INFECTION 2018
FORUM INTERNAZIONALE DI TERAPIA ANTINFETTIVA

Strategie terapeutiche nell'infezione da C. Difficile: ***Il trapianto di feci***

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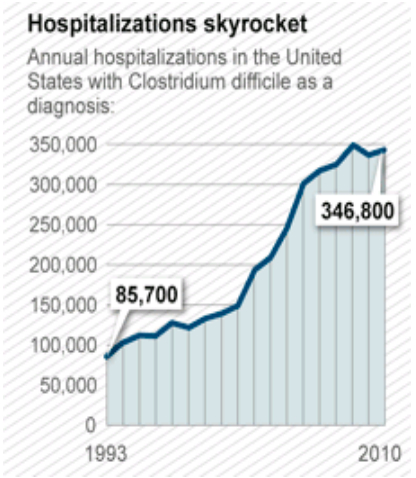
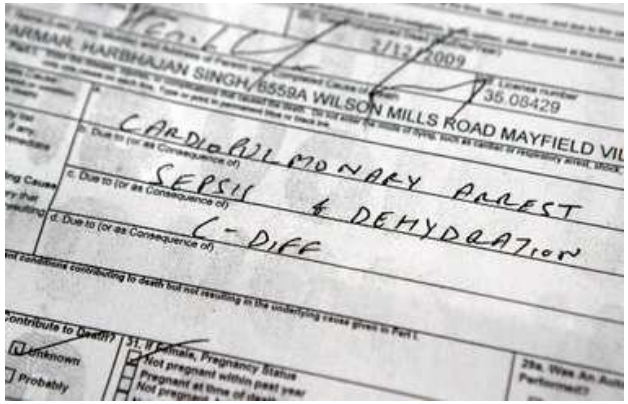
Disclosures (last 5 years)

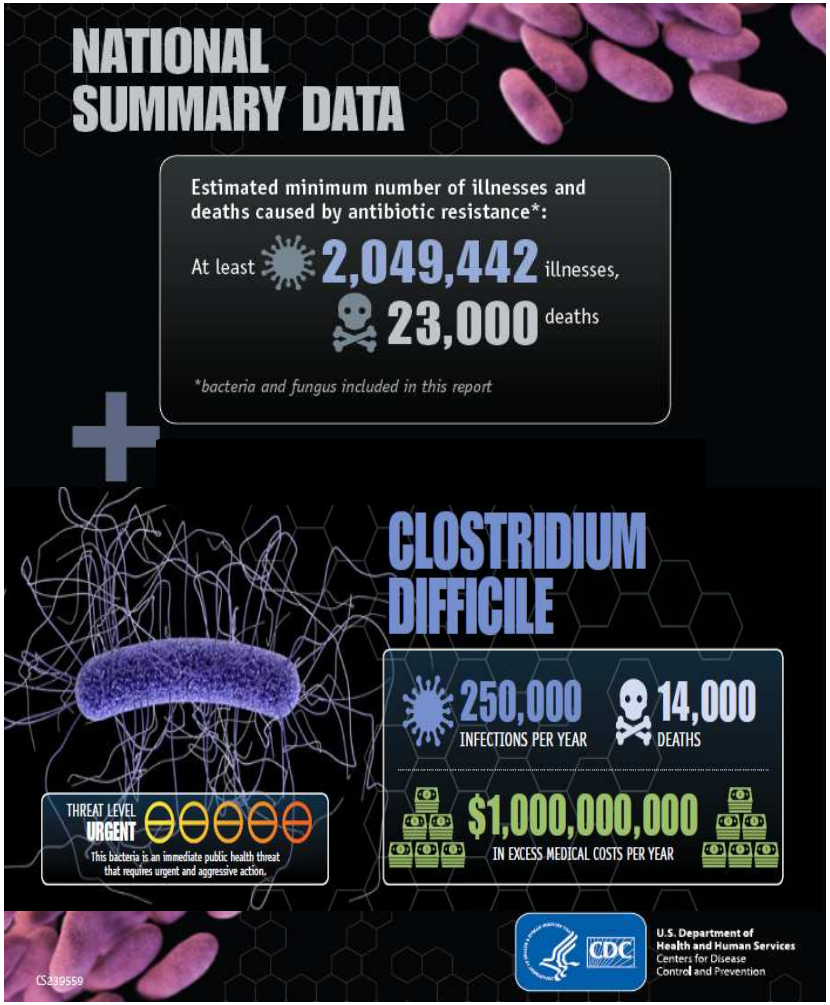
- Advisor/consultant
  - Angelini, Astra Zeneca, Gilead, MSD, Nordic Pharma, Roche.
- Speaker/chairman.
  - Astellas, Astra Zeneca, Gilead, MSD, Novartis, Pfizer.

CDI Epidemiology

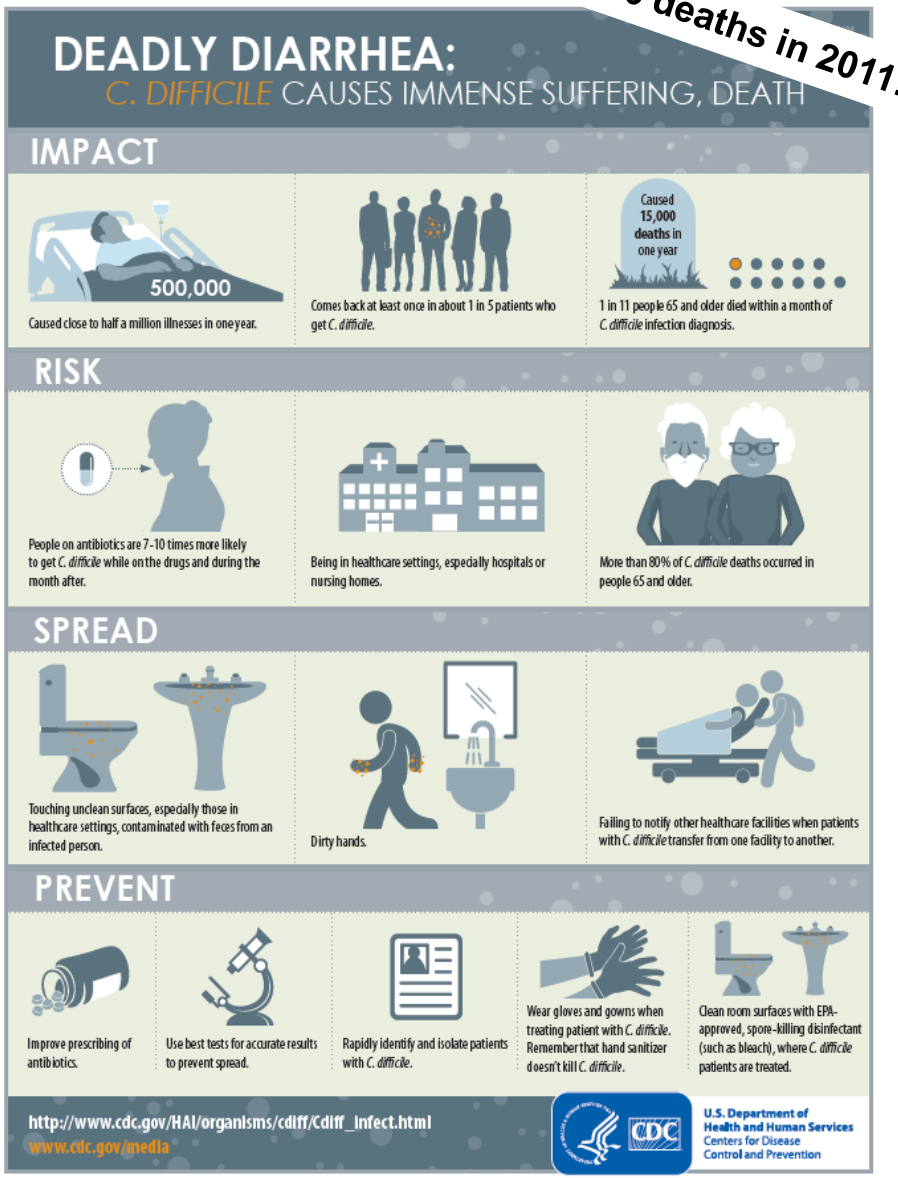


- Commonly occurs in patients in hospitals or nursing homes
- C. diff spores survive cold, hot, or dry surfaces – killed by bleach
- Per death certificates, 14,000 people / year died from C. diff in the U.S.
- Some in CDC estimate that the true number may be the double.





