Current Challenges and Future Options in Management of *C. difficile* Infection

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Faculty/Presenter Disclosure

- **Faculty: Christine Lee**
- **Relationships with commercial interests:**

Advisory Board Member:

Rebiotix

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Disclosure of Commercial Support Slide 2

- **This program has received financial support from in the form: None**
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  - None

Importance of *C. difficile* Infection

- Leading cause of HAI
- Increase in rates in community:
  - HA rates: 1996 (31/100,000)
    2005 (84/100,000)
- 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

Objectives

Objectives

- Efficacy of current treatments for CDI
  - Primary and 1st recurrent episode
  - Recurrent CDI treatment/prevention
    - Anti-infectives
    - Fecal Microbiota Transplantation
    - Monoclonal Antibody
- Prevention

Does this patient have CDI or not?

- 56M admitted for resection of esophageal ca
- Fleet enema, transient loose BMs
- Stool for *C. difficile* toxin : Positive
- Well, Temp 36.4 ^{o}C; WBC 6.0
- Does this patient have CDI?

Diagnosis of CDI: Clinical + Lab

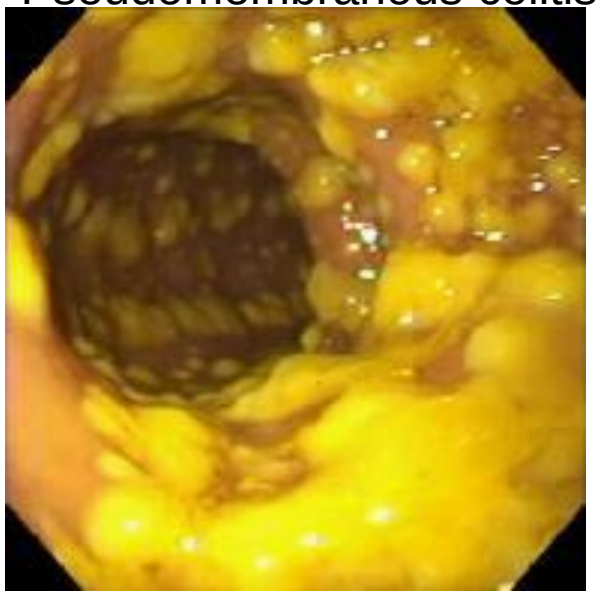
Clinical signs/symptoms

- Watery diarrhea (rarely bloody) $\geq$ 3 in 24 hours
- Abdominal pain
- Anorexia
- Fever
- Abdominal Distention/ileus

Laboratory findings

- Increased WBC
- Electrolyte abnormalities
- Low albumin
- Increased creatinine
- Positive stool toxin assay/endoscopic

Pseudomembranous colitis



Testing for *C. difficile* infection:

Test	Target	Sens (%)	Spec (%)	PPV	NPV	TAT (min)	Cost ($)
EIA	Toxins A + B	60	98	< 60	95	20 – 90	< 20
GDH	Common Ag	90	50	High	Low	20- 90	<20
NA (PCR, LAMP)	Toxin B gene	90	65	High	Low	90 - 200	> 20

Differences in Outcome According to CD Testing Method: Prospective, multicentre diagnostic validation Planche, Lancet Inf Ds 2013.

Stool samples: 15,000;

Inpatient episode: 6500

(Group 1) CTA positive: 435

(Group 2) CC positive and CTA negative: 207

(Group 3) CTA and CC negative: 5880

5927patients survived; 494 died

Mortality : (Group 1) 72/435 [16.6%] vs (Group 2) 20/207 [9.7%] p = 0.044; (Group 3) 503/5880 [8.6%]

Conclusion: multistep algorithms – improved performance characteristics. Higher mortality when CTA positive

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??

- Oral metronidazole 500mg **po** tid
- On Day 2 of therapy, severe nausea
- Options: oral vancomycin 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

- RCT: fidaxomicin 200mg bid vs vancomycin 125 mg qid x 10d.
- ~ 500 patients enrolled
- End point: clinical cure
- Secondary end points:
  - recurrence of CDI
  - cure with no recurrence
- Clinincal cure rates MITT:
  - fidaxomicin and vancomycin 88.2% vs. 85.8%
- Recurrence MITT, PPA:
  - fidaxomicin and vancomycin 13.3 vs. 24% (*P*=0.004)

Louie et. al. N Engl J Med 364 Feb 3. 2011

Potential future options?

- **Multicenter, Randomized Clinical Trial To Compare the Safety and Efficacy of LFF571 (thiopeptide) and Vancomycin for *Clostridium difficile* Infections** K Mullane, CHLee, A Bressler et al. AAC Mar 2015
  - Cure rate: 91% (LFF571); 78% (vancomycin)
  - Recurrence rate
    - Clinical: LFF 571 > vancomycin
    - Toxin-confirmed LFF 571 < vancomycin
- Surotomycin: phase 2 study result
  - Recurrence rate for 250mg bid of surotomycin 17.2 vs vancomycin 35.6% ($P = 0.035$)
- Cadezolid: phase 3
- Summit (SMT 19969): phase 2

Antimicrobial Activities

	MTZ	Vancomycin	FDX	Surotomycin	SMT19969
Clostridial spp.	2	16	256	> 512	> 512
Bacteroides	2	64	512	>512	>512

Drug	Chemical Class	Manufacturer	Status	MIC_{90} μg/mL	Mechanism
Ramoplanin	Lipoglycodepsispeptide	Nanotherapeutics Inc.	Phase 3	0.5	Bacterial cell wall biosynthesis inhibitor
Surotomycin (CB-183,315)	Lipopeptide	Cubist Pharmaceuticals	Phase 3	0.5	Disruption of membrane potential
LFF571	Thiopeptide	Novartis	Phase 2	≤0.5	Protein synthesis inhibitor
Oritavancin	Lipoglycopeptide	The Medicines Co.	Phase 3	1	Disruption of membrane potential; peptidoglycan biosynthesis inhibitor
Cadazolid	Quinoonyl – oxazolidinone	Actelion Pharmaceuticals Ltd.	Phase 2 completed	0.064-0.5	Protein synthesis inhibitor (primary); DNA synthesis inhibitor
CRS3123 (REP3123)	Thienopyrimidone-tetrahydrochroman	Crestone, Inc.	Phase 1	1	Protein synthesis inhibitor
SMT19969	bis (4-pyridyl) bibenzimidazole	Summit PLC	Phase 2	0.125	DNA synthesis inhibitor by binding to DNA
NVB302	Type B lanthionine-containing lantibiotic	Novacta Biosystems Ltd.	Phase 1 completed	1	Bacterial cell wall (CW) biosynthesis inhibitor by binding lipid II

