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Practical Aspects of Faecal Microbiota Therapy (FMT) for recurrent *C. difficile* Infection (CDI)

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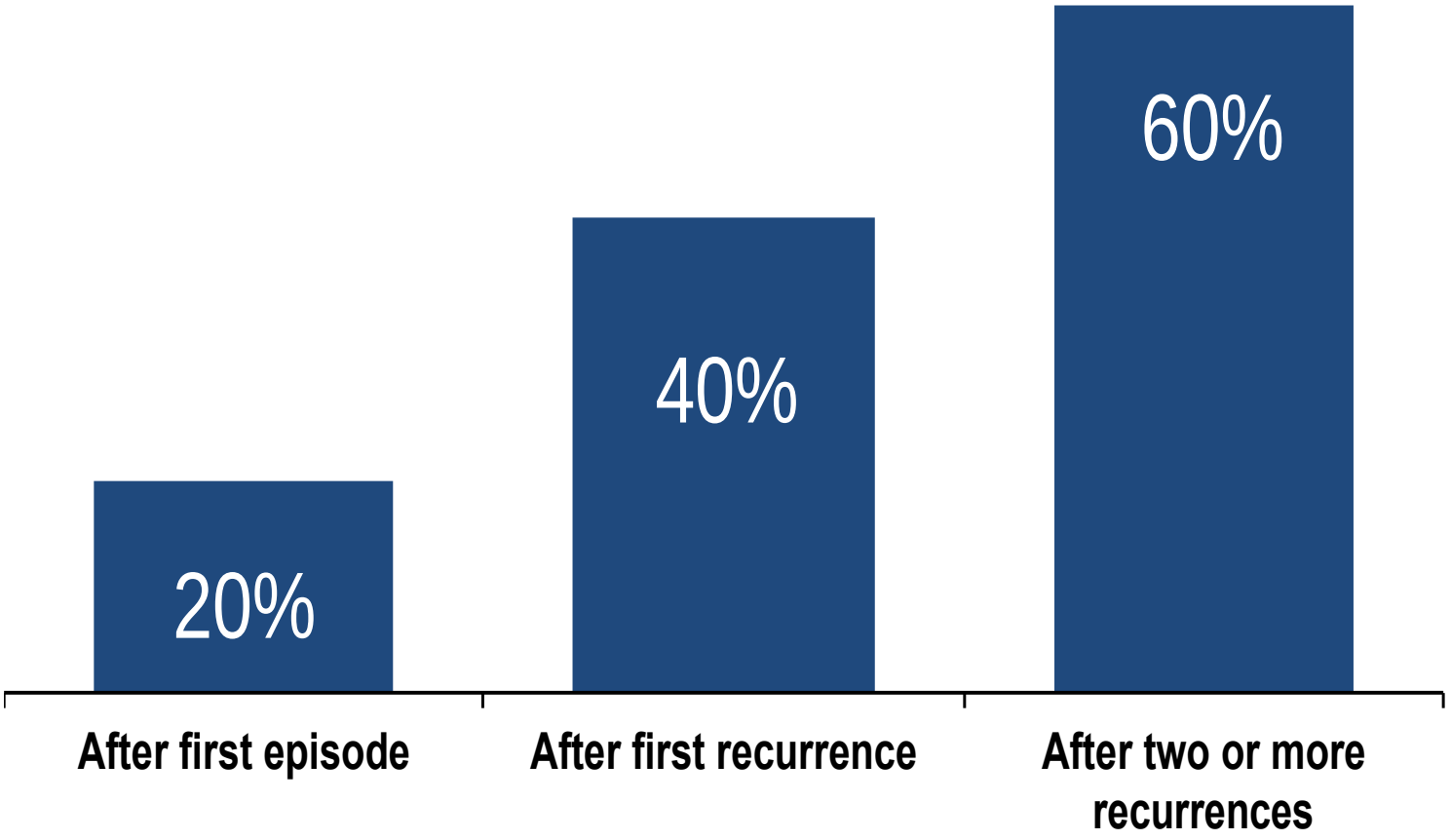
King's College Hospital NHS Foundation Trust

South London and Maudsley NHS Foundation Trust

CDI recurrence rates



Kelly CP, LaMont JT. *N Engl J Med*. 2008;359(18):1932-1940;
Johnson S. *International Journal of Antimicrobial Agents* 33 (2009) S33-S36.

Risk factors for CDI recurrence

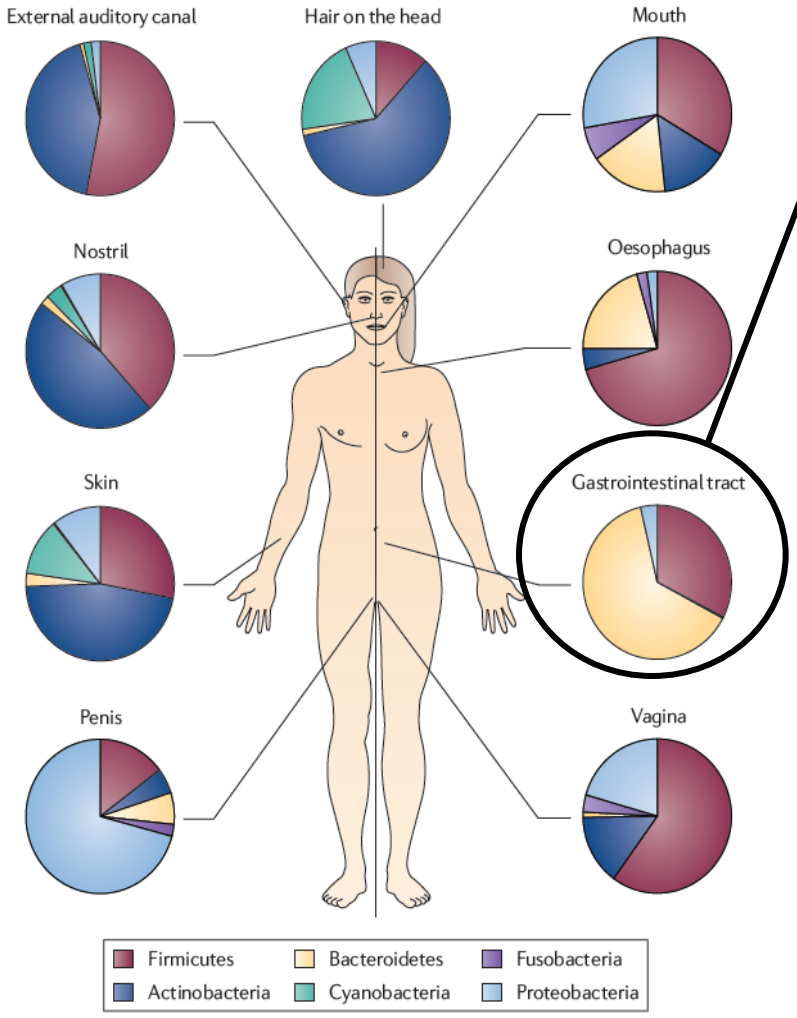
- Age ≥65 years[1-4]
- Severe CDI[1,4]
- Previous episode of CDI[1,3-5]
- Co-morbidities including renal failure[1,4,6,7]
- Exposure to concomitant antibiotics[4]
- Infection with particular strains eg RT 027
- Exposure to PPIs / other gastric acid supressors[8]
- Previous hospital admission[9]

[1] Kyne et al. Lancet 2001; 357: 189-93
[2] Bauer et al. Clin Microbiol Infect 2009; 15: 1067-79
[3] Bauer et al. Lancet 2011; 377: 63-73
[4] Hu et al. Gastro 2009; 136: 1206-14
[5] McFarland et al. Am J Gastroenterol 2002; 97: 1769-75
[6] Do et al. CID 1998; 26: 954-9
[7] Bauer et al. Clin Microbiol Infect 2011; 17: A1-4
[8] Kwok et al. Am J Gastro 2012; 107: 1011-9
[9] Eyre et al. CID 2012; 55: 77-88

