Current Challenges in
Management of *C. difficile* Infection

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Importance of *C. difficile* Infection

- Leading cause of HAI
- Increase in rates in community?
  - HA rates: 2005 (84/100,000)
    2011 (70/100,000)
    2015 (48/100,000 patient-days)
- Reduced efficacy of abx therapy
  - Metronidazole failure rates for uncomplicated CDI: 2.5% vs 18%
  - Following 2 recurrences: > 60% risk of recurrence with abx
- Increased length of stay and hospital costs
  - 4d increase in LOS; additional 12,000 in costs/CDI episode
  - Total costs of CDI: $281M in Canada

Objectives

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- Efficacy of current treatments for CDI
  - Primary and 1st recurrent episode
  - Recurrent CDI treatment/prevention
- Current evidence for use of FMT
- Review of cases

CDI Management

67F. 5 watery bowel movements/day

- Normal temperature, WBC, lactate
- Maintained baseline creatinine
- Empiric treatment?

Mild Case of CDI

- Wait for laboratory confirmation for mild CDI
- Patient's stool: *C. diff*icile toxin positive
- Ongoing diarrhea
- Which antibiotic?
  - Metronidazole 500mg po tid
  - Vancomycin 125 mg po qid
  - Fidaxomicin 200mg po bid
  - Combination therapy??

Vancomycin liquid 125mg po qid

Vancomycin, metronidazole, tolevamer for CDI

- Multinational, RCT. S Johnson. CID Aug 2014
- Tolevamer (TV): 563; vancomycin (VM) 289; metronidazole (MTZ) 266.
- Clinical success of TV was inferior to both MTZ; VM
- MTZ (72.7%)was inferior to VM (81.8%) (p = 0.02)
- Clinical success: 4% (mild); 8.3% (mod); 12.2% (severe cases) more in VM than MTZ

- On Day 2 of therapy, severe nausea
- Options: vancomycin capsules vs fidaxomicin
- Risk factors for recurrence
  - Age, patient on prednisone 30mg od for PMR
  - Inpatient
  - PPI for gastric ulcer
- Based on multiple risk factors for recurrence, switched to fidaxomicin

Fidaxomicin vs. Vancomycin in Treatment of *C. difficile* Infection: Canadian Outcomes

- RCT: fidaxomicin 200mg bid vs vancomycin 125 mg qid x 10d.
- 406 patients enrolled
- End point: clinical cure
- Secondary end points:
  - recurrence of CDI
  - cure with no recurrence
- Clinincal cure rates mITT:
  - fidaxomicin and vancomycin 90.0% vs. 92.2%
- Recurrence mITT, PPA:
  - fidaxomicin and vancomycin 14.4 vs. 28% (*P*=0.001)

Lee et. al. Can J Infect Dis and Med Micro 2016

Back to Mild Case of CDI

- Patient unable to take any oral medications due to intractable nausea and vomiting
- Is IV metronidazole the only option?
- Is it equivalent to oral treatment?

CDI: treat orally

Prospective, cohort study of 250 patients with mild CDI

- Mean patient age: 77; > 50% moderate/severe comorbidity (Charlson index > 2 points
- 121: oral metronidazole
- 42: IV metronidazole
- 42: oral vancomycin
- All cause 30-day mortality rate: 13%
  - 38% in IV metronidazole
  - 7% for oral metronidazole; 10% oral vancomycin group
  - Adjusted for sex, age > 65; severity of comorbidity – risk for death within 30 days > 4-fold higher with IV metronidazole

Wenisch, JM. AAC Apr 2012

Combination Therapy for Critically Ill with CDI

Retrospective: evaluation of mortality for po VAN (44 pts) vs po VAN + iv MTZ (44) for ≥ 3/7 criteria (Rokas. CID 2015)

- Albumin < 25g/L; HR > 90 bpm; mArt Pressure < 60mmHg; WBC ≥ 15 000 cells/mL; age > 60; sCreat 1.5x baseline or T ≥ 38.0 ^{o}C
- Primary outcome: in-hospital mortality
- Patients matched Acute Physiology and Chronic Health Evaluation II scores
- Mortality 36.4% (VAN); 15.9% (VAN + MTZ) p = 0.03
- Clinical cure, length of ICU/hospital stay: no difference

Confounders: VAN + MTZ 4x more received VAN enema; 2x higher dose VAN

- Accuracy of CDI dx as EIA and PCR used
- Mixed data on CDIs: 70% CDI diagnosed after ICU admission
- 2 retrospective studies (Bass. J Hos Infect 2013; Parmar. J Oncol Pharm Pract 2014) did not show superiority for combination treatment; more complications in combination group
- **Combination therapy cannot be routinely recommended for CDI**

Case of ongoing diarrhea

76yM. L BKA – SSI, complicated CDI

- CDI Rx: MTZ, vancomycin 500mg po q6h, enema, FDX
- Referred for FMT for ongoing diarrhea (q20-30min; 2.5 – 5L/d) despite MTZ 500mg IV q8h, VAN 500mg po q6h and FDX 2500mg po q12h
- Normal WBC, creatinine, hemodynamically stable
- Repeat stool for *C. difficile* toxin: negative

Ongoing diarrhea

- When should you consider switching therapy or making an alternate diagnosis?