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

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

52F

- IV vancomycin periop
- Admitted with fever. IV cefazolin.
- Afebrile, planned d/c home

  ¼ BC + CoN Staph
- No bowel movements
- 48hrs later, hypotension → ICU

80M, Clindamycin for dental abscess

- Diarrhea x 2 weeks
- Hypotension, multiorgan failure.

  WBC: 68,000

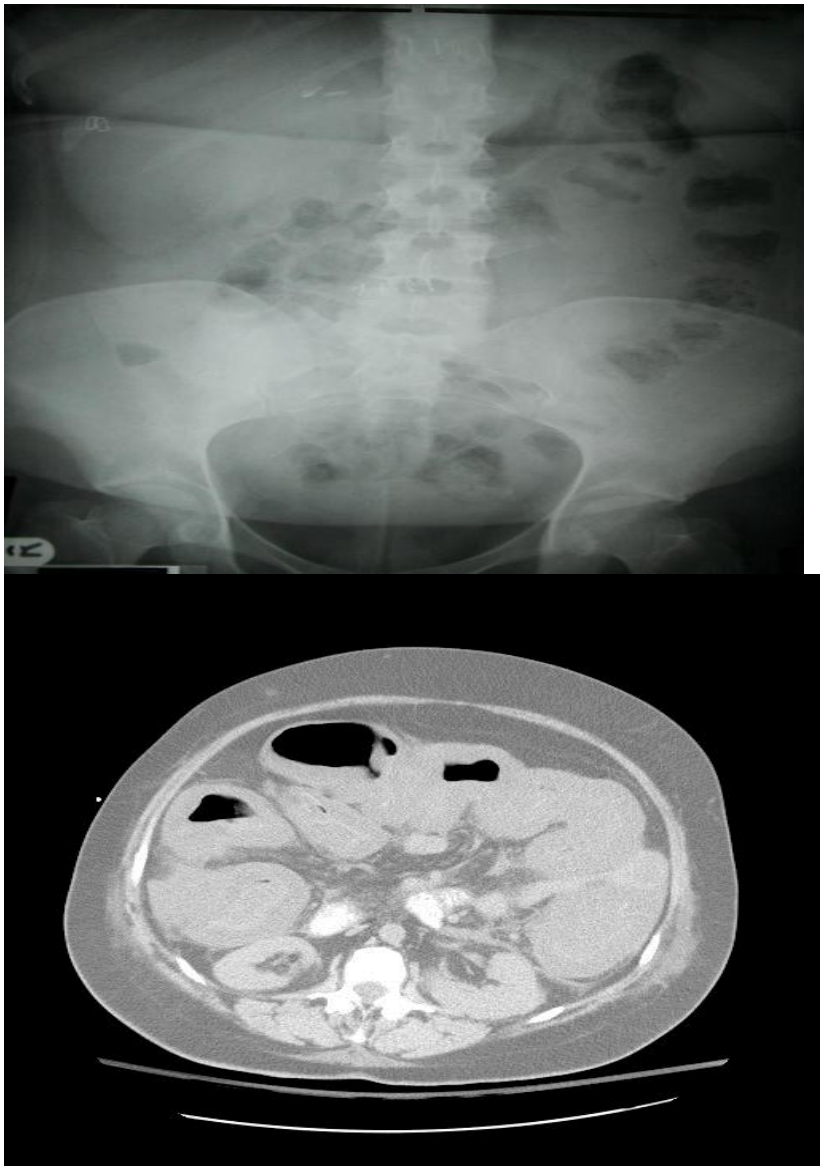
  Lactic acid: 6

Severe *C. difficile*-related colitis

- Definitions:
  - Leading to ICU admission, surgery, death
- 3 – 20% of CDI cases
- Features
  - Pseudomembraneous colitis
  - Marked leukocytosis
  - Megacolon with ↓ colonic motility
  - Hypoalbuminemia
  - Ascites
  - Septic shock

Establishing diagnosis of fulminant colitis

- Abdominal x-ray:
  - Not reliable
- CT
  - Accordion sign
  - Diagnostic
- Sigmoid-proctoscopy
  - Useful to differentiate from ischemic colitis



