Fecal Microbiota Transplant (FMT) in Inflammatory Bowel Disease

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FMT in IBD

– Recurrent *C difficile* infection
– Therapy for IBD
– Safety of FMT
– Bonus slides: FMT basics
FMT FOR RCDI IN IBD PTS.

IBD and CDI: Risk factors

- Ulcerative colitis/colonic Crohn’s
- Antibiotic exposure but not always
- Community acquired
- Younger age
- Steroid use

- CDI in small bowel (UC s/p colectomy)

Berg et al. Inflamm Bowel Dis. 2013
**IBD and CDI: Deadly Duo**

- More complications (toxic megacolon, perforation)
- More colectomies
- Longer length of stay
- Increased mortality


**IBD and CDI**

- CDI and IBD flare difficult to distinguish
  - Diarrhea
  - Abdominal pain
  - Fever
  - Leukocytosis
- Pseudomembranes absent in IBD patients
  (only present in 13%)

IBD and CDI: When to test

- Admitted IBD patients for CDI
- Outpatient IBD patients with flares
- Those without risk factors or antibiotic exposure
- Repeat testing may make sense here (expert opinion)

BASICALLY TEST ANYONE WITH A FLARE OR NOT RESPONDING TO THERAPY

IBD and CDI: How to treat

- Treat both
  - For CDI: start with vancomycin, not metronidazole (expert opinion)
- No initiation or escalation of therapy for IBD for 2-3 days
  - Concern steroids may pose a higher risk for CDI mortality

Ananthakrishnan et al, Inflamm Bowel Dis 2010
IBD and CDI – How to treat

- If not better may need to step up IBD therapy
- Challenging to know when CDI adequately treated
- PCR test for *C diff* very sensitive, some may be carriers
- FMT for *C difficile*, but not for the IBD

Hashash et al Current Gastro Reports 2014

*C difficile* in the small bowel?

- CD enteritis and pouchitis
- Highest in IBD pts post colectomy or IPAA(ileal pouch anal anastamosis) vs non IBD pts
- Risk factors: steroids; colon disease, immune suppression (?not anti TNFs); antibiotics
- Again: test all flares or nonresponders
**C difficile in pouch or small bowel: a therapy challenge**

- Oral antibiotics: metronidazole or vanco
- FMT for refractory cases: often combine enemas with FMT naso duodenal
- Some fatal cases reported (missed dx)

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**Meta analysis: FMT for CDI in IBD**

- 8 studies
  - *C difficile* and IBD
- Results:
  -- All cleared C diff (n=15)
  -- Bottom line: FMT good for RCDI in IBD

  - Anderson et al. Alim Pharm Ther 2012
Increased interest in FMT

- Remarkable efficacy for recurrent *C difficile* infection (90%)
- A “natural” approach, simple
- No immune suppression
- Both *C diff* and IBD have dysbiosis so it might work
Microbiome and IBD

Animals
- Germ free mice do not get IBD
- Colitis can be transferred from dysbiotic mice

Humans
- Diversion of fecal stream heals
- Pouchitis likely related to bacteria in part
- Long term antibiotics treat some cases
- Probiotics helpful in some, pouchitis VSL #3

Microbiome in IBD

Healthy controls/IBD pt

Increased Proteobacteria
- Enterbacteriaceae
- Ruminococcus gnavus
- Desulfovibrio spp

Spor Nature Reviews Microbiology 2011; 9: 279
Quiescent IBD

*Faecalobacterium prausnitzii*
*Lachnospiraceae*
*Akkermansia spp*

Possible probiotics?

FMT- FIRST CASE IN IBD

1989

– Bennett (a physician) had CUC
– Gave himself enemas of stool for 6 months
– Documented clinical and histologic improvement

Bennett JD, Lancet 1989
Initial Studies

Many small case series and case reports
  – Some positive
  – Some negative
    • Some had side effects (fever and elevated CRP)

FMT/ IBD Meta analysis

• 9 studies, no RCTs at that time
• Results:
  – Decreased symptoms 19/25 pts
  – Able to stop meds 13/17
  – Remission 15/24
• Suggests potential efficacy and recommend RCT for IBD

Anderson et al Alim Pharm Ther 2012: 36:503
More recent meta analysis

- 18 studies, one RCT as of May 2014
- 119 patients, mild to severe
- Clinical remission—45% overall
  - Crohn’s (n=79) 60%
  - UC (n=39) 22%
- No Significant Adverse Events
  - Fever
  - Abdominal pain
it is worth pursuing

