Is FMT the answer? Challenging Cases in CDI

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Fecal bacteriotherapy - Wikipedia, the free encyclopedia
en.wikipedia.org/wiki/**Fecal**_bacteriotherapy
Fecal microbiota transplantation (FMT) also known as a **stool transplant** is the process of transplantation of fecal bacteria from a healthy individual into a ...
Procedure - History - In animals - Theoretical basis

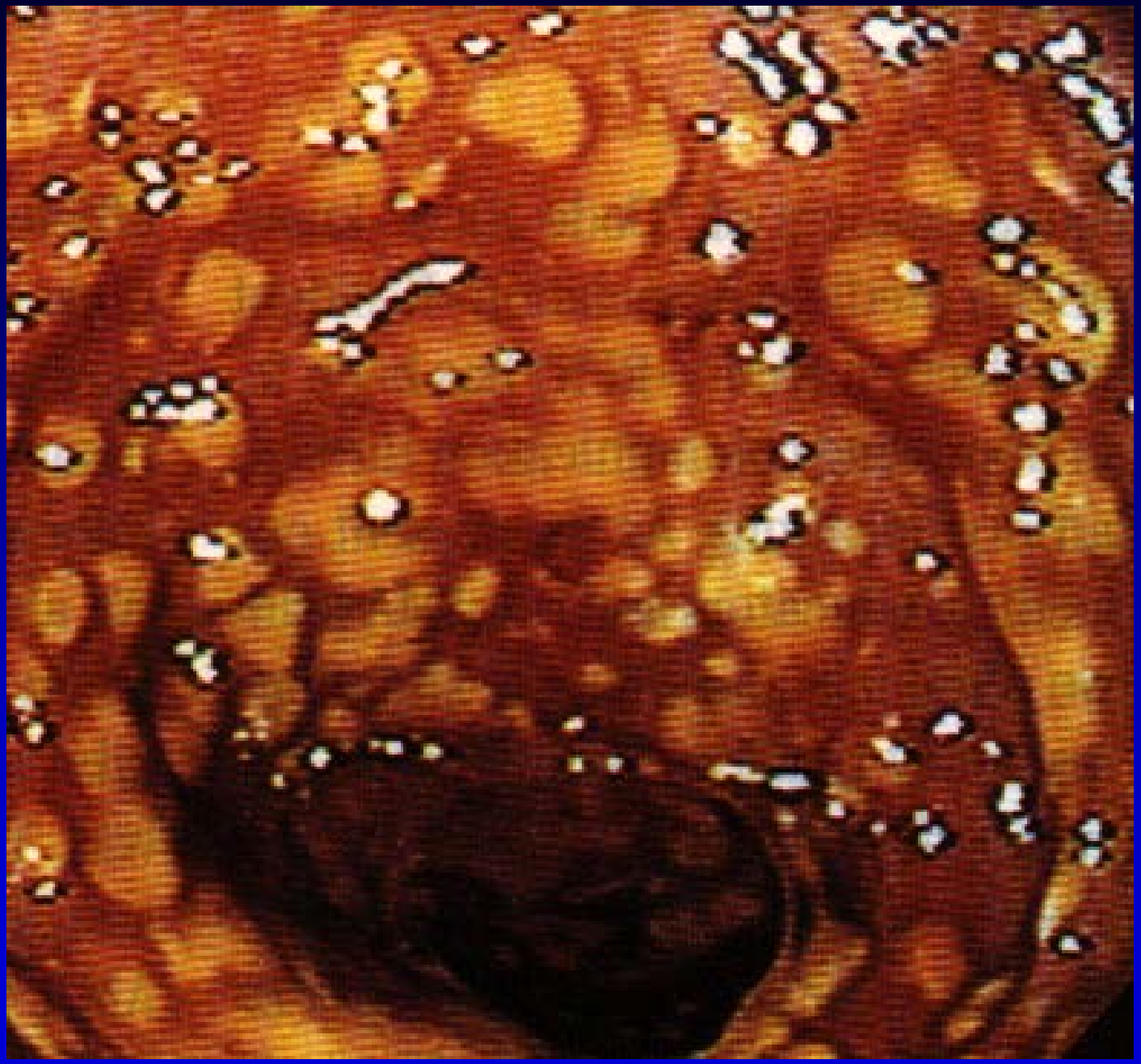
Quick, inexpensive and a 90 percent cure rate - For Medical ...
www.mayoclinic.org/medical.../quick-inexpensive-90-percent-cure-rate
But, he says, one therapy — fecal microbiota transplantation (FMT or **fecal transplantation**) — has proved highly effective at eradicating C. difficile infection and ...

HowStuffWorks "How **Fecal Transplants** Work"

health.howstuffworks.com/medicine/.../**fecal-transplant**.htm
by Nicholas Gerbis
Fecal transplants might just be the next big thing in medicine. Learn about the advantages and challenges of **fecal transplants**.