Dallal Ann Surg 2002;235

Management of fulminant *C. difficile* colitis

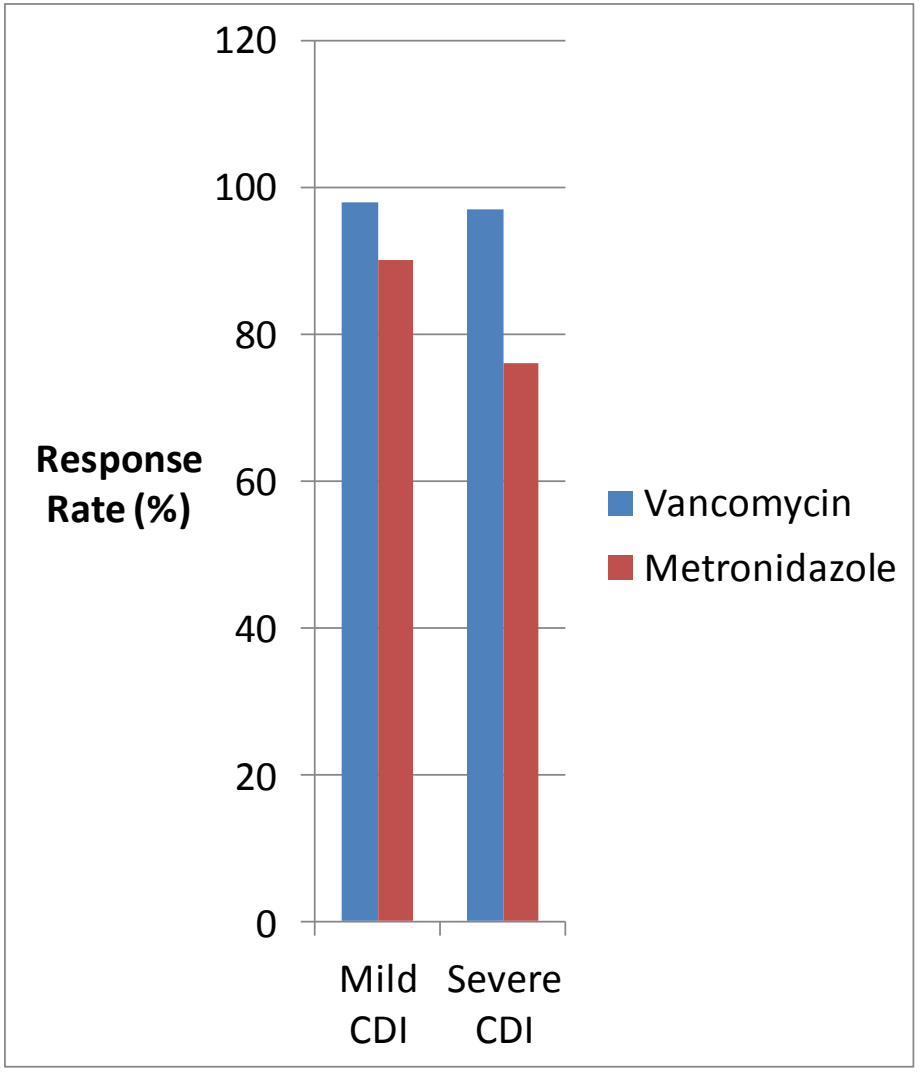
- Oral therapy
  - Vancomycin 250 – 500 mg qid
- Unable to tolerate oral therapy
  - Metronidazole 500mg iv qid plus
  - Vancomycin n/g 500mg q6h; clamp for 1hr or enema 500 mg in 100ml NS q6h via foley
- Surgery (sub-total colectomy & **diverting loop ileostomy**) Annals Surg 2011
  - Progressive colitis despite medical therapy
  - Difficult clinical decision

Response Rates to Vancomycin and Metronidazole Therapy According to Severity of CDI

- Prospective, randomized controlled trial
- Vancomycin 125mg QID vs. metronidazole 250mg QID in 172 patients, stratified by CDI severity
- Similar efficacy in mild CDI

- Vancomycin more effective than metronidazole in severe CDI (97% vs 76%)

Zar et al. Clin Infect Dis 2007;45:302-7.



52F

- Septic shock → ICU
- Multiple antibiotics
- Post-mortem: *C. difficile* colitis

80M, Dental abscess

- Multiorgan failure. WBC: 68,000; Lactic acid: 6
- Colectomy: IV metronidazole; oral vancomycin
- Post-op: vancomycin enema; residual rectal stump

- 60 F, IBS. CDI x 10months
- Recurrent *C. difficile*-related diarrhea despite 2 courses of metronidazole, vancomycin x 3 + *S. boulardii*

Recurrent CDI

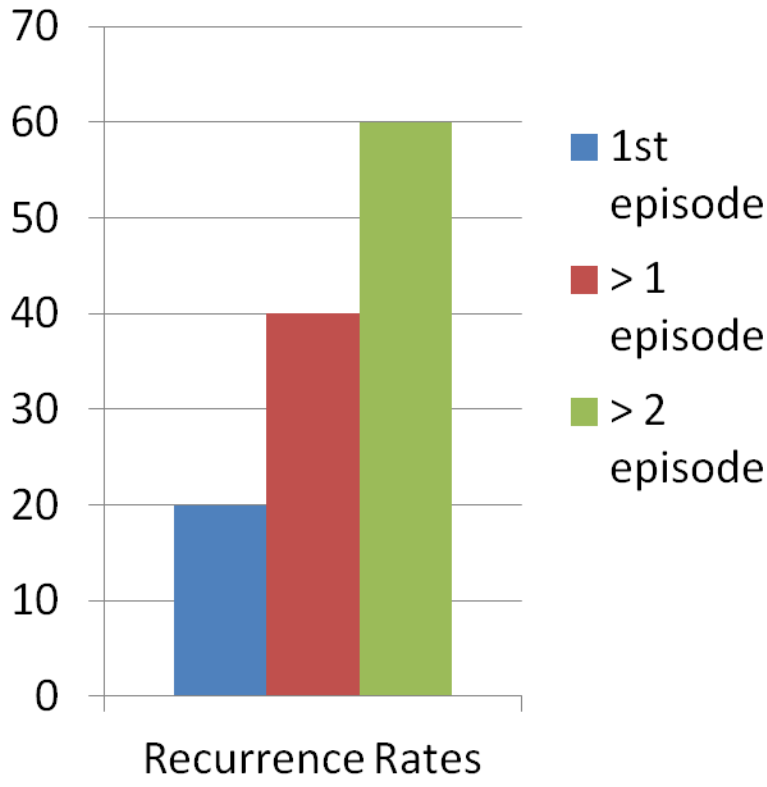
Mechanism

- Resistance to metronidazole/vancomycin: rare
- Presence of persistent *C. difficile* spores
- Persistent disturbance of intestinal flora diversity
- Hypervirulent/pathogenic strains: NAP1/B1/027
- Reinfection (environment)

