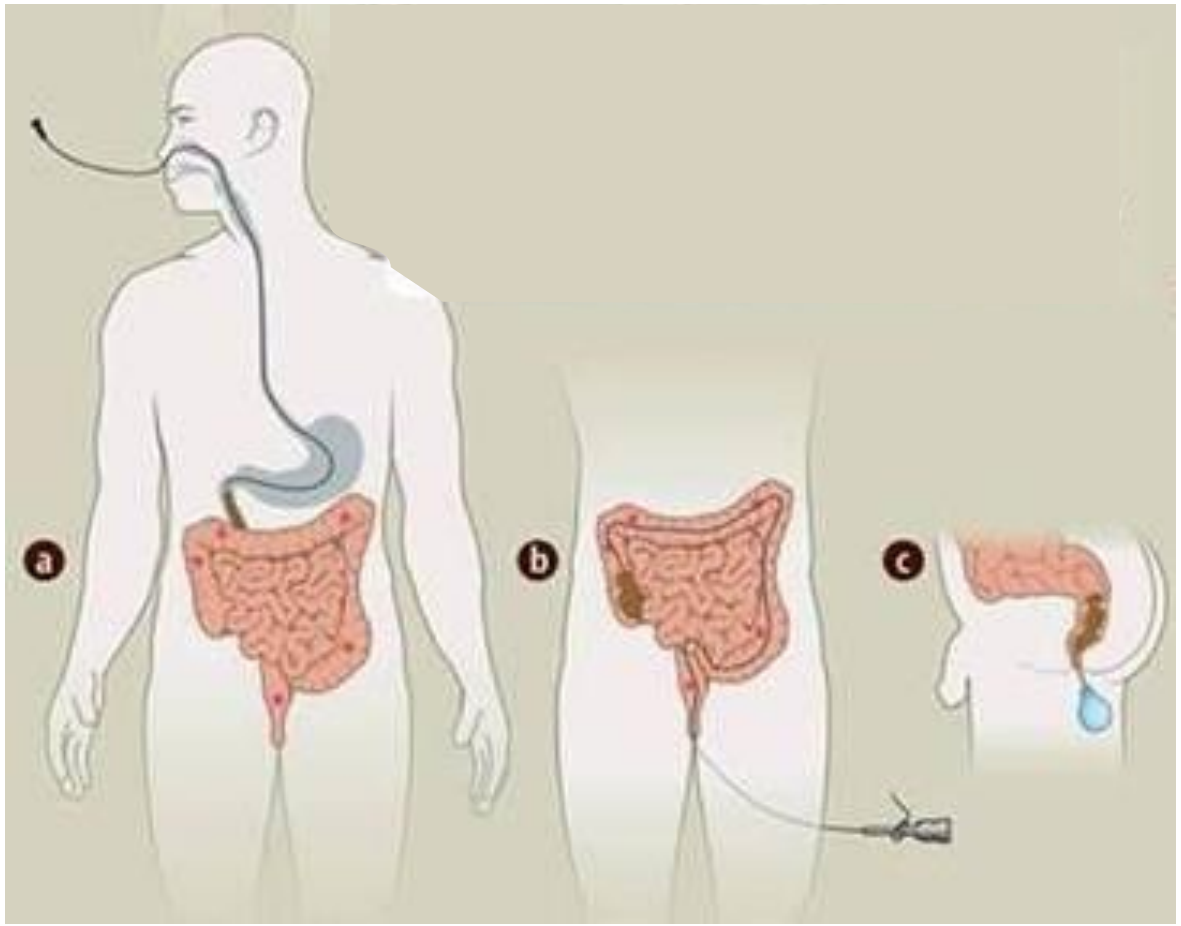
Methodology of FMT—Administration

- Patient preparation
  - Discontinue antibiotics 12-48 hours before FMT
  - Administer proton pump inhibitor before FMT for upper GI tract and oral delivery

(Cammarota et al., 2017)

Methodology of FMT—Administration

- Routes of administration
  - Upper GI tract
    - Endoscopy, nasogastric/ nasointestinal tubes
    - 25-50 ml of stool suspension
  - Lower GI tract
    - Colonoscopy, sigmoidoscopy, rectal tube, enema
    - 200-500 ml of suspension



Nasointestinal tube | Colonoscopy | Enema

(Cammarota et al., 2017; Kelly et al., 2015)

