Cost-effective Treatment of *Clostridium difficile* Infection in the ICU

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Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

Lessa CF et al. NEJM 2015;372:825-34.
Acknowledgements

• Research Funding:
  – Merck & Co
  – Summit PLC
  – Texas Department of State Health Services
Objectives

1. Discuss the epidemiology and presentation of *C. diff* in critically ill patients
2. Compare and contrast pharmacotherapy treatment options for *C. diff* based on efficacy, availability, and cost
Learning assessment questions

• Learning Assessment Questions

• Which severity measure is associated with mortality?
  – Leukocytosis
  – Volume depletion due to diarrhea
  – Low albumin
  – All of the above

• Which of the following antibiotics should NOT be used in patients with severe CDI?
  – Metronidazole
  – Oral vancomycin
  – Fidaxomicin
A History of *C. difficile*

1893 - pseudomembranous colitis first described

1935 - isolated in stool

1978 - *C. difficile* responsible for antibiotic associated diarrhea

1996-2003 CDC reports rate of CDI increased from 31 cases per 100,000 persons to 61 cases per 100,000 persons

2005 – US continues to report increased CDI

2008-11 – England directs significant resources to control CDI (and MRSA)

Current – continued persistence of RT 027 in North America and decrease incidence in Europe

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C. difficile is the main contributor to gastroenteritis-associated deaths in the USA

Analysis of National Center for Health Statistics (NCHS) multiple-cause-of-death mortality data for the years 1999–2007, a 5-fold increase in mortality attributed to CDI was noted

Hall et al. CID 2012;55:216-23
How did we get here?

• Let’s review a few key concepts on CDI to get everyone up to speed
  – Pathogenesis
  – Emergence of ‘hypervirulent’ strains
Pathogenesis of Clostridium difficile-associated diarrhea in adults

Clostridium difficile spores and vegetative cells are ingested.

- Spores
- Vegetative cells

Most vegetative cells are killed in the stomach, but spores can survive the acid environment.

C. difficile multiplies in the colon.

Gut mucosa facilitates adherence to the colonic epithelium.

C. difficile spores germinate in the small bowel upon exposure to bile acids.

Flagellae facilitate C. difficile movement; a polysaccharide capsule discourages phagocytosis.

Pathogenesis of Clostridium difficile-associated diarrhea in adults

C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2), opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhea.
Hypervirulent \textit{C. difficile}
Incidence of hypervirulent strains of *C. difficile*, 2005

Table 1. Isolates of *Clostridium difficile* According to Health Care Facility and the Proportion of Isolates Belonging to the BI/NAP1 Strain.

<table>
<thead>
<tr>
<th>Health Care Facility</th>
<th>Date of Onset of Outbreak</th>
<th>No. of Isolates Tested</th>
<th>BI/NAP1 Strain no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>Oct. 2001</td>
<td>46</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Illinois</td>
<td>July 2003</td>
<td>14</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Maine, Facility A</td>
<td>March 2002</td>
<td>13</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Maine, Facility B</td>
<td>July 2003</td>
<td>48</td>
<td>30 (62)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>June 2003</td>
<td>12</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Oregon*</td>
<td>April 2002</td>
<td>30</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Pennsylvania, Facility A</td>
<td>2000–2001</td>
<td>18</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Pennsylvania, Facility B</td>
<td>Oct. 2003</td>
<td>6</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>187</td>
<td>96 (51)</td>
</tr>
</tbody>
</table>

* Isolates were not collected until after the peak of the outbreak.

Increasing mortality and complications due to CDAD

Table 1: Patients with *Clostridium difficile*-associated diarrhea (CDAD) in the Estrie region of Quebec who died within 30 days after diagnosis or who had complicated CDAD, 1991–2003

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of patients with CDAD*</th>
<th>No. (%) who died within 30 days after diagnosis</th>
<th>Adjusted OR (95% CI)†</th>
<th>No. (%) who had complicated CDAD‡</th>
<th>Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991–1992</td>
<td>169</td>
<td>8 (4.7)</td>
<td>1.0</td>
<td>12 (7.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>1993–1994</td>
<td>217</td>
<td>11 (5.1)</td>
<td>1.7 (0.5–5.3)</td>
<td>14 (6.5)</td>
<td>1.0 (0.4–2.7)</td>
</tr>
<tr>
<td>1995–1996</td>
<td>215</td>
<td>13 (6.0)</td>
<td>1.6 (0.5–5.0)</td>
<td>17 (7.9)</td>
<td>0.9 (0.3–2.2)</td>
</tr>
<tr>
<td>1997–1998</td>
<td>192</td>
<td>11 (5.7)</td>
<td>1.1 (0.4–3.7)</td>
<td>13 (6.8)</td>
<td>0.6 (0.3–1.7)</td>
</tr>
<tr>
<td>1999–2000</td>
<td>248</td>
<td>19 (7.7)</td>
<td>1.5 (0.5–4.6)</td>
<td>28 (11.3)</td>
<td>1.2 (0.5–2.9)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>244</td>
<td>21 (8.6)</td>
<td>1.6 (0.5–4.7)</td>
<td>28 (11.5)</td>
<td>1.1 (0.5–2.5)</td>
</tr>
<tr>
<td>2003</td>
<td>390</td>
<td>54 (13.8)</td>
<td>3.0 (1.1–8.4)</td>
<td>71 (18.2)</td>
<td>2.2 (1.0–4.9)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>&lt; 0.001§</td>
<td>&lt; 0.001¶</td>
<td>&lt; 0.001§</td>
<td>0.001¶</td>
</tr>
</tbody>
</table>

