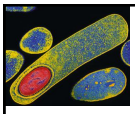
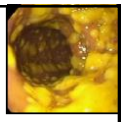
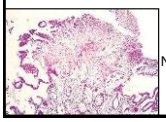




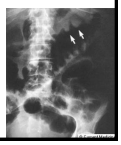
# Challenges in Management of *C. difficile* Infection

Christopher Chang, MD, PhD
Division of Gastroenterology/Hepatology
University of New Mexico School of Medicine
And
New Mexico VA Health Care System



May 14, 2016
National Conference for Nurse Practitioners
Lake Buena Vista, Florida

Kelly '15, Gastroenterol 149:223

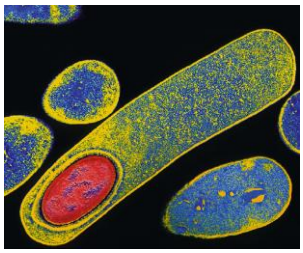


## The Challenges ahead

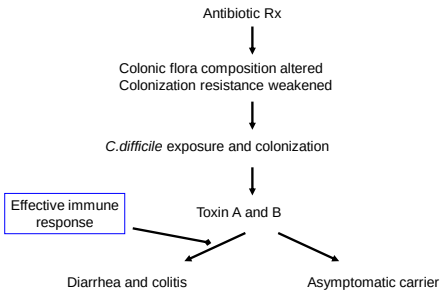
- *C. difficile* infection 101
- Hypervirulent strain
- Community-acquired CDI
- Testing for *C. difficile*
- Severe-fulminant CDI
- Recurrent CDI
- Prophylaxis and prevention
- New and novel therapies

## *Clostridium difficile*

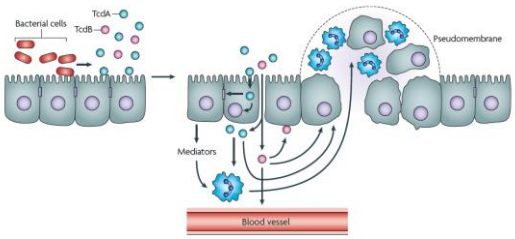
- Anaerobic gram positive bacillus
- Spore-forming
- Ubiquitous
  - Stool of 1-3% healthy adults
  - Community acquired cases
- Enriched in hospital environment
  - Readily cultured from
    - 20-30% hospitalized patients
    - Hospital surfaces
    - Hospital workers
  - Nosocomial infections common and rising



## Pathogenesis of *C. difficile* infection




## *C. difficile* pathogenesis




- Role of biofilms?
- Toxin internalization --> cytoskeletal Δ --> epithelial barrier disruption; cell death; inflammation with neutrophils

## Risk factors for <u>hospital associated</u> CDI

### Major

- Use of antimicrobials
  - Most within 2 weeks
  - Rarely up to 3 months
  - Clindamycin, 2$^{O}$ and 3$^{O}$ cephalosporins, fluoroquinolones
- Age >65
- Severe underlying illness
- Infected roommates

### Other risk factors

- Immunosuppressioin
- Absence of *C. diff* antibody response
- Recent surgery
- NG tube feeding
- Genetic factors (e.g. IL-8 polymorphisms)
- PPI use
- Strain type

7 cases per 1,000 patient discharges and rising.
Estimated 500K cases in US per year with 15-20K deaths.

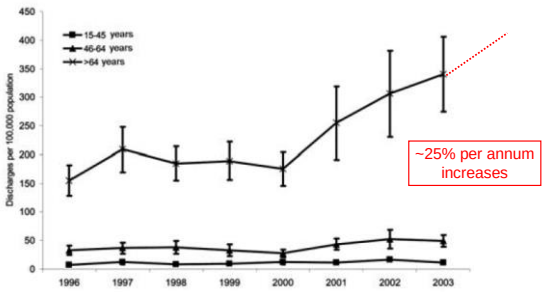
## Treatment recommendations

**(Infectious Disease Society of Am 2010; Am Coll Gastro 2013)**

| | | |
|---|---|---|
| Initial episode:<br>Mild or moderate | WBC <15<br>Cr < 1.5x baseline | **Metronidazole**<br>500 mg po TID x 15d |
| Initial episode:<br>Severe | WBC ≥15<br>Cr ≥ 1.5x baseline | **Vancomycin**<br>125 mg po QID x15d |
| Initial episode:<br>Severe/complicated | Hypotension<br>Shock<br>Ileus<br>Megacolon | Vancomycin 500 mg PO/NGT QID plus<br>Metronidazole 500 mg IV q 8hrs plus<br>± Vanco enemas if complete ileus |
| First recurrence | | Same as for initial episode |
| 2nd recurrence | | Tapered and/or pulsed vancomycin |

## Rising CDI among hospitalized elderly:

Acute care hospital discharge diagnoses



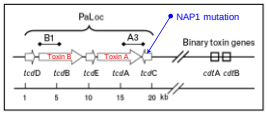

McDonald ,06 Emerg Infec Dis 12:409

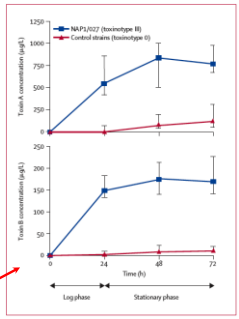
## The epidemic *C. difficile* strain

- Quebec 2004: 3-fold increase CDI with more severe outcomes (ICU, colectomy, death)
  - 30 day mortality jumped 4.7% to 13.8%
  - Typically 1-2%
- 82.2% isolated strains from Quebec hospitals were NAP1/027
- Isolated from 67% hospital-associated and 37% community-acquired CDI in US-European study
- Found widely in US institutions that had higher rates of CDI
- In 2007, NAP1/027 strain found in 38 US states

