Current Challenges and Future Options 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: 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

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

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 oC; WBC 6.0
- Does this patient have CDI?

Diagnosis of CDI: Clinical + Lab

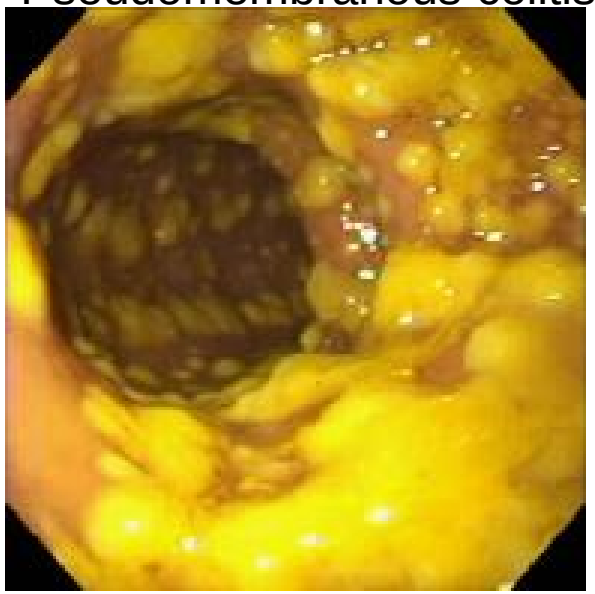
Clinical signs/symptoms

- 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% ($P = 0.035$)