How to Safely do a **Fecal Transplant** at Home - DIY Instructi...
thepowerof**poop**.com/epatients/**fecal-transplant**-instructions/
Everything you want to know about **fecal transplant** at home, but were afraid to ask, including DIY Instructions, testing protocols and FAQs.

http://2.bp.blogspot.com/-EPw7VzDBDWw/TkGcgq0Ht_I/AAAAAAAAH20/QOFeQPP8giM/s1600/diarrhea+cartoon.jpeg



What is FMT?

Instillation of (products derived from)
donor feces for treatment of a disease or condition

AKA “fecal microbial transplantation”, “stool transplant”, “Human biotherapy”

Proven indications:

- Relapsing or refractory CDI

Under investigation:

- IBD
- Metabolic syndrome
- MDR organism decolonization

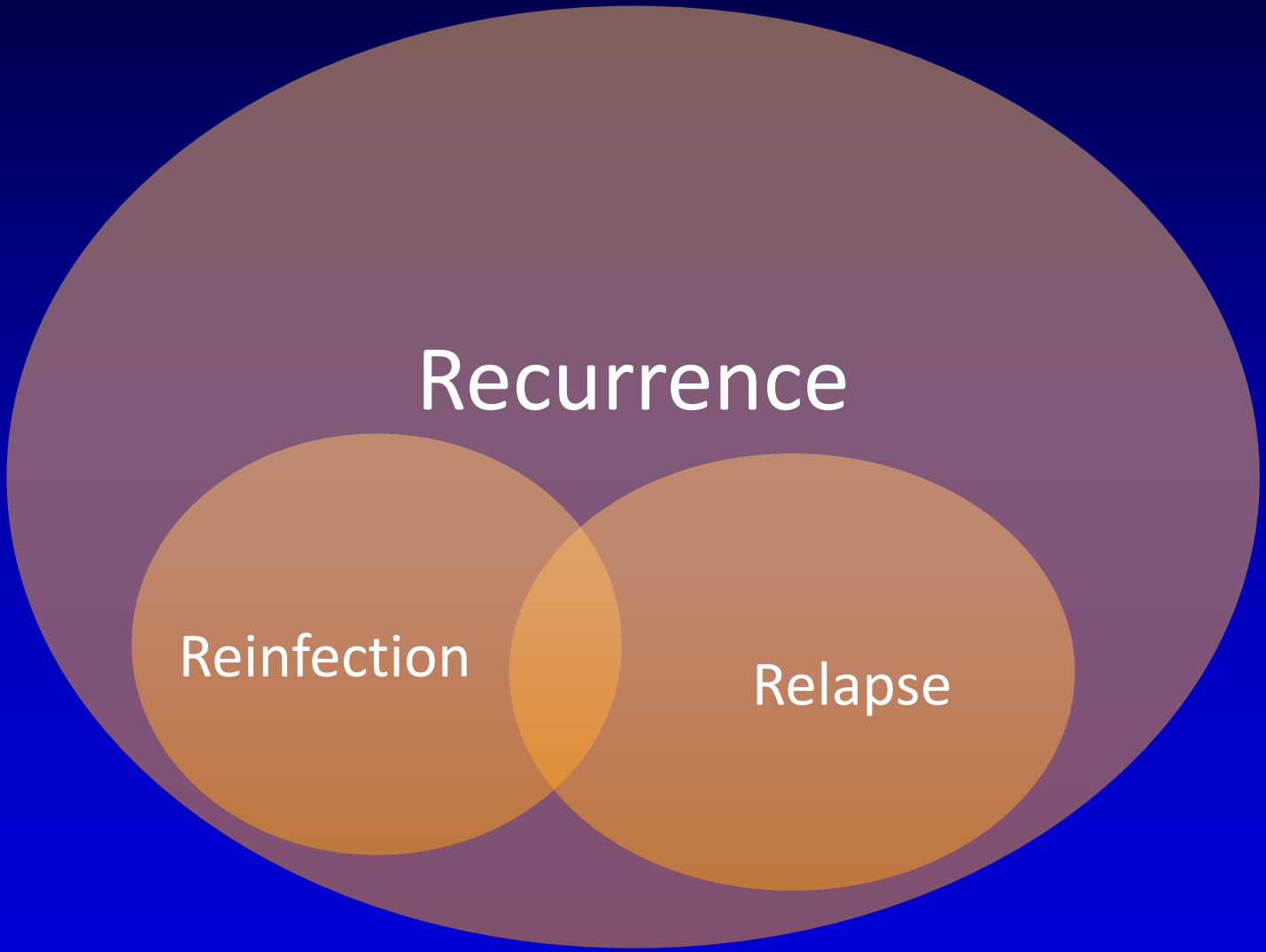
Challenges with FMT

- Is it really CDI?
- If it is, are all the symptoms due to CDI?
- If not, will eliminating C. diff/restoring microbiota make the symptoms better?
- What if it doesn’t work?