Loo '05, NEJM 353: 2442, McDonald '05 NEJM 353:2433, Wamy '05 Lancet 366:1079

## Hypervirulent strain secretes more toxin




- Tox A and B glycosylate rho proteins to disrupt cell signaling --> cytoskeletal actin disintegration and apoptosis
- Mutation in repressor gene tcdC leads to up-regulation of Tox A and Tox B production
- NAP1/027 strain produces 16x Tox A and 23x Tox B than non-hypervirulent strains

Warny '05

## Community-acquired CDI

(Not admitted to healthcare facility >3 months since diarrhea onset)

- Often no antibiotic exposure
- Chronic GI conditions (IBD, diverticulitis, cirrhosis)
- Possible exposures-reservoirs
  - Spores in soil
  - Contaminated home surfaces
  - Colonized family members
  - Pets
    - Visitation dogs in Canadian hospital: 58% colonized by *C.diff*
- Higher risk for
  - Young children
  - Post-partum and pregnant
  - PPI users, IBD patients
- 7 cases per 100,000 person-years
- 1 case per 5,500 outpatient antibiotic prescriptions

MMWR 2005 54:1201, McFarland 2008,
Nat Clin Prac Gastro/Hep 5: 40

## Epidemiology of community-acquired CDI

- Olmsted County data '91-'05
- Increased CDI rates overall; outpatient 41%
- Fewer of usual risk factors in outpatient group
  - Younger (ave 50 vs 72 yrs old)
  - Women (76% vs 60%)
  - Less severe disease (20% vs 31%)
- Pregnancy and severe CDI: 10 cases reported '05-'06
  - Hospitalized / ICU
  - Colectomy (7), death (3)

Khanna, Am J Gastro 2011

## CDI in inflammatory bowel disease

- Rates 2x higher in Crohn's; 3x higher in UC
- More severe disease; younger; higher mort
- Antecedent abx use not essential
- Risk factors:
  - Immunomodulation
  - Colonic disease
- +/- pseudomembranes on colonoscopy
- Use vancomycin as first-line therapy

## CDI and PPI use

- 2 recent meta-analyses: Increased risk CDI
  - 65% increase risk in 1 study
  - Risk further increased with Abx use
  - Decreased risk with H2-blocker use
- Findings consistent with increased risk of acute infectious gastroenteritis and PPI use

Janathan, Am J Gastro2012, Kwok, Am J Gastro 2012

## Diagnosing CDI: Clinical tools

- Toxin enzyme immunoassays (EIA)
  - Sensitivity of single EIA ~80% (frequent false negative)
  - 3 specimens recommended to r/o CDI (evidence weak; DON'T)
  - Some strains only produce Tox A or B (~2%)
  - BUT…easier and quick (2-4 hours)
- Cytoxicity assay
  - Gold standard (>90% sensitivity and specificity)
  - Requires tissue culture set up and 24-48 hr assay; $$
- Real time PCR
  - Detects conserved regions of the Toxin B gene (*tcdB)*
  - Fast (<3 hrs); >90% sensitivity and specificity
  - [illegible] GOLD STANDARD
- Bedside flexible sigmoidoscopy
  - Clinical suspicion but negative stool studies
  - Unprepped; can obtain more stool samples
  - Immediate diagnosis possible
- Clinical suspicion should trump test findings
- Empiric Rx if suspicious for CDI

## What if tests are negative for *C. difficile*?

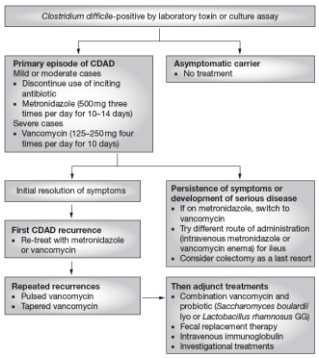
- Low *C. diff* toxin levels in stool sample
- Improper handling and storage of stool sample by lab
- Consider other causes of diarrhea, pain, leukocytosis
  - MRSA
  - *Klebsiella oxytoca* --> right-sided colitis
  - IBD flare
  - Undiagnosed celiac disease
  - Ischemic colitis

## Treatment algorithm for CDI

Why metronidazole?
- Reported equivalency
- VRE risk
- $$ (vanco > $1000)

But recent reports
- higher risk of complicated CDI
- Increased recurrence
- Longer duration

….on metronidazole vs vanco




## Oral vancomycin more effective than metronidazole for severe CDI

≥2 points = SEVERE

1 point:

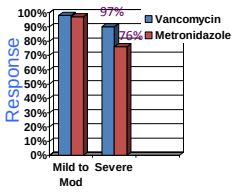
| | |
|---|---|
| Age | >60 |
| Temp | >101 F |
| Albumin | <2.5 |
| WBC > 15K | |

2 points:

Pseudomembranes on colonoscopy

ICU patient

172 patients enrolled; 150 completed

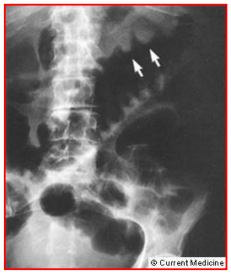



P = 0.02 for severe CDI

Zar '07, Clin Infec Dis 45:302

## Fulminant CDI: toxic megacolon and paralytic ileus

- Severe-fulminant CDI may present as acute abdomen and /or mimic colonic pseudo obstruction
- Little or no diarrhea
- Post-op setting, on narcotics
- Abdominal pain severe, tenderness and distention
- Dilated and inflamed colon on X-ray or CT
- Elevated WBC, CRP, Cr, lactate; decreased albumin
- Fever, anorexia, nausea, malaise