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

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

Recurrent CDI

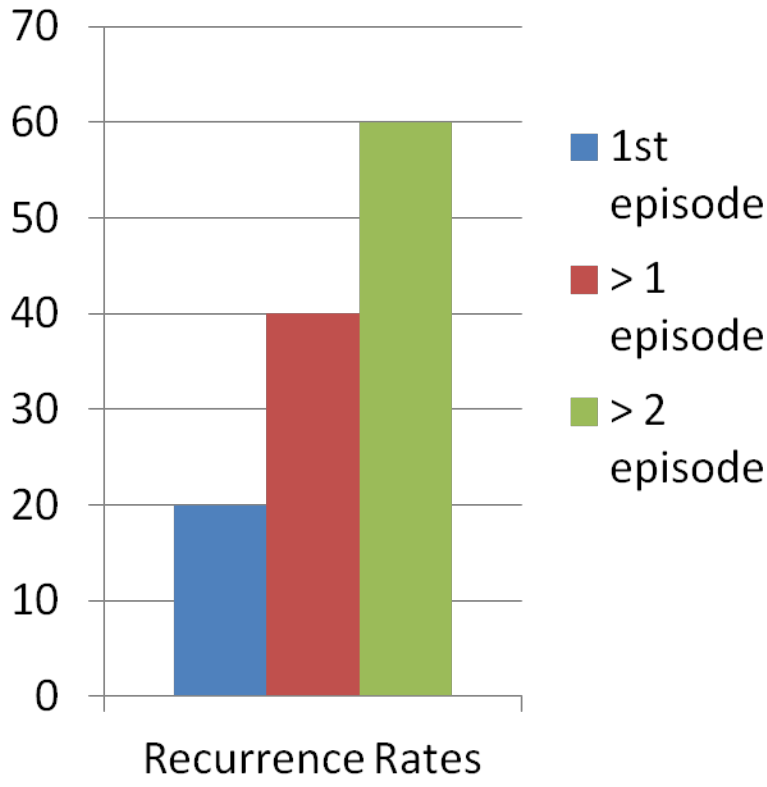
Mechanism

- 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

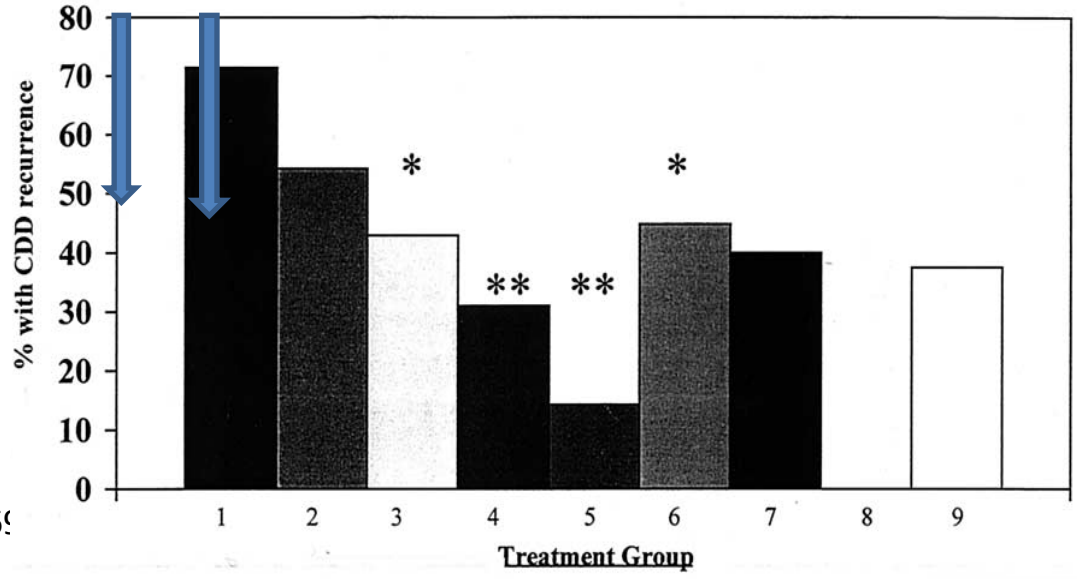
- Additional antibiotic therapy
- Age > 65 years
  - 60% risk of recurrence
- Severe underlying illness
  - ICU stay
  - Prolonged hospital stay
- Immunodeficiency: proper IgG response

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

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

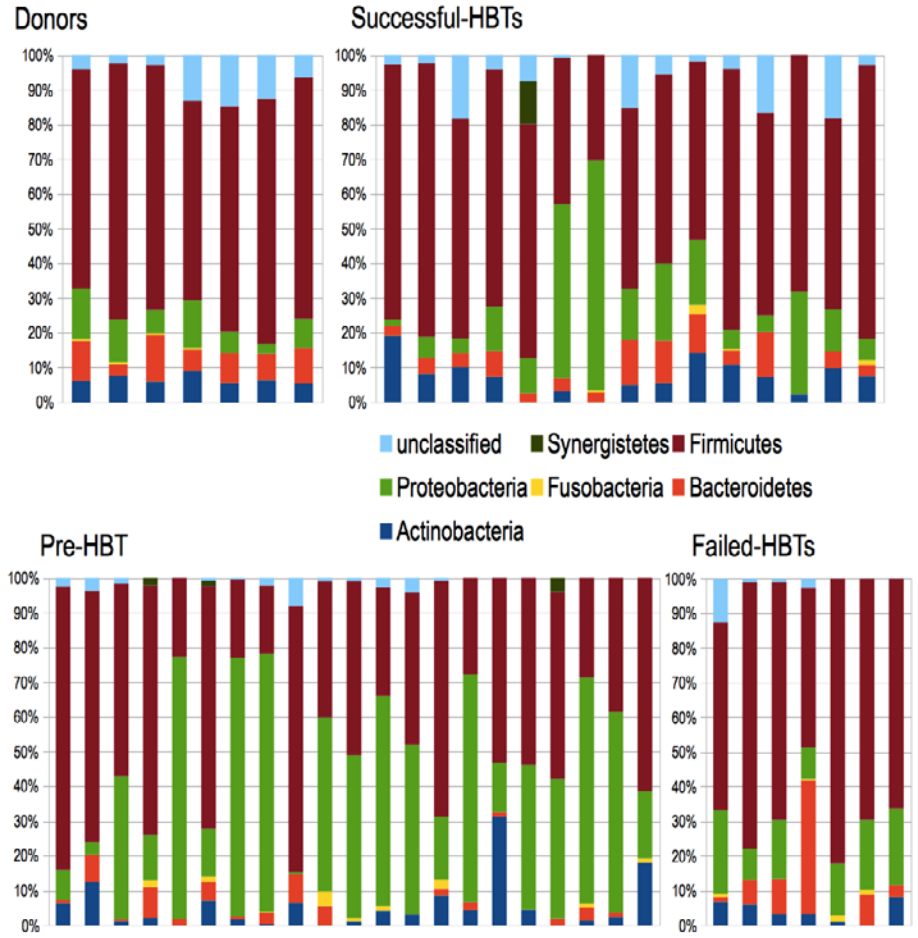
FMT x 1 (SJHH)

