# Fecal Transplants 2013

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# Relapse

- 18% of cases relapsed in a hospital based survey in Europe (Lancet 2011:377:63-73)

- Once one recurrence risk of 2nd is 45% (Gastroenterol Hepatol 2011:8:17-26)

- 60% after 2 recurrences Kelly et al. *N Engl J Med.* 2008;359(18):1932-1940.

# First Case

- 71 y.o. Female -2003
- 3 years of CIDP on prednisone 30 mg/day
- Brief outpatient cipro for UTI
- *C. diff*
- Hospitalized in Lindsay with dehydration, azotemia (Cr=325)
- Rapid worsening of weakness on metronidazole

# First case

- oral vanco 125 QID x 14D- symptomatic improvement- home
- Relapse 2 weeks off Rx – rapidly deteriorated- hospitalized ICU- fluids+ dopamine +Vanco 250 QID PO
- Home to finish 2 weeks
- Relapse post treatment- hospitalized for IV fluids- acute renal failure- Vanco 500 QID sent home + referred as outpatient

- Attempt at slow taper of vanco over 4 weeks (expensive as no insurance coverage) with oral sacchromyces
- relapse once reach 125 mg/day
- Attempt at Rifampin + Vanco failed eradication
- Cholestyramine failed maintenance

- Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube
- 16/18 successful
- Johannes Aas, Charles E. Gessert, and Johan S. Bakken: Clinical Infectious Diseases 2003;36:580–585

- Concern re: NG tube- invasive + If goes into lungs- disaster so need radiology confirmation
- Colonoscopy-  Plug scope?- No GI would do it
- Least invasive is enema
- Check out “Shoppers drug mart”
- Average over the counter fleet size 250cc’s
- Need to make a slurry so 50cc’s stool + 200 cc’s saline

- Screen with C+S, O+P x2, *C. diff* toxin, microspora
- Serologies: HIV, Hep A IgM, Hep B profile, Hep C, HTLV I+II, Syphilis, *H. pylori Ab*
- Negative on screening

- Lab- micro only place where stools routinely processed.
- We are not trained.- many explanations re only need a blender in hood, then pour in empty enema bag.
- We don’t have a blender.
- Patient purchases blender for ~30$ at Canadian tire for disposal after

- Nurses- We are not trained.
- I discuss in detail.
- Retain supine as long as possible on left (~1-3 hrs).
- Stop Vanco 48 hrs before, but continue sacchromyces for 30 days after

- Come to ER when donor needs to have BM (in AM, Patient evacuates first).
- I arrive “it’s a good thing my chron’s is not acting up”.
- Cancelled
- Repeat with son once re-screened lab AND clinical- no GI history including reflux or dyspepsia, irritable bowel, polyps etc.., no antibiotics or hospitalization within 3 months, no cancer

- No diarrhea after 1 year follow-up
- 2 more successful
- Interview on CBC- large demand follows from across Canada
- Administration- we need a formal review by all “relevant” committee’s- no committee agrees to review- therefore stopped
- Family members nurses
- “We are going to do it anyway with or without you”

- I do screening
- Only patients who with documented toxin + (now PCR+) and failure of two courses of metronidazole then vancomycin 125QIDx14days, then vanco 500QID, then vacomycin taper with sacchromyces

# Clinical Gastroenterology and Hepatology
2010;8:471–473

- **Success of Self-Administered Home Fecal Transplantation for Chronic**
- ***Clostridium difficile* Infection**
- MICHAEL S. SILVERMAN, IAN DAVIS, and DYLAN R. PILLAI
- Case series of the first 7 home transplants
- 7/7 successful

- Widely reported in lay press
- Update after 1 year- 19/21 (90.5%)

# New Consults

- “Thank You Dr Silverman for saving my life!!”-Rush to give hug
- But you just walked in?
- “I already did the transplant at home. I found your protocol on the internet. I know I shouldn’t do it without screening the donor first, but I was desperate”. “Can you screen me now for diseases?”
- Husband just diagnosed with duodenal ulcer
- Patient *H.pylori* seropositive but asymptomatic

# Fecal Transplants

- Van Nood E et al. NEJM 2013 Jan 16
- Netherlands open-labelled RCT in adults with recurrences
- 3 arms
- Oral vanco for 14 days (standard)
- Oral vanco for 14 days with bowel lavage
- Oral vanco for 4-5 days then bowel lavage and then infusion of donor feces via Nasoduodenal tube