Recurrent *C.difficile* Infection

- Impaired host-response
- Altered intestinal microbiome

The Human Microbiome

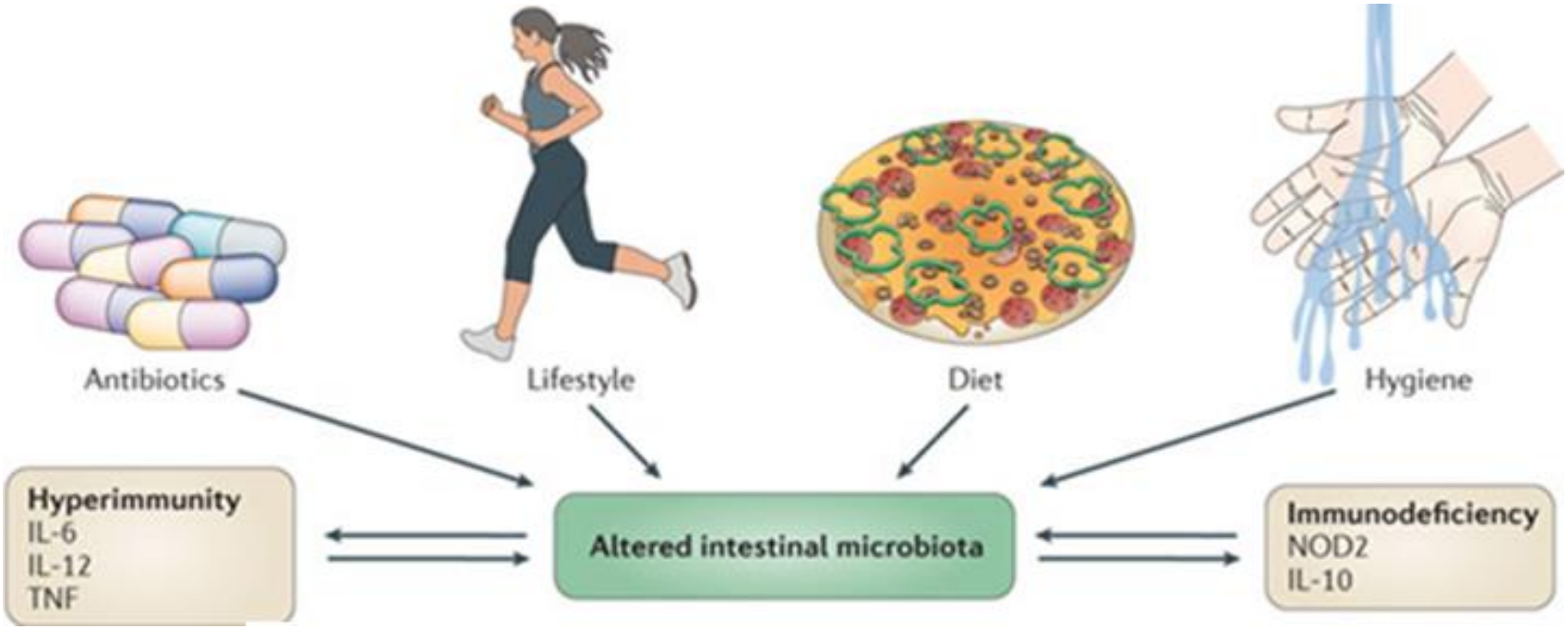


The Gut Microbiota

- Human gut is home to ~ 100 trillion bacterial cells
- Density of 10^{11} to 10^{12} per gram in the colon weighing ~2kg
- Genome size of microbiota at least 100-fold greater than human
- Large numbers species present (200-1000 species), most uncultured

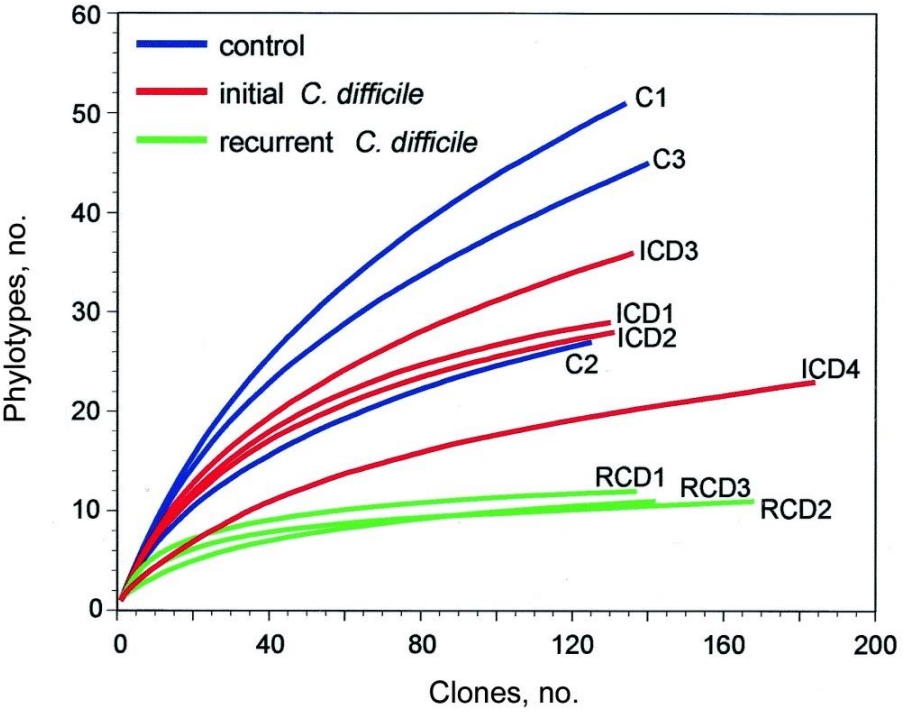
Nat. Rev. Micro. 2011;9:279-290

Factors shaping intestinal microbial composition



Sommer F, Nat Rev Microbiol. 2013 Apr;11(4):227-38

Decreased Diversity of the Faecal Microbiome in Recurrent *C.difficile*



- Patients with recurrent *C.difficile* have decreased phylogenetic richness

Chang JY, et al. J Infect Dis 2008:197;435-8

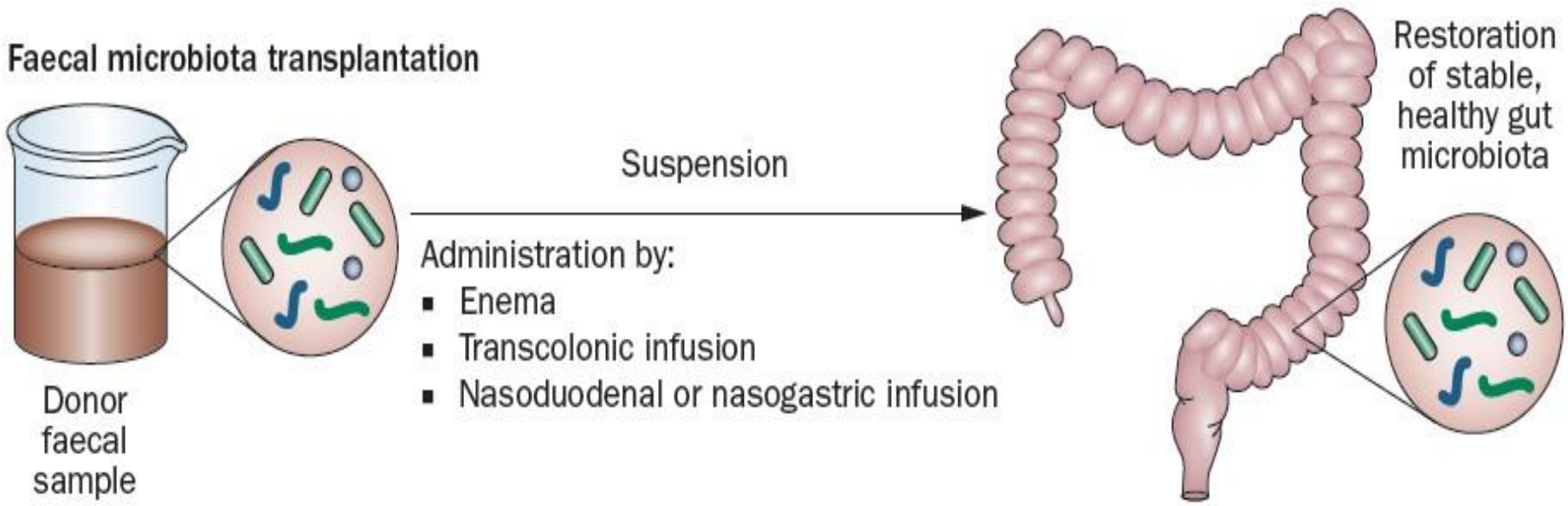
- After antibiotics some bacteria remain disrupted for long periods:

