C difficile 2021 and Beyond

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IDAC April 15, 2022 Virtual Meeting
Conflicts of Interest 2021

• Advisory Boards:
• Acurx Pharmaceuticals LLC
• Bio K +
• Merck Pharmaceuticals
• Shionogi
• Speakers Bureau: Merck
Outline

• Epidemiology
• Pathogenesis
• Testing
• COVID Effect?
• Therapy  IDSA recommendations & Potential NEW changes
  • FDX vs Vanco
  • Bezoltoxomab
• New Agents
  • Research Drugs  Ridinilazole, Ibezapolstat (ACX-362E), Ribaxamase, DAV 132
  • Vaccines
  • Fecal Transplants
Epidemiology of CDI

Over the past 15 years

• Increased Incidence 147.2/100,000 pop. 7.4/10,000 pt. days
• Increased Severity 027 & 078 strains
• 237% increase in CDI related hospitalizations
• In 2013, 250,000 pts. Hospitalized due to CDI
• Attributable Mortality 2.2% → 4.5%
• Length of Stay Increased of 55.3%
• Cost: $6 billion ($3,427-$9,960/ case)
• CDC classified CDI as URGENT Global Threat
Asymptomatic C. difficile colonization

Acquisition of a toxigenic strain of *C. difficile* and failure to mount anamnestic Toxin A, B IgG antibody response results in CDI.

CID, 51: 1306, 2010
C difficile carriage in healthy infants - France

• 1 year follow-up study of 10 infants
  – ALL 10 infants acquired C. difficile and were carriers for several months

• Additional 1-point study of 85 infants
  – 38/85 (45%) carried C. difficile
  – 11% had toxigenic isolates
  – Abx use (mother or infant) and “food diversification” had a positive association

Rousseau et al CID 2012; 55:1209
Lower Socio-economic Status linked to Community Assoc CDI

- Up to 20% of those diagnosed with CA-CDI have no hx of recent abx therapy or outpt health care exposure
- CDC studies 35 counties in 10 states; 9,682 cases CA-CDI 2014-2015
- Three factors accounted for 95% of variance

**Higher Incidence**
- Poverty  (RR=1.19; 95%; CI 1.15-1.22)
- Foreign born  (RR=1.05; CI 1.02-1.08)
- High Income  (RR=0.95; CI 0.92-0.97-)

**Lower Incidence**

Skrobarcek KA, CID 2021 doi:10.1093/cid/ciab042
<table>
<thead>
<tr>
<th>Meat product</th>
<th>No. tested</th>
<th>Ribotype 078/Tox V (%)</th>
<th>Ribotype 027/Tox III (%)</th>
<th>Total pos. (%)</th>
<th>Total by species of origin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground beef</td>
<td>26</td>
<td>10 (38.5)</td>
<td>3 (11.5)</td>
<td>13 (50.0)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Summer sausage</td>
<td>7</td>
<td>0</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Ground pork</td>
<td>7</td>
<td>2 (28.6)</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Braunschweiger</td>
<td>16</td>
<td>7 (43.8)</td>
<td>3 (18.8)</td>
<td>10 (62.5)</td>
<td>19 (41.3)</td>
</tr>
<tr>
<td>Chorizo</td>
<td>10</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>2 (20)</td>
<td></td>
</tr>
<tr>
<td>Pork sausage</td>
<td>13</td>
<td>2 (15.4)</td>
<td>2 (15.4)</td>
<td>4 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Ground turkey</td>
<td>9</td>
<td>4 (44.4)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>90</strong></td>
<td><strong>26 (28.9)</strong></td>
<td><strong>11 (12.2)</strong></td>
<td><strong>33 (36.7)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*C. difficile* Isolates from Retail Meats, United States

Songer JG et al. Unpublished data
Kaiser Permanente Northern CA
May 2011- July 2014
9,986 cases vs 2,230,354 controls
Cases tended to be older (> 65 yo 59% vs 21%) females, 61 % vs 53%
hospitalized (69% vs 10%), ED visits (51 % vs 14%),
ECF stays (25% vs 0.6%) , PPI use (36% vs 7%)
Charlson score 3 (11% vs 2%), with specific Co-morbidities
- PNA (21% vs 1%), CKD (26% vs 4%), CAHD (22% vs 3%),
- CHF (22% vs 2%) DM (23% vs 6%),
- ABX 81% vs 11%

Using hospital discharge as the IDRSA, our risk score model yielded excellent performance in predicting the likelihood of developing CDI in the subsequent 31–365 days (C-statistic of 0.848)
Cardiac Surgery Risk factors for CDI