# Exclude Many Potential Donors

- Screening of blood from candidate donors.
- **Cytomegalovirus (IgG and IgM)**
- **Epstein-Barr Virus (VCA IgM, VCA IgG, VCA, antiEBNA)**
- **Hepatitis A (total antibodies**, and if positive also Hepatitis A IgM)
- Hepatitis B (HbsAg, antiHbsAg)
- Hepatitis C (anti HCV)
- HIV-1 and HIV-2 (Combined HIV Antigen/Antibody test)
- Human T-lymphotropic virus types I and II (HTLV) (antibodies)
- Treponema pallidum (TPHA)
- Entamoeba histolytica (agglutination and dipstick test)
- Strongyloides stercoralis (ELISA)
- Fecal tests: Bacteriological evaluation by local standards
- Parasitological evaluation by local standards (triple feces test)
- Test for Clostridium difficile (toxin ELISA **and culture**)

# Excluded Donors

- **age > 60 years**
- behaviour associated with an increased risk for (contracting) infectious diseases in the phase between screening and donation of feces (such as a recent visit to a tropical area in the last three months, risky sexual behaviour defined as a new sexual contact in the last six months, recent needle stick accident, receiving blood products, or getting a tattoo);
- any gastrointestinal illness or gastrointestinal complaints (abdominal discomfort, regularly loose stools, or constipation)
- **a family history of intestinal cancer or inflammatory bowel disease**
- a general illness or use of medication that could be excreted in feces and pose a potential risk for recipients
- **25/70 donors accepted**

# Nasoduodenal Tube

- Feces were diluted with 500 cc sterile saline (NaCl 0.9%).
- The feces were poured in a container with saline (NaCl 0,9%), approximately 100 cc at a time, and stirred with spatulas or a small rudder. The upper part ("supernatant") of stirred
- feces was poured in a funnel, in which two unfolded gauzes (10x10 cm) served as a sieve and collected in a bottle that was closed after filling. This procedure was repeated
- until all saline was dissolved and a 500 cc bottle was filled.

# Primary outcome –cure ie resolution of diarrhea and 3 consecutive negative stool tests without relapse at 10 weeks

- Repeat transplants from other donors allowed
- Trial stopped after interim analysis
- 13/16 (81%) cured after first transplant and 2/3 remaining cured after re-transplant from a different donor
- 4/13 (31%) in Vanco only group and 3/13 in Vanco+lavage group (23%) ($p<0.001$)
- No significant adverse events from transfusion

# British Guidelines for multiple recurrences

- Stop PPI's
- If very mild diarrhea and no abdo symptoms- consider anti-motility agents
- Vanco Taper
- Trial of fidaxomycin 200mg PO BID x10-14 days
- IV Ig (based on study of 4 patients)
- Fecal Transplant

# Now definitely evidenced based

- Will all hospitals set up programs?
- Best approach- NG tube/ Colonoscope/ Rectal infusion- (high versus low volume)
- Could we have a stool bank?

# Frozen Minnesota Popsicles

- Forty-three consecutive adults with recurrent *C. difficile* infection
- 10 who received fresh material from patient-selected donors, 12 who received fresh material from standard donors, and 21 who received frozen material from standard donors.
- Rates of infection clearance (defined as resolution of diarrhea and negative stool-test results 2 months postprocedure) were 70%, 92%, and 90%, respectively, after a single infusion of donor fecal material.
- Avoids delay with screening and finding donors *Am J Gastroenterol* 2012 May; 107:761

# Microbiome- what is happening?

- PCR amplification of ribosomal DNA before and after transplant in donor+ recipients

| Study Features | Khoruts *et al.* | Shahinas, Silverman+ Pillai | van Nood *et al.* |
|---|---|---|---|
| Number of FT patients | 1 | 6 | 9 |
| FT method | Colonoscope | Enema | Naso-duodenal infusion |
| Microbiota analysis method | T-RFLP confirmed by cloning and sequencing | 454 deep sequencing | Phylogenetic microarray |
| PCR amplification of 16s rRNA prior to analysis | Yes | Yes | Yes |
| Diversity | Not available | Lowest pre-FT<br>Increased post-FT<br>Highest in donors | Lowest pre-FT<br>Highest post-FT |
| Pre-FT profile | *C.difficile* dominance<br>Abundant Proteobacteria | *C.difficile* presence<br>Abundant Proteobacteria | *C.difficile* presence<br>Abundant Proteobacteria |
| Post-FT profile | Abundant Firmicutes and Bacteriodetes | Abundant Firmicutes and Bacteriodetes | Abundant Firmicutes and Bacteriodetes |
| Significant common finding | Restoration of butyrate producing bacteria post-FT | (Inhibits colonic endothelial autophagy and C.diff growth) | |