Colman, J Crohns Colitis 2014:8: 1569

FMT Induces Remission in Patients With Active Ulcerative Colitis (RCT)

- 75 pts with active UC (FMT 38; Placebo 37)
- Lower route for FMT
- Donor stool enemas weekly x 6 wks vs water enemas
- Continued immune suppressive RX.
- End points: Clinical remission and endoscopy
- Terminated study early for futility

Moayyedi et al. Gastro 2015; 149: 102
Remission results

**FMT**
- 4/27, 15%
- 9/27, 24%

**Placebo**
- 2/26, 8%  NS
- 2/26, 5%  now p=.03

**One week later…..**
- 9/27, 24%

**7 of 9 had the same donor! Donor B**

Donors B and F had similar efficacy

*Gastroenterology, 149 2015: 102–109*
Moreover...

- Remission in 3 of 4 with UC less than a year
- Compared to 6 of 34 with UC longer than 1 yr.
  - So maybe earlier in course is better?

RCT of FMT for Patients With Ulcerative Colitis

- Nasoduodenal FMT (donor stool) at one wk. and 3 wks later after gut lavage
- Control was their own stool
- Measured clinical remission via colitis activity scores and endoscopy at 12 wks.

Rossen et al. Gastroenterology 2015: 149:110
## Results

<table>
<thead>
<tr>
<th>DONOR STOOL</th>
<th>CONTROL</th>
</tr>
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<tbody>
<tr>
<td><strong>Intention to treat</strong></td>
<td></td>
</tr>
<tr>
<td>• 7/23 30%</td>
<td>• 5/25 20% p=.51</td>
</tr>
<tr>
<td><strong>Per protocol</strong></td>
<td></td>
</tr>
<tr>
<td>• 7/17 41%</td>
<td>• 5/20 25% p=.29</td>
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### OTHER RESULTS

- Recipient resembled donor at 12 wks.
- No donor effect
- No IBD flares
- 2 pts with fever
- May have been underpowered
Why different results?

• Patient selection
• Different treatment protocol
  – Route/placebo
  – Some continued other meds
  – Gut lavage can change microbiome
• “Donor B “ effect?
• Length of follow up
• Were studies underpowered?

More questions...

1. is it effective?
   – Primary or adjunct therapy?
   – Which route is best?
   – Short or long term?

2. which patients will benefit and when in the course is optimal?

3. If successful, will it need to be long term?
   Bennet had an enduring remission off meds
How long do changes last?

- FMT eradication of *C difficile* in 8 children (5 with IBD)
- FMT successful in all, stool like donor
- At 6 months: returned to pre FMT baseline in those with IBD (abnormal, decreased *Bifidobacteria* and *Firmicutes* and increased in *Proteobacteria*)

Hourigan et al. Alim Pharm Ther 2015; 42:741

FMT COMPLICATIONS AND SAFETY DATA
FMT Complications

<table>
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<tr>
<th>Relatively Common</th>
<th>Uncommon - Case reports</th>
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<tr>
<td>• Transient fevers • Constipation • Bloating • Change in gas</td>
<td>• IBD flares • Norovirus • Diverticulitis • Weight gain • Aspiration pneumonia – Upper-route FMT – During sedation</td>
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Long-Term Follow-Up Study: FMT

- 77 patients—5 centers in US
- Follow-Up: 3 months to 5 ½ years
- Success rate: 82% → 98% (second infusion)
- New conditions: 4 patients
  - Rheumatoid Arthritis
  - Sjogren’s Syndrome
  - ITP (Idiopathic Thrombocytopenic Purpura)
  - Peripheral Neuropathy

Brandt, et al. Amer J Gastroenterol 2012; 107
FMT in Immune Compromised Patients

- Retrospective series from 16 institutions
- 80 patients, SOT, IBD, HIV, etc.
- Effective
  - 78% cured single FMT; 89% Overall
- Good safety overall
  - No infections related to FMT
  - Serious adverse events: IBD flares, hospitalizations in 12, 4 related to FMT and 5 possibly


Immune compromised series

2 deaths (1 related to FMT procedure)
- Aspiration during sedation for colonoscopy, pt had advanced esophageal cancer
- The other pt had pneumonia before and after FMT
Infection in IBD pt after FMT

- 51 y.o. woman with 3 yr history of ulcerative colitis on TNF inhibitor
- Receives antibiotics for tooth infection and develops *C difficile* diarrhea
- Severe diarrhea continues despite treatment of *C diff*