- CDI 3\textsuperscript{rd} most common infection post cardiac surgery
- Of 12,235 pts following cardiac surgery, 143 (1.2\%) developed CDI
- Hyperlactatemia and Decreased Lactate Clearance perturbations of the perioperative acid-base balance increase the risk of CDI

Rzucidło-Hymczak A et a (Poland). PLOS One 3-17,2021 Poland
## Risk Stratification of Antibiotics

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td><strong>macrolides</strong></td>
<td><strong>Doxycycline</strong></td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td><strong>Intravenous b-lactam/b-lactamase inhibitors</strong></td>
<td><strong>Tigecycline</strong></td>
</tr>
<tr>
<td><strong>Carbapenems</strong></td>
<td></td>
<td><strong>Azithromycin</strong></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td></td>
<td><strong>Metronidazole</strong></td>
</tr>
</tbody>
</table>

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Elimination of healthcare associated fluoroquinolone-resistant, but not fluoroquinolone-susceptible *Clostridium difficile*

Dingle K et al. Lancet ID 2017;17:411-421
Populations at Risk: Patients Taking Antibacterial Drugs

Antibiotic Exposure and Risk of CDI

**Antibiotic Exposure and Risk of CDI**

- **Hazard ratio compared to <4 antibiotic days**:
  - 4 - 7 days: 1.4
  - 8 - 18 days: 3.0
  - > 18 days: 7.8

- **Hazard ratio compared to only 1 antibiotic received**:
  - 2 antibiotics: 2.5
  - 3 or 4 antibiotics: 3.3
  - 5 or more antibiotics: 9.6

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C difficile associated with poor outcomes in End-Stage Renal Disease

<table>
<thead>
<tr>
<th>National Inpatient sample Database</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% sample of US hospitals in 44 states</td>
<td></td>
</tr>
<tr>
<td>184,139 cases ESRD</td>
<td></td>
</tr>
<tr>
<td>2.8% had CDI</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>+ CDI</th>
<th>w/o CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Hosp. Mortality</td>
<td>13.2%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>17.3 days</td>
</tr>
<tr>
<td>Cost</td>
<td>$124,846</td>
</tr>
</tbody>
</table>

CDI is associated with significantly worse outcomes in patients with ESRD

Laboratory Diagnosis of CDI

Enzyme Immunoassay (EIA)

**Glutamate Dehydrogenase (GDH)**

**Cell Culture Neutralization Assay (CCNA)**

**Toxigenic Culture (Culture and CCNA)**

**Molecular Based (PCR Or LAMP)**

- Test only **unformed** stools
- Do **NOT** test asymptomatic pts.
- Stool culture is the most sensitive
Guidelines recommend only Grades 5 to 7 should be tested for *C. difficile* toxin.
### Types of CDI Test 2021

Summary of available tests for CDI in decreasing order of analytical sensitivity

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Substance detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic culture</td>
<td>High</td>
<td>Low(^a)</td>
<td><em>C. difficile</em> vegetative cells or spores</td>
</tr>
<tr>
<td>NAAT</td>
<td>High</td>
<td>Low/moderate</td>
<td><em>C. difficile</em> nucleic acid (toxin genes)</td>
</tr>
<tr>
<td>GDH</td>
<td>High</td>
<td>Low(^a)</td>
<td><em>C. difficile</em> common antigen</td>
</tr>
<tr>
<td>CCNA</td>
<td>High</td>
<td>High</td>
<td>Free toxins</td>
</tr>
<tr>
<td>Toxin A/B EIA</td>
<td>Low</td>
<td>Moderate</td>
<td>Free toxins</td>
</tr>
</tbody>
</table>

Adapted from McDonald et al.

- Labor Intense

**Multiplex Test for enteric Pathogens** - **Problematic**
Over diagnosis of CDI in the Molecular Test Era

• Prospective observational study ¹
  – 2010-2012   UC Davis
• 293/1416 pts Tested + PCR
• 131/293 (44.7%) + for Toxin
• “Virtually all CDI-related complications and deaths occurred” with + toxin assay
• “Treat the Patient, Not the Test” ²

2. Debberke & Burnham JAMA Intern Med 9-8-15
Impact of Diagnostic Method

Larger difference in patients diagnosed with methods that detect toxin in stool

Difference (95% CI):
-15.4 (-22.0, -8.7)
-9.7 (-16.8, -2.5)

% Participants With rCDI (MODIFY I and II pooled data)

- Toxin EIA + CCA: Bezlo toxumab 17.6% (55/312), Placebo 33.3% (107/324)
- tgPCR + Toxigenic Culture: Bezlo toxumab 23.6% (74/313), Placebo 33.3% (99/297)