- Up to 2 years following treatment with clindamycin
- Up to 4 years after H. pylori eradication therapy

Sadowsky et al. The Fecal Bacteria, 2011

Faecal Microbiota Transplantation (FMT)

Instillation of stool from a healthy person into another person to cure a certain disease



Faecal Microbiota Transplantation (FMT)

Rationale: A perturbed imbalance in intestinal microbiota (dysbiosis) is associated with or causes disease and can be corrected by re-introduction of donor faeces

- Avoids prolonged, repeated courses of antibiotics
- Re-establish normal diversity of the intestinal microbiome, thus restoring "colonization resistance"

Early History of FMT

<u>4th century</u>: Ge Hong described use of human faecal suspension by mouth for diarrhoea and food poisoning

"Zghou Hou Bei Ji Fang"

Handy Therapy for Emergencies

<u>16th century:</u> Li Shizhen prescribed fermented faeces for abdominal diseases with diarrhoea, abdominal pain, fever,
vomiting and constipation; "yellow dragon soup"

"Ben Cao Gang Mu "

Compendium of Materia Medica

Early History of FMT

17th century: veterinary medicine:

Transfaunation (transfer of cecal contents or fresh faeces) from healthy horses to treat horses with chronic diarrhoea

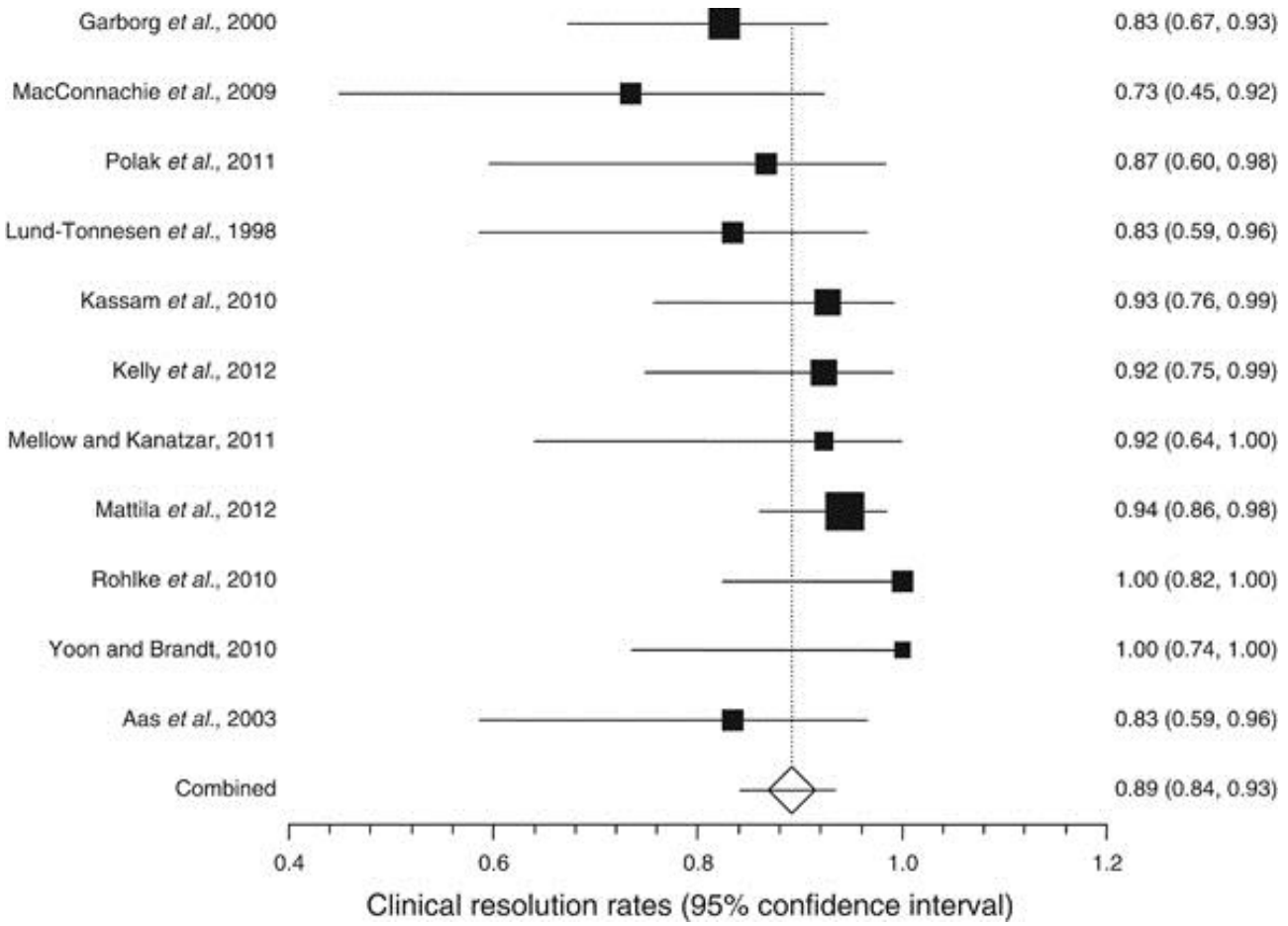
Rumen transfaunation is used to 'refaunate' cows that have been off-feed because of illness e.g mastitis

Later History of FMT

- 1958: *Eismann et al*. 4 patients with fulminant pseudomembranous colitis treated with FMT enema
- 1983: *Schwann, et al*. CDI treated with FMT enema
- Other methods of FMT
  - 1991: NG tube (*Aas, Gessert, Bakken*)
  - 1998: gastroscopy and colonoscopy (*Lund-Tønnesen, Persky, Brandt*)
  - 2010: self-administered enemas (*Silverman, Davis, Pillai*)

Eisman et al. Surgery 1958; 44: 854-9
Scwann. Lancet 1983; 2(8354): 845

Meta-analysis of Clinical Resolution Rates (11 of 2709 reports, 273 patients)



Clinical resolution rate 89% overall

(95% CI= 84-93%)

No AEs

Kassam et al . AM J Gastroenterol, 2013

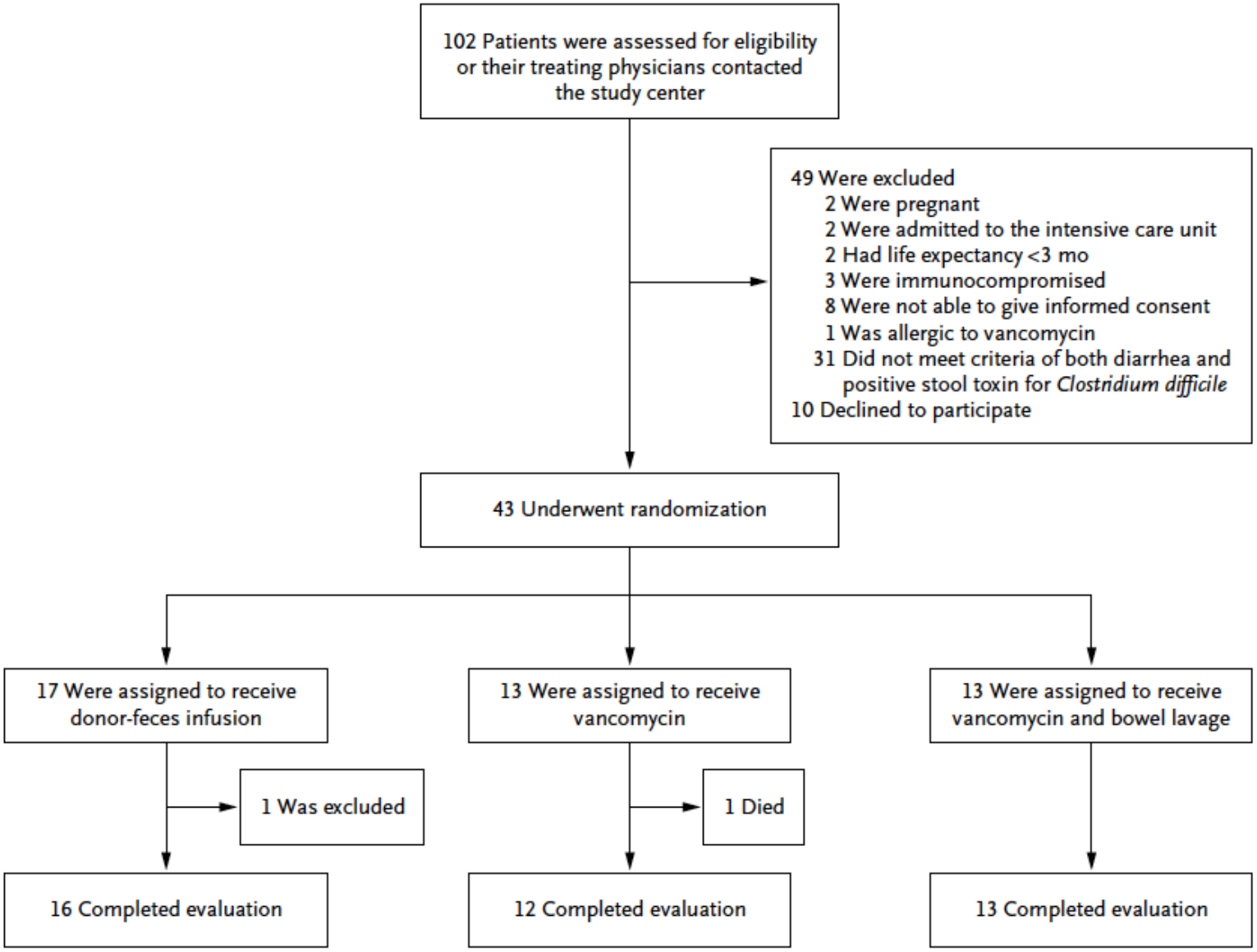
FMT for Treatment of *CDI:* A Systematic Review