## Management of severe-fulminant CDI

- Vancomycin 500 mg po/NGT QID
- Partial ileus:
  - Metronidazole 500-750 mg IV TID **plus**
  - Vancomycin 500 mg via NGT QID
- Complete ileus:
  - Metronidazole 500-750 mg IV TID **plus**
  - Vancomycin 500 mg QID via foley enema (in 100 ml NS; clamp 60 min)
- Progressive and refractory; critically ill
  - Surgical evaluation for possible colectomy
  - Consider IVIG 400 mg/kg

## Surgery for severe fulminant CDI

- Indications: toxic megacolon, perforation, "septic" picture, incresed pain, WBC, and failure to respond to medical Rx
- Total vs. partial colectomy:
  - Retrospective 14 cases. Overall mortality 36%
  - Total colectomy mortality 11%
  - Left hemi-colectomy mortality 100%
- Does emergent colectomy improve outcomes?
  - Retrospective cohort study in Quebec (hypervirulent strain)
  - 165 pts in ICU for CDI
  - 53% died within 30 days of ICU admit

Koss 2006, Colorec Dis 8:149,
LaMontagne 2007, Ann Surg 245:267

## Emergent surgery for fulminant CDI

- 53% died within 30 days of ICU admission
  - Predictors: WBC >50, lactate ≥ 5, age ≥ 75, immunosuppression, and hypotension requiring pressors
  - Medical therapy (127 pts) 58% died
  - Colectomy (38 pts) 34% died
  - Colectomy Vs med Rx reduces death: adjusted OR = 0.22
- Colectomy most likely to benefit:
  - Age ≥ 65
  - Immunocompetent
  - WBC ≥ 20
  - Lactate 2.2 - 4.9

LaMontagne 2007

## CDI treatment in IBD patients

- Vancomycin as first-line therapy
- Continue immunosuppression , but hold steroids if possible
- Refrain from starting or increasing immunosuppression until CDI controlled

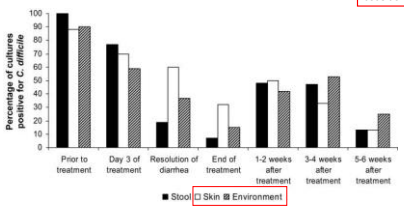
C. Surawicz, recommendations

## Recurrent CDI: reservoir of persistent contamination and colonization

- Carrier state of asymptomatic colonization by *C. difficile*
  - Infants 50-70%
  - Hospitalized adults 14%
  - Post-successful Rx 20%
  - Healthy adult < 1%

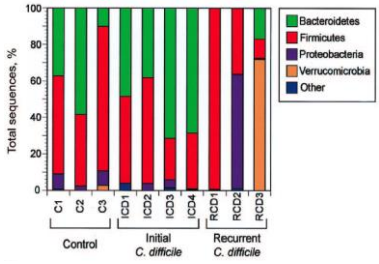
Skin: Chest, abd swab

Environment: bed rail, bedside table, call button




Seth 2010, Infec Control Hosp Epi 31:21

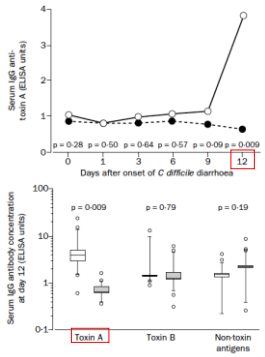
## Altered fecal microbiota in recurrent CDI




- Decreased overall diversity in recurrent CDI flora vs non-recurrent vs normals
- Altered Bacteroidetes: Firmicutes ratio

Chang '08, J Infec Dis 197:435

## Antibody response to toxin A protects against recurrent *C. diff* diarrhea

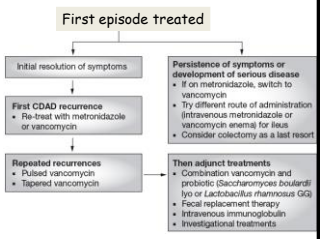



- Prospective study of 63 pts w/ nosocomial *C.diff* diarrhea
- Of the 44 survivors, 22 had recurrent CDI
- Pts with only single episode CDI had higher serum IgG values against Toxin A than those with recurrent CDI; p = 0.009; OR= 48
- Asymptomatic carriers of *C.diff* also have high concentration of this IgG against Toxin A

Kyne '01 Lancet 357:189
Kyne '00 NEJM 342:390

## Recurrent CDI treatment strategies

- Common:
  - ~20% after first CDI
  - ~40% after first recurrence
  - >60% after 2 or more recur
- Not due to V or M resistance
- > 50% new infections
- Inadequate immune response (low anti-toxin A IgG)



## Recurrent CDI: Tapered vs pulse vancomycin

Start vancomycin 500 mg qid x 2 wks

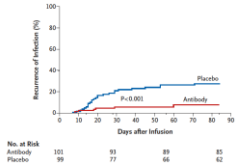
| Tapered vancomycin: | Pulse vancomycin |
|---|---|
| 125 mg qid x 1 wk | 250 mg bid x 5 days |
| 125 mg bid x 1 wk | 250 mg bid qod x 1 wk |
| 125 mg qd x 1 wk | 250 mg bid q 3d x1 wk |
| 125 mg qod x 1 wk | 250 mg bid q 4d x1 wk |
| 125 mg q3 days x 2 wks | Cont until q 10d, then stop |

