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

Objectives

• Efficacy of current treatments for CDI
  – Primary and 1\textsuperscript{st} 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 °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:

<table>
<thead>
<tr>
<th>Test</th>
<th>Target</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV</th>
<th>NPV</th>
<th>TAT (min)</th>
<th>Cost ($)</th>
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</thead>
<tbody>
<tr>
<td>EIA</td>
<td>Toxins A + B</td>
<td>60</td>
<td>98</td>
<td>&lt; 60</td>
<td>95</td>
<td>20 – 90</td>
<td>&lt; 20</td>
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<tr>
<td>GDH</td>
<td>Common Ag</td>
<td>90</td>
<td>50</td>
<td>High</td>
<td>Low</td>
<td>20- 90</td>
<td>&lt;20</td>
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<tr>
<td>NA (PCR, LAMP)</td>
<td>Toxin B gene</td>
<td>90</td>
<td>65</td>
<td>High</td>
<td>Low</td>
<td>90 - 200</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

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
5927 patients 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. difficile* 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
- Clinical cure rates MITT:
  - fidaxomicin and vancomycin 88.2% vs. 85.8%
- Recurrence MITT, PPA:
  - fidaxomicin and vancomycin 13.3 vs. 24% ($P=0.004$)

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

<table>
<thead>
<tr>
<th></th>
<th>MTZ</th>
<th>Vancomycin</th>
<th>FDX</th>
<th>Surotomycin</th>
<th>SMT19969</th>
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</thead>
<tbody>
<tr>
<td>Clostridial spp.</td>
<td>2</td>
<td>16</td>
<td>256</td>
<td>&gt; 512</td>
<td>&gt; 512</td>
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<tr>
<td>Bacteroides</td>
<td>2</td>
<td>64</td>
<td>512</td>
<td>&gt; 512</td>
<td>&gt; 512</td>
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<tr>
<td>Drug</td>
<td>Chemical Class</td>
<td>Manufacturer</td>
<td>Status</td>
<td>MIC$_{90}$ $\mu$g/mL</td>
<td>Mechanism</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>Lipoglycodepsispeptide</td>
<td>Nanotherapeutics Inc.</td>
<td>Phase 3</td>
<td>0.5</td>
<td>Bacterial cell wall biosynthesis inhibitor</td>
</tr>
<tr>
<td>Surotomycin (CB-183,315)</td>
<td>Lipopeptide</td>
<td>Cubist Pharmaceuticals</td>
<td>Phase 3</td>
<td>0.5</td>
<td>Disruption of membrane potential</td>
</tr>
<tr>
<td>LFF571</td>
<td>Thiopeptide</td>
<td>Novartis</td>
<td>Phase 2</td>
<td>$\leq$0.5</td>
<td>Protein synthesis inhibitor</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Lipoglycopeptide</td>
<td>The Medicines Co.</td>
<td>Phase 3</td>
<td>1</td>
<td>Disruption of membrane potential; peptidoglycan biosynthesis inhibitor</td>
</tr>
<tr>
<td>Cadazolid</td>
<td>Quinoonyl – oxazolidinone</td>
<td>Actelion Pharmaceuticals Ltd.</td>
<td>Phase 2 completed</td>
<td>0.064-0.5</td>
<td>Protein synthesis inhibitor (primary); DNA synthesis inhibitor</td>
</tr>
<tr>
<td>CRS3123 (REP3123)</td>
<td>Thienopyrimidone-tetrahydrochroman</td>
<td>Crestone, Inc.</td>
<td>Phase 1</td>
<td>1</td>
<td>Protein synthesis inhibitor</td>
</tr>
<tr>
<td>SMT19969</td>
<td>bis (4-pyridyl) bibenzimidazole</td>
<td>Summit PLC</td>
<td>Phase 2</td>
<td>0.125</td>
<td>DNA synthesis inhibitor by binding to DNA</td>
</tr>
<tr>
<td>NVB302</td>
<td>Type B lanthionine-containing lantibiotic</td>
<td>Novacta Biosystems Ltd.</td>
<td>Phase 1 completed</td>
<td>1</td>
<td>Bacterial cell wall (CW) biosynthesis inhibitor by binding lipid II</td>
</tr>
</tbody>
</table>
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

- 1st episode
- > 1 episode
- > 2 episodes
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

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 1 year, 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)
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

<table>
<thead>
<tr>
<th>Blood</th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Parasites</td>
</tr>
<tr>
<td>HTLV 1-2</td>
<td><em>C. difficile</em> toxin/gene</td>
</tr>
<tr>
<td>HAV, HBV, HCV</td>
<td>Enteropathogenic bacteria</td>
</tr>
<tr>
<td><em>Treponema pallidum</em></td>
<td>Adeno/rota/norovirus</td>
</tr>
</tbody>
</table>
Efficacy and safety of FMT
3 systematic reviews

  • 11 studies [245/273 (89.1%)] patients – resolution
  • NG/NJ – peritonitis, UGI bleed, enteritis
  • Additional 5 case series identified by Canadian Association of Gastroenterology (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*

- 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

• 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

232 patients enrolled and randomized

118 randomly allocated fresh FMT
- 4 excluded
  - 7 withdrew before FMT

111 (94.1%) included in mITT analysis
- 24 excluded
  - 24 received antibiotic in between FMT and did not adhere to protocol

87 (73.7%) included in the PP analysis
- 84 (96.6%) had cumulative clinical cure at 13-week follow-up

114 randomly allocated frozen FMT
- 6 excluded
  - 4 withdrew before FMT
  - 2 met exclusion criteria

108 (94.7%) included in mITT analysis
- 17 excluded
  - 17 received antibiotic in between FMT and did not adhere to protocol

91 (79.8%) included in the PP analysis
- 87 (95.6%) had cumulative clinical cure at 13-week follow-up
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 12 to 24-month follow-up

Brandt. Am J Gastroenterol 2012
Ruben, Bakken. Anaerobe 2013
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: mAb 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
Pseudomembranous 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


• 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