Site of FMT	# of Pts	Dose of FMT (mean g/mls)	Success Rate (%)
Stomach	109	25/68	81
Duod/Jejunum	97	63/252	86
Caecum/Asc Colon	214	93/281	93
Distal Colon	116	58/272	84

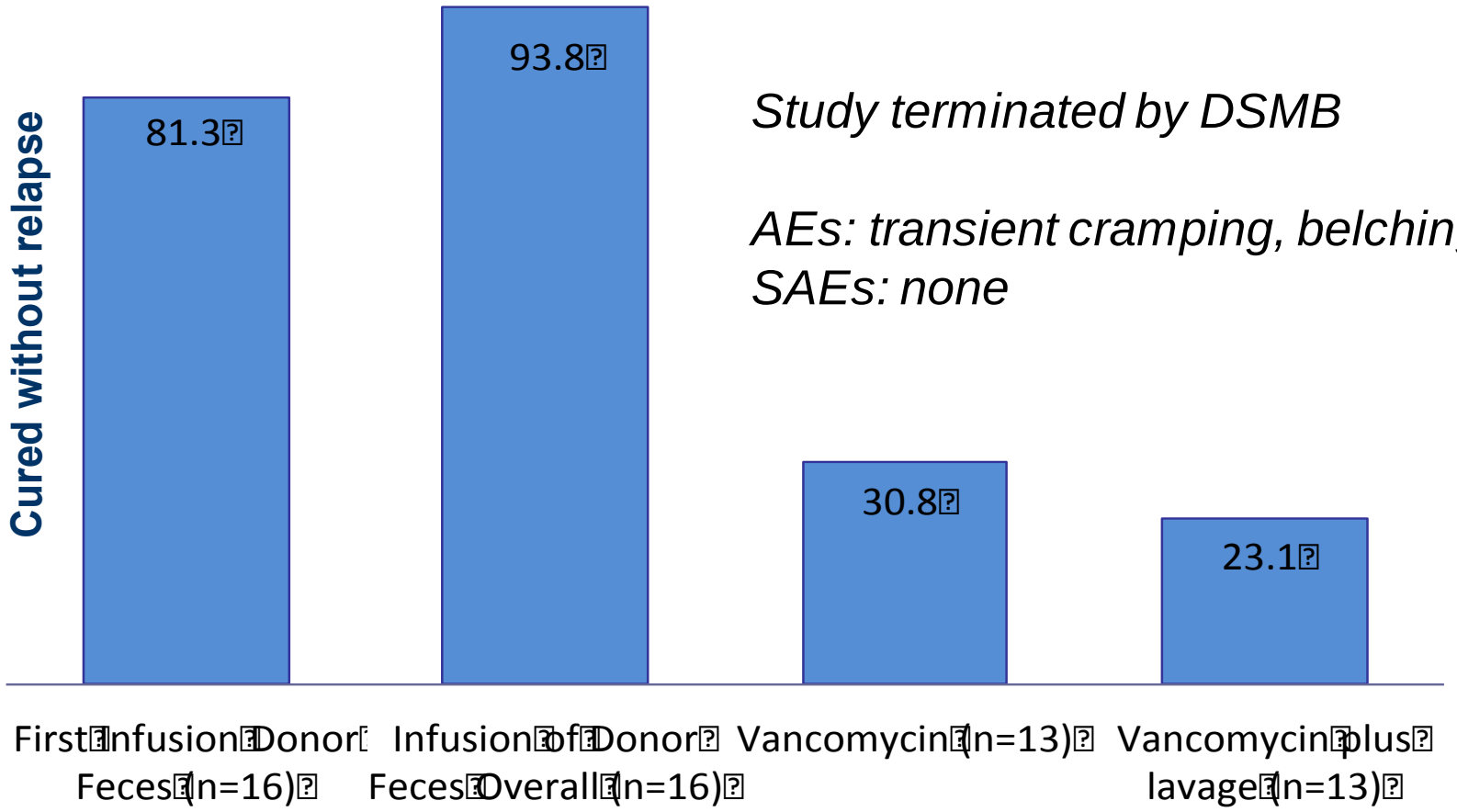
Cammarota G, Ianiro G, Gasbarrini, A. J Clin Gastroenterol, 2014

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

van Nood et al. NEJM 2013 368:5, 407-15



Nasoduodenal FMT for Recurrent *CDI: a RCT*



Study terminated by DSMB

AEs: transient cramping, belching
SAEs: none

van Nood E , Vrieze A , Nieuwdorp M et al. N Engl J Med 2013;368:407–15

Follow-up Survey
77 patients > 3 months after FMT

- Symptomatic response after FMT
  - mean of 6 days
  - <3 days in 74%

- Primary cure rate (Resolution within 90 days): 91 %
  Secondary cure rate (resolution after one further course of vancomycin +- FMT): 98.7%

- 97% of patients would have another FMT for recurrent CDI and 58.3 % would choose FMT as their preferred Rx