## Recurrent CDI: Alternative therapies (investigational, off-label)

- Rifaximin "chaser": 14 patients, severe recurrent CDI
  - Vancomycin course --> rifaximin 400 mg BID x 2 wks
  - 12/14 no further relapses (Johnson'09 Anerobe 15:290)
- Vancomycin 2g po qd x10d --> *Saccharomyces boulardi* 500 mg po BID on day 7 x 28 days Vs placebo probiotic
  - *S. boulardi* group recurrence: 16.7%
  - Placebo group recurrence: 50.0% p = 0.05
  - Lower vanco doses or metronidazole: no significant difference
  - (Surawicz '00 CID 31:1012)

- Humanized Mab against tox A and B
  - RDBPCT phase II trial. Single infusion 10mg/kg in 200 CDI pts receiving metronid or vanco
  - 1º endpt recurrence w/in 84 d after infus.
  - Placebo recurrence 25%
  - Anti-toxin Ab recurrence 7% (p<0.001)

  (Lowy '10 NEJM 362:197)




## CDI prophylaxis with probiotics

- Prospective trial: *Lactobacillus casei, L. bulgaricus,* and *Streptococcus thermophilus* (Hickson '07 BMJ 335:80)
  - RDBPCT of 113 pts from 3 London hospitals
  - Pts randomized to the probiotic yogurt drink or placebo within 48 hrs of antibiotics being started; probiotic continued 1 wk after abx.
  - CDI rates: Probiotic 0%
  - Placebo 17% p = 0.001
  - Strict exclusion criteria: pts < 50 yrs excluded (?); high risk abx (clinda, cephalos) excluded (?)
  - Other trials with other probiotics less promising
- Retrospective study: compared incidences of two hospitals in AZ. One prescribed *L. acidophilus, Bifidobacterium longum and B. bifidum* routinely with Abx. (Graul '09 Med Hypoth 73:194)
  - 66% reduction in CDI incidence resulting from probiotic use (p=0.0027)

## CDI prevention and control

Most cases in healthcare setting--3 main strategies:

- Prudent use of antimicrobials (especially broad-spectrum Abx)
  - Shorter duration use
  - Avoid broad spectrum if possible
- Prevent cross infections (fecal-oral spread of resistant spores)
  - Isolate suspected CDI pts ASAP
  - Enhanced environmental and equipment cleaning
  - Appropriate protective clothing and hand washing (alcohol gels less effective)
- Active surveillance of infections: timely feedback, detect outbreaks and monitor effectiveness of infections

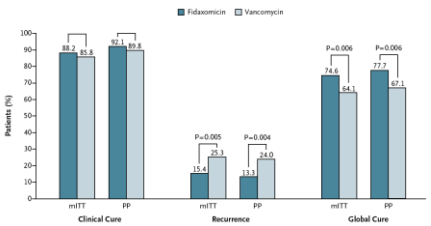
Monaghan 2008, Gut 57:850

## New/novel therapies for CDI

- Fidaxomicin: Poorly absorbed abx active against gram positive anaerobes (Poxton'10 Future Microb 5:539)
  - 2 phase III trials (n> 2000); 200 mg BID x 10 d
  - Initial and recurrence effectiveness comparable to vanco 125 mg QID
  - Recurrence only 13% vs 25% for vanco
- IVIG: Used off-label for severe CDI. Mixed results. Higher mortality in treated patients
- Tolevamer: Anionic resin that binds toxin A and B. Phase II trial showed non-inferiority to vanco in achieving "time to resolution" of diarrhea.
- Non-toxigenic *C. diff*: Colonization by these strains confers resistance to toxigenic *C. diff* in hamster models. Human trials underway.
- *C.diff* toxoid vaccine: small trials successful for recurrent CDI (Sougioultzis '05 Gastro 128:764). Phase trial II underway in UK-US. DNA-based vaccines in progress (safer?)

## Fidaxomicin vs vancomycin

Van Nood '13, NEJM 368:407



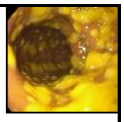

- Fidaxomicin 200mg bid vs vanco 125 qid for 10 days
- Multicenter DBRCT with 629 pts
- 8x greater *in vitro* activity (bactericidal) than vanco (bacteriostatic)
- Less activity against normal gut flora
- Recurrence not reduced in the NAP1 hypervirulent strain

## Fidoxamicin vs Vancomycin

- 200 mg BID x 10 days → $2800 (vs $1700)
- Equivalent efficacy to vancomycin
  - Cure: 88.2% vs 85.8%
  - Hypervirulent strain cure: 78.7% vs 80.7%
- Less disruption to colonic flora → less recurrence ?
  - 15.4% vs 25.3% (overall CDI).
  - Same recurrence rate for hypervirulent strain.