Risk Factors

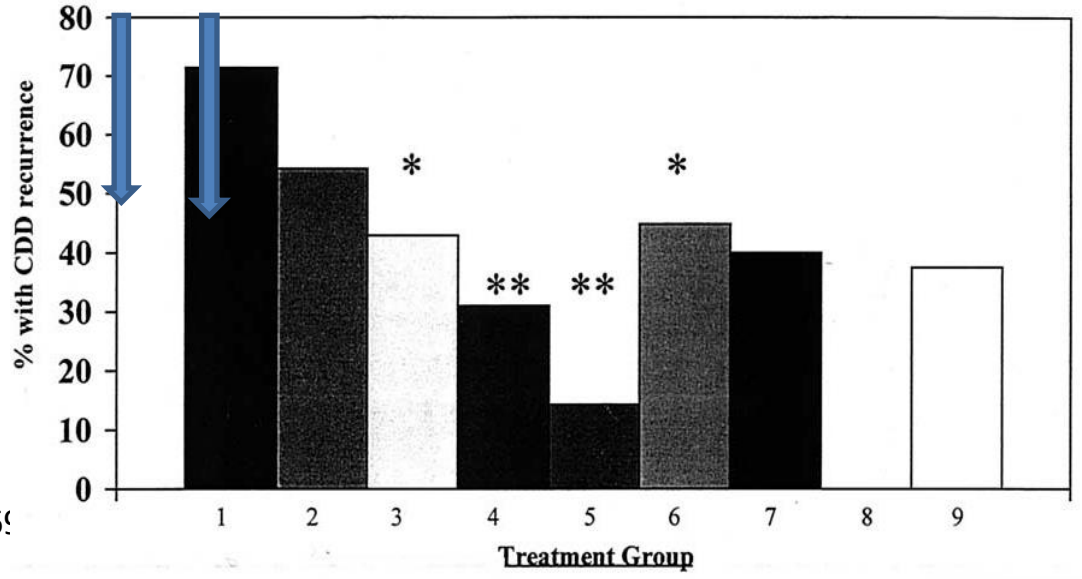
- Additional antibiotic therapy
- Age > 65 years
  - 60% risk of recurrence
- Severe underlying illness
  - ICU stay
  - Prolonged hospital stay
- Immunodeficiency: proper IgG response

Rates of recurrence



Treatment of Recurrent CDI

- Observational study of 163 patients treated for recurrent CDI
- Tapering vancomycin regimen (#4) and pulse vancomycin dosing (#5) resulted in significantly fewer recurrences at 2 months after their treatment completion



McFarland et al. Am J Gastroenterol 2002;97:176

Treatment of Recurrent CDI

60 F, IBS. CDI x 10months

- Disinfection of household bathrooms with hypochlorite
- Treated with po vancomycin x 4 weeks + rifampin x 14d
- F/up at 2 yrs : no recurrence

1st Recurrence:

- Treat as 1st episode, based on disease severity

2nd and subsequent recurrence

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

Treatment of recurrent CDI

- Unacceptable failure rates using conventional antibiotic regimen
- Need alternate approach

http://www.cbc.ca/player/22+Minutes+Clips+and+Shorts+-+Site+only/ID/2288940951/

75 M recurrent CDI x 1year, admitted with refractory CDI, 40lb weight loss, albumin 18

- FMT x 1: resolution of diarrhea within 24 hrs. albumin 35 in 2 weeks.

•At 2-year follow up - remained cured; 40lb +

85F gastric cancer

Annual follow-up: chemotherapy? Stomatitis. Oral abx

Multiple rCDI > 5 courses of vancomycin + taper

FMT x 2 (home)

Vancomycin

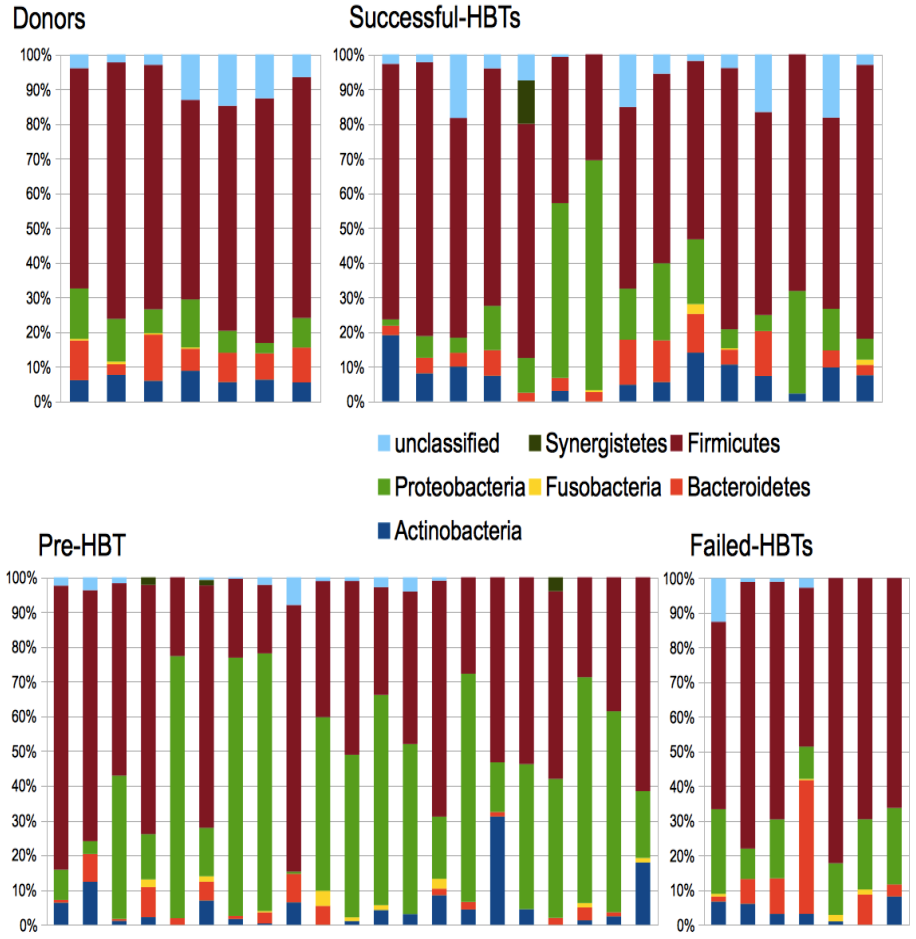
FMT x 1 (SJHH)