# Phyla

## FIRMICUTES

- **Bacilli, order Bacillales**
- *Bacillus*
- *Listeria*
- *Staphylococcus*
- **Bacilli, order Lactobacillales**
- *Enterococcus*
- *Lactobacillus*
- *Lactococcus*
- *Leuconostoc*
- *Pediococcus*
- *Streptococcus*
- **Clostridia**
- *Acetobacterium*, *Clostridium* *Eubacterium*, *Heliobacterium*, *Heliospirillum*, *Megasphaera*, *Pectinatus*, *Selenomonas*, *Zymophilus*, *Sporohalobacter*, *Sporomusa*, **Erysipelotrichix**

## Proteobacteria

- Gram negative facultative anerobes such as *Escherichia*, *Salmonella*, *Vibrio*, *Helicobacter*

# American GI Association asked FDA for Opinion

- April 27th/2013- Fecal Transplants are a drug
- Not licensed for any indication yet.
- Need Investigational New Drug (IND) application for each procedure
- Good Pharmaceutical practices needed
- System shut down in US
- Advantage of home fecal transplants- lots of interest

# Re-poopulate

- *Emma Allen-Vercoe Guelph*
- -*Microbiome* 2013, **1**:3  doi:10.1186/2049-2618-1-3
- 23 strains from 1 female donor grown in strict anaerobic conditions then administered by colonoscopy
- 2/2 successful administrations