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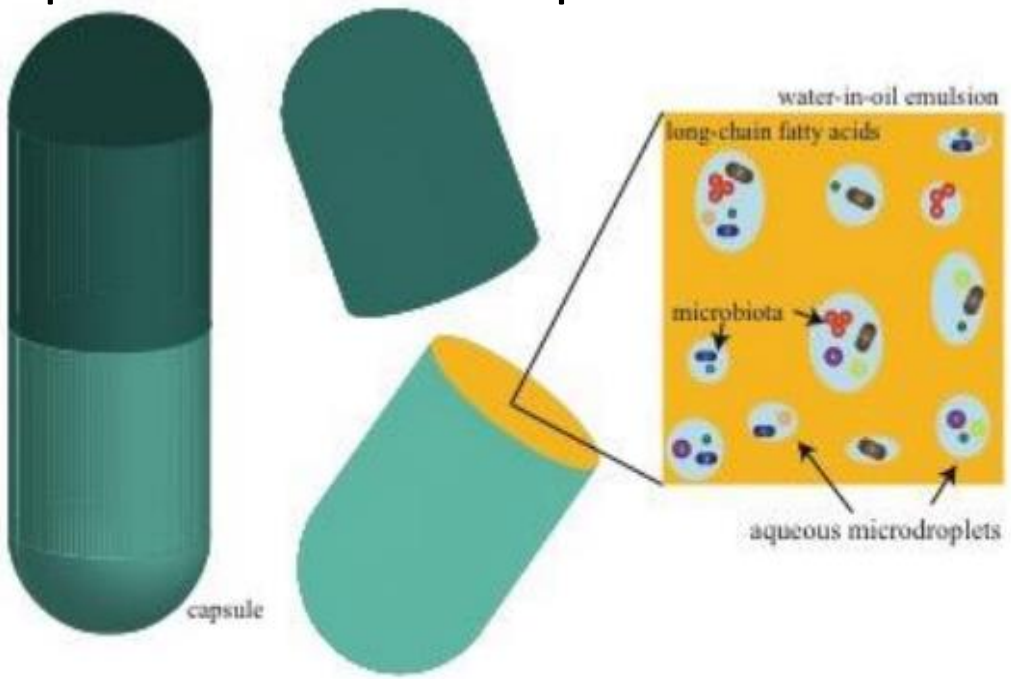
Methodology of FMT—Administration

- Routes of administration
  - Oral—Capsules
    - Dose: ~30 capsules
    - Contain same amount of stool material in traditional FMT
    - Advantages:
      - Non-invasive
      - Eliminate procedure-related cost
      - More aesthetically appealing

OpenBiome's FMT Capsule



FMT Capsule G3 Ingredients: Frozen human fecal microbiota filtered to 330 microns, theobroma oil, glycerol, hide bovine gelatin, sodium lauryl sulfate, colorants FD&C, titanium dioxide

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Efficacy of FMT in rCDI

- Rapid resolution of symptoms within days
- High cure rate

Systematic review by Li et al. in 2016

- Included 18 cohort and case series studies
- Involved 611 patients
- Long-term follow-up duration (≥90 days)
- Pooled primary cure rate: 91.2% (95% CI 86.7–94.8%)
- Overall recurrence rate: 5.5% (95% CI 2.2–10.3%)