Remains cured 6-month f/up

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 Selection:

- Prior to 2011 a family member was the most frequent donor
- Recently, a pool of screened donors has been built
- No standardized exclusion criteria identified but most commonly cited criteria in literature include:
- ***Exclusion criteria:***
  - Known HIV, HCV or HBV or exposure within past 12 m
  - High-risk sexual behaviours
  - Illicit drugs
  - Tattoo or body piercing within 6 months
  - Incarceration or history of incarceration
  - Known current communicable disease
  - RF for Creutzfeldt-Jacob disease
  - Travel within the last 6 months to areas where enteric pathogens are endemic or risk of travel diarrhea is high

FMT

Donor Selection:

- ***Exclusion criteria Cont'd:***
  - IBD
  - IBS
  - Chronic constipation
  - History of GI malignancy or known polyposis
  - Antibiotic use in the past 3 months
  - Major immunosuppressive medications
  - Antineoplastic agents
  - Recent ingestion of a potential allergen

- ***Relative Contraindications:***
  - Major GI surgery
  - Metabolic syndrome
  - Autoimmune conditions
  - Allergic diseases
  - Eosinophilic disorders of the GI tract
  - Chronic pain syndromes

FMT

Donor Screening:

- No standardized donor screening

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

Efficacy and safety of FMT
3 systematic reviews

- Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-analysis. Kassam, et. al *Am J Gastroenterol* 2013
    - 11 studies [245/273 (89.1%)] patients – resolution
    - NG/NJ – peritonitis, UGI bleed, enteritis
    - Additional 5 case series identified by Canadian Association of Gasteroenterology (CAG) after initial review
- Systematic Review of Intestinal Microbiota Transplantation for Recurrent CDI. Gough et. al. Clin Inf Ds. 2011
    - 27 studies 92% resolution.
- Systematic Review: Faecal Transplant for Treatment of CDAD Guo et. al. 2012 Aliment Pharmacol Ther 2012. 124 patients with recurrent/refractory CDI.
    - 83% resolution

Efficacy and safety of FMT

1 Randomized Controlled Trial.

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

DISRUPTION OF GUT MICROBIOTA

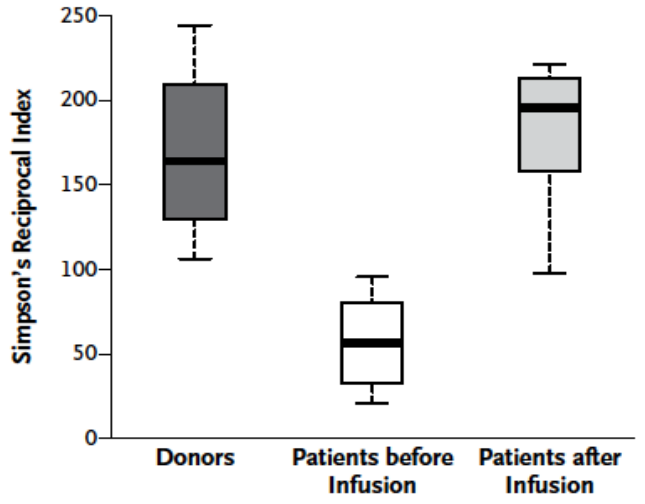


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Microbiota diversity is expressed as Simpson's Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes).

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*
van Nood, et al. (2013)

Decreased diversity of gut microbiota in patients with CDI prior to FMT

Diversity improved significantly post FMT

Study also noted quantitative changes in relevant groups of intestinal bacteria:

↑ Numbers of Bacteroidetes by 2-4 times

↓Proteobacteria by factor of up to 100

Oral, Capsulized, Frozen FMT for Relapsing CDI

- Open-label, single-group, feasibility study. MGH 2013-14. Youngster. JAMA. Oct 2014
- 20 patients with ≥3 mild to moderate CDI; failed tapering vancomycin
- 15 frozen capsules on 2 consecutive days, followed for symptom resolution and AE for 6 months
- 14/20 resolved; 4/6 resolved following retreatment. 90% clinical resolution

A Multi-Centre, Randomized, Double-Blind Trial of Fresh *versus* Frozen-and-Thawed Human Biotherapy for Recurrent *Clostridium difficile* Infection