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

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

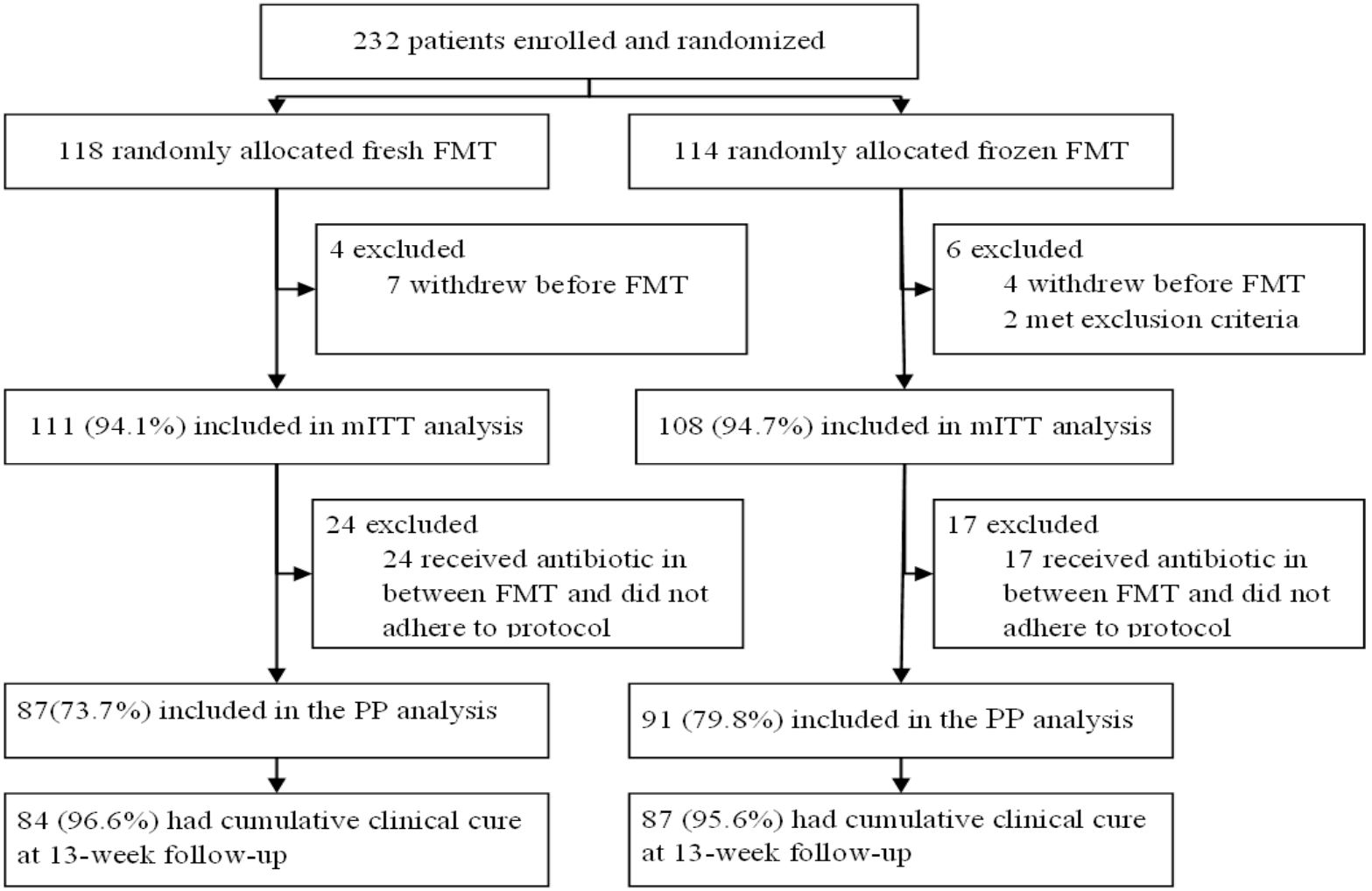
Block Randomization: Age, number of recurrences, hospital vs. community associated CDI

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



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

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

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