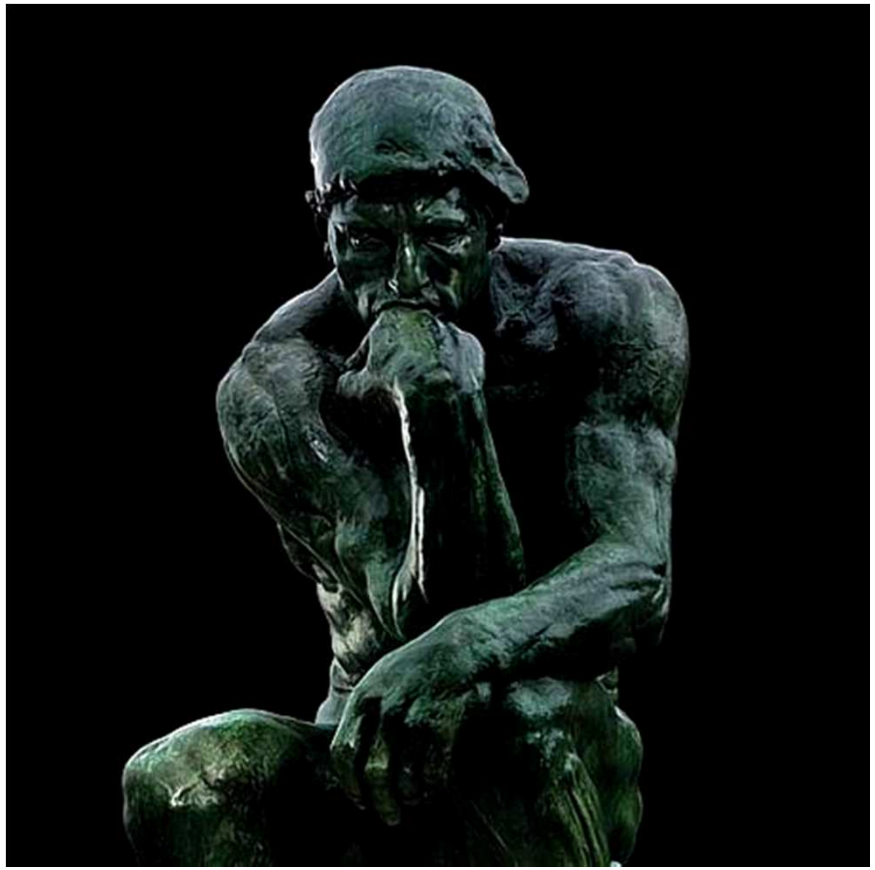
*29,000 deaths in 2011!



*based on the latest data by Lessa et al., *N Engl J Med* 2015

CDI Treatment

- Antibiotics
- 20% of patients relapse
- Repeated antibiotics



Host factors for **recurrent** CDI

- Age ≥ 65 years
- Immunosuppression
  - recipients of organ transplants (3-11%), chemotherapy, corticosteroids, HIV, IBD, ESRD, ESLD
- PPI use ≥ 3-fold
- Hospitalization, long-term care facilities
  - After 1 week 13%, after 4 weeks > 50% colonization rate
- Previous recurrent CDI

Hookman P, Barkin, JS. World J Gastroenterol. 2009;15:1554-1580.

2. *APIC. Guide to the Elimination of Clostridium difficile in Healthcare Settings. 2008.*
3. *Makris AT, Gelone S. J Am Med Dir Assoc. 2007;8:290-299.*
4. *Cohen SH, et al. Infection Control and Hospital Epidemiology. 2010;31(5):431-455.*
5. *Goodhand JR, et al. Ailment Pharmacol Ther. 2011;33:428-441.*
6. *Aseeri M, et al. Am J Gastroenterol. 2008;103:2308-2313.*
7. *Schaier M, et al. Nephrol Dial Transplant. 2014;19:2432-2436*

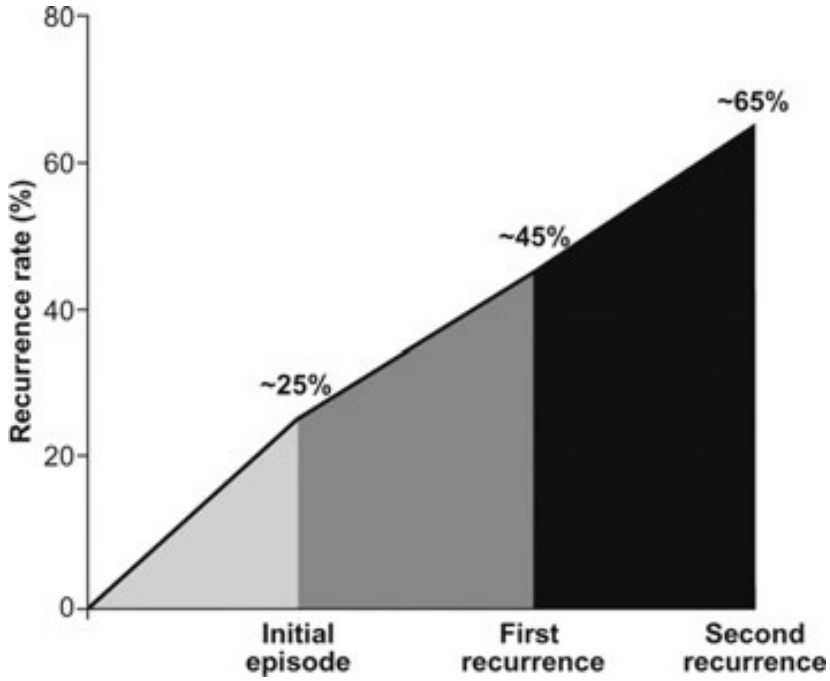
The burden of CDI recurrence

➢ Most patients with an initial episode of CDI will respond to treatment with either oral metronidazole or vancomycin (87 and 97%, respectively).

➢ However, many patients will experience a recurrence of diarrhoea within days to weeks of stopping treatment for the first attack (**15-25%** of cases).

➢ Of these, **40-45%** of patients will experience a second recurrence after the treatment.

➢ After 2 or 3 recurrences, **60-65%** of patients will have multiple recurrences.



Relapse or re-infection ?

- Current guidelines argue that it is impossible in daily practice to distinguish between relapse and re-infection, and "recurrence" is therefore used as a generic term for both.

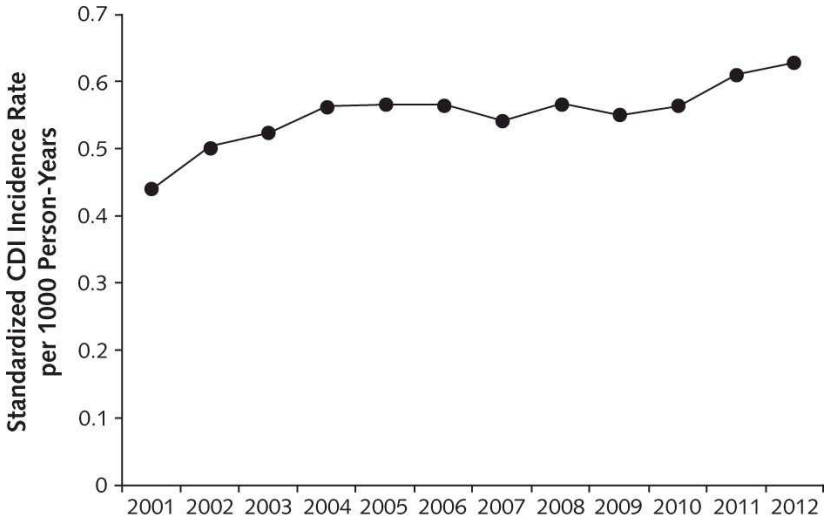
- Infection occurring after symptom resolution within 8 weeks of a previous infection is more likely to be a relapse, whereas infection occurring >8 weeks is more likely to result from re-infection.