Note: OR = odds ratio, CI = confidence interval.
*Includes only patients for whom enough information was available to assess these outcomes.
†Adjusted for age, sex, initial treatment, immune status, and tube feeding and surgery in the 2 months preceding diagnosis; 1991–1992 was used as the baseline period.
‡Presence of one or more of the following: megacolon, perforation, colectomy, shock requiring vasopressor therapy, death within 30 days after diagnosis.
§χ² test for trend.
¶χ² test, comparing 2003 with all other years.
Toxins A and toxin B are produced in the Pathogenicity Locus (PaLoc) of *C. difficile*

**Diagram:**
- **Codes for toxin B**: tcdC deficient strain = Lots more production of toxins A and B!
- **Codes for toxin A**: Negative regulator of tcdA and tcdB

Time course of toxin production by hypervirulent strain compared to control

Warny Lancet 2005;366:1079
Michigan: Derivation (n=310/34 severe) and validation (n=433/45 severe) of predictors of severe CDI (ICU admission, colectomy, or death). After accounting for disease presentation severity, ribotype did not predict outcome.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Derivation OR (95% CI)</th>
<th>P Value</th>
<th>Validation OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervirulent ribotype:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>027/078 vs non-027/078 (reference)</td>
<td>0.82 (.07–10.0)</td>
<td>.874</td>
<td>1.34 (.53–3.16)</td>
<td>.516</td>
</tr>
<tr>
<td>White blood cell count:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;4000 cells/mL) vs normal (reference)</td>
<td>4.27 (1.14–19.46)</td>
<td>.041</td>
<td>2.32 (1.07–5.18)</td>
<td>.035</td>
</tr>
<tr>
<td>Low albumin level (g/dL)</td>
<td>0.25 (.07–.77)</td>
<td>.025</td>
<td>0.47 (.25–.87)</td>
<td>.018</td>
</tr>
</tbody>
</table>
..and there are more ribotypes than just 027

A lot of ribotypes are associated with CDI

Many ribotypes are virulent, including 027

<table>
<thead>
<tr>
<th>Ribotype</th>
<th>Severe CDI presentation</th>
<th>Severe CDI outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>027 (n=170)</td>
<td>54.7%</td>
<td>18.9%</td>
</tr>
<tr>
<td>014-020 (n=118)</td>
<td>22.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>FP11 (n=70)</td>
<td>31.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>078-126 (n=42)</td>
<td>21.4%</td>
<td>9.5%</td>
</tr>
<tr>
<td>001 (n=35)</td>
<td>42.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>FP24 (n=35)</td>
<td>37.1%</td>
<td>22.9%</td>
</tr>
<tr>
<td>17 (n=23)</td>
<td>39.1%</td>
<td>17.4%</td>
</tr>
<tr>
<td>FP8 (n=19)</td>
<td>36.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>053-163 (n=16)</td>
<td>37.5%</td>
<td>6.25%</td>
</tr>
<tr>
<td>FP16 (n=16)</td>
<td>35.3%</td>
<td>11.8%</td>
</tr>
<tr>
<td>FP9 (n=16)</td>
<td>25.0%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

Aitken et al. ICHE 2015
So, why do you really have bad outcomes due to CDI?