Efficacy of FMT in rCDI – Clinical trials

- Two clinical trials comparing efficacy of FMT with vancomycin

van Nood et al., 2013

Resolution of rCDI occurred in

- FMT group: 13/16 (81%) of patients
- Vancomycin group: 4/13 (31%) of patients

Cammarota et al., 2015

Resolution of rCDI occurred in

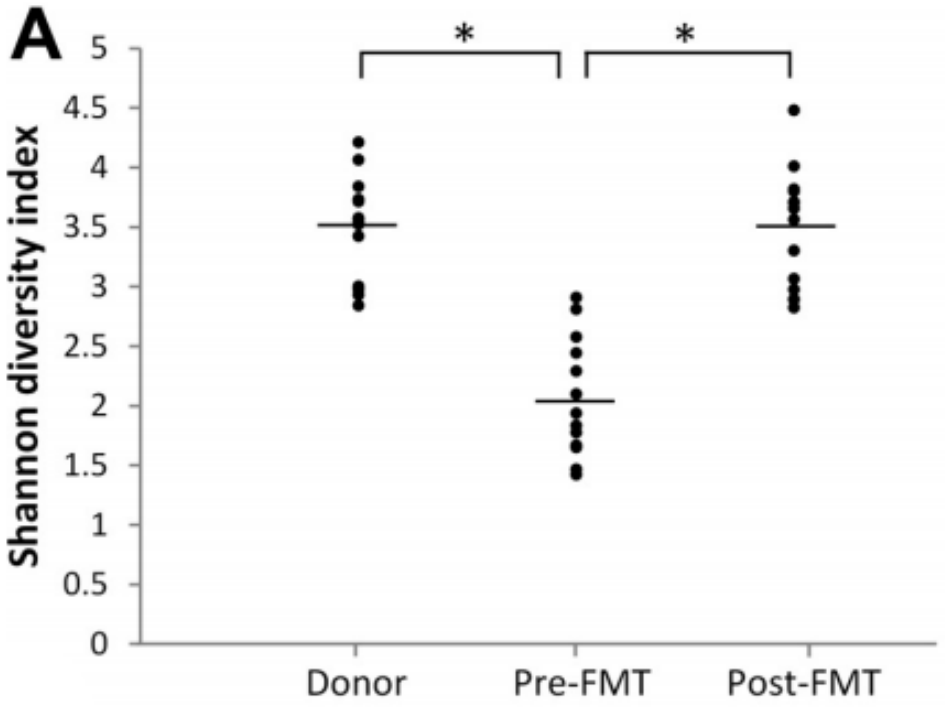
- FMT group: 18/20 (90%) of patients
- Vancomycin group: 5/19 (26%) of patients