Number of participants: 232 Timeline: 24 months

Participating sites: Hamilton, Kingston, Vancouver

- 6 academic and 17 community hospitals

FMT Enema: 50% Fresh; 50% Frozen-and Thawed

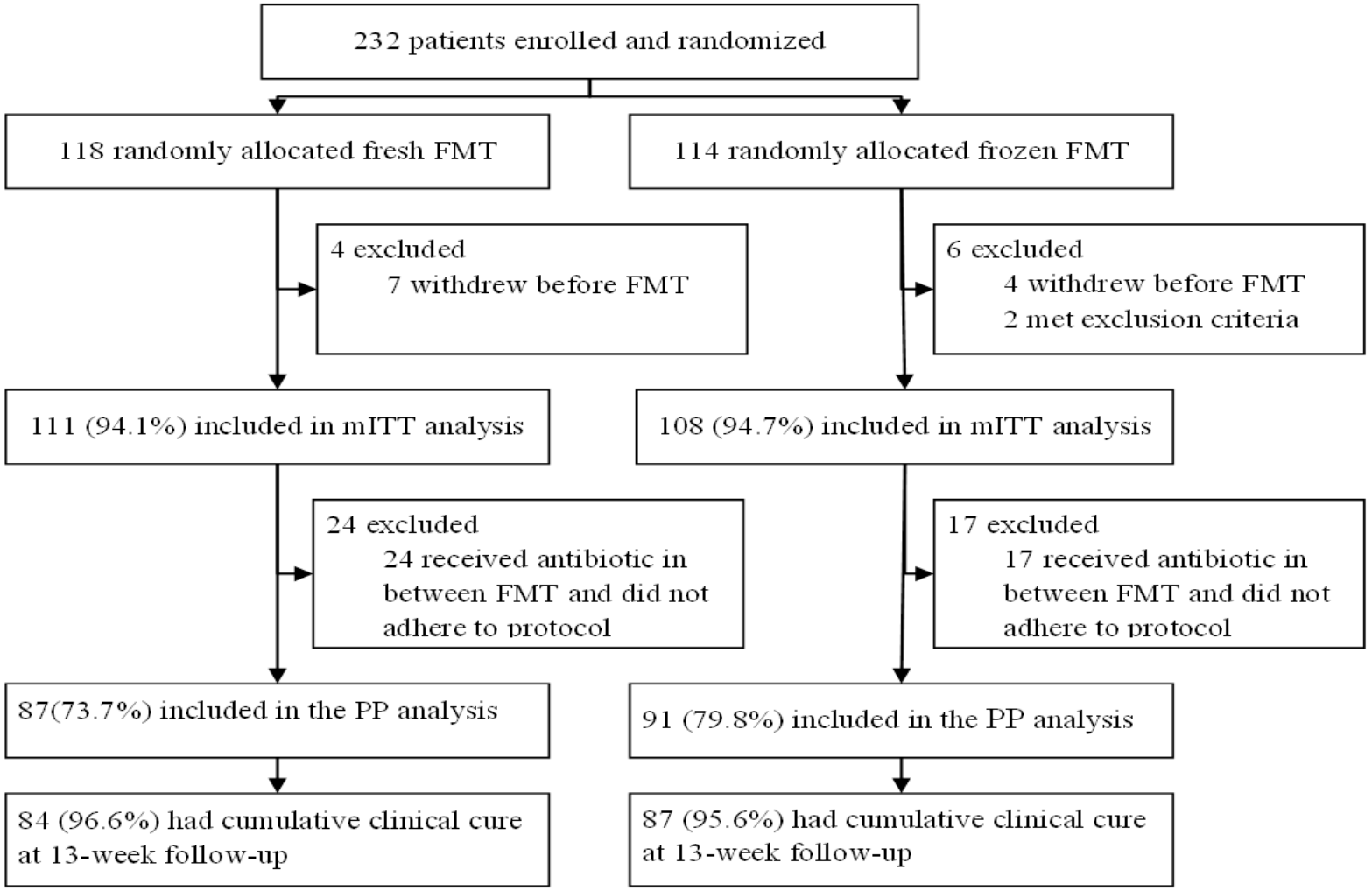
Block Randomization: Age, number of recurrences, hospital vs. community associated CDI

Outcome Measures:

- To evaluate the safety of fresh and frozen-and-thawed FMT
- To compare the clinical response, treatment failure and relapse rate in patients treated with fresh FMT compared to those treated with frozen-and-thawed FMT for recurrent CDI