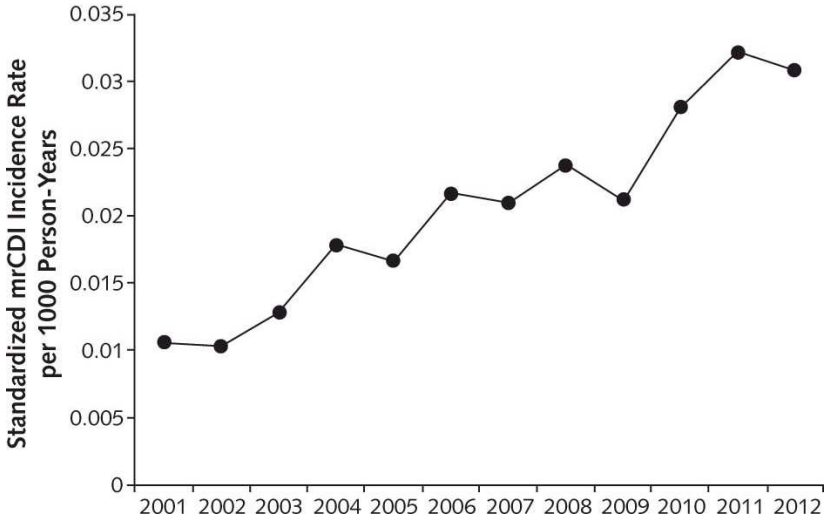
Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

The American Journal of GASTROENTEROLOGY

Increasing Incidence of Multiply Recurrent Clostridium difficile Infection in the United States – A Cohort Study

GK Ma, et al. Ann Intern Med 2017





From 2001 to 2012, the annual incidence of CDI and mrCDI per 1000 person-years increased by 42.7% (from 0.4408 to 0.6289 case) and 188.8% (from 0.0107 to 0.0309 case), respectively.

The increase in mrCDI incidence was independent of known risk factors for CDI.

Conclusion:

Relative to CDI, mrCDI incidence has disproportionately increased, indicating a rising demand for mrCDI therapies

Age- and sex-standardized incidence rates per 1000 person-years for CDI (top) and mrCDI (bottom) were computed using direct standardization, with the 2007 OptumInsight population used as the reference. CDI = Clostridium difficile infection; mrCDI = multiply recurrent Clostridium difficile infection.

Why Do We Get Recurrent CDI ?

- Virulence of infection
- Impaired host-response
- Altered intestinal microbiome

  “Dysbiosis”

Dysbiosis

- Dysbiosis is a general term to characterize an intestinal (predominantly colonic) microbiome that is altered from its normal state, generally a decreased diversity and abundance of bacteria.

Dysbiosis

- Adults, even when colonized, tend not to have overt CDI develop without dysbiosis developing first.

- With a disruption of the intestinal microbiota, most commonly by antibiotics, *C. difficile* can take advantage of the dysbiotic state and cause infection.

SCIENTIFIC AMERICAN™

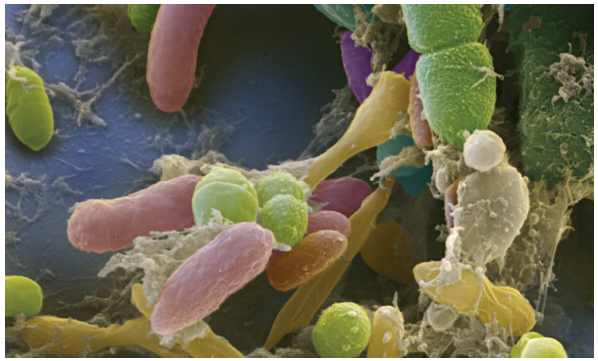
Fecal Transplants For Gut RePOOPulation

A laboratory-made slurry of healthy bacteria could replace human fecal matter in stool transplants to treat bacterial infections. Gretchen Kuda Kroen reports.

Fecal microbiota transplantation

- What is it?
  - Administration of fecal material containing distal gut microbiota from a healthy person to a patient with a disease or condition related to dysbiosis

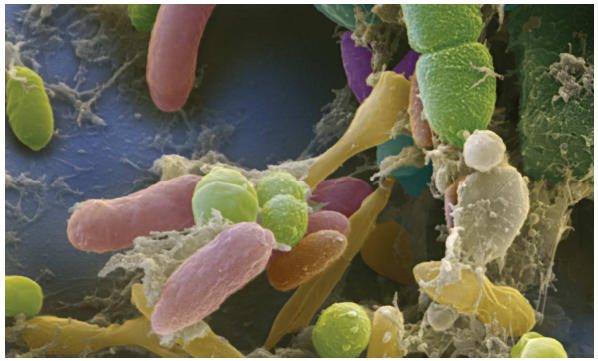
- Why do it?
  - Restore phylogenetic diversity and therefore microbiome physiological functions
  - Replace and or inhibit pathogenic species



1. Van Nood et al. Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile* NEJM 368;5
2. Kelly et al. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms and Outlook. Gastroenterology 2015; 149: 223-237

Fecal microbiota transplantation

- Does it work?
  - For recurrent *C. difficile* infections the efficacy of FMT is now undisputed, with cure rates of **85-90%** in case series
  - One randomised trial: efficacy was 81% for a first infusion and 93,8% with a second infusion vs 30% for vancomycin



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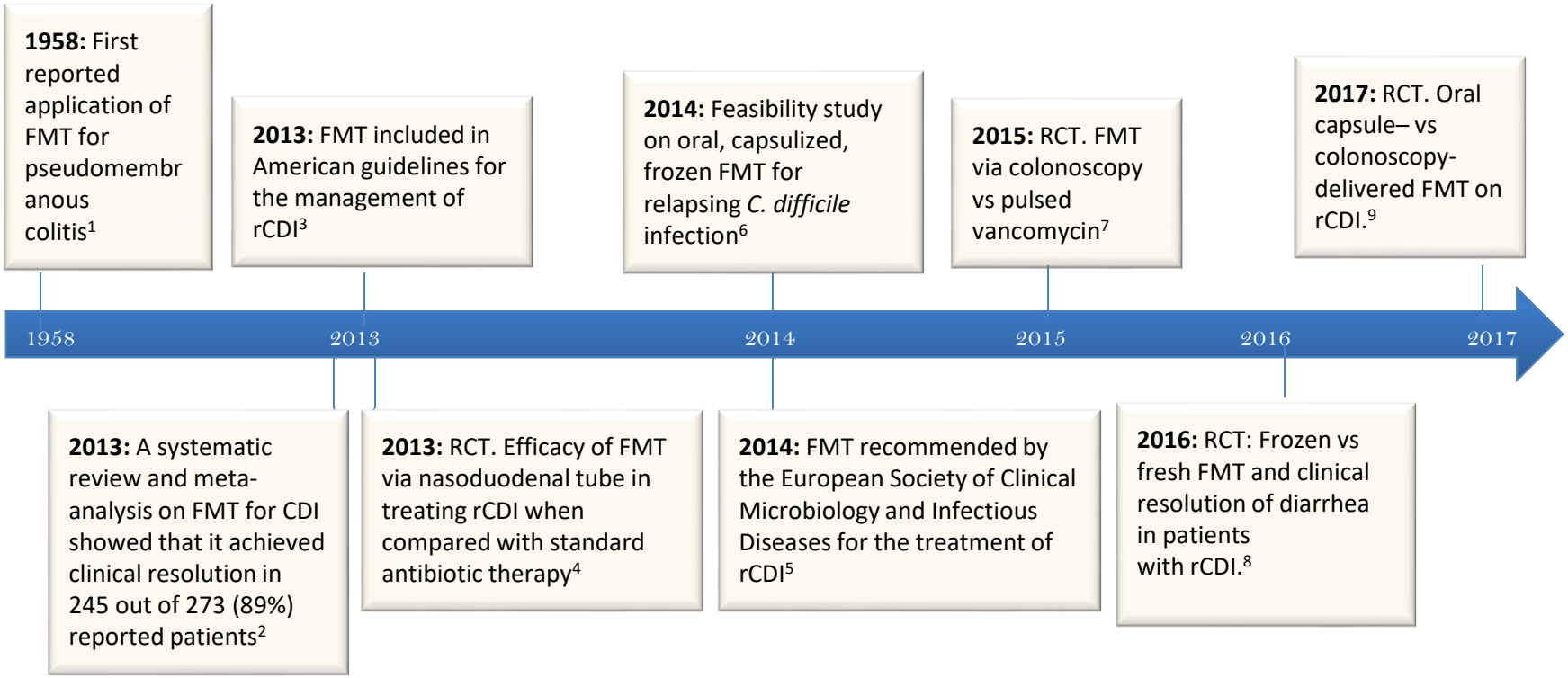
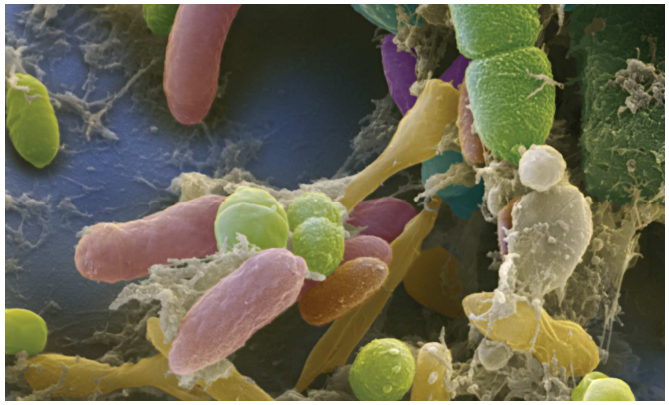
History of FMT for CDI