Larger difference in patients diagnosed with methods that detect toxin in stool.
Monthly Fecal *C. difficile* Detection from Week 6 to 6 Months

Gerding DN et al JAMA 2015;313:1719, May 5, 2015, Supplementary Material
# CDI Outcomes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>10-38%</td>
</tr>
<tr>
<td>Colectomy</td>
<td>8.7 per 1,000 CDI cases</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>3-9%</td>
</tr>
<tr>
<td></td>
<td>90% of CDI deaths in the elderly</td>
</tr>
<tr>
<td>Costs</td>
<td>Average cost is approximately $25,000 per episode</td>
</tr>
<tr>
<td></td>
<td>$4.8 billion in excess costs to US Acute care facilities</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>55% increase</td>
</tr>
</tbody>
</table>

CDI Problems 2019
Increasing Recurrences; Patient PTSD

Each additional episode of CDI associated with:
- Increased morbidity and mortality
- Increased healthcare cost
- Limited treatment options

Recurrent CDI associated with increased perturbation of the gut microbiota
- Mainstay therapy (metronidazole and vancomycin) associated with increased dysbiosis

Increasing Risk of Recurrence

<table>
<thead>
<tr>
<th>Infection</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>~25%</td>
</tr>
<tr>
<td>2nd</td>
<td>~45%</td>
</tr>
<tr>
<td>3rd</td>
<td>~65%</td>
</tr>
</tbody>
</table>
# 2017 IDSA Update Rx of CDI

<table>
<thead>
<tr>
<th>Initial Episode</th>
<th>Non-severe</th>
<th>Vanco 125 QID or FDX 200 bid</th>
<th>Strong/ High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MTZ if only available</td>
<td>Weak/ High</td>
</tr>
<tr>
<td>Initial Episode</td>
<td>Severe</td>
<td>Same except NOT MTZ</td>
<td>Same</td>
</tr>
<tr>
<td>Fulminant</td>
<td></td>
<td>Vanco 500 QID po/ng Rectal if Ileus MTZ + Vanco</td>
<td>Strong/Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Strong/Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Strong/Moderate</td>
</tr>
<tr>
<td>First Relapse</td>
<td>Taper Vanco 2-8 weeks FDX x 10 days</td>
<td>Weak/Low</td>
<td></td>
</tr>
<tr>
<td>Second or later relapse</td>
<td>Vanco + rifaximin taper FDX Fecal Transplant</td>
<td>Weak/Low</td>
<td></td>
</tr>
</tbody>
</table>

Weak/Low
“Metronidazole is medicine for your mother-in-law
Vancomycin is for your mother”

Prof. Sherwood L Gorbach
Tufts Univ School of medicine
Co-discoverer of C. difficile

Inf Dis Clin Practice
1992
“ Medicines for your mother-in-law ”
Summarizes the current evidence on the efficacy and adverse

No evidence supports the use of high dose oral vancomycin in the
treatment of severe CDI

Weak evidence from observational studies supports the use of
high dose oral vancomycin in addition to intravenous metronidazole

Weak evidence for high dose vancomycin retention enema in
fulminant CDI.

Vancomycin retention enema can be used in severe CDI when oral
administration is not possible, or in conditions when the oral
formulation cannot reach the colon such as Hartman’s pouch,
ileostomies, or colon diversions.
Focused Update on *C. difficile* Infection Treatment Guidelines: Fidaxomicin and Bezlotoxumab

Session 55: IDSA Case-based Clinical Guideline Overview and Update
ID Week 2020 *Virtual Meeting*
October 23, 2020

Stuart Johnson, MD
Hines VA Hospital
Loyola University Medical Center
Chicago, IL
Background

- Since publication of the 2017 Clinical Practice Guidelines for CDI in early 2018, new relevant evidence for fidaxomicin and bezlotoxumab was published

- Literature reviewed (all CDI treatment) through May 2020
  - Fidaxomicin vs vancomycin
    - 3,609 articles screened, 18 full text review, 5 kept for qualitative analysis
  - Bezlotoxumab
    - 239 articles screened, 12 full text review, 7 kept for qualitative analysis

- Focus of review limited to adult patients

- Did not reassess recommendations for FMT but noted the FDA safety alerts documenting transmission of pathogenic *E. coli* from donor to FMT recipients and concern for transmission of SARS-CoV-2
Summary