- All late recurrences occurred in setting of subsequent unrelated antibiotics

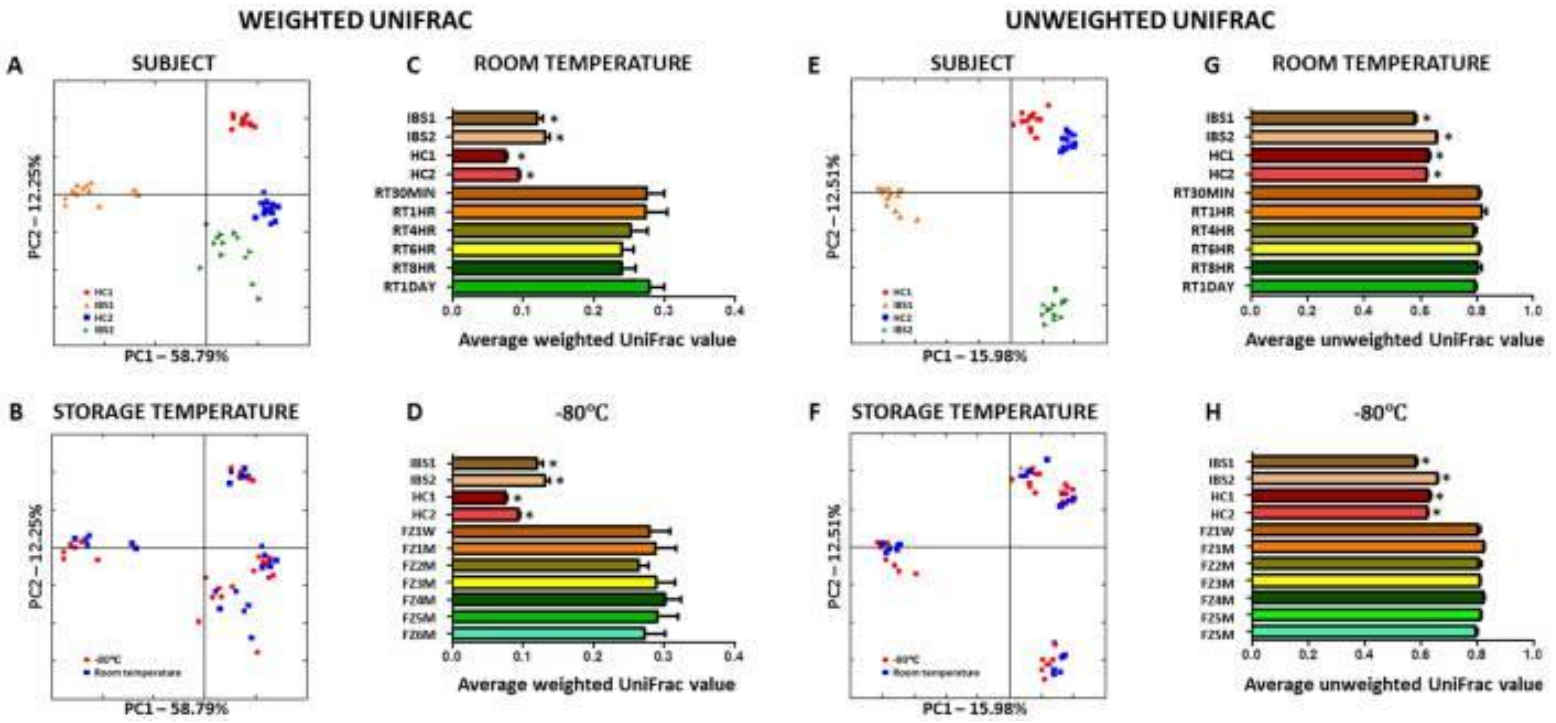
Brandt LJ, et al. Am J Gastroenterol, 2012 **107**:7, 1079-87

Cure Rates and AEs in 146 Patients > 65 years of Age

CDI (n)	Primary cure rate	Secondary cure rate	Transient AEs	Serious AEs
Recurrent-CDI (89)	82%	94.4%	11.2%	2.2%
Severe-CDI (45)	88.8%	97.7%	4.4%	4.4%
Complicated-CDI (12)	67%	100%	0%	16.6%
Total (146)	82.8%	95.8%	7.5%	4.1%

Agrawal M, Aroniadis O, Brandt L, et al, DDW, 2014

Frozen Donor Stool Retains its Diversity



High-throughput pyrosequencing of the 16S rRNA gene demonstrates stability of microbiota in faecal samples at seven time points during a six month storage period at -80oC.

Carroll I, PLoS One. 2012; 7(10): e46953

Standardized Frozen Preparation for Transplantation of Faecal Microbiota

Donor material	Mean age years	% female	Mean number of relapses	Success rate (%) Symptom resolution and negative PCR @ 2 months
Individual donor n=10	61	70%	6.2	7/10 (70%)
Standard donor, fresh n=12	55	83%	6.4	11/12 (92%)
Standard donor, frozen n=21	59	67%	5.2	19/21 (90%)
Total N=43	59	72%	5.9	37/42 (86%)

Hamilton et al. Am J Gastroenterol 2012 107:5, 761-7

OPENBIOME

OpenBiome is a nonprofit organization dedicated to expanding safe access to fecal microbiota transplantation (FMT) therapies.

www.openbiome.org

Oral, Capsulized, Frozen FMT

Healthy volunteer donors screened
FMT EC capsules were generated and stored at −80° C.

Patients received 15 capsules on 2 consecutive days and were followed up for symptom resolution and adverse events
Primary endpoint: clinical resolution of diarrhoea with no relapse at 8 weeks

Resolution of diarrhea was achieved in 14 patients (70%; 95% CI, 47%-85%) after a single capsule-based FMT.

All 6 non-responders were re-treated; 4 had resolution of diarrhoea, resulting in an overall 90% (95% CI, 68%-98%) rate of clinical resolution of diarrhoea (18/20).

Youngster et al. JAMA 2014 2014;312(17):1772-1778

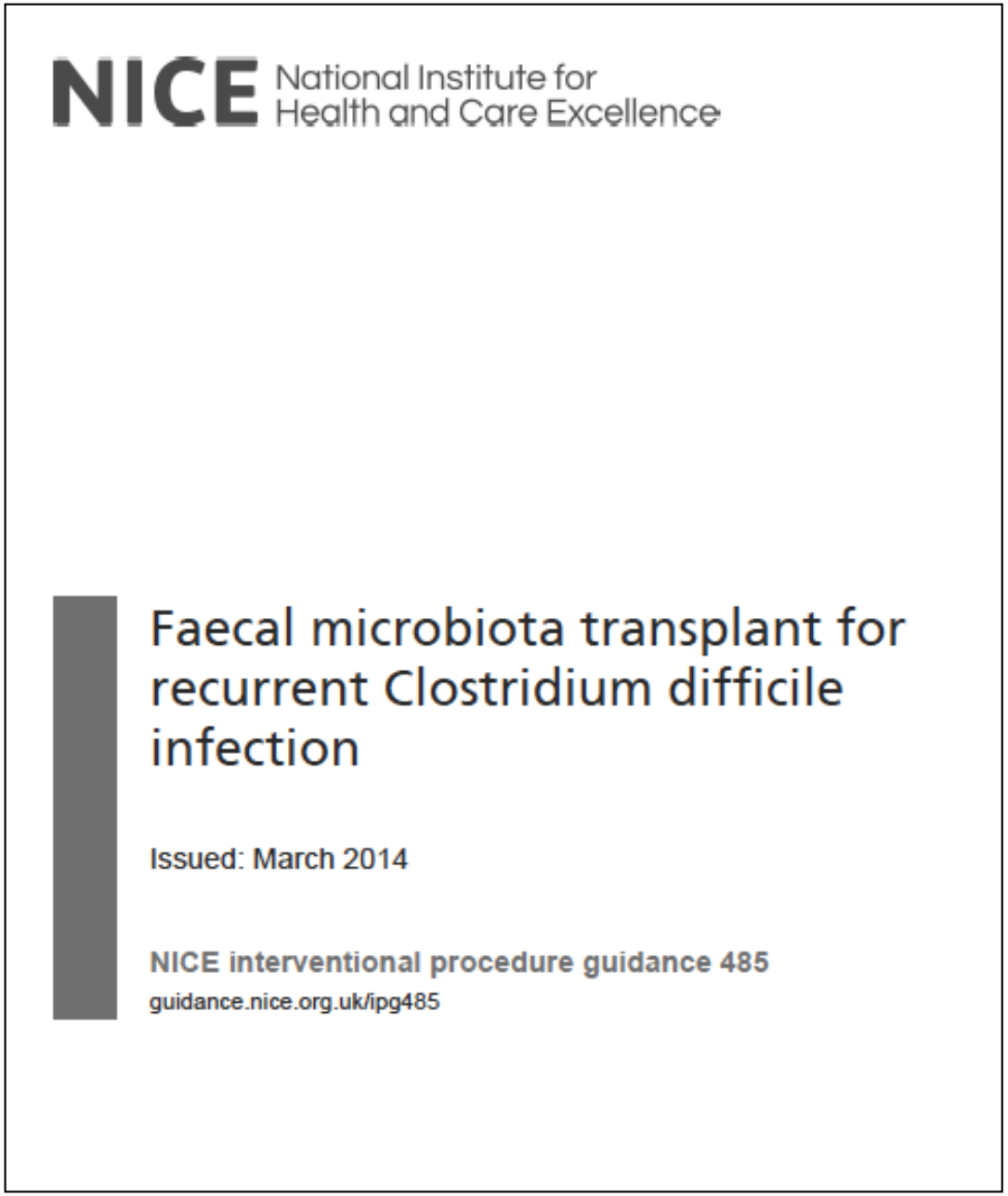
European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for Clostridium difficile Infection