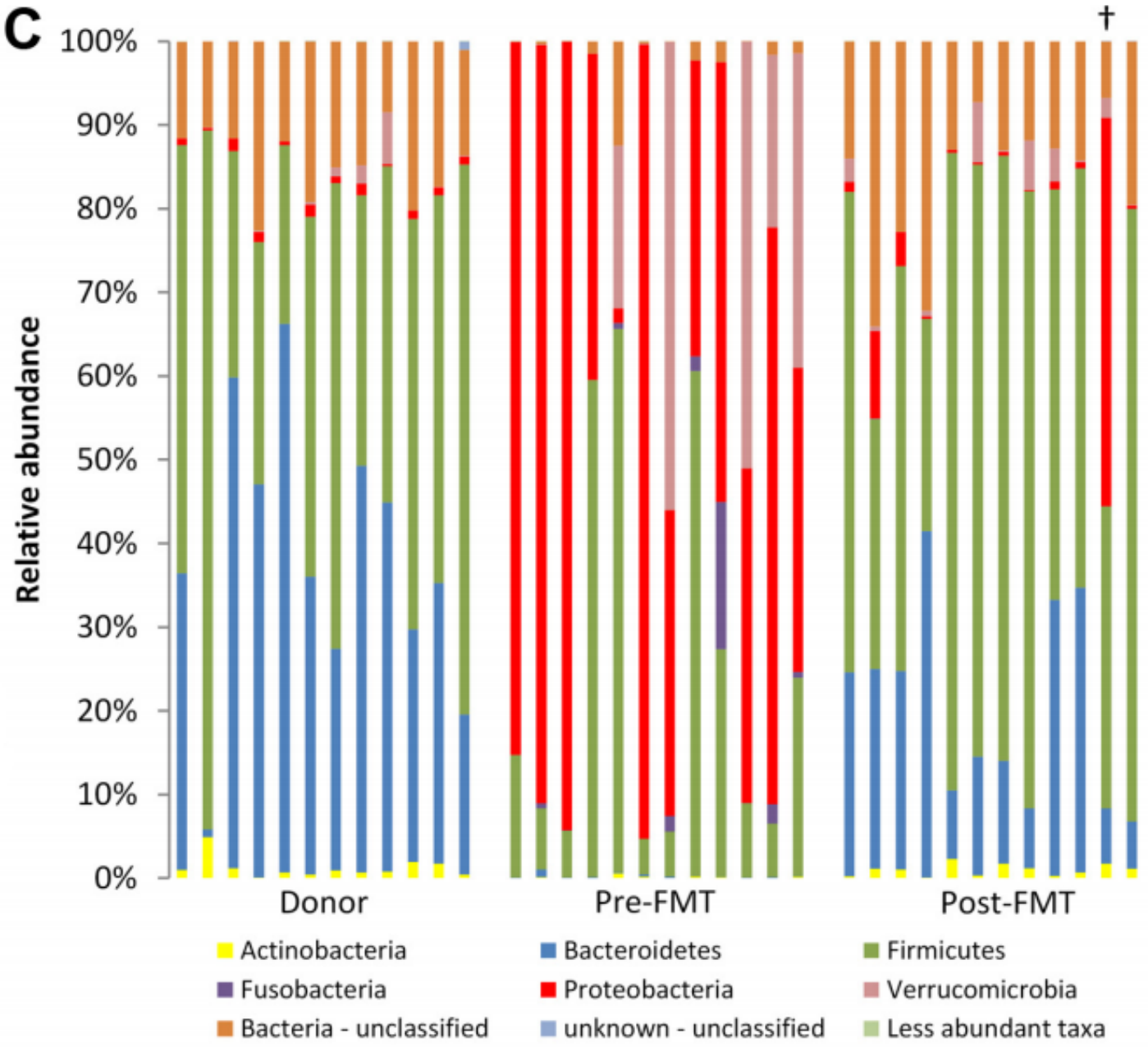
Mechanisms of FMT in treating RCDI

- Characteristics of rCDI patient's gut microbiota:
  - Loss of microbial diversity
  - ↓ Abundances of Bacteroidetes and Firmicutes
  - ↑ Abundances of Proteobacteria
    (Weingarden et al., 2015)
- FMT normalizes microbial diversity & community structure of patient's gut microbiota
  - Normalization was observed as early as 24 h after FMT
    (Weingarden et al., 2014)

Study by Weingarden et al., 2015

- 12 patients & 2 donors
- 16S rRNA sequence characterization on stool sample





Mechanisms of FMT in treating rCDI

Two mechanistic categories

Direct interaction of donor gut microbiota with *C. difficile*

- Antimicrobial peptides
- Bile-acid-mediated inhibition

Microbiota mediated effects on host immune responses

(Khoruts and Sadowsky, 2016)

Mechanisms of FMT in treating rCDI

- Antimicrobial peptides — Bacteriocins

Thuricin CD
(Rea et al., 2010)

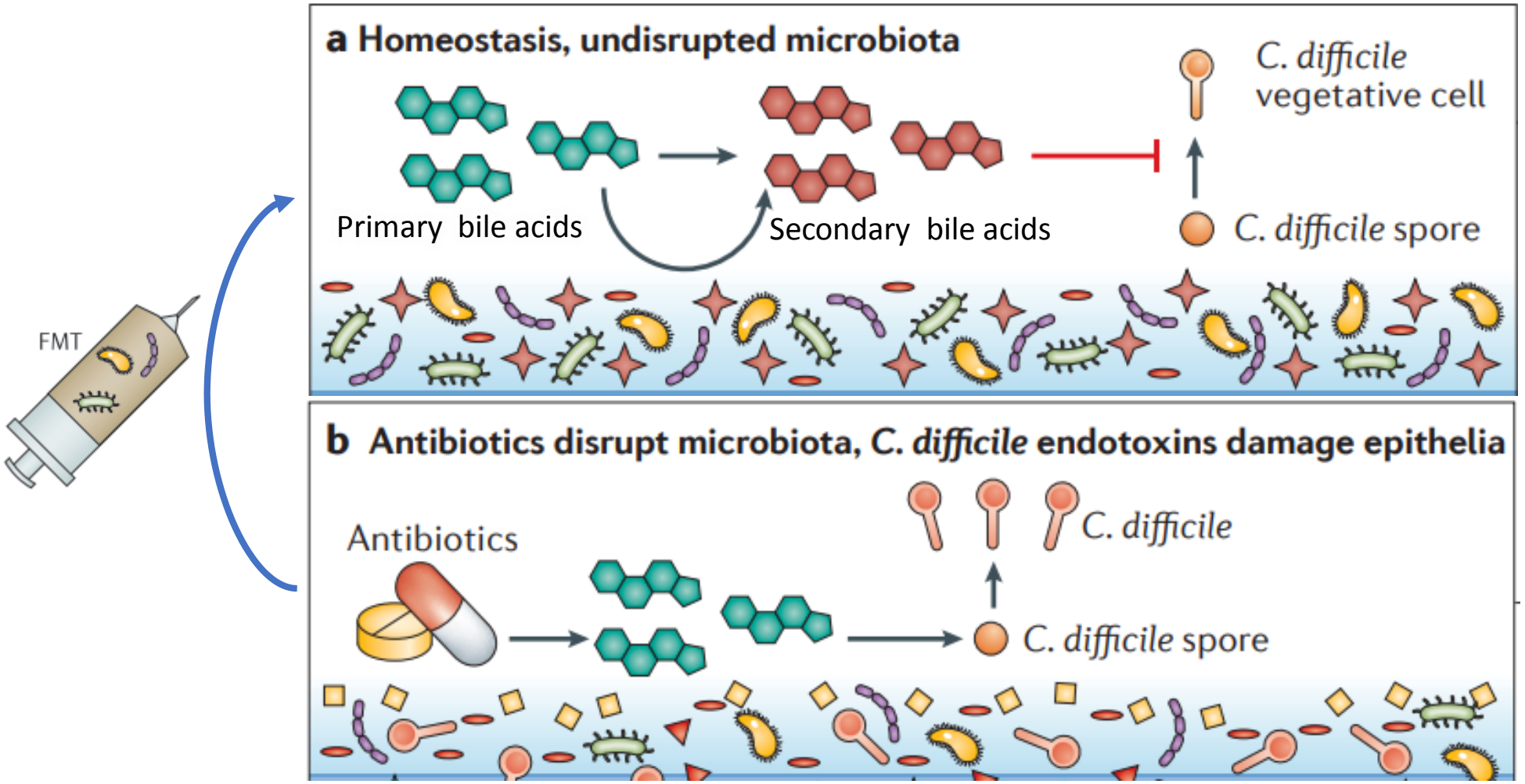
- Produced by *Bacillus thuringiensis*
- Narrow spectrum and highly effective against *C. difficile*