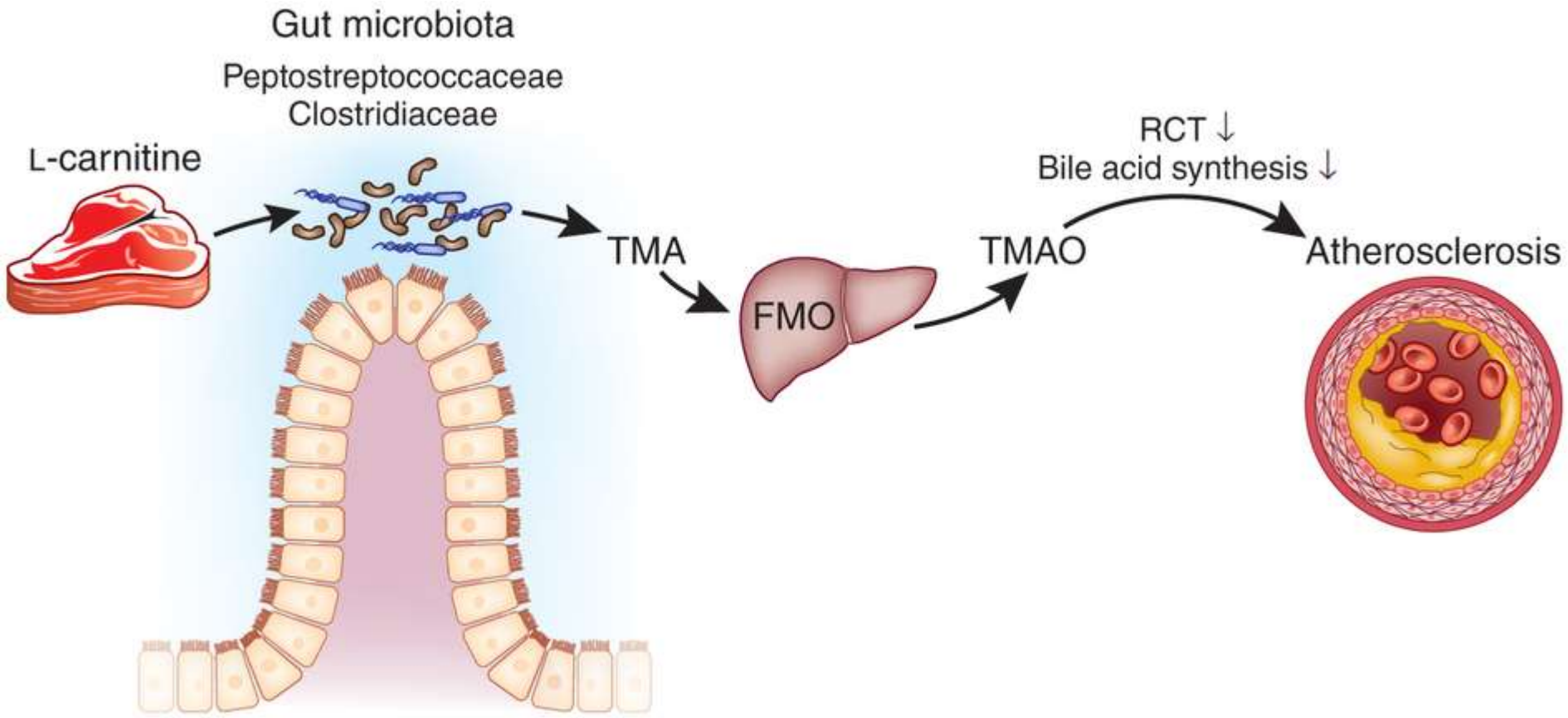
# Crap-Caps

- Tom Louie- Calgary
- Capsules from fresh donor stools made on site
- 24-30 capsules- after bowel prep
- 27/27 success, but thereafter 2 failures
- Proof of principle that capsules can work, but not yet ready for rollout

# Can changing the microbiome impact Atherosclerosis?

- trimethyamineoxide (TMAO) is a new pro-atherogenic molecule
- in a three-year follow-up of 4,000 stable subjects undergoing elective cardiac evaluation high plasma concentrations of TMAO were associated with a high risk of a major adverse cardiac event after adjustment for traditional risk factors. Tang, W.H.W. *et al*. *N. Engl. J. Med. April 25, 2013*

dietary L-carnitine is metabolized by the gut microbiota, potentially  taxa belonging to the Peptostreptococcaceae and Clostridiaceae families, into TMA. TMA is further metabolized into TMAO by flavin monooxygenases (FMOs) in the liver. TMAO may increase atherosclerosis by suppressing reverse cholesterol transport (RCT) and bile acid synthesis. Nature Medicine 19, 533–534 (2013)



# Production related to dietary habits leading to evolution of the gut microbiome

- Clostridiaceae and Peptostreptococcaceae were positively associated with both an omnivorous diet and TMAO production in humans
- vegan subject did not produce any TMAO after an L-carnitine challenge test.
- Omnivores did but not if pretreated with antibiotics

- fed atherosclerosis-prone *Apoe*$^{-/-}$ mice a diet supplemented with L-carnitine
- significantly increased atherosclerotic plaque burden. This increase was abrogated when the *Apoe*$^{-/-}$ mice were treated with antibiotics

- gut microbiota is altered in malnourished children compared with their well-nourished, healthy twin siblings and that the altered microbial ecology contributes to weight loss in mice fed a typical Malawian diet.
- RCT showed improved survival with Ampicillin or cephalosporin in malnourished Malawian children Smith, M.I. *et al*. *Science* **339**, 548–554 (2013).

# Can we prevent CDI with probiotics?

- Meta-analysis of Trials (Johnston et al. Ann Intern Med Dec 18, 2012)
- Of 1659 studies 20 RCT's found that were of adequate quality and were reviewed
- Size of studies ranged from n=17 to 239. In and Outpatients. Total n=1974 on Rx and 1844 controls
- 14/20 used some form of *lactobacillus (rhamnosus, acidophilus, casei, plantarum)*
- 6/20 used *S.boulardii*
- Multiple different doses
- Follow-up often short (3 had ≤7 day post treatment follow-up, only 9/20 followed for >14days post antibiotic
- No statistical evidence of publication bias

- Use of a probiotic was associated with a reduced incidence of CDAD 66% (pooled relative risk=0.34 [95%CI 0.25-0.49])
- Possible improved impact in studies that used several species of lactobacilli rather than mono-therapy (interaction p=0.06)
- No difference between higher or lower dose studies, and no difference between 2 main organisms tested (*S.boulardii* and *L.rhamnosus*)
- In a population with a 5%CDAD risk probiotic prophylaxis in 1000 people would prevent 33 episodes
- Within studies NNT=26 (23-34)

- Adverse events in 9.3% of treated patients versus 12.6% of controls (RR 0.82 p=0.17) (most GI symptoms). Borderline more **serious** adverse events in the control arm (RR 0.85 p=0.05), none definitely related to the probiotic (no therapeutic organisms identified in blood etc..)
- Overall “Moderate Quality” evidence suggests that probiotic prophylaxis results in a large reduction in CDAD without an increase in clinically important adverse events.