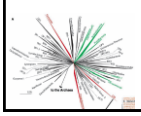
## CDI Take home points

- Incidence (15-30% of hospitalized pts) and severity of CDI is rising
- A hypervirulent strain produces more toxin and is responsible for recent outbreaks in N. America
- Community acquired CDI rising; large potential reservoir
- Clinical suspicion for CDI should supersede neg lab test in initiating empiric antibiotics
- Oral vancomycin 125-250mg QID is best choice for severe CDI, whereas oral metronidazole 500 mg TID is first choice for milder disease
- Emergent total colectomy improves outcomes in select population with fulminant CDI
- Multiple recurrences of CDI should be treated by prolonged vancomycin taper or pulse dosing
- Several new therapies show promise for recurrent CDI
- Promise of probiotics not yet met; in contrast, fecal transplant appears quite effective in preventing relapsing CDI



## FECAL MICROBIOTA TRANSPLANTATION: THE REAL POOP

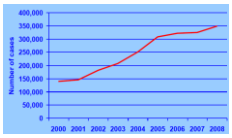
Christopher Chang MD, PhD



## Overview

- Recurrent *C. difficile* infection (CDI)
- Fecal microbiota *transplant* (FMT)??
- What is the gut microbiota?
- Early studies using FMT
- Promising large studies and RCT
- FMT for IBD
- The yuck factor
- How to do FMT
- Potential future applications

## The *C. difficile* infection problem

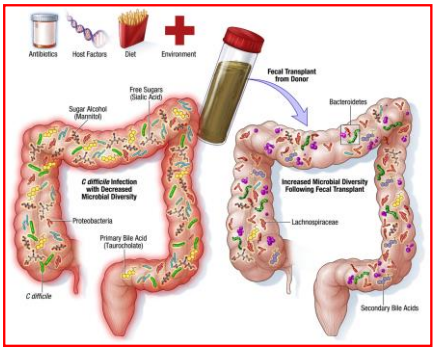

- Estimated 3 million cases CDI per year in US hospitals and LT-care facilities. Continued rise in past decade.
- 14,000 deaths per year; 90% in the elderly population
- 336,600 hospitalizations; 1% of all stays.
- 20-30 community-associated CDI per 100,000 population; >20% of CDI cases

Evans '15 Clin Infec Dis 60: S66

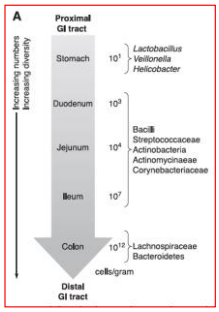
## Recurrence is a major problem

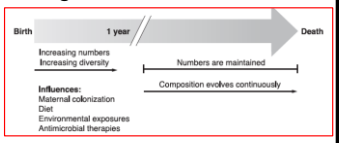
- Hypervirulent NAP1/027 strain
- Recurrent infection common after treatment
  - 15-30% recurrence after first infection
  - 40% recurrence after second infection
  - Up to 65% recurrence after third infection
  - Up to 200,000 recurrent infections in US per year
- Recurrence is treated with MORE ANTIBIOTICS

## Simple approach to alter gut microbiome: Fecal Microbiota Transplant (FMT)

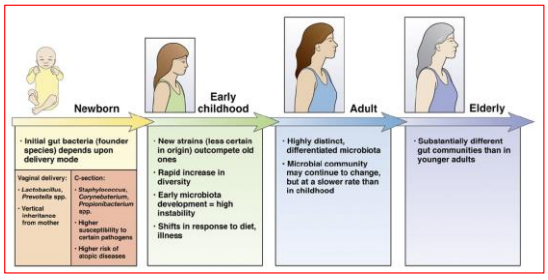



## Gut flora varies with location and changes during life

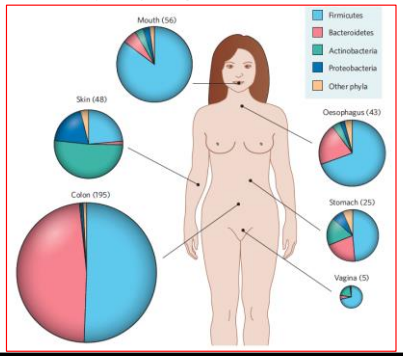



## Early, diverse microbiota converges onto adult core microbiota

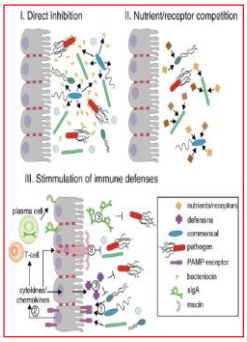


## Human microbial communities dominated by 4 groups of bacteria

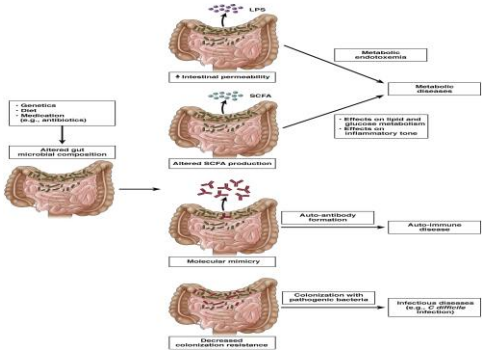



## Beneficial effects of gut microbiota

- Colonization resistance
- Immune system development
  - Antigenic stimulation
  - Tolerance
- Epithelial growth and differentiation
- Nutrition and metabolism
  - Fermentation of non-digestible residues to SCFA
  - Vitamin and bile metabolism
  - Drug metabolism




## How gut microbiota changes can lead to disease




Smits 2013 Gastroenterol

## Earliest uses of FMT

- 4th century traditional Chinese medicine doctor Ge Hong gave human fecal suspensions by mouth to cure food poisoning and severe diarrhea
- 16th century China "yellow soup" used to treat various GI ailments
- 17th century veterinary description of cud transfer from healthy ruminant to mouth of sick animal with recovery
- "Transfaunation" part of veterinary practice to treat colitis and rumination disorders

## First case series (1958): FMT cures pseudomembranous colitis

- *C. difficile* not recognized as cause of PMC until '78
- 3 of 4 treated patients with life-threatening PMC despite multiple Rx
- Fecal retention enemas used
- Dramatic resolution of symptoms within 48 hours