1) Eiseman B, et al. *Surgery* 1958; 44: 854–859.
2) Kassam Z, et al. *Am J Gastroenterol* 2013; 108: 500–508.
3) Surawicz C, et al. *Am J Gastroenterol* 2013; 108: 478–498.
4) van Nood E, et al. *N Engl J Med* 2013; 368: 407–415.
5) Debast SB, et al. *Clin Microbiol Infect* 2014; 20 (suppl. 2): 1–26.
6) Youngster I, et al. *JAMA* 2014; 312: 1772–1778.
7) Cammarota G, et al. *Aliment Pharmacol Ther* 2015; 41: 835–843.
8) Lee CH, et al. *JAMA* 2016; 315:142-149.
9) Kao D, et al. *JAMA* 2017; 318: 1985-1993.

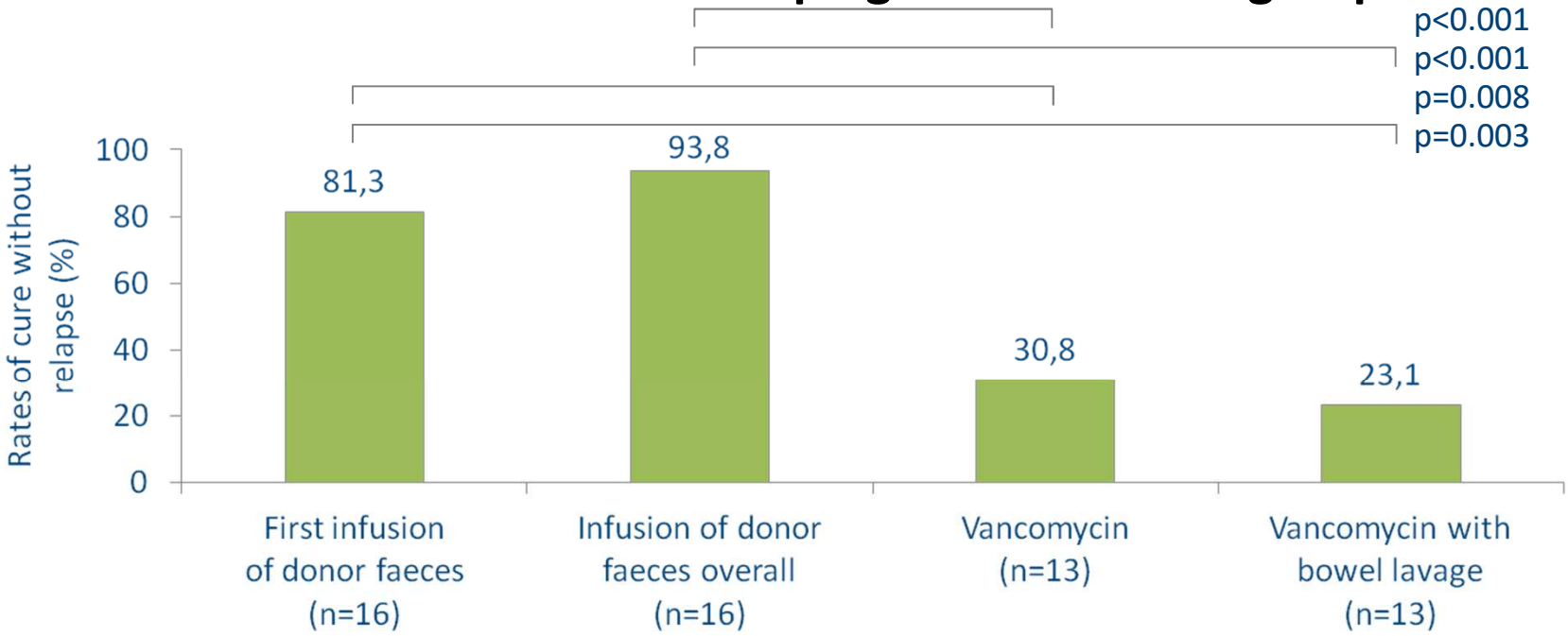


- The FMT from a healthy donor into a recipient is comparable to classic organ transplantation; the idea that there is a human organ made up of microbes is novel, but well supported by modern science

- FMT is simpler to perform than other organ transplantations—there is no need for immunological matching of the donor and recipient, or for immunosuppression after the procedure

Duodenal FMT vs vancomycin plus lavage

- **Study stopped after interim analysis**
- **No significant differences in AEs between groups, except for mild diarrhoea and abdominal cramping in the infusion group**



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

The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals.

- A multicenter, long-term follow-up study was performed with demographic, pre-FMT, and post-FMT data collected from elderly patients with RCDI, SCDI, and CCDI, through a 47-item questionnaire.
- 146 patients
- FMT was performed for RCDI in 89 (61%), SCDI in 45 (30.8%), and CCDI in 12 (8.2%) patients.
- The primary and secondary cure rates were 82.9% and 95.9%, respectively.
- Early and late recurrences occurred in 25 and 6 patients, respectively.

Agrawal M et al. J Clin Gastroenterol 2015

Clinical Infectious Diseases

MAJOR ARTICLE

Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD Study

Robert Orenstein,[1] Erik Dubberke,[2] Robert Hardi,[3] Arnab Ray,[4] Kathleen Mullane,[5] Darrell S. Pardi,[6] and Mayur S. Ramesh[7]; for the PUNCH CD Investigators[a]