- Additional RCTs since publication of the 2017 Clinical Practice Guidelines for CDI support the **superiority of fidaxomicin over vancomycin for sustained clinical response after treatment**.
- This effect was evident for patients with primary CDI as well as patients with recurrent CDI, although **the certainty of evidence was low for patients with recurrent CDI**.
- Extended-pulsed dosing of fidaxomicin shows promise for treatment of recurrent CDI although additional studies with more appropriate comparators are needed to clarify the role of this dosing strategy.
- **Bezlotoxumab given as adjunctive therapy can improve outcomes** in patients at high risk for recurrence, including age >65, immunocompromise, severe CDI, and prior CDI episodes.
- **Once approved, these recommendations will be incorporated into the previous over all recommendations (2017) for treatment of CDI.**
### Evidence summary for patient-important outcomes, PICO 1 (patients with an initial CDI episode): Vanco vs Fidaxo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained response of CDI</strong></td>
<td>1,673 (4 RCT)</td>
<td>MODERATE</td>
<td>RR 1.16 (1.09 to 1.24)</td>
<td>Risk with vancomycin: 631 per 1,000</td>
</tr>
<tr>
<td>(follow up: 4 weeks after EOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CDI initial clinical cure</strong> *</td>
<td>1,673 (4 RCT)</td>
<td>MODERATE</td>
<td>RR 1.00 (0.96 to 1.04)</td>
<td>Risk with vancomycin: 856 per 1,000</td>
</tr>
<tr>
<td>(follow up: 2 days after EOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug-related adverse events</strong></td>
<td>1,721 (4 RCT)</td>
<td>LOW</td>
<td>RR 1.02 (0.76 to 1.36)</td>
<td>Risk with vancomycin: 95 per 1,000</td>
</tr>
<tr>
<td>(follow up: 4 to 12 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>1,721 (4 RCT)</td>
<td>MODERATE</td>
<td>RR 0.90 (0.66 to 1.23)</td>
<td>Risk with vancomycin: 87 per 1,000</td>
</tr>
<tr>
<td>(follow up: 4 to 12 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Forest plot, PICO 1: Sustained response 1 month after end of treatment (patients with an initial CDI episode)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louie</td>
<td>214/287</td>
<td>198/309</td>
<td>1.16 [1.05, 1.30]</td>
<td>2011</td>
</tr>
<tr>
<td>Cornely</td>
<td>193/252</td>
<td>163/257</td>
<td>1.21 [1.08, 1.36]</td>
<td>2012</td>
</tr>
<tr>
<td>Guery</td>
<td>124/177</td>
<td>106/179</td>
<td>1.18 [1.01, 1.38]</td>
<td>2018</td>
</tr>
<tr>
<td>Mikamo</td>
<td>70/104</td>
<td>71/103</td>
<td>1.02 [0.85, 1.24]</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>820/1040</strong></td>
<td><strong>853/1013</strong></td>
<td><strong>1.16 [1.09, 1.24]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.51 (P < 0.00001)

PICO 2: In patients with recurrent CDI episode(s), should fidaxomicin be used rather than vancomycin?

- Previous guidelines included 3 options for treatment of a first CDI recurrence (vancomycin, fidaxomicin, tapered-pulsed vancomycin); rationale for choice was based on treatment used for initial episode

- We considered evidence in subgroup analyses from 3 RCTs comparing fidaxomicin with vancomycin; randomization was stratified for the number of previous episodes. 1 study compared an extended-pulsed fidaxomicin regimen with a standard vancomycin regimen

- Patient important outcomes considered:
  - sustained response (1 mo after EOT)
  - sustained response (3 mo after EOT)
  - initial clinical cure (2 d after EOT)
  - Serious AEs
  - all-cause mortality
Extended-pulsed fidaxomicin regimen

  - **Day 1 to 5:** fidaxomicin 200 mg twice daily
  - **Day 6 to 26:** fidaxomicin 200 mg once every other day
- Has only been compared to standard vancomycin dosing
- Some data suggest that the initial treatment phase (twice daily dosing for 5 days) might be suboptimal in duration

- *Poster presentation #797* Xing Tan, et al.: Management of Patients with Multiple *Clostridioides difficile* Infection Recurrences using a Tapered-Pulsed Fidaxomicin Strategy (‘IDWeek Trainee Award’)
Evidence summary for patient-important outcomes, PICO 2 (patients with one or more recurrent CDI episodes):