Eiseman 1958, Surgery 44:854

## FMT case series 2011-2012

- 2011 systematic review: 317 pts from 27 case series and reports; disease resolution in 92%. Death and AE uncommon (Gough, Clin Inf Dis 53:994)
- Resolution of diarrhea in 24/26 relapsing CDI (Kelly ,et al, J Clin Gastro 46:145)
- 43 patients receiving transplant from individual (family, friend) and standard volunteer donors (Hamilton, et. al, AJG 107: 761)
  - Fresh and frozen material used, delivered by colonoscopy
  - Success rate comparable between fresh vs frozen (92% and 90%, respectively) and was better than patient-identified donor (70%). Combined success rate: 86%
- 70 patients receiving fresh transplant via colonoscopy in Finland (Mattila, et al, Gastro 142: 490)
  - All non-hypervirulent CDI patients resolved diarrhea/CDI within 12 weeks
  - 36 pts with hypervirulent strain had 89% resolution; 4 non-responders later died of colitis. Overall response rate 94% to FMT
  - 4 relapsers after 1 year, all after abx use; CDI resolved with either abx or repeat FMT.

## 5 center long term f/u of FMT

- 77 of 94 eligible pts contacted retrospectively; 10-20 pts from each center (Montefiore, Brown, Oklahoma City, East Bay, Harborview-Seattle)
- 36 item questionnaire completed
- Outcomes:
  - Primary cure rate: resolution of sx without recurrence within 90 days of FMT
  - Secondary cure rate: resolution of sx after 1 further course of vancomycin with or w/o repeat FMT
- Donors:
  - Spouses/partners 60%
  - First degree or other relatives 27%

Brandt '12, Am J Gastro 107: 1079

## Patient charcteristics

- 73% women (56/77)
- Mean f/u 17 months (3-68)
- Sx duration 11 months (1-28)
- Diarrhea
  - < 3 BM/day 5%
  - 3-6 BM/day 27%
  - > 6 BM/day 68%
- Abdominal pain 73%
- Weight loss 68%
- Fatigue 91%

Brandt 2012

**Table 2. Post-FMT data**

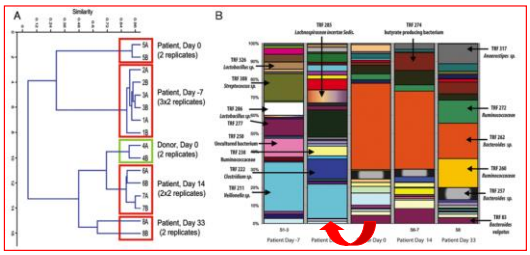
| | |
|---|---|
| Total number of patients | 77 |
| *Diarrhea* | |
| No improvement | 1 (1%) |
| Improved | 13 (17%) |
| Resolved | 63 (82%) |
| Mean days to improvement/ resolution (range) | 5 (1–60 days) |
| *Abdominal pain* | |
| Not present before FMT | 21 (27%) |
| No improvement | 4 (5%) |
| Improved | 13 (23%) |
| Resolved | 39 (70%) |
| Mean days to improvement/ resolution (range) | 10 (1–120 days) |
| *Fatigue* | |
| Not present before FMT | 3 (4%) |
| No improvement | 5 (7%) |
| Improved | 31 (42%) |
| Resolved | 38 (51%) |
| Mean weeks to improvement/ resolution (range) | 4 (1–28 weeks) |
| *Weight* | |
| Increased | 41 (53%) |
| Remained the same | 34 (44%) |
| Decreased | 2 (3%) |

## Long term follow up

- Total # recurrences 15 (out of 77 study pts)
  - Early recurrence (≤ 90 days) in 7pts. All responded to Abx or repeat FMT, except 1 pt who died in hospice w/o Rx.
  - Late recurrence (> 90 days) in 8 pts
  - Primary cure rate 91% (70/77)
  - Secondary cure rate 98% (76/77)
- Recurrences distributed equally among 5 centers
- Patient satisfaction in survey was high
  - 97% would repeat FMT for recurrent CDI
  - 53% would choose FMT as first Rx before antibiotics

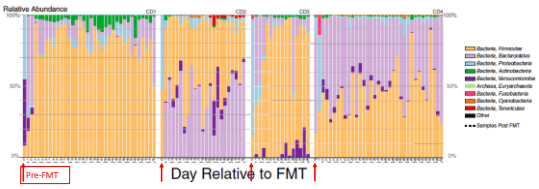
Brandt 2012

## Durable alteration of microbiome after FMT




Khoruts 2012, J Clin Gastro 44:354

## Durable yet Dynamic Changes to Microbiota after FMT




- Fecal samples collected through day 84 post-FMT → high throughout sequencing
- Rapid normalization of marked dysbiotic state in recipient (compared to Human Microbiome Project data)
- Both recipient and donor microbiota diverge variably, but remain "healthy"

Weingarden, et al. *Microbiome*. 2015;3:10.