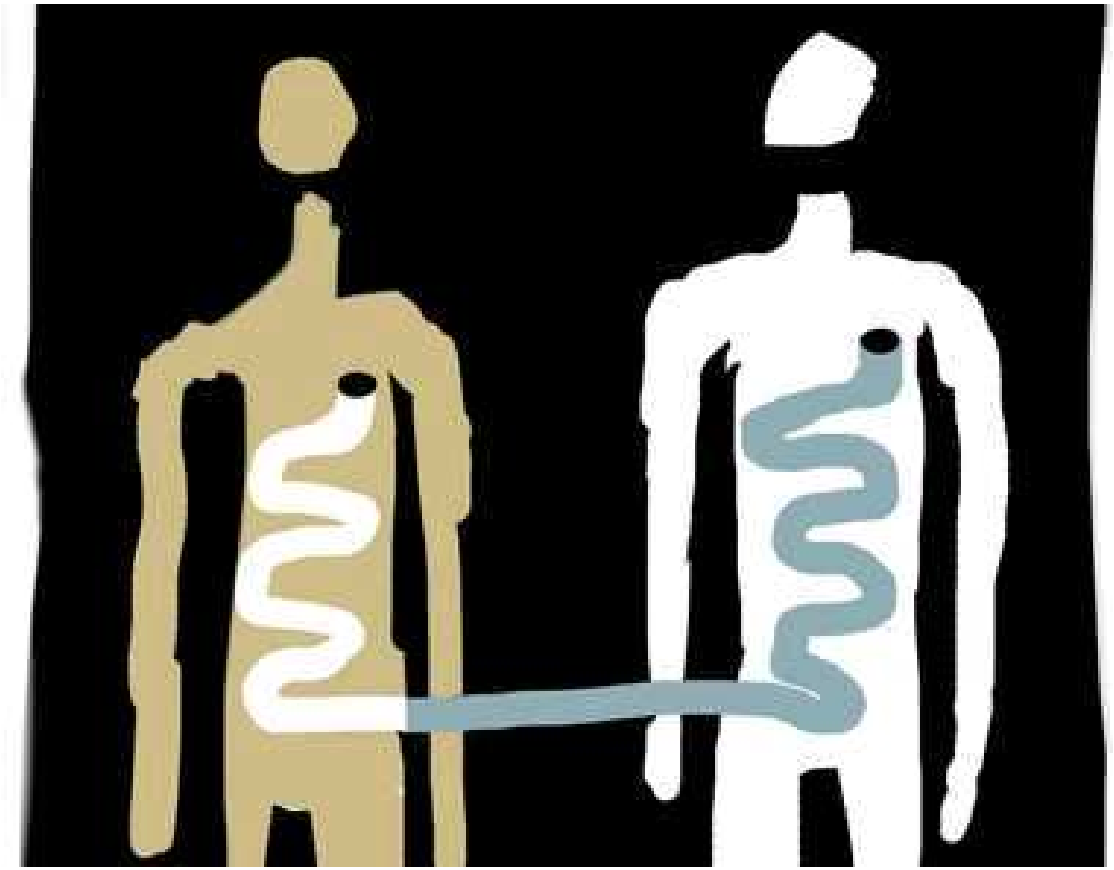
- Prospective, multicenter open-label study of RBX2660 a commercially prepared FMT drug manufactured using standardized processes and available in a ready-to-use format administered via enema.
- The primary objective was product-related AEs. A secondary objective was CDI-associated diarrhea resolution at 8 weeks.
- Among patients with recurrent or severe CDI, administration of RBX2660 via enema appears to be safe and effective.

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

Which are the FMT technical tips?



FMT “how To”

1. Donor Selection

1. Donor Screening

1. Stool collection and preparation

1. Patient preparation and stool administration

Donor selection and screening

- Unrelated volunteer vs family, partner or friend
- Chosen donor must be healthy and devoid of any microbiota associated (IBS, Obesity, constipation, GI malignancy) or potentially transmittable illness
- Donor must not have taken antibiotics recently
- Only 30% of candidates were acceptable when screened at one facility [2]

1. Kelly et al. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms and Outlook. Gastroenterology 2015; 149: 223-237
2. Costello et al. Establishing a fecal microbiota transplant service for the treatment of *Clostridium difficile* Infection. CID 2016: 62 April 1

Donor selection and screening

Table 1. Donor Screening Criteria

Medical interview (exclusions)
Age: <18 or >65
Antimicrobial therapy or probiotics in the past 3 mo
Active medical illness or symptoms
Any medications
International travel in last 6 mo to areas at high risk of travelers' diarrhea
High risk sexual activity (unprotected sex in last 3 mo outside of a monogamous relationship, men who have sex with men, sex for drugs or money)
Illicit drug use
Tattoo or body piercing within 6 mo
Known HIV or viral hepatitis exposure in the last 12 mo
Incarceration or a history of incarceration.
Family history of colorectal carcinoma involving 2 or more first degree relatives
Household members with active GI infection
Medical history and Examination (exclusions)
Any gastrointestinal disorder
Obesity (BMI > 30),hypertension, type 2 diabetes and dyslipidaemia
Malnutrition (BMI < 18)
Autoimmune disease
Atopic disease
Depression
Infection with HIV, Syphilis, Hepatitis B or C
Malignancy
Chronic pain syndromes, neurologic or neurodevelopmental disorders
Blood screening
Full blood count
Electrolytes, Urea and Creatinine
Liver function tests
Human T-cell lymphotropic virus 1 and 2 serology
Epstein Barr Virus IgM and IgG
Cytomegalovirus IgM and IgG
Syphilis (Rapid plasma reagin)
Strongyloides stercoralis, *Entamoeba histolytica*, *Helicobacter pylori* serology
Hepatitis A virus IgM
Hepatitis B surface Antigen, Hepatitis B core Antibody, Hepatitis C virus Antibody
HIV type 1 and 2 Antibody and p24 antigen
Antinuclear antibody
Fasting lipids and Blood sugar level
C-Reactive Protein and Erythrocyte Sedimentation Rate
Stool screening
Microscopy and Culture
Rotavirus, Norovirus, and Adenovirus PCR
Clostridium difficile toxin PCR
Egg, cysts and parasites (including Cryptosporidium spp., Giardia spp., *Dientamoeba fragilis* and *Entamoeba histolytica* PCR)
Vancomycin resistant enterococcus screen

Abbreviations: BMI, body mass index; GI, gastrointestinal; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

1. Costello et al. Establishing a fecal microbiota transplant service for the treatment of *Clostridium difficile* Infection. CID 2016: 62 April 1

Stool collection and preparation

Fresh stool in ziplock container

Blended with 400ml saline in new magic bullet

Filter out larger particles

Place into barium enema kit

Donor produces stool directly into bag then cable tie bag closed

↓

Deliver in cooler box for processing within 1 hour

↓

Blend with Glycerol (10%) and Normal Saline (65%) for 1 minute

↓

Divide blend into 200ml aliquots

↓

Label pots with donor number and date and record in donor register

↓

Freeze immediately at -80°C in stool bank

Figure 2. Stool preparation.

1. Costello et al. Establishing a fecal microbiota transplant service for the treatment of *Clostridium difficile* Infection. CID 2016: 62 April 1

Patient preparation and route of administration

- Stop antibiotics 24h-72h before
- Colonoscopy preparation the night before
- Main routes
  - Retention enema
    - Patient is laying down in slight tredelenburg position
    - Turns over during the procedure
    - Usually waits 30 minutes after complete infusion
  - Colonoscopy
  - Naso-duodenal infusion
  - Oral pills of encapsulated fecal material

Frozen Encapsulated Stool in Recurrent *Clostridium difficile*:

Table 1. Frozen encapsulated stool protocol

(1) All patients had a positive Clostridium difficile toxin determined via PCR and were nonresponsive to standard CDI therapy.
(2) Double-encapsulated fecal pills were obtained from a public stool bank, whose rigorous donor screening and workflow has been previously reported (3).
(3) Anti-CDI antibiotics were held 1 day before FMT, and PPI b.i.d. therapy was initiated 1 day before FMT and was continued for 2 days subsequently.
(4) Frozen encapsulated stool pills were ingested under clinical supervision at one sitting, and were well tolerated in all patients.

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; PPI, proton-pump inhibitor.

Figure 1. Frozen encapsulated stool.