<table>
<thead>
<tr>
<th>Outcomes (follow-up)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained response of CDI (follow up: 30 days after EOT)</td>
<td>253 (2 RCT)</td>
<td>★★★★ LOW ab</td>
<td>RR 1.40 (1.11 to 1.77)</td>
<td>450 per 1,000</td>
</tr>
<tr>
<td>Sustained response of CDI (follow up: 90 days after EOT)</td>
<td>75 (1 RCT)</td>
<td>★★★★★ VERY LOW abc</td>
<td>RR 1.56 (0.99 to 2.44)</td>
<td>410 per 1,000</td>
</tr>
<tr>
<td>CDI initial clinical cure * (follow up: 2 days after EOT)</td>
<td>253 (2 RCT)</td>
<td>★★★★ LOW ad</td>
<td>RR 1.02 (0.91 to 1.14)</td>
<td>822 per 1,000</td>
</tr>
<tr>
<td>Serious adverse events (follow up: 90 days)</td>
<td>75 (1 RCT)</td>
<td>★★★★★ VERY LOW abde</td>
<td>RR 0.68 (0.35 to 1.29)</td>
<td>410 per 1,000</td>
</tr>
<tr>
<td>All-cause mortality (follow up: 90 days)</td>
<td>75 (1 RCT)</td>
<td>★★★★★ LOW e</td>
<td>RR 0.81 (0.20 to 3.38)</td>
<td>103 per 1,000</td>
</tr>
</tbody>
</table>

Risk with vancomycin

Risk difference with fidaxomicin (95% CI)

PICO 3: In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard of care (SOC) antibiotics rather than SOC alone?

- Bezlotoxumab is a mAb directed against *C. difficile* toxin B and has been studied as an adjunctive therapy in patients receiving SOC antibiotics (metronidazole, vancomycin, or fidaxomicin)

- Evidence was available from 2 large RCTs (>1,000 participants) where bezlotoxumab was administered in conjunction with SOC antibiotics compared with SOC alone; A subgroup analysis was identified for patients at high risk for recurrence defined as age >65, immunocompromise, severe CDI, prior CDI episode (w/in 6 mo)

- Patient important outcomes considered:
  - CDI recurrence after ICC (3 mo f/up)
  - CDI-associated hospital readmission (1 mo f/up)
  - Drug-related AEs (1 mo f/up)
  - all-cause mortality (3 mo f/up)
Forest plot, PICO 3: Post-hoc subgroup analysis of CDI recurrence – Number of prior CDI episodes

PICO 3: In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard of care (SOC) antibiotics rather than SOC alone?

• Recommendation: For patients with a CDI RECURRENT episode and at least one risk factor of recurrence, we suggest using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, high certainty of evidence).

• Comment: Risk factors for CDI recurrence (or poor outcome) include age >65 years, immunocompromised host, severe CDI on presentation, and prior episode of CDI in the last six months. The FDA warns that “in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk”.

Provisional Recommendation
Bezlo for the prevention of rCDI

• Bezlo study MODIFY II
• 19 day ½ Life Detectible in serum 6 months
• 130/293 participants stools 6, 9, & 12 months
• Same as any prior ribotype 44%- 6 m; 64% -9 m. 61%- 12 m.
• rCDI < 2% at 12 months in Bezlo group
• Efficacy due to prevention rather than delayed onset rCDI

Goldstein et al CID 2020;71:1102-5
Preventative Oral Vanco for CDI

• 3 Clinical studies found **Oral Vanco Prophylaxis** reduced the risk of RCDIs and should be considered on a case-by-case basis. Caution is warranted before routine use is implemented because the impact on long-term outcomes has not been assessed and the optimal regimen has not been defined.


• For elderly patients with frequently relapsing C. difficile, prolonged vancomycin once daily at a dose of 125 mg orally was effective in preventing further relapse.

  Zhang K et al. *BMC Infect Dis* 2019;19:51
Oral Vanco Prevention of CDI

SW Johnson et al. CID 2020;71:1133-9

North Carolina, Randomized Prospective, open label study

100- similar patients except for ABX exposure

(Vanco 125 mg po Q day,
Average 12 doses)

Zero HCFO-CDI for VOP group
6 (12%) for Control group

Literature review of 8 studies
Dosage varied Once daily (3)
Twice daily (3) QID (1)

Five studies showed significance
Ridinilazole

• Non absorbable
• Does not act through cell wall inhibition
• Nor via lipid, protein, RNA or DNA synthesis
• Likely impairs cell division- elongates cells and inhibits sporulation
• Narrow spectrum

Less Microbiome change compared to vancomycin
Bactericidal with Inhibition of Toxin Production

Ridinilazole arrests *C. difficile* cell division

Dose dependent inhibition of septum formation

Ridinilazole inhibits toxin production

Ridinilazole is bactericidal

Direct attachment to C diff spores

(1) Basseres *et al*: JAC 2016; Anaerobe 2021
(2) Corbett *et al*: JAC 2015
No Safety Concerns Identified
Comparable rates of adverse events across the two treatment groups