# Other prevention strategies

- CamSA — a taurocholate analog that inhibits *C.diff* germination in vitro- not absorbed orally
- Given orally to mice before massive challenge with C.diff spores+clindamycin
- 5/5 mice getting this were asymptomatic and no histologic evidence of disease vs 5/5 getting placebo developed severe diarrhea
- No benefit if fed vegetative forms
- ?will be given prophylactically to hospitalized patients?
- Howerton *et al J Infect Dis* 2013 Feb 18

# Could using different antibiotics prevent *C.diff*?

- Long debate about pip/tazo
- Doxycycline use?
- UCSF use doxy/ceftriaxone for large numbers of CAP
- Retrospectively assessed 2734 hospitalizations 2005-2010 which received ceftriaxone; of these 1066 (39%) got doxy (tended to be older, more likely to have CAP and less likely to be surgical) and had HIGHER Charleson comorbidity index, and received shorter courses of other antibiotics, but had similar total length of stay before and after treatment and duration of ceftriaxone.
- Incidence of CDI was 1.67/10,000 patient days in those who received doxy and 8.11/10,000PD (still relatively low) in those who didn't. For each extra day of doxy there was a 27% lower risk of CDI (95% CI 0.56-0.96, p=0.03)

- When compared CAP Rx alone: 5days of ceftriaxone/ doxy had an 85% lower incidence of CDI vs ceftriaxone/macrolide (95%CI 0.03-0.77) and 87%lower than ceftriaxone/quinolone (95%CI 0.03-0.62)
- ?from doxy activity vs *C.diff* or due to minimal impact on bowel flora due to high absorption in small bowel (ie absence of the bad drug quinolone or macrolide)?
- Need further studies to confirm
- Doernberg et al. CID 2012:55:615-20

# Efficacy of Fidaxomicin in first relapse cases

- Using data from Lancet+NEJM papers
- 128 in the per-protocol population had another recent episode of CDI prior to the CDI diagnosis at study enrolment.
- initial response to therapy was similar for both drugs (>90% cure).
- recurrence within 28 days occurred in 35.5% of patients treated with vancomycin and 19.7% of patients treated with fidaxomicin (−15.8% difference; 95% confidence interval, −30.4% to −0.3%;*P* = .045).
- Early recurrence (within 14 days) was reported in 27% of patients treated with vancomycin and 8% of patients treated with fidaxomicin (*P* = .003).
- In patients with a first recurrence of CDI, fidaxomicin was similar to vancomycin in achieving a clinical response at end of therapy but superior in preventing a second recurrence within 28 days.
- Clin Infect Dis. 2012 August 1; 55(Suppl 2): S154–S161.

# Fidaxo “chaser” after Vanco in Multiple relapses?

- Case series of 3 patients with success in 2 and 3rd relapsed after brief Rx for UTI (CID 2013:56 (15 January) pg 309)
- Ajax 3 patients referred for fecal transplant who had private drug coverage
- 60 yoF failed on first try but retry success
- 70 yoF failed
- 62 yoM after Rx ongoing cramps/soft stools/toxin+, went to ER given hysocine butylbromide 20 mg TID x 4 days. Symptoms markedly improved. Now 1 stool every day or other day and occasionally watery (no constipation) toxin+, doesn’t want further Rx
- 75yoM- failed
- ?2/4 success

# Would you be a donor/ recipient?

- I DON'T GIVE A S**T, AND I DON'T TAKE NO CR*P FROM NOBODY!!
- Large patient “pent up demand”
- Big problem with non-*C.diff* “indications” from self theorization- Ulcerative Colitis, Chrons then really out there “RA, Ankylosing Spondylitis, Fibromyalgia, Parkinsons, Autism”