Clin Microbiol Infect 2014; 20 (Suppl. 2): 1–26

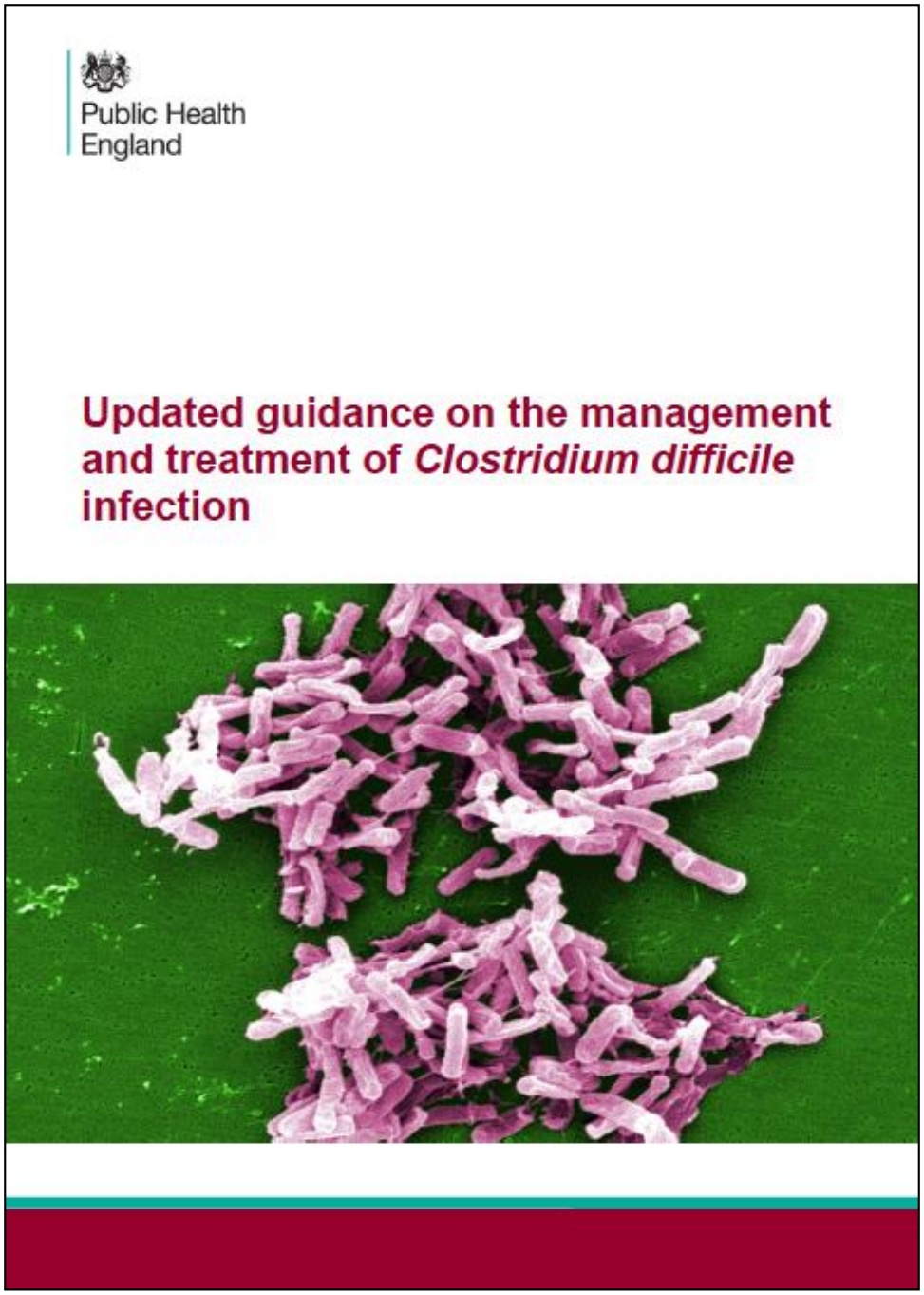
TABLE 22. Recommendations on non-antibiotic treatment (in combination with antibiotic treatment) of recurrent *Clostridium difficile* infection (CDI) (more than one relapse)

Type of intervention	Treatment	SoR	QoE	Ref(s)	Comment(s)
Faecal or bacterial instillation	Vancomycin, 500 mg four times daily, 4 days + bowel lavage + nasoduodenal infusion donor faeces	A	I	[145]	Also many observational studies and meta-analyses. [164,186,189–191].
Probiotics	Vancomycin or metronidazole + *Saccharomyces boulardii*	D	I	[126]	Comparison of relapse rates: in subgroup analysis efficacy in recurrent CDI, but *not* in initial CDI. Evidence-based review: [137].
	Vancomycin or metronidazole + *Lactobacillus* spp.	D	I	[147,148]	Evidence-based review: [137].
Passive immunotherapy with immune whey	Colostral immune whey	D	I	[149]	Study interrupted early.

"For multiple recurrent CDI unresponsive to repeated antibiotic treatment, faecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I)."



"This procedure should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments."



"Consider donor stool transplant in cases of recurrent CDI"

Protocol for FMT in Recurrent CDI

Choose donor

- any healthy person – friend/family (donor directed), anonymous
- universal donor

Questionnaire screening

-Risk factors for BBV etc

Donor testing

- serum and stool
- archived aliqouts

Donor Exclusions:

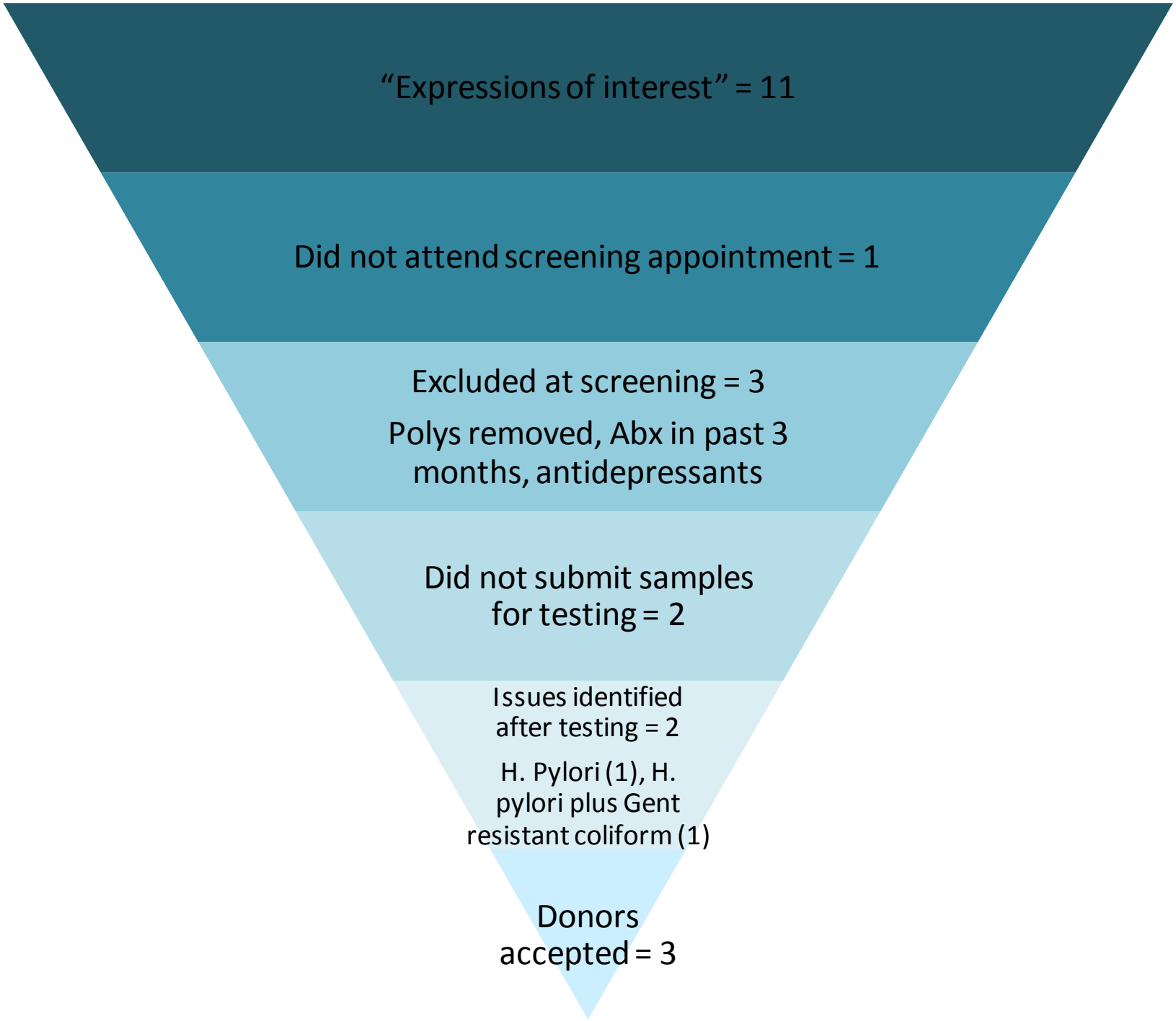
- Age <18 or >60
- Obesity (BMI >30)
- In receipt of any regular prescribed oral medication (except oral contraceptive pill)
- Known to be infected with HIV, HTLV, or Hepatitis A, B, C, or E
- Known exposure to HIV, HTLV, or Hepatitis A, B, C, or E in the last 12 months
- Active diarrhoea (≥3 loose or watery stools per day for at least 2 consecutive days)
- High risk sexual behaviour (sexual contact with known HIV or hepatitis patients, men who have sex with men within the past 12 months, sex workers)
- Use of recreational drugs and/or novel psychoactive substances drugs
- Tattoos or body piercing within the last 6 months
- Incarceration or history of incarceration within past 12 months
- History of inflammatory bowel disease
- History of irritable bowel syndrome
- History of gastrointestinal malignancy or known polyposis syndrome
- Use of antibiotics within last 3 months
- Major immunosuppressive agents (e.g. calcineurin inhibitors, exogenous corticosteroids, biological agents)
- Systemic antineoplastic agents

