Treatment and Prevention Options for *Clostridium difficile* Infection (CDI)

Dale N. Gerding, MD
Professor of Medicine
Loyola University Chicago Stritch School of Medicine
Research Physician
Hines VA Hospital
Disclosures: Holds patents for the treatment and prevention of CDI licensed to ViroPharma; is a consultant for Merck, ViroPharma, Pfizer, GSK, Roche, Novartis, Optimer, Cubist, TheraDoc, BioRelix, Cangene, Medicines Co., and Actelion; and holds research grants from Merck, GOJO, Optimer, Sanofi-Pasteur, and Cubist.

Unapproved Use: Metronidazole, rifaximin, and nitazoxanide for treatment of CDI do not have US FDA approval, but are available for other indications.
C. difficile is causing many Americans to suffer or die

- Other healthcare-associated infections declined in recent years, but *C. difficile climbed to historic highs and remains at these unacceptable levels*
- Linked to 14,000 deaths - Deaths related to *C. difficile increased 400% between 2000 and 2007*
- More than 335,000 hospitalizations per year - Hospital stays caused by *C. difficile tripled in the 2000s*
- People most at risk are those who take antibiotics *and also receive medical care in any setting. This could include a nursing home, hospital, doctor’s office, outpatient surgery etc.*
- Risk generally increases with age; children are at lower risk and older adults are at higher risk
- Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older
CDC Update on *C. difficile* Infection (CDI): March 9, 2012

- Almost all (94%) of *C. difficile* infections occur in people who recently received medical care in or out of hospitals.

- 75% of *C. difficile* infections have their onset in nursing homes or occur in people recently cared for in an outpatient setting.

- Hospitals still play a central role.
  - 25% of all *C. difficile* infections have onset in hospitals.
  - In hospitals:
    - 50% of cases are present on admission in patients who transfer from another healthcare setting or patients recently discharged from another facility.
    - 50% of cases are a result of care in that specific facility.
Current CDI Treatment and Prevention Challenges

- Treatment of severe complicated or fulminant CDI (Shock, Life Threatening)
- Reduction of recurrence of CDI (now 25%)
- Treatment of multiply recurrent CDI (repeated episodes)
- Management of CDI due to an epidemic BI/NAP1/027 strain of *C. difficile*
- Primary prevention of CDI
  - Vaccines
  - Immunologics
  - Biotherapeutics
New CDI Treatment Strategies: Inside and Outside the Box

• Use an antimicrobial treatment that spares the normal flora (Fidaxomicin, New Agents)

• Avoid antimicrobial treatment entirely using luminal (oral) toxin binders or antibodies (toxin binding polymer = tolevamer, bovine milk-derived antibodies = MucoMilk)

• Use a biotherapeutic approach to restore the protective effect of the flora (fecal transplants, nontoxigenic C. difficile)

• Supplement or increase the antibody response to C. difficile toxins (active: vaccines, passive: monoclonal antibodies)
Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic toxin A IgG antibody response results in CDI.

CDI Future Prevention Strategies Include Biotherapeutics, Immunologics, and Vaccines

C. difficile acquisition

Antimicrobial(s)

Give Non-toxigenic C. difficile, other biotherapeutics or monoclonal antibodies.

Asymptomatic C. difficile colonization

Hospitalization

Vaccinate or give monoclonal Antibodies to prevent CDI.

Antibiotic Rx plus monoclonal antibodies or vaccine or fecal transplant or non-toxigenic C. difficile

Gerding DN, Discovery Medicine 13(68):75-83, January 2012]
Lower Cure Rates for BI (BI/NAP1/027) vs. non-BI Isolates of *C. difficile*

<table>
<thead>
<tr>
<th></th>
<th>BI</th>
<th>Non BI</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>214/247</td>
<td>445/472</td>
<td>659/719</td>
</tr>
<tr>
<td>Fidaxomycin</td>
<td>105/120</td>
<td>225/236</td>
<td>330/356</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10/9</td>
<td>12/7</td>
<td>220/236</td>
</tr>
</tbody>
</table>

- *P = 0.030* for BI vs. non-BI isolates in Total.
- *P = 0.009* for BI vs. non-BI isolates in Fidaxomycin.
- *P < 0.022* for BI vs. non-BI isolates in Vancomycin.

*Petrella L et al ICAAC 2011, Chicago, IL Sept 19, 2011*
Good News: New CDI Antibiotic Treatments in Clinical Trials

- LFF571, Novartis, (Antibiotic – Phase II)
- ACT-179811, Actelion (Antibiotic – Phase II)
- CB-183,315, Cubist, (Antibiotic – Phase III?)
- Tigecycline, Pfizer, (Antibiotic – Phase II?)
- Metronidazole delayed release formulations vs. standard Metronidazole, Dr. Reddys, (Antibiotic - Phase II)
### Good News: CDI Vaccines and Immunologics: Current Status

<table>
<thead>
<tr>
<th>Product</th>
<th>Antigen</th>
<th>Formulation</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur ACAM-CDIFF Vaccine</td>
<td>Formalin Inactivated toxins A and B from VPI 10463</td>
<td>+/- Alum adjuvant, IM injection days 0, 7, and 28-30</td>
<td>Phase II for primary CDI prevention</td>
</tr>
<tr>
<td>Intercell IC84 Vaccine</td>
<td>Recombinant fusion protein of toxin A and B binding regions</td>
<td>+/- Aluminum salt adjuvant, IM injection days 0, 7, and 21</td>
<td>Phase I volunteer safety and immune response</td>
</tr>
<tr>
<td>Merck Monoclonal Antibodies</td>
<td>Monoclonals target toxin binding epitopes</td>
<td>Human Monoclonal Antibody</td>
<td>Two Phase III clinical trials</td>
</tr>
</tbody>
</table>
Good News: BioTherapeutics Under Development

- VP20621, ViroPharma, (Non-Toxigenic *C. difficile*, Phase II)
- Fecal Transplant vs. Tapering Vancomycin, U. Health Network, Toronto (Phase II)
- *Lactobacillus reuteri*, AAD and CDI Prevention (Bulgarian Hospital)
- Probiotic Drink, Danone, (U. Sussex, Phase ?)
- Probiotic, Danisco, (U. of Turku, Phase ?)
- Synthetic Stool, Queens University, Canada, (Phase ?)
- *Saccharomyces boulardii*, (Bernard Nocht Institute for Tropical Medicine)
- *Lactobacillus Acidophilus/Rhamnosus* Complex, Prevention of AAD (and CDI), Jamieson Laboratories Ltd, Canada (Phase II)