Nisin
(Lay et al., 2016)

- Produced by *Lactococcus lactis*
- Inhibits *C. difficile* vegetative cells growth and spore germination

Mechanisms of FMT in treating rCDI

- Bile-acid-mediated inhibition



(Modified from Figure 1. Khoruts & Sadowsky, 2016)

Challenges faced by FMT

Safety

Applications

Replacement

Challenges faced by FMT—Safety

- Short term adverse effects
  - Minor events
    - e.g. Diarrhoea, abdominal cramps, belching, and constipation
    - Common; Resolve within hours post-FMT
  - Serious events
    - Rare
    - Procedure-related
      - Endoscopy: Perforation and bleeding
      - Sedation: Aspiration
    - Infectious complications
      - Uncertain relationship to FMT

(Cammarota et al., 2015; Khoruts and Sadowsky, 2016; Weingarden et al., 2013)

Challenges faced by FMT—Safety

- Potential Long-term effects
  1. Possible transmission of infectious agents through FMT
     - e.g. Hepatitis C and HIV
     - Not examined in short-term follow-up
     - Other possible unrecognized infectious agents
  2. Induction of chronic disease related to alterations of microbiota
     - Disease/condition related to gut microbiota:
       Obesity, diabetes, colon cancer etc.

To assess the long-term safety of FMT,

Clinical follow-up of patients over years
Analysis of banked donor and recipient specimens } are required

(Cammarota et al., 2017; Kelly et al., 2015)

Challenges faced—Applications other than rCDI

- Refractory CDI
  - Pooled results of 7 case-series studies (Drekonja et al., 2015)
    Overall resolution rate 55%, range 0-100%
- Inflammatory bowel disease (IBD)
  - In a systematic review included 53 studies (Paramsothy et al., 2017)
    36% [201/555] of ulcerative colitis
    50.5% [42/83] of Crohn's disease
    patients achieved clinical remission

Challenges faced—Applications other than rCDI

- Obesity
  - Randomized control study of Vrieze et al., 2012
  - Obese male subjects received FMT
    of allogenic (lean donor) or autologous (self) stool material
  - After 6 weeks, the allogenic group had
    - Improved insulin sensitivity
    - Increased diversity in gut microbiota
    - Increased abundance of butyrate-producing bacteria

Challenges faced—Applications other than rCDI

- Promising preliminary data
- Not efficacious as treating rCDI
- Large randomized controlled studies are required
- Optimization of FMT protocol is required
  - e.g. Antibiotic pretreatment & Multiple rounds of FMT

Challenges faced by FMT—Replacements

- Products with defined microbial consortia are more favoured
- Examples of treating rCDI
  - SER-109
    - Orally administered capsule developed by Seres Therapeutics
    - Contains mixture of bacterial spores purified from human faeces
    - Current in phase 3 trial
  - RePOOPulate (Petrof et al., 2013)
    - Collection of 33 strains isolated from healthy human faeces
    - Administration by infusion through colonoscopy
    - Achieved clinical remission of 6 months in 2 patients

Take-home messages

Fecal microbiota transplantation (FMT) is

- Grafting donor's gut microbiota to a recipient through fecal transplant
- To normalize gut microbiota diversity and composition

FMT has shown to

- Be an highly effective treatment for recurrent CDI
- Have promising results in treating other diseases

FMT lacks

- Assessments on long-term adverse effects
- Optimal protocols

FMT may be replaced by products with defined microbial consortia

https://aboveaverage.com/wp-content/uploads/2015/02/poop-emoji-thumbnail.jpg

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