ClinicalTrials NCT01398969

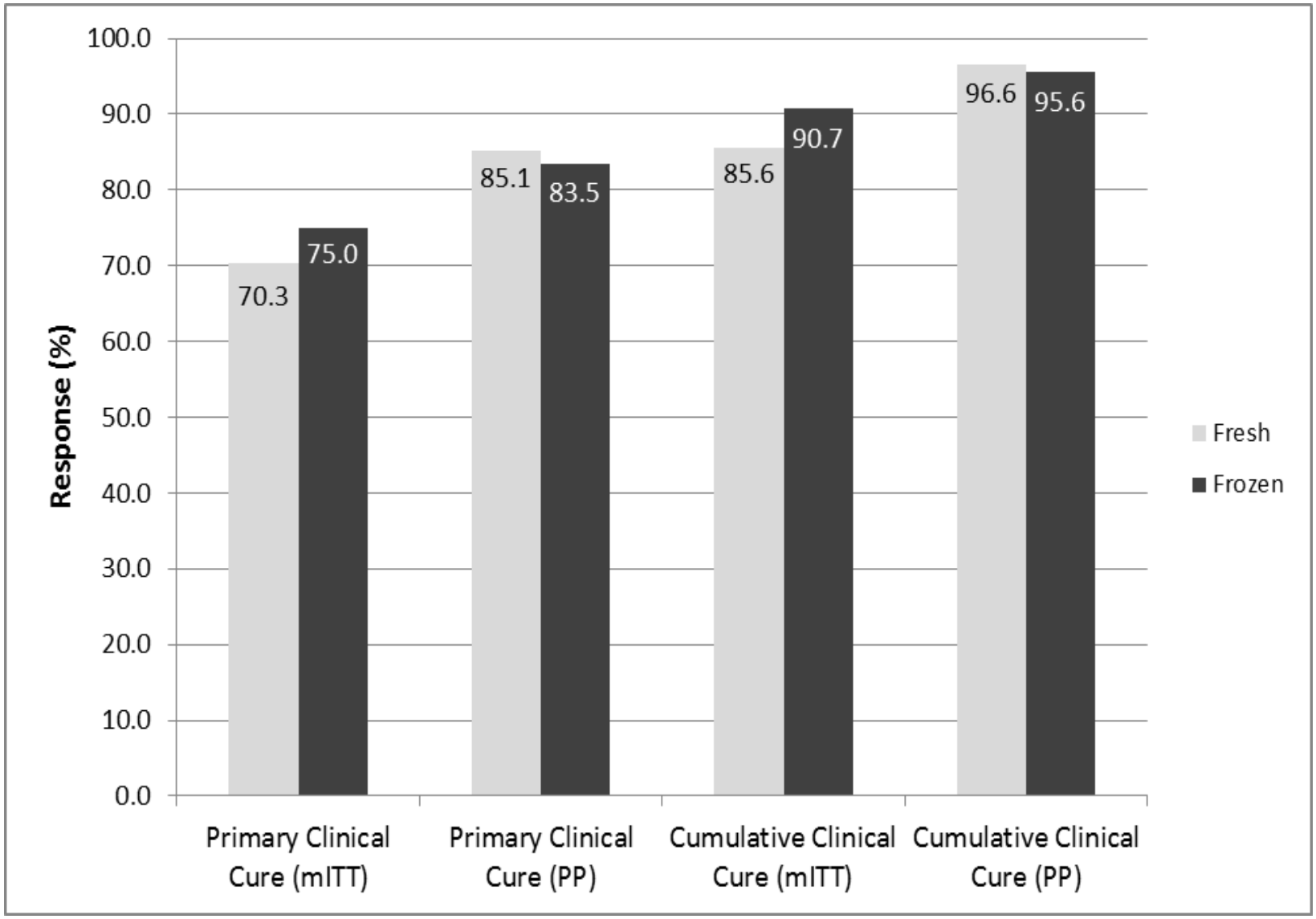
Patient Distribution and Outcome



Primary Efficacy Outcome in mITT and PP According to Subgroup

Subgroup	mITT			PP		
	Fresh	Frozen	P value	Fresh	Frozen	P value
	Cure rate, n/N (%)			Cure rate, n/N (%)		
Age						
< 65 years	17/27 (63.0)	22/27 (81.5)	0.129	17/21 (81.0)	21/24 (87.5)	0.545
≥ 65 years	61/84 (72.6)	59/81 (72.8)	0.975	57/66 (86.4)	55/67 (82.1)	0.499
Admission status at time of FMT						
Inpatient	45/60 (75.0)	35/51 (68.6)	0.456	41/46 (89.1)	32/41 (78.1)	0.160
Outpatient	33/51 (64.7)	46/56 (82.1)	0.040	33/41 (80.5)	44/49 (89.8)	0.211
Severity of CDI at baseline						
Mild	28/33 (84.9)	33/41 (80.5)	0.624	28/31 (90.3)	31/37 (83.8)	0.494*
Moderate	29/51 (56.9)	34/49 (69.4)	0.195	26/35 (74.3)	32/41 (78.1)	0.070
Severe	21/27 (77.8)	14/18 (77.8)	1.000*	20/21 (95.2)	13/13 (100.0)	1.000*
Strain type						
Non-027 ribotype	18/20 (90.0)	15/20 (75.0)	0.408*	16/17 (94.1)	15/17 (88.2)	1.000*
Ribotype 027	10/14 (71.4)	10/15 (66.7)	0.408*	9/11 (81.1)	10/12 (83.3)	1.000*
Not tested	50/77 (64.9)	56/73 (76.7)	0.113	49/59 (83.1)	51/62 (82.3)	0.908
Immunocompromised†	14/17 (82.3)	14/18 (77.8)	1.000*	13/14 (92.9)	14/15 (93.3)	1.000*
IBD	5/7 (71.4)	5/10 (50.0)	0.6221*	5/6 (83.3)	5/6 (83.3)	1.000*

Primary Cure Rate and Cumulative Clinical Cure Rates



Outcome of Patients Unresponsive to FMT

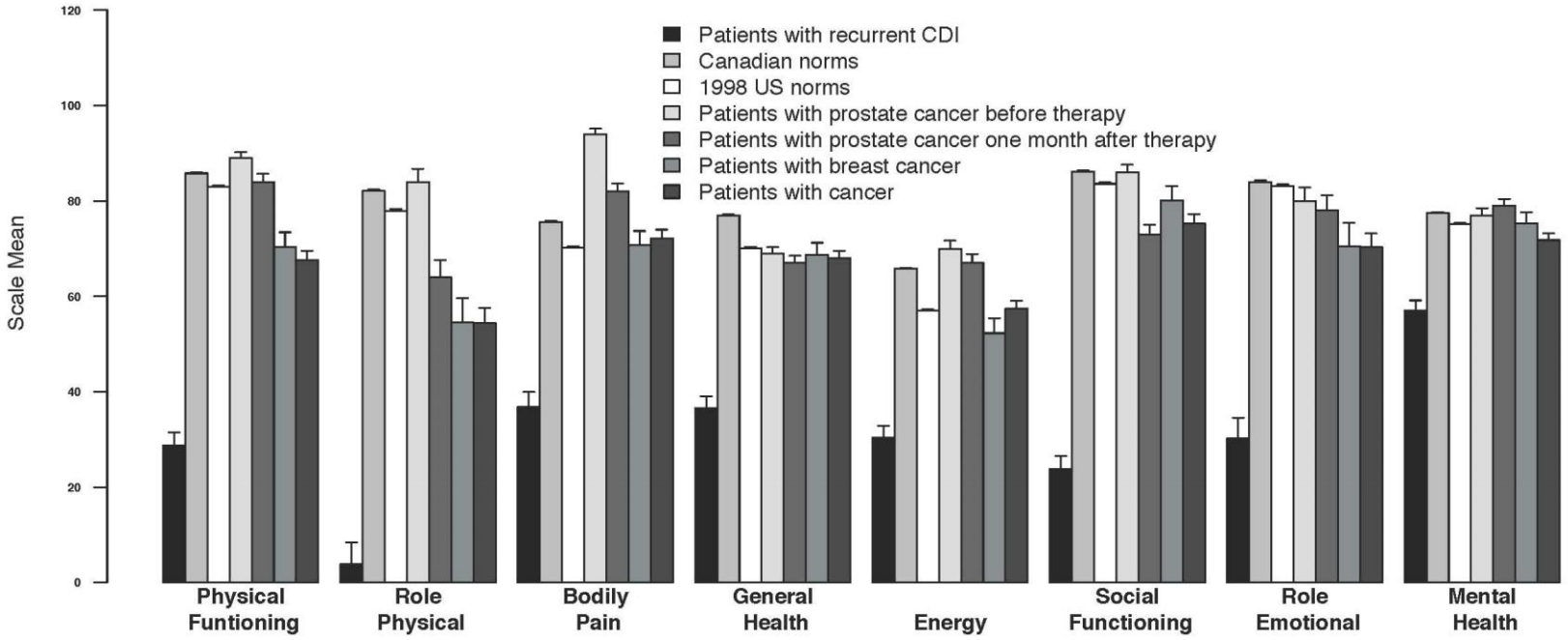
- Pts refractory to CDI
- Multiple FMTs – no response
- Response to oral vancomycin post FMT relapse
  - 4/94 in SJHH observational study
  - 6/232 in RCT
    - 4/6 unresponsive to oral vancomycin pre-FMT
    - 6/6 post FMT, symptom-free on vancomycin 125mg od at 12to 24-month follow-up