Is it really relapsing CDI?

- Stool PCR can stay positive for months after successful treatment (and can be negative quickly on treatment)
- PCR+EIA+ samples more likely to be true positives in acute disease, but no data on relapses (JAMA Intern Med. 2015 Nov;175(11):1792-801)
- The smell and color of stool are not helpful (Clin Infect Dis. 2013 Feb 15; 56(4): 615–616) and can mislead patients (but not dogs!)

CDI recurrences



Is CDI really causing the symptoms?

- Post-infectious IBS common after repeated episodes
- Chronic abdominal pain conditions can follow repeated infections or can be slow to resolve

Example case 1

- 59 yo woman with multiple recurrences with disabling abdominal pain
- Psychiatric comorbidities (anxiety, somatization d/o, PTSD)
- On chronic narcotics, benzodiazepines
- Ongoing severe pain on suppressive vancomycin, but worse diarrhea when she stops

What would you do?

A. Continue suppressive vancomycin
B. Stop vancomycin and give FMT
C. Stop vancomycin and give trial of fidaxomicin
D. Taper vancomycin and repeat stool PCR for *tcdB*

Case 1 (cont)

- Patient given FMT
- No recurrence of severe diarrhea, but ongoing abdominal pain, dizziness, occas. loose stools
- Still requiring narcotics for abdominal pain but improved energy and sense of well being

What now?

A. Repeat stool PCR and restart vancomycin if positive
B. Repeat stool PCR and repeat FMT if positive
C. Repeat FMT
D. Continued observation

Case 1 outcome

- No FMT or repeat testing done
- No recurrence of diarrhea
- 6 mos post FMT—ER visit with Abd pain, high CRP/WBC, diarrhea—stool neg for TcdB
- No subsequent FMT or relapses

Case 1 teaching points

- FMT can cure recurrent CDI even in the presence of severe IBS
- IBS takes much longer to resolve
- CDI is due to toxin production, epithelial injury, and inflammation
  - Diarrhea present in the vast majority of cases

What about co-morbid GI illness?

- FMT safe in immune-compromised (Am J Gastroenterol. 2014 Jul;109(7):1065-71)
- FMT in IBD patients very complicated
  - Role of medications?
  - How to tell IBD flare from CDI?
  - Risk of disease exacerbation after FMT (14% in study above)
- No specific data on FMT in patients on prednisone

Recurrent CDI in IBD—case 2

- 25 yo man with UC dx in 2009 (after receiving Abx)
- Ongoing activity on 5-ASA
- Stool tested + for C. diff in 2011—response to MTZ/vanco several times but sxs recurred off abx with bloody diarrhea, pain
- Admitted to hospital—colonoscopy showed only mild colitis: put on prednisone and vancomycin

What would you do for this patient?

A. Taper prednisone and continue vancomycin
B. Taper vancomycin and continue prednisone
C. Taper both drugs and see if he recurs
D. Stop vancomycin and give FMT

Case 2 (cont.)

- Sxs gone on vancomycin + prednisone—returned after both tapered off, so restarted on both
- Vanco stopped but prednisone continued (30 mg with taper).
- FMT 2 doses 1 wk apart, but sxs returned d10.
- 2 more doses FMT plus cholestyramine, but no improvement—back on vanco and prednisone, and sxs settled

Now what?

A. Try more FMT while on prednisone (different donor)
B. Taper prednisone and continue suppressive vancomycin
C. Continue prednisone and try fidaxomicin
D. Start biologic for steroid-refractory UC

Case 2 outcome

- Slowly tapered off prednisone, and stable on low-dose vanco
- Currently asymptomatic
- Will plan to re-treat with FMT

CDI in IBD—case 3

- 21 yo man with ?crohn's colitis dx in 2006
- Failed several biologics (including anti-TNF, investigational agents)
- Found C. diff + in 2012 and responded to MTZ
- CDI recurred in 2013—put on vanco with resolution and maintained on OD-BID for 2 years
- Referred for FMT on vanco but no meds for IBD

What would you do?

A. Stop vancomycin and give 1 dose FMT
B. Stop vancomycin and give 2 doses FMT
C. Start patient on 5-ASA and then give FMT
D. Choose alternative to FMT (e.g. Kefir, rifaximin, fidaxomicin)

CDI in IBD—case 3 (cont)

- Received 1 dose FMT—well for 3 weeks
- Loose stools returned, + cramps, 0 blood
- Given dose #2, but next day sxs worse so self-started on vancomycin
- 1 wk later, no better; stool – for TcdB; self-stopped vancomycin—advised to go to hospital. Was started on prednisone
- 1 wk later presented to hospital with no improvement; required emergency colectomy

Teaching points—cases 2,3

- IBD itself causes dysbiosis due to inflammation
- IBD associated with inability to shut off physiologic inflammation after infection
- IBD patients are smart and have learned to self-manage
  - This isn't always a good idea
- IBD sucks!!