Informed consent is obtained to perform serological testing for:

- HIV 1+2 serology
- HTLV I/II Ab
- Hepatitis A IgG (and if positive IgM)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis C (HCV Ab)
- Hepatitis E
- Syphilis
- CMV/EBV IgG/M
- *Strongyloides stercoralis* (ELISA)

Stool for:

- Culture (*Campylobacter*, *Salmonella*, *Shigella* and *E. coli* O:157)
- Ova, cysts and parasites by concentration x3
- *C. difficile* test, Norovirus
- Screen for gentamicin and carbapenem resistant Gram negative organisms
- Screen for MRSA
- Helicobacter pylori antigen
- *Entamoeba histolytica* PCR

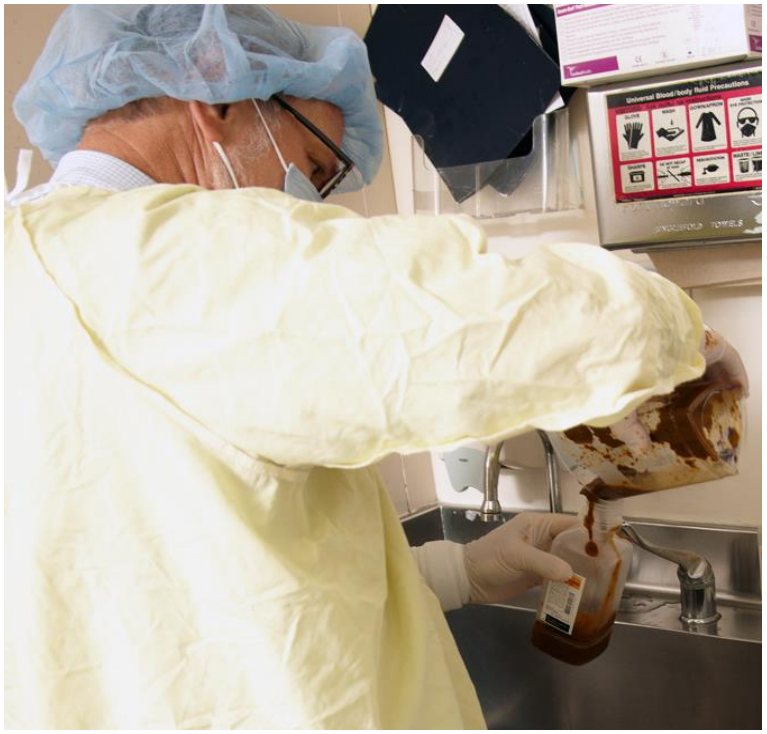

"Expressions of interest" = 11
Did not attend screening appointment = 1
Excluded at screening = 3
Polys removed, Abx in past 3 months, antidepressants
Did not submit samples for testing = 2
Issues identified after testing = 2
H. Pylori (1), H. pylori plus Gent resistant coliform (1)
Donors accepted = 3

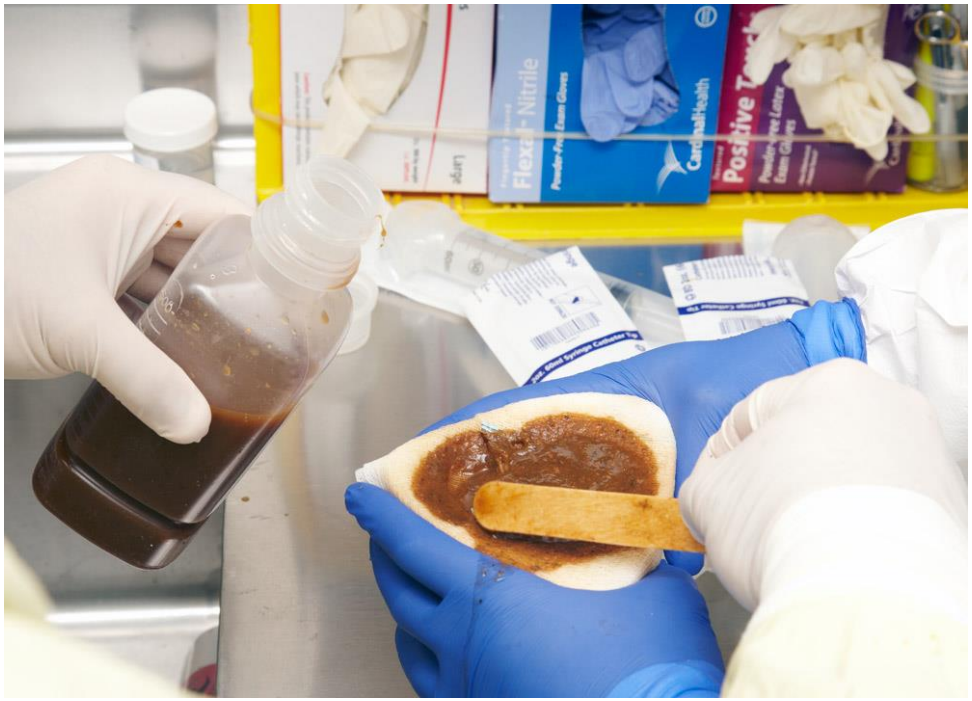
Protocol for Colonoscopic FMT in Recurrent CDI

Stool Transplant Preparation

- Donor stool >50g → suspension with non-bacteriostatic saline to make a 'slurry'

  mix by hand/blender/shaker
- Filtered through gauze into container
- Use of a biosafety hood
- Final volume (~250-300mL) adjusted with 12.5% glycerol
- Stored at -80^{o}C for up to 6 months





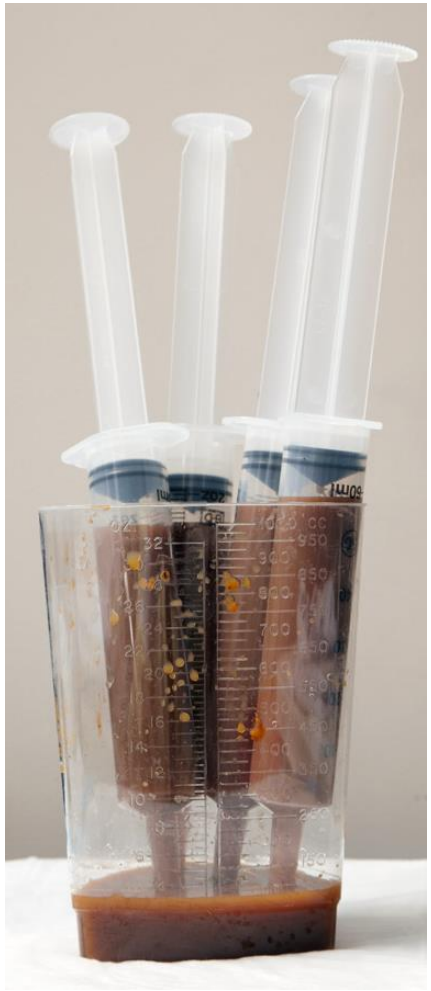
Courtesy of Dr Lawrence Brandt, Albert Einstein College of Medicine, NY