Stollman N et al. Am J Gastroenter 2015

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): update of the treatment guidance document for Clostridium difficile infection (CDI)

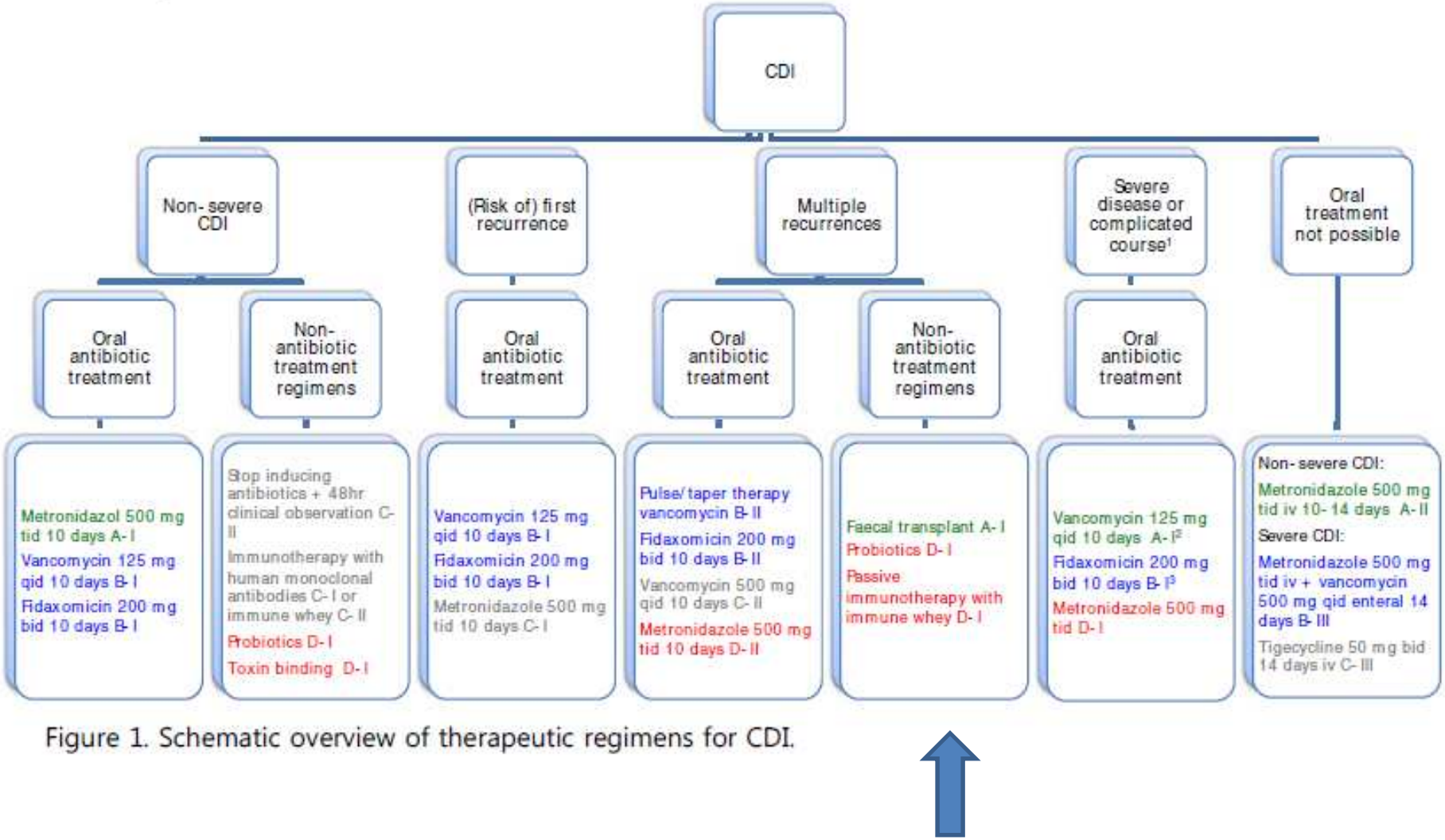


Figure 1. Schematic overview of therapeutic regimens for CDI.

Debast SB et al. Clin Microb Infect 2013

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

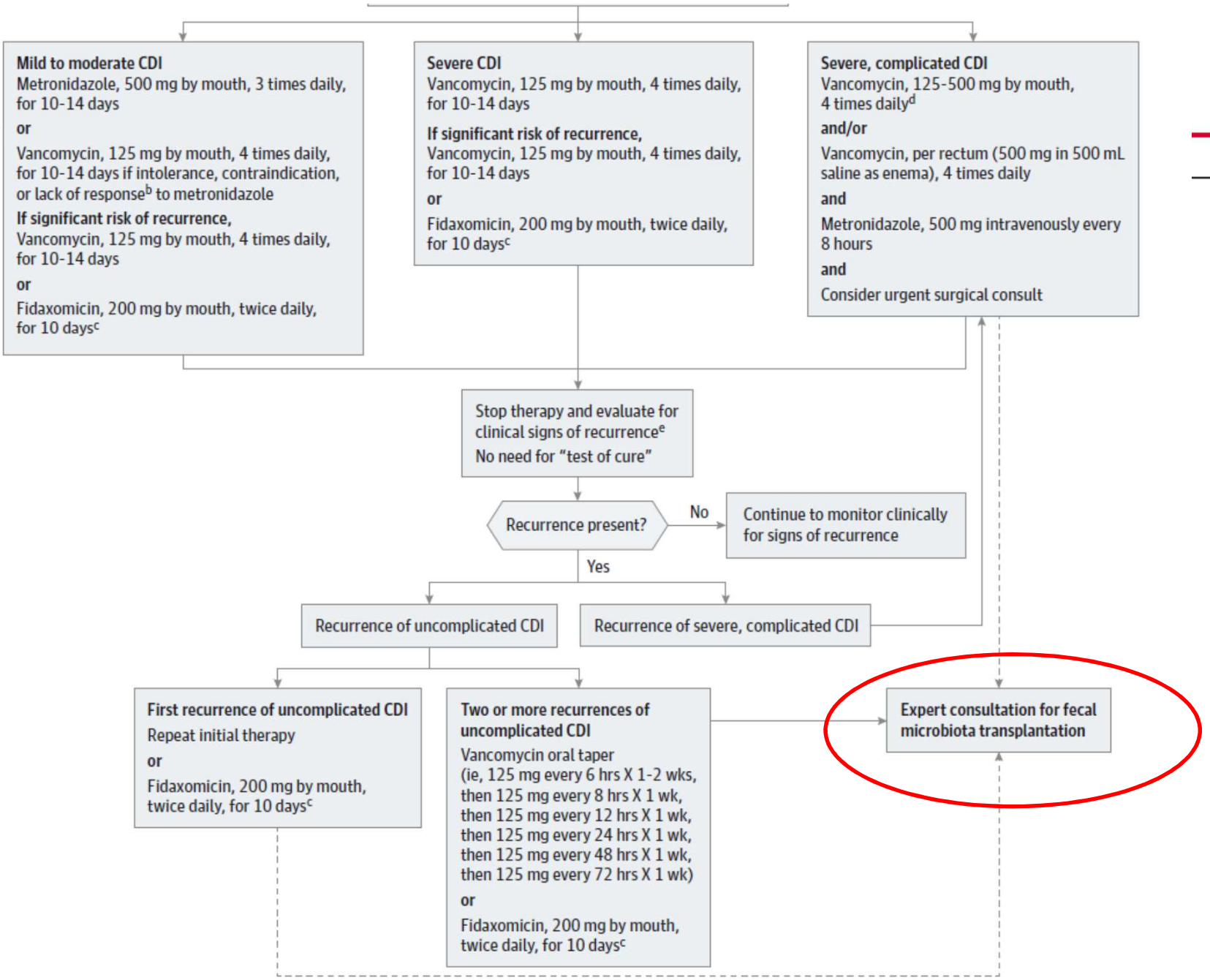
Christina M. Surawicz, MD[1], Lawrence J. Brandt, MD[2], David G. Binion, MD[3], Ashwin N. Ananthakrishnan, MD, MPH[4], Scott R. Curry, MD[5], Peter H. Gilligan, PhD[6], Lynne V. McFarland, PhD[7,8], Mark Mellow, MD[9] and Brian S. Zuckerbraun, MD[10]

