Challenges in Management of *C. difficile* Infection

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

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
    - colonization of hospitalized patients
    - hospital surfaces
    - hospital workers
  - Nosocomial infections common and rising
Pathogenesis of *C. difficile* infection

- Antibiotic Rx
  - Colonic flora composition altered
  - Colonization resistance weakened
- Effective immune response
- Toxin A and B
- Diarrhea and colitis
- Asymptomatic carrier

*C. difficile* pathogenesis

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

Risk factors for hospital associated CDI

**Major**
- Use of antimicrobials
  - Most within 2 weeks
  - Rarely up to 3 months
  - Clindamycin, 2nd and 3rd cephalosporins, fluoroquinolones
- Age >65
- Severe underlying illness
- Infected roommates

**Other risk factors**
- Immunosuppression
- 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)

<table>
<thead>
<tr>
<th>Initial episode: Mild or moderate</th>
<th>WBC &lt;15 Cr &lt; 1.5x baseline</th>
<th>Metronidazole 500 mg po TID x 15d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode: Severe</td>
<td>WBC ≥15 Cr ≥ 1.5x baseline</td>
<td>Vancomycin 125 mg po QID x15d</td>
</tr>
<tr>
<td>Initial episode: Severe/complicated</td>
<td>Hypotension Shock Ileus Megacolon</td>
<td>Vancomycin 500 mg P.O/NGT QID plus Metronidazole 500 mg IV q 8hrs plus Vanco enemas if complete ileus</td>
</tr>
<tr>
<td>First recurrence</td>
<td>Same as for initial episode</td>
<td></td>
</tr>
<tr>
<td>2nd recurrence</td>
<td>Tapered and/or pulsed vancomycin</td>
<td></td>
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</tbody>
</table>

Rising CDI among hospitalized elderly:
Acute care hospital discharge diagnoses

- 25% per annum increases

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
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

Wamy SS

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
- Higher risk for
  - Young children
  - Post-partum and pregnant
  - PPI users, IBD patients
- Higher risk for
  - 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)

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%)

Nat Clin Prac Gastro/Hep 5: 40
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

Diagnosing CDI: Clinical tools

- Toxin enzyme immunoassays (EIA)
  - Sensitivity of single EIA ~80% (frequent false negative)
  - 3 specimens recommended to rule out CDI (evidence weak; DON'T)
  - Some strains only produce Tox A or B (~2%)
  - BUT...easier and quick (2-4 hours)
- Cytotoxicity assay
  - Gold standard (>90% sensitivity and specificity)
  - Requires tissue culture set up and 24-48 hr assay; $$$
  - Detects conserved regions of the Toxin B gene (tcdB)
  - Fast (~3 hrs); ~90% sensitivity and specificity
- Real-time PCR
  - Detects conserved regions of the Toxin B gene (tcdB)
  - Fast (<3 hrs); >90% sensitivity and specificity
  - THIS IS BECOMING THE GOLD STANDARD
- Bedside flexible sigmoidoscopy
  - Clinical suspicion but negative stool studies
  - Unprepared; 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
  - *A. avycoeta* → right-sided colitis
  - *MRSA*
  - Undiagnosed celiac disease
  - Ischemic colitis

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### Treatment algorithm for CDI

#### Why metronidazole?
- Reported equivalency
- VRE risk
- $\$5$ (varies $>\$1000$)
- 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

<table>
<thead>
<tr>
<th>≥2 points = SEVERE</th>
<th>1 point:</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥60</td>
</tr>
<tr>
<td>Temp</td>
<td>&gt;101 F</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;2.5</td>
</tr>
<tr>
<td>WBC &gt; 15K</td>
<td></td>
</tr>
</tbody>
</table>

2 points:
- Pseudomembranes on colonoscopy
- ICU patient

172 patients enrolled; 150 completed


P = 0.02 for severe CDI
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, increased 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
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. Busetz, 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%

Seth 2010, Infect Control Hosp Epi 31:21

Skin: Chest, abd, extd
Environment: bed rail, bedside table, call button
Altered fecal microbiota in recurrent CDI

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

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

Recurrent CDI treatment strategies

- Common:
  - ~50% after first CDI
  - ~40% after first recurrence
  - >50% after 2 or more recurrences
  - Not due to V or M resistance
  - >50% new infections
  - Inadequate immune response (low anti-toxin A IgG)
Recurrent CDI: Tapered vs pulse vancomycin

**Tapered vancomycin:**
- 125 mg qid x 1 wk
- 125 mg bid x 1 wk
- 125 mg qd x 1 wk
- 125 mg qod x 1 wk
- 125 mg q3 days x 2 wks

**Pulse vancomycin:**
- 250 mg bid x 5 days
- 250 mg bid qod x 1 wk
- 250 mg bid q 3d x 1 wk
- 250 mg bid q 4d x 1 wk
- 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 Aneurese 15:290]
  - Vancomycin 2g po qd x 2 wks → *S. boulardii* 500 mg po BID on day 7-28 vs. placebo probiotic
    - 3/14 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
  - 1 yr endpt recurrence w/in 84 d after infusion
  - 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 335:90)
  - 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.
  - CIDI rates: Probiotic 0%
  - Placebo 17% p = 0.001
  - Strict exclusion criteria: pts < 50 yrs excluded (?); high risk abx (clinda, ceph) 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=0.0037)
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
- **Tolerafer**: 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

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
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

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 (75%). 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%

Patient characteristics

- 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%

<table>
<thead>
<tr>
<th>Table 2: Post FMT data</th>
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<tbody>
<tr>
<td>Feature of patients</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>No improvement</td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>Normal</td>
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<tr>
<td>Mean days for improvement</td>
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<td>Abdominal pain</td>
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<td>Not present before FMT</td>
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<td>Weight</td>
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<td>Normal for same</td>
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<td>Normal</td>
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</tbody>
</table>

Long term follow up

- Total # recurrences 15 (out of 77 study pts)
  - Early recurrence (< 90 days) in 7 pts. 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
Durable alteration of microbiome after FMT

Khoruts 2012, J Clin Gastro 44:354

Pre-FMT


Durable yet Dynamic Changes to Microbiota after FMT


Finally, an RCT

The NEW ENGLAND JOURNAL OF MEDICINE

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile


- 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 relapers got infusion with 83% cure
- Day of infusion:
  - Diarrhea 94%, cramping 31%, belching 19%
  - Resolved within 3 hrs
- Constipation 19% at t/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

- 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”
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 '09, Am J Gastro 105:135

Physicians 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:

<table>
<thead>
<tr>
<th>Reason</th>
<th>Total no.</th>
<th>IBD</th>
<th>GI-ID</th>
<th>Academic-private</th>
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<tbody>
<tr>
<td>Did not know how to perform FMT</td>
<td>7 (9%)</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Had concern regarding the safety of procedure</td>
<td>4 (3%)</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Not enough evidence in support of FMT</td>
<td>3 (17%)</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Concern about patient acceptance of therapy</td>
<td>3 (17%)</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unfavorable nature of therapy</td>
<td>1 (1%)</td>
<td>6</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Not reimbursement to talk to the patient about FMT</td>
<td>0</td>
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<td></td>
<td></td>
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<tr>
<td>Not feasible in patient with recurrent CDI</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected long term results of therapy</td>
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Sofi '13, Am J Gastro 108:1661

Donor screening for FMT

Kelly '15, Gastroenterol 149:223.
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”

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

- 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 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 J. Gastroenterol Clin N Am 41:781

Future targets for FMT

- Gut microbiome as a therapeutic target

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