## Finally, an RCT


The NEW ENGLAND JOURNAL of MEDICINE

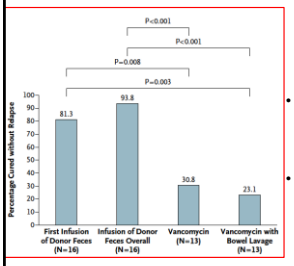
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

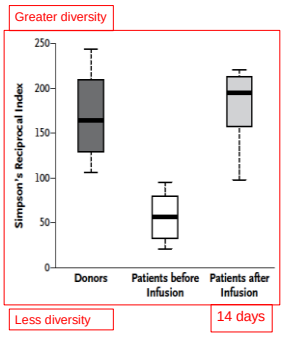
- Open-label RCT comparing 3 regimens:
  1. Initial vancomycin 500 mg QID x 4d, followed by bowel lavage and infusion donor feces thru NGT
  2. Vancomycin 500 mg QID x 14d
  3. Vancomycin 500 mg QID x 14d followed by lavage
- Primary end point: resolution of diarrhea without relapse within 10 weeks
- Secondary end point: resolution without relapse after 5 wks

# FMT more effective than vanco




- Feces from 15 pre-screened donors
- 40 pts per group planned
  - 43 enrolled in first 2 yrs
  - High relapse rate in controls
  - Trial terminated after interim efficacy analysis
- Median time to recurrent CDI 23-25 days in control groups
  - 18 relapsers got infusion with 83% cure
- Day of infusion:
  - Diarrhea 94%, cramping 31%, belching 19%
  - Resolved within 3 hrs
  - Constipation 19% at f/u visits

# Recipient microbiota increases diversity after FMT




- Fecal microbiota evaluated in 9 patients
- Human Intestinal Tract Chip (HITChip microarray)
- PCA showed major shift in recipient microbiota toward that of donor
- Q-PCR analysis showed:
  - Increased Bacteroidetes
  - Increased Clostridium
  - Decreased Proteobacteria (by up to 100-fold)

# Patients receptive toward FMT

| Conditions | Antibiotics + FR, No. (%) | Antibiotics Alone, No. (%) |
|---|---|---|
| After reading scenario 1 | 162 (85%) | 29 (15%) |
| After reading scenario 2 (disclosure of FR specifics) | 154 (81%) | 37 (19%) |
| • If FR provided as colorless, odorless liquid given by NGT, enema, or colonoscopy | 158 (83%) | 33 (17%) |
| • If FR provided as colorless, odorless pill | 171 (90%) | 20 (10%) |
| • If FR (in any form) recommended by doctor | 179 (94%) | 12 (6%) |

| Reason for Choosing Antibiotics Alone | Scenario 2 (Disclosure of FR Specifics) |
|---|---|
| Do not think FR will work | 2 (5%) |
| Concerns about safety of FR | 16 (43%) |
| FR is too gross | 13 (35%) |
| Safety + gross | 3 (8%) |
| Other | 3 (8%) |

- Survey describing hypothetical "flora reconstitution" treatment scenarios for rCDI completed by 192 outpts
- Physician recommendation influences acceptance
- Most unappealing:
  - "need to handle stool"
  - "receiving FMT by NGT

Zipursky '12 Clin Infec Dis 55:1652

## Physicians attitudes toward FMT 2009

- Aesthetically unappealing? Logistically challenging?
- 73 physicians surveyed at DDW 2009
  - 38% from outside US
  - 10% had performed FMT or knew colleague who had
- 27% had never heard of FMT
- 48% had heard of FMT and would be willing to try it
- 34% not willing to try, despite familiarity
- Barriers to FMT cited by this group:
  - 71% patient acceptance and tolerability
  - 60% safety
  - 57% efficacy
  - 41% physician education
  - 34% endorsement by professional societies

Kelly '10, Am J Gastro 105:135

## Physician attitudes toward FMT 2013

- 200 Physicians emailed using on-line Survey-Monkey
  - Mix of GI and ID; even split academic vs practice;
  - 118 responded.
- 86.4% willing to use FMT for recurrent CDI ( vs 48% in 2009)
- 9.3 % unwilling to use FMT (vs 34% in 2009)
- Reasons for not considering FMT:

| | Total no. | M:F | GI:ID | Academic:private |
|---|---|---|---|---|
| Do not know how to perform FMT | 7 (63%) | 5:2 | 3:4 | 3:4 |
| Skeptical regarding the safety of procedure | 4 (36%) | 4:0 | 2:2 | 2:2 |
| Not enough evidence in support of FMT | 3 (27%) | 2:1 | 2:1 | 2:1 |
| Unsure about patient acceptance of therapy | 3 (27%) | 3:0 | 2:1 | 1:2 |
| Unpleasant nature of therapy | 1 (9%) | 1:0 | 1:0 | 0:1 |
| Feel embarrassed to talk to the patient about FMT | 0 | — | — | — |
| Never treated a patient with recurrent CDI | 0 | — | — | — |
| Skeptical about long-term results of therapy | 0 | — | — | — |

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; GI:ID, gastroenterologist:infectious disease specialist; M:F, male:female.

Sofi '13, Am J Gastro 108:1661

## Donor screening for FMT

| Serological | Stool | Consider | Possibly |
|---|---|---|---|
| Hepatitis A virus/immunoglobulin M | *C difficile* toxin B (preferably by polymerase chain reaction) | Giardia | Cytomegalovirus |
| Hepatitis B surface antigen<br>Antibody to hepatitis C virus | Culture for enteric pathogens<br>Ova and parasite examination, if travel history suggests | *Cryptosporidium*<br>*Isospora and Cyclospora* | Human T-cell lymphoma virus<br>Epstein–Barr virus |
| Human immunodeficiency virus 1 and 2 enzyme immunoassay<br>Rapid plasma reagin (RPR) | | *E coli* O157 | *Dientamoeba fragilis* |
| | | Rotavirus<br>Listeria<br>Vibrio<br>Norovirus | *Blastocystis hominis*<br>*Strongyloides stercoralis*<br>*Entamoeba histolytica*<br>*H pylori*<br>*Schistosoma*<br>JC virus<br>Vancomycin-resistant enterococci<br>Methicillin-resistant *Staphylococcus aureus* |

**Box 1. Criteria for selecting a donor for FMT**

Donors should meet the following criteria:
- No known communicable disease.
- No recent (3 months) antibiotic use.
- No history of diarrhea.
- No history of an immune disorder.
- No concurrent immunosuppressive agents.
- No history of inflammatory bowel disease, chronic constipation, or irritable bowel syndrome.
- No history of malignancy – non-melanoma skin cancer excluded.
- No recent (6 months) travel to endemic diarrhea areas.
- No current antineoplastic agent therapy.
- No current gastrointestinal symptoms.
- No risk factors – intravenous drug abuse, high-risk sexual behaviors, tattoos, current or historical incarceration, or body piercing (if male).