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Ridinilazole n patients (%)</th>
<th>Vancomycin n patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>180</td>
<td>183</td>
</tr>
<tr>
<td>TEAEs</td>
<td>41 (82)</td>
<td>40 (80)</td>
</tr>
<tr>
<td>Severe drug related TEAEs</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>SAEs</td>
<td>8 (16)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>TE SAEs</td>
<td>8 (16)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Drug related TE SAEs</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Withdrawals due to AEs</td>
<td>2(4)</td>
<td>1(2)</td>
</tr>
<tr>
<td><strong>SOC Preferred Term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>20 (40)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>12 (24)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12 (24)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>11 (22)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>10 (20)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>9 (18)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6 (12)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>5 (10)</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>
Rationale for Ibezapolstat (ACX-362E) Development

- **A New Class of antibiotic**

  Targets DNA Pol IIIC
  
  “pol” for DNA polymerase”; “stat” for enzyme inhibitor

  - Guiding principles (Tarantino, AAC 1999)
    - **DNA Pol IIIC** essential for replication of low G+C content Gram-positive bacteria
    - DNA Pol IIIC strongly conserved across broad spectrum of low G+C Gram-positive pathogens
    - DNA Pol IIIC possesses a unique active site which renders it specifically susceptible to inhibition

  - ACX-362E designed as
    - inhibitor based upon competitive inhibition of dGTP

  ![ACX-362E](ACX-362E.png)

  ![dGTP](dGTP.png)
Phase 2 Trial

- Transition to Segment 2B: Double-blind, vancomycin-controlled

- Expectation of ibezapolstat therapeutic success supported by:
  - In vitro potency against *C. difficile*
  - In vivo efficacy in the hamster model
  - Excellent human safety profile to date
  - High human fecal concentrations (3 logs above MIC)
  - Favorable microbiome effects
  - 100% 1° efficacy (clinical cure) in 10 Phase 2A patients
  - 100% 2° efficacy (sustained clinical cure) in 10 Phase 2A patients
Ibezapolstat Mechanism of Action*: Association with DNA Pol IIIC

Template-directed elongation is blocked by the inhibitor through simultaneous binding to the cytosine of the DNA strand and near the active site of DNA Pol IIIC.

Figure A: Ternary complex of inhibitor ACX-362E, DNA, and PolC.

Figure B (2D Interactions): H-bonding between inhibitor molecule dGTP/362E and a cytosine residue of DNA (DNA-C5).

*Van Eijk, ECCMID 2012
Docking of dGTP vs Ibezapolstat (ACX-362E)

- Superimposition of dGTP and ACX-362E docking positions
- dGTP has its guanine positioned similarly to that of ACX-362E, interacting with DNA-C5
- Phosphate tail of dGTP leads to different direction of other parts of ACX-362E, forming different interactions with protein residues
Phase 2A Adverse Event Profile (450 mg BID x 10 days)

Ibezapolstat was very well-tolerated, with 7 AEs in 4 subjects

<table>
<thead>
<tr>
<th>AE DESCRIPTION</th>
<th>INTENSITY</th>
<th>RELATIONSHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADACHE</td>
<td>MILD</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>TEMPORAL HEADACHE</td>
<td>MILD</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>MIGRAINE HEADACHE EXACERBATION*</td>
<td>SEVERE</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>INTERTRIGINOUS CANDIDIASIS*</td>
<td>MODERATE</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>VOMITING*</td>
<td>MODERATE</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>NAUSEA*</td>
<td>MODERATE</td>
<td>UNRELATED</td>
</tr>
<tr>
<td>NAUSEA</td>
<td>MODERATE</td>
<td>PROBABLY RELATED</td>
</tr>
</tbody>
</table>

*4 AEs reported in the same subject
Ribaximase (SYN 004)
A Therapy to protect the Microbiome from antibiotic collateral damage

• Ribaxamase a **Class A β-lactamase** - single amino acid modification

• Formulated for oral pH-dependent delivery at pH > 5.5 (proximal small intestine)

• For use with selected IV beta-lactam antibiotics (Ceftriaxione)

• Intended to degrade excess antibiotics excreted into the intestine via the bile
**Clostridium difficile Infection (CDI)**

- No CDI patients reported previous CDI
- P-values are 1-sided based on the pre-specified Z-test
- The study was powered at 80% with 1-sided alpha=0.05
Analysis of the Change in Relative Abundance of AMR Genes

Collection point T0 to T1, Placebo vs. Ribaxamase-treated patients

**T0**

**Placebo**

**Ribaxamase**

**T1**

Comparison of Patients with Enterococcal Mono-domination

> 30% of taxa present were enterococci at T1 or T2 based on 16S sequencing

![Graph showing comparison of AMR genes at T0 and T1, with Placebo and Ribaxamase treatments, and a bar chart showing number of VRE (Vancomycin-Resistant Enterococci) in Placebo and Ribaxamase groups, with a P-value of 0.004.](image-url)
COVID-19 and CDI- Co-Infection?
With all the Abx used do we expect an Increase?