Table 3. CDI severity scoring system and summary of recommended treatments

Severity	Criteria	Treatment	Comment
Mild-to-moderate disease	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria	Metronidazole 500 mg orally three times a day for 10 days. If unable to take metronidazole, vancomycin 125 mg orally four times a day for 10 days	If no improvement in 5–7 days, consider change to vancomycin at standard dose (vancomycin 125 mg four times a day for 10 days)
Severe disease	Serum albumin <3 g/dl plus ONE of the following: WBC ≥15,000 cells/mm^3, Abdominal tenderness	Vancomycin 125 mg orally four times a day for 10 days	
Severe and complicated disease	Any of the following attributable to CDI: Admission to intensive care unit for CDI Hypotension with or without required use of vasopressors Fever ≥38.5 °C Ileus or significant abdominal distention Mental status changes WBC ≥35,000 cells/mm^3 or <2,000 cells/mm^3 Serum lactate levels >2.2 mmol/l End organ failure (mechanical ventilation, renal failure, etc.)	Vancomycin 500 mg orally four times a day and metronidazole 500 mg IV every 8 h, and vancomycin per rectum (vancomycin 500 mg in 500 ml saline as enema) four times a day	Surgical consultation suggested
Recurrent CDI	Recurrent CDI within 8 weeks of completion of therapy	Repeat metronidazole or vancomycin pulse regimen	Consider FMT after 3 recurrences

Am J Gastroenterol 2013; 108:478–498; doi:10.1038/ajg.2013.4; published online 26 February 2013

Figure 3. F



Bagdasarian N et al. *JAMA 2015; 313: 398-408*

European Consensus Conference on Faecal Microbiota Transplantation in Clinical Practice*

G. Cammarota, G. Ianiro, H. Tilg, M. Rajilić-Stojanović, P. Kump, R. Satokari, H. Sokol, P. Arkkila, C. Pintus, A. Hart, J. Segal, M. Aloi, L. Masucci, A. Molinaro, F. Scaldaferri, G. Gasbarrini, A. Lopez-Sanroman, A. Link, P. de Groot, W.M. de Vos, C. Högenauer, P. Malfertheiner, E. Mattila, T. Milosavljević, M. Nieuwdorp, M. Sanguinetti, M. Simren, A. Gasbarrini; *The European FMT Working Group*

Excerpt:

INDICATIONS

Key issue: Clostridium difficile infection

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**

Gut 2017

Excerpt:

INDICATIONS

Key issue: Clostridium difficile infection

FMT for refractory Clostridium difficile infection

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

Quality of evidence: **low**

Strength of recommendation: **strong**

Gut 2017

Excerpt:

INDICATIONS

Key issue: Clostridium difficile infection

FMT for the first episode of CDI

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**

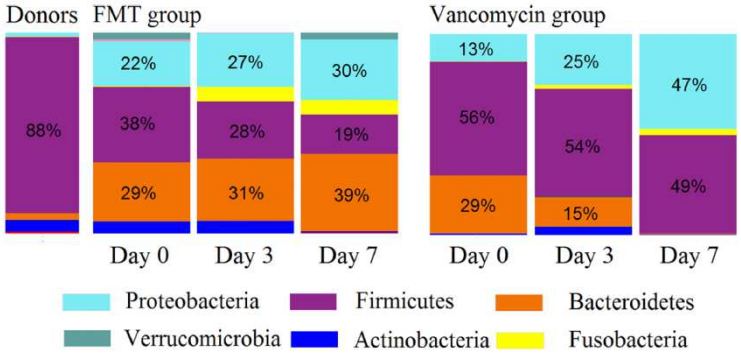
Strength of recommendation: **weak**

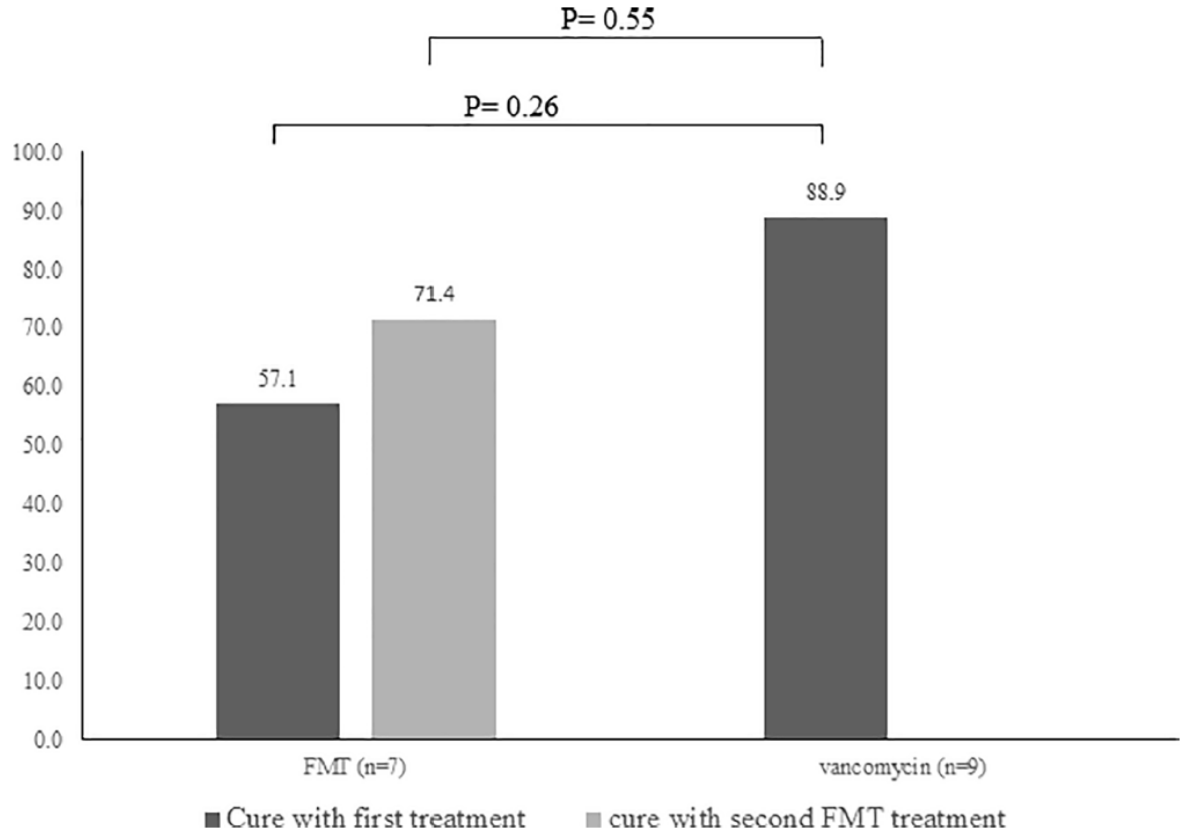
Gut 2017

RESEARCH ARTICLE

Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial *Clostridium difficile* infection in intestinal microbiome

Adrián Camacho-Ortiz[1,2], Eva María Gutiérrez-Delgado[2], Jose F. Garcia-Mazcorro[3], Soraya Mendoza-Olazarán[4], Adrián Martínez-Meléndez[5], Laura Palau-Davila[1], Simon D. Baines[6], Héctor Maldonado-Garza[4], Elvira Garza-González[4]*





PLOS ONE | https://doi.org/10.1371/journal.pone.0189768 December 20, 2017

Safety of FMT

- Multiple theoretical risks associated with FMT
  - Transmission of infection
  - Transmission of microbiota associated disease
  - Complications during the procedure
- Health Canada now requires registration
- FMT is generally very well tolerated

NEJM RANDOMISED TRIAL

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

1.Van Nood et al. Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile* NEJM 368;5

Adverse events in faecal microbiota transplant: a review of the litterature

Baxter et al. Journal of hospital infection 92 (2016) 117-127

- Compiled n= 1555 patients
  - 1190 treated for CDI, 186 for UC, 67 for CD
- Serious complications CDI:
  - 2 deaths related to aspiration pneumonia
  - 2 perforations during colonoscopy
  - 1 related bacteremia (24h after)
  - Exacerbated IBD in 6 cases

Adverse events in faecal microbiota transplant: a review of the litterature

Baxter et al. Journal of hospital infection 92 (2016) 117-127

Table VI

Overall rates of the most common adverse events using the denominator as the total number of cases receiving faecal microbiota transplant for inflammatory bowel disease (IBD)

Effect	Number of patients	Overall % ($N = 265$)
Diarrhoea	28	10.57%
Abdominal distension/bloating	24	9.06%
Abdominal pain/cramping/tenderness	20	7.55%
Fever	14	5.28%
Flatulence	10	3.77%
Deterioration of IBD	6	2.26%
Raised C-reactive protein	6	2.26%
Constipation	5	1.88%
Blood in stools	4	1.50%
Vomiting	3	1.32%