Although not strict contraindications to donor eligibility, the following items are appropriate to consider with regard to excluding a donor:
- Diabetes mellitus type II or metabolic syndrome.
- History of major gastrointestinal surgery.
- Chronic pain syndromes.
- Systemic autoimmune disorders.
- Atopic diseases including eczema, asthma, or eosinophilic disorders of the gastrointestinal tract.

Kelly '15, Gastroenterol 149:223.
2013 Trends in Micro 21:443

## Methods: Delivery by colonoscopy

- Donors screened: *C.diff*, O+P, enteric bacterial pathogens, Giardia, Cryptosporidium, Isospora, Rotavirus, HAV, HBV, HCV, HIV, Hp,and *T. pallidum* infection
- Fecal transplant procedure:
  - Night before: PEG bowel prep (recipient); consider MOM for donor. Stool should be used within 6-8 hours.
  - Abx held for 48-72 hours before transplant
  - 3 hours before– 50 gm donor stool manually homogenized with 250 ml sterile saline and filtered through gauze pads
  - Stool suspension delivered via colonoscope biopsy channel into cecum/ileum/R-colon (60 cc syringes )
  - Consider loperamide 1-2 hrs before transplant to help retain transplanted stool for 4-6 hrs

Brandt 2013

## Latest methods of FMT delivery

- Open label study with 20 subjects. Oral, frozen FMT capsules. 15 ingested on 2 consecutive days. Overall 90% response rate for recurrent CDI.
- RCT of 232 pts with recurrent/relapsing CDI, receiving fresh vs frozen/thawed FMT via enema. Very similar rates of diarrhea resolution achieved.

Youngster ,'14 JAMA 312:1772
Lee'16 JAMA 315:142

## FDA to the "rescue"


NATURE BIOTECHNOLOGY | NEWS

Fecal transplants to follow FDA rules

Jeffrey L Fox

Nature Biotechnology 31, 583 (2013) | doi:10.1038/nbt0713-583

Published online 09 July 2013

US Food and Drug Administration (FDA) officials in April declared that fecal microbiota transplants (FMT) will be considered and regulated as biologic drugs. Anyone conducting such procedures is now required to file an investigational new drug application (IND). Although this regulatory change began taking shape two years ago, the April announcement brought forth critics...

HOSPITAL
C.DIFFICILE

- FMT requires IND application for each use
  - Paperwork
  - 30 day waiting period
- Feces to be regulated as a "biologic drug"


In the News

ISSUE: OCTOBER 2013 | VOLUME: 49

FDA Reverses Course on Fecal Transplantation for C. Difficile

Swayed by Pleas From Doctors, Patients to Not Require INDs

By George Ochoa

After stating that the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* infection would require an Investigational New Drug Application (IND), the FDA reversed course after a public outcry, and announced that it would not require INDs for this therapy, at least for the time being.

- FDA backs off on IND requirement
- Informed consent still needed
  - Investigational nature
  - Discussion of potential risks

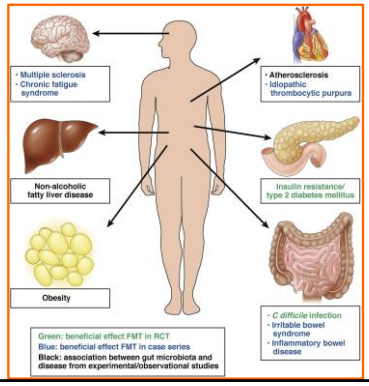
Stay tuned. This is an evolving situation

## Not Ready for Prime Time: Gut flora alteration and other diseases

- Metabolic syndrome (e.g. obesity, diabetes)
  - Gut flora role in energy metabolism
  - FMT from lean donors in resulted in marked fasting triglyceride reduction and improved insulin sensitivity, compared to controls (n=18)
- Parkinson's disease and myoclonic dystonia
  - Case reports of antibiotic treatment improving stool irregularity and profound improvement in movement disorder
- Chronic severe constipation
  - Improvement in 40/45 pts in 1 study; long term improvement in 60%
- Improvements in other extra-intestinal diseases
  - Chronic fatigue syndrome
  - Autism

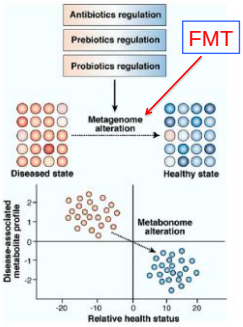
Borody'12, GI Clin of N Am 41:781

## Future targets for FMT




Smits'13, Gastroenterol

## Gut microbiome as a therapeutic target



## Fecal transplant take home points

- Prevalence of CDI and recurrent CDI has increased
- FMT is ~90% successful in treating recurrent CDI in large case series and first RCT
- Response rapid and durable, leading to changes in fecal microbiota of recipients
- Studies of FMT for IBD promising but limited to case series
- “Yuck” factor is exaggerated; majority of patients are willing
- Other potential uses for FMT await more rigorous studies