What if FMT fails?

- Exclude other causes of sxs (e.g. other infections, IBS, microscopic colitis)
- Try again
- Cholestyramine
- Try again (different donor?)
- Try again
- Try again

Case 4

- 74 yo woman, previously healthy, h/o mild IBS
- Several episodes of CDI since 2011 without relapse
- Relapsing CDI since early 2014—completely well on vancomycin; hospitalized within days of stopping each time

Case 4 (cont)

- FMT#1: did well for 2 weeks, then relapse
- FMT#2: did well for 3 weeks, then relapse (PCR+)
- Fidaxomicin x 10 d then FMT#3: relapsed again after 3 weeks, back on vanco
- FMT#4: relapse after 1 week, back on vanco for 1 month
- FMT#5: did well, then abrupt onset N/V, then typical diarrhea

Case 4 (cont)

- FMT#6, did well, then relapse within a month
- FMT#7,8 4 days apart: improving but still some sxs at 1 wk
- FMT#9: 5 d later, in ER, back on vanco
- FMT#10-12 in 1 week: relapsed in 1 month
- FMT#13-17 within 10 days
- Has remained well since then; still on cholestyramine!!

Case 4 (cont)

- Pt agreed to give blood for measurement of T cell responses to TcdA/B
- PDF: “the CD4 percentage was really low”
- Sent blood to clinical lab: CD4=280 (HIV neg)

- No reports of CDI in idiopathic CD4 lymphopenia

Teaching points—case 4

- Success of FMT caps at around 95%
- We still don’t understand risk factors for refractory relapsing disease
  - Role of CD4+ T cells?
- Repeat dosing with FMT does generally improve success rates

Future of FMT

- Oral capsule delivery
  - Stool
  - Bacterial pellet
  - Lyophilized stool
- Stool-free systems
  - SERES
  - RePOOPulate

Alternatives to FMT

- Vancomycin pulse with kefir (case series)
- Fidaxomicin “chaser” (case series) (Open Forum Infect Dis. 2014 Aug 25;1(2)
- Rifaximin “chaser” (several case series)
- Chronic vancomycin suppression
- Bezlotoxumab ?
  - Not yet available

Actoxumab/bezlotoxumab

- Humanized mAbs against TxA and TxB
- Given I.V. as single dose
- Phase II trial: 70% reduction in recurrence rate vs placebo (p=0.0004)
- Trend towards less severe disease after treatment (p =0.06)
- Phase III trials recently completed

Lowy et al, DDW 2009, 751b

Actox/Bezlo Phase III results

Efficacy and Safety of Bezlotoxumab (BEZ) alone and with Actoxumab (ACT) for Prevention of Recurrent *C. difficile* Infection (rCDI) in Patients on Standard of Care (SoC) Antibiotics (MODIFY II)

	ACT+BEZ		BEZ alone		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
rCDI[†]	58/390	(14.9)	62/395	(15.7)	97/378	(25.7)
Global Cure[‡]	224/390	(57.4)	264/395	(66.8)	197/378	(52.1)
rCDI by Subgroup						
Metronidazole	28/191	(14.7)	24/189	(12.7)	42/182	(23.1)
Vancomycin	29/187	(15.5)	36/190	(18.9)	51/184	(27.7)
Fidaxomicin	1/12	(8.3)	2/16	(12.5)	4/12	(33.3)
Inpatient	35/269	(13.0)	33/273	(12.1)	54/259	(20.8)
Outpatient	23/121	(19.0)	29/122	(23.8)	43/119	(36.1)
History of CDI in past 6 months	21/104	(20.2)	27/113	(23.9)	47/110	(42.7)
Infected with 027 Ribotype	5/37	(13.5)	9/40	(22.5)	19/58	(32.8)
Severe CDI at study entry	9/80	(11.3)	6/55	(10.9)	13/65	(20.0)
Age ≥ 65 years	42/241	(17.4)	32/205	(15.6)	61/206	(29.6)
Immunocompromised	11/75	(14.7)	11/82	(13.4)	15/53	(28.3)

ID week, 2016

Conclusions

- FMT is a very safe and effective treatment for relapsing CDI
- Real world success lower than in case series
  - Reporting bias
  - Inconsistent definitions
- No major safety concerns yet
  - Exercise caution in IBD patients
  - Ensure proper donor screening

Acknowledgments

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