Recurrent CDI

- 60 F, IBS. CDI x 10months
- MTZ x 2
- VAN x 3+ *S. boulardii*

Recurrent CDI

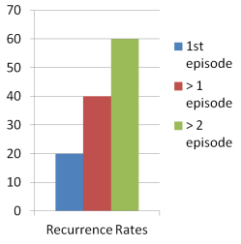
Mechanism

- Resistance to metronidazole 0%; vancomycin-rare
- Reinfection (environment)
- Proper immune response is important Risk factors

Risk Factors

- Additional antibiotic therapy
- Age > 65 years
- Severe underlying illness
  - ICU stay
  - Prolonged hospital stay
- Immunodeficiency

Rates of recurrence



Treatment of Recurrent CDI

60 F, IBS. CDI x 10 months

- Disinfection of household bathrooms with hypochlorite
- Treated with tapering vancomycin regimen
- F/up at 2 yrs : no recurrence

1st Recurrence:

- Vancomycin/fidaxomicin x 10d

2nd and subsequent recurrence

- Vancomycin 125mg po qid x 10d followed by tapering/pulsed
- Metronidazole not recommended
- Fecal transplant
  - Efficacy > 85%

Fecal Microbiota Therapy **(FMT)** at SJHH

- Commenced: Oct 2008
- Support from Administration, colleagues
- Engaged Nurses, IPAC
- Dedicated medical student
- Committed donors
- Willing patient

Patient #1

- 2008: 75 M recurrent, admitted with refractory CDI, 40lb weight loss, albumin 18 FMT x 1: resolution of diarrhea within 24 hrs. albumin 35 in 2 weeks.
- 2010: remained cured; 40lb +

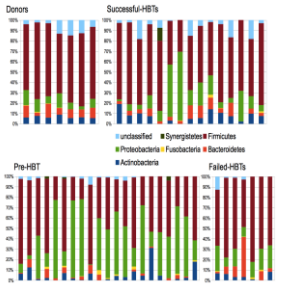
"Teamwork: Simply stated, it is less me and more we." Unknown

"A championship team is a team of champions."
Unknown

How Does FMT Work?

- Mechanism not yet understood
- Recurrent CDI
  - Decreased diversity, promotion of *C. difficile* growth
- FMT:
  - restoration of healthy microbiome → Resistance to *C. difficile* (Colonic Resistance)

Fecal Microbiota Results of Patients pre and post FMT: Relative Abundance



FMT Donor Screening

- Prior to 2011 a family member was the most frequent donor
- A pool of universal screened donors: OpenBiome, Rebiotix, Hamilton
- No standardized exclusion criteria
- ***Exclusion criteria:***
- positive for any of the following: HIV, HCV, HBsAg, HTLV1/II, syphilis, VRE, MRSA, ESBL, CRO, *Salmonella*, *Shigella*, *E.coli* O157 H7, *Yersinia* and *Campylobacter*
- Detection of ova, protozoa, *C. difficile* toxin, norovirus, adenovirus, rotavirus
- History of risk factors for acquisition of blood-borne pathogens; prion or any neurological disease as determined by the donor questionnaire,
- History of gastrointestinal comorbidites, e.g., inflammatory bowel disease, irritable bowel syndrome, chronic constipation or diarrhea
- Antibiotic use or any systemic immunosuppressive agents in the 3 months prior to stool donation
- Receipt of any type of live vaccine within 3 months prior to stool donation
- Ingestion of nut or shell fish 3 days preceding donation
- History of depression, anxiety or panic disorder
- History of GI cancer
- Family history of colon cancer
- History of any type of active cancer or autoimmune disease
- Body mass index > 29

FMT

Donor Screening:

- No standardized donor screening
- Completion of donor questionnaire

Blood	Stool
HIV	Parasites
HTLV 1-2	*C. diffilce* toxin/gene
HAV IgG, HBV, HCV	Enteropathogenic bacteria
Treponema pallidum	Adeno/rota/norovirus
	MRSA/VRE/ESBL/CRO