Cost-Effectiveness of Fecal Microbiota Transplantation in the Treatment of Recurrent Clostridium Difficile Infection: A Literature Review

Leor T. Arbel [1] , Edmund Hsu [2] , Keegan McNally [3]

	Cost (millions)	QALY	Cost/QALY	Cost in USD (millions)		Cost in USD/QALY
FMT (age ≥ 18y)	$253	11,941	$21,187.51	$255.90		$21,430.40
Current practice (age ≥ 18y)	$309	11,410	$27,081.51	$312.54		$27,391.97
FMT (age 18 -59y)	$43	3,016	$14,257.29	$43.49		$14,420.74
Current practice (age 18 - 5y)	$49	2,928	$16,734.97	$49.56		$16,926.82
FMT (age 60 -79y)	$95	4,695	$20,234.29	$96.09		$20,466.26
Current practice (age 60- 79y)	$118	4,480	$26,339.29	$119.35		$26,641.24
FMT (age ≥ 80y)	$114	4,230	$26,950.35	$115.31		$27,259.31
Current practice (age ≥ 80y)	$142	4,002	$35,482.26	$143.63		$35,889.03

2017 Arbel et al. Cureus 9(8): e1599. DOI 10.7759/cureus.1599

Clinical Practice and Infrastructure Review of Fecal Microbiota Transplantation for *Clostridium difficile* Infection

Challenges to incorporating FMT into clinical practice

- First, methods of fecal bacterial community processing vary, as do methods of FMT administration.
- Second, the optimal dosing strategy and expected benefit of FMT for refractory CDI, particularly for severe and severe complicated cases, are uncertain.
- Third, the US Food and Drug Administration (FDA) considers FMT an investigational treatment.
- Fourth, insurance reimbursement for FMT usually falls short of FMT administration costs.

CHEST 2018; 153(1):266-277

Excerpt:

BASIC REQUIREMENTS FOR IMPLEMENTING A FMT CENTRE

FMT centre	Statement	QoE	SoR
Clinical requirements and facilities	Implementation of referral centres in proficient hospitals is encouraged	Moderate	Strong
	FMT staff should be trained	Low	Strong
	FMT staff should be multidisciplinary	Low	Strong
	Availability of general facilities	Low	Strong
	Clinical governance is mandatory	Low	Strong
Microbiological requirements and facilities	Safe processing of human samples is mandatory	Low	Strong
	Documentation stored for at least ten years	Low	Strong
Regulatory requirements	Implementation of registers to collect data is recommended.	Low	Strong
	If any, specific national rules should be followed	Low	Strong

Gut 2017

Excerpt:

CLINICAL MANAGEMENT AND FAECAL DELIVERY

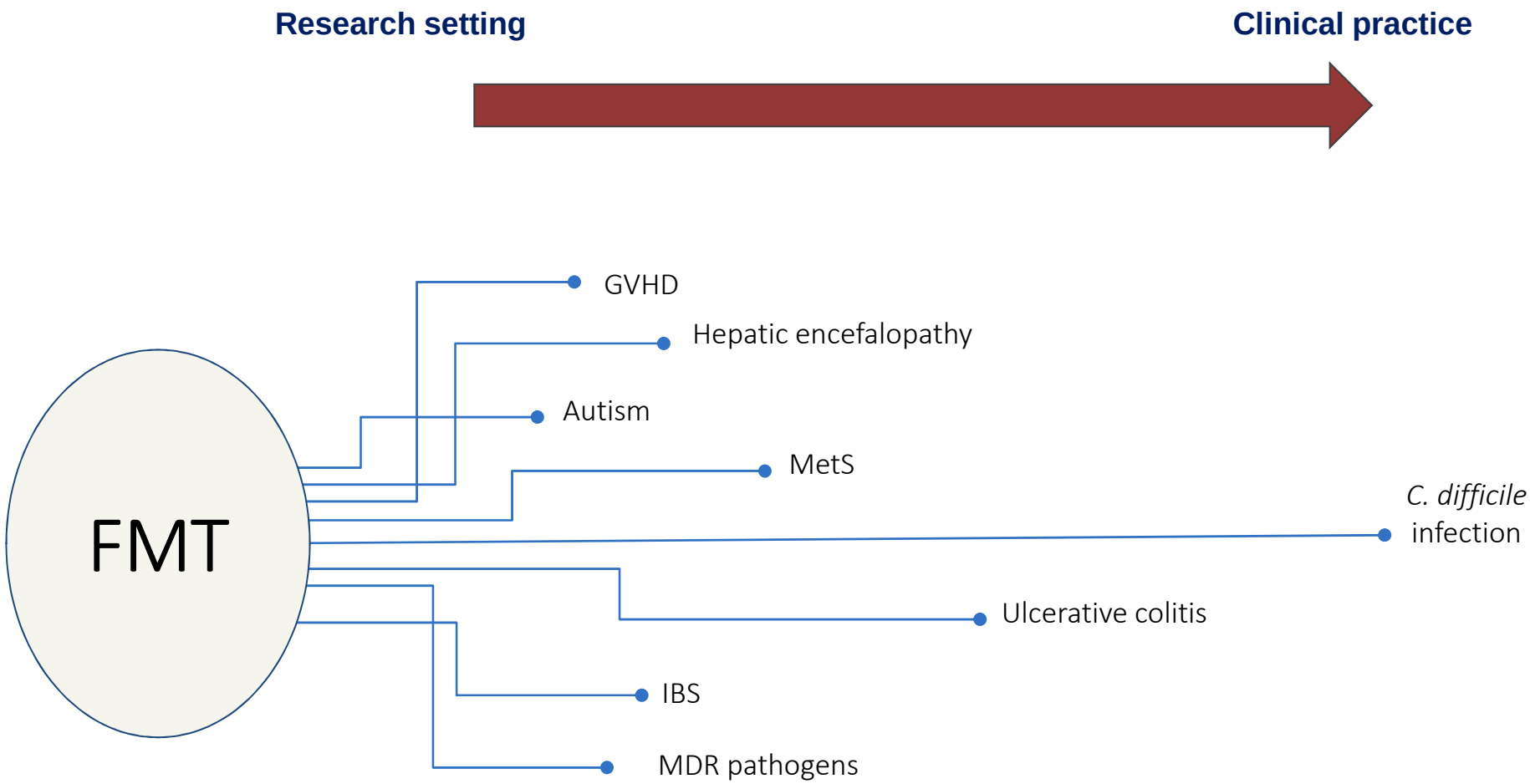
Faecal delivery and follow-up	Statement	QoE	SoR
Recipient preparation:			
· **Antibiotics**	A 3-day antibiotic pre-treatment course is suggested for recurrent CDI before FMT. Stop antibiotics 12 to 48 hours before stool infusion	Moderate	Strong
· **Bowel lavage**	Bowel cleaning before FMT should be performed	Low	Strong
Route of faecal delivery:			
· **Colonoscopy**	Apply stool in right colon in CDI patients; if not possible or in severe colitis, apply stools in left colon.	High	Strong
· **Enema(s)**	Apply one or more enemas in usual manner.	Low	Strong
· **Upper GI tract**	Via endoscope, NGT, NJT, or gastrostomy. Keep patients in upright position after infusion.	High	Strong
Safety considerations	In critically ill patients consider infusion by enema	Low	Strong
Repeated faecal infusion	Faecal infusion can be repeated after treatment failure	High	Strong

Gut 2017

Summary of FMT

- FMT is a simple, acceptable and currently the most efficacious treatment for recurrent CDI---may play a role in the treatment of variety of GI and non-GI diseases
- FMT via the upper tract seems to be less efficacious than via the lower tract
- Long-term safety remains unknown
- The Future… “Artificial stool” or targeted bacteriotherapy

FMT INDICATIONS in 2018 - SUMMARY



Human Gut Microbiome: Expanding Clinical Frontier

2011

Fecal transplant for recurrent *Clostridium difficile* (rCDI)

2018