• Rawson et al\textsuperscript{1}:
  – 72\% of 2,010 COVID-19 patients received antibiotics in the hospital
  – Only 8\% actually had a bacterial and fungal co-infection.

• Italy\textsuperscript{2}:
  – Among 16,654 patients who died of COVID-19, ‘superinfections’ were reported in 11\% of cases.

• Wuhan\textsuperscript{3}:
  – 191 patients
  – 15\% of patients developed secondary bacterial infections, and half of those who did died.
  – Most common antibiotics used were respiratory quinolones

\textsuperscript{1}Rawson TM, et al. Clin Infect Dis. 2020
CDI in COVID-19 patients
Detroit Medical Center Hospitals, Mar-Apr 2020

9 cases of co-infection with SARS-CoV-2 and C. difficile
• 3 had prior CDI
• 2 had diarrhea & positive for C. diff on admission; 7 developed CDI after COVID-19 diagnosis (median lag in diagnosis, 6 days)
• All had received antibiotics (mean duration prior to CDI, 5 days)
• 4 patients died & 1 was discharged to hospice

Underlying characteristics:
• Median age, 75; F, 78%; median ATLAS score, 6
• Required ICU & vasopressors, 4
• Median ferritin, 1,459.4 ng/mL
• mean WBC 12.0 10^9/L
• mean Cr 4.22 mg/dL (3 were on HD)

Sandhu A et al Emerg Infect Dis 2020; Sep Ahead of Print
**Clostridioides difficile** in the COVID-19 Era

- 311/4,973 inpatients tested for **GI infections** 204 COVID +; 107 -
- **COVID +**
  - Overall 10%
  - **CDI** 5.1%
  - Non CDI 11%
- **COVID -**
  - Overall 22%
  - **CDI** 8.2 % \( p = 0.33 \)
  - Non CDI 22%

**CDI and non-CDI decreased during the pandemic**

NYC: Columbia, Mt. Sinai & Sloan Kettering

Italy- during the pandemic (2020) HA-CDI incidence was significantly lower with respect to the previous years Bentivegna E et al Amer J Inf Control Oct 5, 2020

Ireland- NYC Decrease in HA-CDI in the pandemic year. Hazel K et al. ICHE 2021;
❖ **Seems Infection Prevention measures work**
DAV 132 (Da Volterra) Microbiota Protector

• "first-in-class microbiota protector," patented **colon-targeted adsorbent**
• orally administered formulation that releases **5 gm of activated charcoal** from a 7.5gm dosage into, or after passage through the ileum.
• Phase 2 Trial (SHIELD) multicenter, randomized, parallel-group comparative trial in 4 European countries (Germany, Romania, Bulgaria, and Serbia)
• 7.5gm of DAV132 **three times daily**
• 260 elderly patients (median age 71) receiving **oral or IV fluoroquinolone** for the treatment of
  • LRTI
  • cUTI
  • Prophylaxis for febrile neutropenia
  • for a mean duration of 7.5 days.
• demonstrated **protection against antibiotic-induced disruption of intestinal microbiota**.
DAV 132 (Da Volterra) Microbiota Protector

- DAV132 while developed for the prevention of *Clostridioides difficile* infections,
- and for the prevention of intestinal colonization by multi-drug resistant organisms and their dissemination.
- Is anticipated to provide a significant clinical benefit, in combination with antibiotics, for
  - Patients undergoing allogeneic hematopoietic stem-cell transplantation (HSCT) in collaboration with the European-based COMBACTE-NET consortium
  - Cancer patients treated with immune checkpoint inhibitors.
<table>
<thead>
<tr>
<th>Development Stage</th>
<th>Valneva VLA 84</th>
<th>Pfizer</th>
<th>Sanofi</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>50+ years</td>
<td>65+ years</td>
<td>50+ years</td>
<td>Chandrabali Ghose, Symbiotic Health, Rockefeller University</td>
</tr>
<tr>
<td>Recombinant Protein</td>
<td>Toxoids A and B</td>
<td>Toxoids A and B</td>
<td>Replicating Single-Cycle Adenovirus</td>
<td></td>
</tr>
<tr>
<td>Development Stage</td>
<td>Phase I &amp; II completed, Phase III on hold</td>
<td>Phase I &amp; II completed, Phase III ongoing</td>
<td>Phase III Suspended due to “futility”</td>
<td></td>
</tr>
</tbody>
</table>
Safety, immunogenicity, and efficacy of a Clostridioides difficile toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial