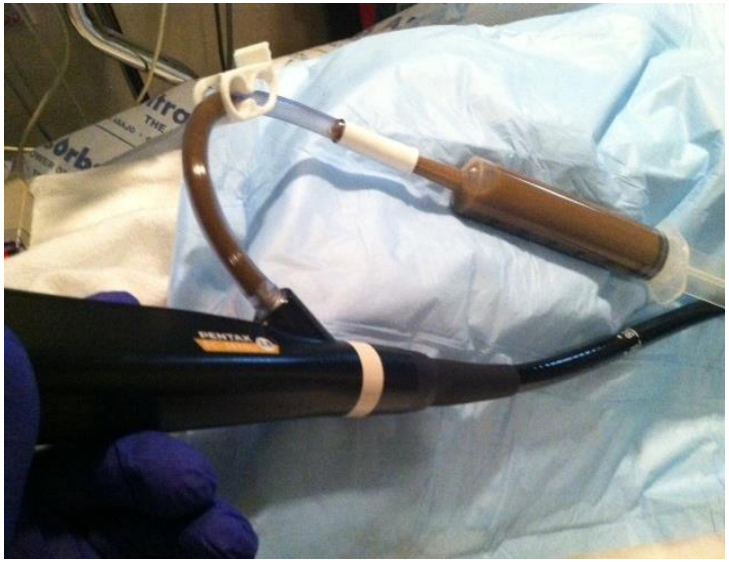
Protocol for Colonoscopic FMT in Recurrent CDI

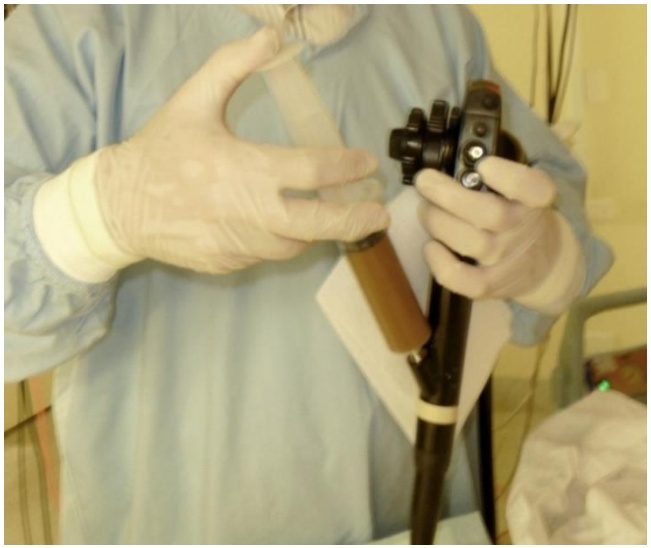
Recipient

- Recipient serum archived pre-tranplant

- Antibiotics (oral vanc) 3-5 days before procedure (stop 24 hours before)
- Large-volume colonoscopy prep the evening before procedure
- Loperamide immediately before procedure
- Approx 300mL instilled into patient (approx 2/3rd into caecum)







Courtesy of Dr Lawrence Brandt, Albert Einstein College of Medicine, NY

How Do Patients Feel About FMT?

- Hypothetical case scenarios given to clinic attendees (n=192)
  - efficacy data alone (described as Floral Reconstitution) (85%)
  - awareness of faecal nature of FR (81%)
  - FMT chosen if by pill (90%) or if physician recommended (94%)

- FMT issues found most unappealing
  - need to handle stool (65%)
  - receiving FMT by NGT (75%)
  - women: all aspects of FMT unappealing, “gross” (odour, handling stool)
  - men: concerned with safety issues
  - no signif difference in age or education level
  - older patients: FMT less unappealing

Zipursky, et al. Clin Infect Dis, 2013

Patient email

“Dear Dr Irving and Dr Goldenberg, I just thought I would drop you an email to let you know that I am feeling so much better, I am convinced the transplant has worked. In fact people have commented that I am looking so much better (little do they know what I have done) I have a lot more energy and not feeling tired. I can start re'living' my life again.”

Challenges with faecal transplants

- Risks of transmission of viruses and bacteria that are yet uncharacterised (even with careful donor screening)
- Unclear sample stability – if fresh, needs to be used within a short period of time but unclear exactly how long it is stable
- "Yuk" factor – steps involved to prepare a faecal transplant sample are unappealing
- Difficult to QC, given variability between donors and within the same donor over time
- Unclear potential for long term complications (diabetes, cancer, *etc*) and difficult to study (each donor and host will be different)

Weight gain following FMT: a case report

32 year old female with recurrent CDI underwent FMT – pre transplant weight stable (BMI 26)

Donor (patients 16 year old daughter) was overweight at time of transplant (~140 lbs / BMI 26.1) and later increased to 170lbs

Recipient presented 36 months after FMT with unintentional weight gain of 41 lbs (BMI 34.5) despite medically supervised diet and exercise programe

The hypothesis of FMT triggering or contributing to obesity is supported by animal models demonstrating that an obese microbiota can be transmitted

Alang and Kelly, Open Forum Infect Dis, 2015, 2 (1): doi:10.1093/ofid/ofv004

Barriers to widespread adoption

Survey of 161 UK Infection and Gastroenterology specialists from 86 Trusts/Boards

Factor	Favours use %	Inhibits use %	Neither %	Don't know %
Evidence base	**96.4**	0	1.4	2.2
Benefit vs risk	**90.8**	0.7	5.7	2.8
Overall cost	**41.8**	9.9	29.8	18.4
Antimicrobial resistance	**61**	3.5	29.1	6.4
Patient safety	**55.3**	12.1	26.2	6.4

Porter, Clin Microbiol Infect, 2015, in press

Barriers to widespread adoption

Factor	Favours use %	Inhibits use %	Neither %	Don't know %
Patient acceptance	23.4	**41.1**	26.2	9.2
Donor selection	9.3	**47.9**	32.1	10.7
Cost to local laboratory	10	32.9	**45.7**	11.4
Availability of prepared stool	33.6	**47.1**	11.4	7.9
Feasibility / practicality of procedure	24.8	**57.4**	13.5	4.3
Local expertise	32.1	**45.7**	17.1	5

Porter, Clin Microbiol Infect, 2015, in press

Synthetic stool / stool substitute

"RePOOPulate"

33 strains chosen at relative ratios matching a metagenomic database of health stool donors

Final product delivered to 2 patients with recurrent CDI via colonoscopy: both remained symptom free at 6 month follow up

Acidaminococcus intestinalis
Bacteroides ovatus
Bifidobacterium adolescentis (two different strains)

Bifidobacterium longum (two different strains)

Blautia producta
Clostridium cocleatum
Collinsella aerofaciens
Dorea longicatena (two different strains)

Escherichia coli
Eubacterium desmolans
Eubacterium eligens
Eubacterium limosum
Eubacterium rectale (four different strains)

Eubacterium ventriosum
Faecalibacterium prausnitzii
Lachnospira pectinoshiza
Lactobacillus casei/paracasei
Lactobacillus casei
Parabacteroides distasonis
Raoultella sp.
Roseburia faecalis
Roseburia intestinalis
Ruminococcus torques (two different strains)

Ruminococcus obeum (two different strains)

Streptococcus mitis[b]

Petrof et al. Microbiome 2013, 1:3

Summary

- Success rate of ~90% when FMT is used to treat recurrent CDI
- Prescreening of donors is critical to prevent transmission of currently known pathogens
- Currently over 800 cases reported in the literature
- FMT is an appropriate salvage therapy for multiply recurrent CDI

  - More robust (RCTs) data are needed which include cost effectiveness analysis
  - Concern for long-term sequelae
- FMT may be replaced by bioengineered product/synthetic stool

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