Brandt. Am J Gastroenterol 2012

Ruben, Bakken. *Anaerobe* 2013

Lee, et. Al. Eur J Clin Microbiol Infect Dis 2014

Quality of Life for Patients with Recurrent CDI



Safety of FMT

Immune Thrombocytopenia

- 84 yF: rCDI (CA), CRF and type 2 DM
- Severe CDI: WBC 34K/µL; Creatinine: 360 → 663µmol/L
- Oral vancomycin 250mg qid
- FMT: platelet (pre-FMT: 103K; post FMT 20K)
  - Possibilities
    - Inflammatory process
    - Oral vancomycin
    - Donor feces

Malnick, J Clin Gastroenterol 2015

Safety of FMT

Weight gain post-FMT

- 32F rCDI, weight: 136 lbs, BMI: 26 (18.5 -25)
- Donor (daughter): 16F, weight 140 lbs, BMI 26.4
- 16 months post-FMT, pt and donor weight gain
  - Patient: 170 lbs
  - Donor: 170 lbs
- Microbiome sequencing of donor and patient, not done

Alang. OF Inf Dis. 2014

Deaths attributable to FMT

- Aspiration pneumonia post enteroscope-assisted FMT. GA. Rx: IV metronidazole, meropenem. CID. Mar 2015
- Toxic megacolon, septic shock. CID. 2014

rCDI Prevention

A Study of MK-3415, MK-6072, and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-001) (MODIFY I)

- mAb vs. toxins A, B or A & B
- Completion of 2 large (> 1000 pts) phase 3 trials. NCT01513239 NCT01241552
  - 4 arms: mAb toxin A; toxin B; toxins A & B or placebo
  - 3 arms: m Ab toxin B; toxins A & B or placebo
- Overall efficacy: toxin B and toxins A & B ~ 70%
- No major adverse events, increase risk of thrombotic events (rare)

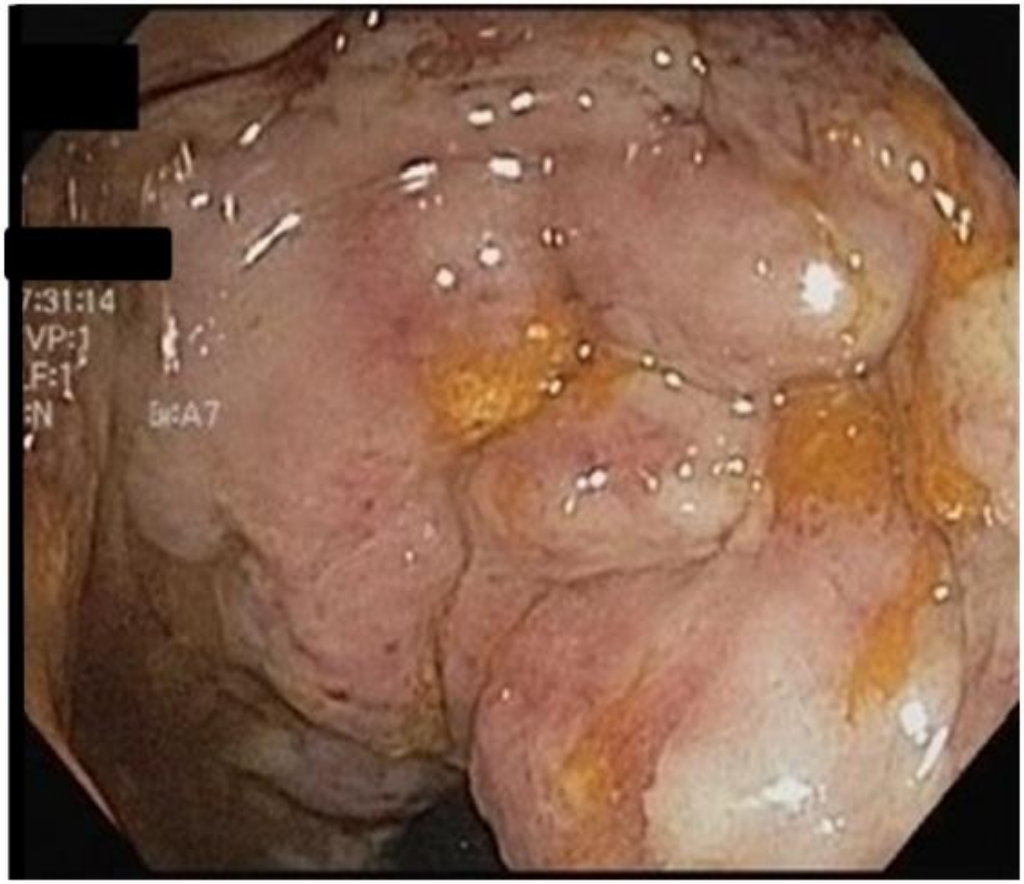
45 F admitted with profound diarrhea, fever.

WBC >20,000 Neutrophilia

Stool C. difficile toxin: positive by EIA

Negative PCR

Oral vancomycin: no improvement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VP:1
F:1
N
BrA7

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

Prevention, prevention, prevention

- Judicious use of antibiotics
- Adherence and Promote IPAC Team
- Does doxycycline protect against CDI? Doernberg, CID 2012
  - CDI risk: 1.61/10,000 pt days.
  - Rate of CDI 27% lower (95% confidence interval, .56–.96)

Probiotics – current status

Cochrane Review (2013 May 31): Probiotics for prevention of CDAD in adults and children. Goldenberg JZ, et.al

- Systematic review and meta-analysis of 23 RCT (4213 patients)
- Moderate quality of evidence for efficacy and safety
- Limitations:
  - Significant missing CDAD data (5 – 45%)
  - Exclusion of immunocompromised patients

Conclusion

- CDI associated with significant M &M
- FMT effective for rCDI;
  - Need results from RCTs
- Implement registry for long-term follow-up
- Prevention is the key