- **Sanofi** 27 countries
- 7-30-2013 to 11-17-2017 9,302 Participants (6,201 Vaccine gp)
- > 50 years, 2 Hosp stays + abx or planned surgery + abx
- **Vaccine IM Day 0, 7 and 30** 100 µg toxoid
- **Highly purified TcdA & TcdB** ATCC 43255
- 3 loose stools **PCR +** followed for 3 years
- Terminated at first planned interim analysis due to "futility"
- Adverse events 4.8 % both groups
A Phase 2 Study Evaluating the Safety, Tolerability, and Immunogenicity of Two 3-Dose Regimens of a Clostridium difficile Vaccine in Healthy US Adults Aged 65 to 85 Years

• **Pfizer** July 2013 to March 2017 855 adults 65-85 y.o.
• 15 US Centers 3:3:1 randomization IM toxoid 2 strains
• 100 or 200 µg or placebo 0,1 & 6 mos. Or 1,8 & 30 days
• Serum Toxin A & B specific neutralizing Antibodies
• 200 >100 µg dose response remained elevated for 12 mos.
• Response peaked 7 mos. (month) vs 37 days (day) regimen
The Gut Microbiome

Khanna S, Montassier B et al Ailment Pharmacol Ther 2016;44:715-27
The Gut Microbiome Predicts Treatment Response & Relapse
Probiotics in the Coronavirus Era

Lynne V. McFarland, PhD
Seattle, Washington
Dose-Response Study of a Lactobacillus Combination Probiotic in Prevention of AAD and CDI

Comparative CDI Rates Pierre-LeGarde Hospital vs Similar Hospitals in Quebec

Enhanced CDI prevention with a pharmacy controlled policy that adds a 3-strain *Lactobacillus* probiotic to most antibiotic users

Mazaide et al. CID In Press 2021

- Pierre-Le Gardeur Hospital, in the outskirts of Montreal, Quebec, Canada 2016-2019
- quinolone antibiotic use restricted azithromycin → doxycycline
- Adult inpatients prescribed two or more days of antibiotics were flagged by the hospital pharmacy to receive the probiotic daily within the first 24 hours
- 13922 inpatient hospitalizations of adults Rx antibiotics
- 4383 patients observed 12-months & 6079 18-months
- When 70% of antibiotic users took a probiotic (BioK+) HA-CDI was significantly lower during the intervention, 5.2 cases per 10 000 patient day compared to the observation period, 8.6, P=.002
# Proposed Mechanisms of Probiotic Action

<table>
<thead>
<tr>
<th>Product</th>
<th>Proposed Mechanism</th>
</tr>
</thead>
</table>
| *Saccharomyces boulardii*     | • Secretes a protease that degrades Toxins A & B  
                                 | • Inhibits binding receptors                                                     |
| *Lactobacillus rhamnosus GG*  | • Avidity of mucosal cells  
                                 | • Reduction of permeability defects                                              |
| Bio K + combination           | • Enhances intestinal immunity                                                    |
| *Lactobacillus acidophilus*   |                                                                                   |
| *Lactobacillus casei*         |                                                                                   |
| *Lactobacillus rhamnosus*     |                                                                                   |
| *Lactobacillus rhamnosus*     |                                                                                   |
| *Lactobacillus rhamnosus*     |                                                                                   |
| *Lactobacillus rhamnosus*     |                                                                                   |

2020 AGA Guidelines: Prevention of *C. difficile* infections:

In adults and children on antibiotic treatment:

- *S. boulardii* CNCM I-745 [Florastor®] (based on 9 RCTs)
- 2-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R [Bio K+] (based on 3 RCTs)
- 3-strain combination of *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, and *B. bifidum* (only 1 RCT)

[Su GL et al. 2020 Gastro]
Fecal Biotherapy/ Transplant

Upper or Lower Endoscopy
Home Enemas
Capsules
Fecal Transplants for r CDI

- **Directed Donor**
- **Open Biome** Non profit stool bank [www.openbiome.org](http://www.openbiome.org)
  - issues with CRE, Corona virus
  - **will expand availability of FMT preparations for all scheduled patients, May 3, 2021. RT-PCR testing- donors & stools**
- **RBX-2660** (Ferring Pharmaceuticals)
  - Suspension of “human derived” microbiota as rectal enema
  - **PUNCHCD3** NCTO3244644
- **SER 109** Donor derived purifies spores
  - 89 pts reduced rates of CDI but did not meet clinical significance Phase 2
  - McGovern B et al CID 2020 NCT02437487
  - Phase 3 underway, 289 pts enrolled 88.9% sustained response preliminary analysis Contagion Feb 2021
Thank you  Any Questions?