Efficacy and safety of FMT

9 Randomized Controlled Trials.

Duodenal Infusion of Donor Feces for Recurrent *C. difficile*

van Nood, et. al . N Eng J Med. 2013

- 3 treatment groups (NJ infusion of FMT: oral vancomycin; bowel lavage and oral vancomycin
- ***Study halted following interim analysis as FMT superior to other treatments (P* <0.001)**
  - FMT 13/16 (81% , 1st infusion); 2/3 resolved with 2nd infusion: overall efficacy 94%
  - Vancomycin 4/13 (31%)
  - Bowel lavage and oral vancomycin 3/13 (23%)
  - Similar AE's between 3 groups; mild diarrhea and abd cramps in FMT group

Variability of FMT Efficacy

85F gastric cancer

- Annual follow-up: chemotherapy?
  - Stomatitis: cephalexin
- Multiple rCDI > 5 courses of oral vancomycin/tapering
- Home FMT x 2
  - Oral vancomycin
- SJHH FMT x 1
  - Remains cured,18-month

Outcome of Patients Non-Responsive to FMT

- Pts refractory to CDI
- Multiple FMTs – no response
- Response to oral vancomycin post FMT relapse
  - 4/94 in SJHH observational study
  - 6/232 in RCT
    - 4/6 unresponsive to VAN pre-FMT
    - 6/6 post FMT, symptom-free on VAN 125mg[1] 24 – 36m f/up
  - Ruben, Bakken. *Anaerobe* 2013
  - Brandt. Am J Gastroenterol 2012
  - Lee, et. al. Eur J Microbiol Infect Dis 2014

FMT Next Steps

- Lyophilized FMT
- Open-labelled to include ≥ 12 yrs rCDI
  - Rapid results and reduce costs
- Advantages:
  - Long shelf-life, greater accessibility
  - Minimize donor screening, variability

Cost Comparison: on-site FMT vs. LYO-FMT

LTCF: 4 patients with refractory CDI

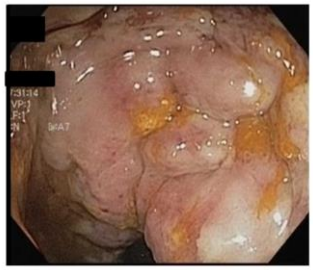
2 visits: via OPT transfer from Mississauga to St. Joseph's Outpatient Dept.			
Cost for OPT:	$ 514.20	$ 2,056.80	*OPT: [(88 x 2)+(2.2 x 136)+39 x 4 patients]
Nurse from Malton Vill.	$ 120.00	$ 480.00	*$30 x 4 hours x 4 patients
FMT	$ 4.64	$ 18.56	*4.64 per enema x 4 patients
Outpatient Nurse	$ 40.00	$ 160.00	*$40 per hour x 4 patients
Patient Assessment	$ 13.40	$ 53.60	*$13.40 per patient x 4 patients
Outpatient Visit	$ 288.00	$ 1,152.00	*$288 base cost x 4 patients
		$ 3,920.96 x 2 = $ 7841.92	

Lyophilized Treatment: Sending to Malton Village			
FMT Cost	$9.64	77.12	*9.64 x 8 treatments
Shipping Costs	$70.00	$70.00	
		147.12	

FMT Summary/Future Directions

- Most effective for rCDI
- Promising for UC
- RCTs
  - Colonoscopy versus oral capsules
  - Tapering vancomycin
  - Pediatric
- Registry for long-term safety and efficacy
- BCaLM Program

45F admitted with profound diarrhea, fever.
WBC >20,000 Neutrophilia
Stool *C. difficile* toxin: positive by EIA
Negative PCR
Oral vancomycin: no improvement



Pseudomembraneous colitis

Infectious
- *C. difficile*
- *Campylobacter*
- *Salmonella*
- E. coli O157
- CMV
- *Strongyloides*

Non-infectious
- Collagenous colitis
- Glutaraldehyde exposure

- Antibiotic switched to oral metronidazole
- Within 48 hours; clinical improvement

- 52yF. Recurrent CDI x 10 months
- Cured following FMT
- 3 months post-FMT, recurrence of diarrhea
- What next?

Repeat Stool Testing

- *C. difficile* Ag +/toxin negative EIA
  - Toxin gene positive
- Stool for O & P
- Stool culture
  - Positive for *Salmonella enteritica*
- Does she have both CDI and *S. enteritica?*
- Management?

- 85yF, referred for FMT for recurrent/refractory CDI. Radical cystectomy, bladder ca in Aug. 2015
- Oral vancomycin
- WBC 28,000; creatinine normal

- FMT –performed
  - Resolution of confusion
  - WBC 32,000

- CT of abdomen:
  - Necrotic lesion in pelvic area
- Pathology of lesion
  - Necrotizing poorly differentiated carcinoma

Take Home Message

- CDI associated with significant M &M
- Team effort
- Discontinue offending antibiotic
- Empiric therapy for ill patients only
- Mean time to response: 3 – 5 days
- Treat for 10 days for 1st episode of CDI
- Do not perform test of cure assays

Thank you!