Courtesy of Dr. Elizabeth Broussard

- Immunotherapy changed and responds
- *C difficile* recurs
- Symptoms do not get better with therapy and *C difficile* still positive in stool
- Referred for fecal microbiota transplant, donor is daughter
- Severe colitis
Worse diarrhea, steroids increased 20 to 40 mg

Obtunded, presents to local ER

Transferred to UW medical center

07/25 07/27 07/28 07/30 07/31

• Local ER: Chest xray, head CT normal
  – CT abdomen: severe colitis
  – Given one dose each of vancomycin and piperacillin-tazobactam
  – This prob saved her life

• Transferred to UW Medical Center

• LP: grew *Listeria monocytogenes*

• Did well with Rx and went for colectomy
Questions from this case

• Difficult to manage CDI and IBD but RCDI is good indication for FMT
• Co therapy necessary, I wonder about steroids
• FMT not without risk—severity of colitis allowed translocation?
• Screening cannot eliminate all bugs (Listeria carriage transient, asymptomatic)

What do we tell our patients?

• FMT for IBD should be done in research setting
  – Don’t try this at home
• We do not know long term safety
• Concern re future immune diseases from one long term follow up study
• The field is moving quickly
  – Likely we will have specific cocktails at some time
  – Stick with proven traditional therapy for now
Diet and the Microbiome

- Prebiotics (inulin) can increase *Bifidobacteria* and *F prausnitzii*, so consider?
- Healthy diet, more plant based
- Avoid processed foods
- Consider fermented foods
  - Kimchee; kefir, sauerkraut
  - ROLE OF DIET THERAPY FOR IBD IS UNDER STUDY

Summary

- FMT effective for RCDI
- Role in primary Rx of IBD is being studied
- This may all change quickly.....
- Bonus slides: practical aspects of performing FMT

• THANK YOU FOR YOUR ATTENTION
FMT methods: Patient Selection

- Recurrent C difficile infection
  - 3 or more recurrences with adequate treatment
    - Vanco pulse regimen 125 mg qid x 10 d, then one pill every 3 days for 10 more doses
  - I make sure it is RCDI and not post infectious IBS
- Recommended by ACG guidelines for 3d recurrence (2013) and strongly recommended for multiple recurrences by European Society Clinical Microbiology and Infectious Diseases (2014)

Surawicz et al, Am J Gastroenterol 2013:108;478-498; Debast et al Clin Infect 2014: 20(suppl 2); 1-26
Donor Selection

• Usually family, friend or stool bank
• If no suitable donor, we schedule on same day and divide stool or ask donor to deliver again another day, donor insurance pays
• Extensive initial questionnaire, like for blood donation, including
  – Cancer
  – Autoimmune disorders
  – Metabolic syndrome
  – GI disease or GI symptoms

Did fecal transplant make woman obese?

Woman gained 40 lbs and rising after FMT (32 yo, 16 yo daughter, BMI 26, but wt went from 140 lb to 170 lb)

Her BMI: 26 to 33

Not able to lose weight

Alang and Kelly, Open forum infectious diseases November 2014
Donor Screening - Blood

- Hepatitis A, B, C
  - Hep A IgM
  - Hep B surface antigen and core antibody
  - Hep C antibody

- HIV 1 and 2
- Syphilis

Consider: CMV, EBV, Strongyloides, Ameba

Donor Screening - Stool

- Enteric pathogens, expanded, includes Yersinia
- C difficile PCR
- O&P (one)
- Acid fast stain: cyclospora and isospora (sp)
- Giardia antigen
- Rotavirus EIA
- Consider Norovirus, Listeria, Vibrio, MRSA, VRE
We are now using prescreened frozen stool

- Excellent patient acceptance
- Much easier and probably cheaper in the long run
- Patient selected donors need to be screened for blood and stool pathogens as which can be expensive

Donor Preparation- Stool

- Take a laxative the night before and inform us if any change in health
- Avoid allergens like nuts if pt has allergies
- Put sample in disposable container
- Prefer fresh, 6 hrs., ice not needed
- We weigh (200 gm or more best), mix by hand, filter thru gauze. 6 fifty cc syringes full into colon
Patient Preparation

- Baseline blood work for Hep A, B, C, HIV and syphilis
- Prep for colonoscopy—want excellent
- Consent: not guaranteed to work, could have risks of unknown infection or short or long-term consequences; investigational
- After procedure get loperamide and stay for 2 hours
- Follow up phone calls at 24 hr., 2 wks. and clinic visit at 3 months

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