**Table 5 (European guidelines): Prognostic markers to determine severe CDI**

<table>
<thead>
<tr>
<th>Characteristic (Major goal)</th>
<th>SoR</th>
<th>Associated poor outcomes</th>
<th>Associated with</th>
<th>Associated with</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity</td>
<td>B</td>
<td>30-d mortality</td>
<td>Yes</td>
<td>Yes</td>
<td>Vulnerable population</td>
</tr>
</tbody>
</table>

**Major goal of treatment:**
Stop the fluid loss (diarrhea) and make sure it doesn’t come back!
You are all now expert C diff ribotypers

• 027 is definitely a virulent ribotype
• .....but, there are lots of ribotypes that are equally virulent
  – Treat the patient, not the bug!
• Without a doubt, the ribotype 027 strain has put a large focus on the value of strain typing in *C. difficile*.
• Now, let’s use some antibiotics!
Expanding treatment goals for CDI

**Essential:**  Correct dysbiosis  Kill the organism  Adaptive immunity

**Optional but nice:**  Safe and convenient  Also affects toxins and spores  Short vs. long-term

Adamu and Lawley. Curr Opin Microbiol 2013
There has been an explosion in treatment possibilities for CDI

**Current:** Probiotics
- FMT
- Metronidazole
- Vancomycin
- Fidaxomicin
- IVIG

**Future:** 2nd generation FMT
- non-tox C diff M3
- Ecobiotics
- Surotomycin
- Cadazolid
- SMT-19969
- Monoclonal antibodies vs. C diff toxins
- Toxoid vaccines
### Current US IDSA CDI guidelines 2010

<table>
<thead>
<tr>
<th>Episode</th>
<th>Clinical Signs</th>
<th>Severity</th>
<th>Recommended agent</th>
<th>Dosing Regimen</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>WBC &lt; 15,000 and SrCr &lt; 1.5 X premorbid level</td>
<td>Mild or moderate</td>
<td>Metronidazole</td>
<td>500 mg PO three times daily</td>
<td>A-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>WBC ≥ 15,000 or SrCr ≥ 1.5 X premorbid level</td>
<td>Severe</td>
<td>Vancomycin</td>
<td>125 mg PO four times daily</td>
<td>B-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-14 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>Hypotension, shock, ileus, megacolon</td>
<td>Severe, complicated</td>
<td>Vancomycin + metronidazole IV</td>
<td>Vancomycin: 500 mg PO or NG four times daily +</td>
<td>C-III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metronidazole: 500 mg IV q8hours. For ileus, consider adding rectal instillation of vancomycin</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>(1st recurrence)</td>
<td>--------------</td>
<td>Same as initial</td>
<td>Same as initial</td>
<td>A-II</td>
</tr>
<tr>
<td>Third</td>
<td>(2nd recurrence)</td>
<td>--------------</td>
<td>Vancomycin</td>
<td>PO tapered and/or pulsed</td>
<td>B-III</td>
</tr>
</tbody>
</table>

Cohen SH, Gerding DN, et al. Infection control and hospital epidemiology. 2010 (May); 31(5)
Current European CDI guidelines

CDI

Non-severe CDI
- Metronidazole
- Vancomycin
- Fidaxomicin

(Risk of) first recurrence
- Vancomycin
- Fidaxomicin
- Metronidazole

Severe disease or complicated course
- Vancomycin
- Fidaxomicin
- Metronidazole

Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use
More recently, metronidazole has been shown to be globally inferior to vancomycin (televamer phase III RCT)

# Summary of metro vs. vanco clinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>n</th>
<th>Single center</th>
<th>Blinded</th>
<th>Randomized</th>
<th>Metro dose</th>
<th>Vanco dose</th>
<th>Clinical failure</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teasley, 1983</td>
<td>82-83</td>
<td>MN</td>
<td>101</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>250 mg QID</td>
<td>500 mg qid</td>
<td>2 of 37 (5.4%)</td>
<td>0 of 45 (0%)</td>
</tr>
<tr>
<td>Wenisch, 1996</td>
<td>93-95</td>
<td>Austria</td>
<td>62</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>500 mg TID</td>
<td>500 mg tid</td>
<td>2 of 31 (6%)</td>
<td>2 of 31 (6%)</td>
</tr>
<tr>
<td>Musher, 2006</td>
<td>02-04</td>
<td>USA (Houston)</td>
<td>34</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QID</td>
<td>125 mg qid</td>
<td>6 of 34 (17%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Zar, 2007</td>
<td>94-02</td>
<td>Chicago</td>
<td>150</td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QID</td>
<td>125 mg qid</td>
<td>13 of 79 (16%)</td>
<td>2 of 71 (3%)</td>
</tr>
<tr>
<td>Johnson, 2013</td>
<td>05-07</td>
<td>World</td>
<td>552</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>375 mg QID</td>
<td>125 mg qid</td>
<td>76 of 278 (27%)</td>
<td>49 of 259 (19%)</td>
</tr>
</tbody>
</table>
There may have been a MIC creep with metronidazole over the decades

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Time period</th>
<th>Isolates</th>
<th>MIC50</th>
<th>MIC90</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecht et al</td>
<td>Various</td>
<td>1983–2004</td>
<td>110</td>
<td>0.125</td>
<td>0.25</td>
<td>0.025–0.5</td>
</tr>
<tr>
<td>Edlund et al</td>
<td>Sweden</td>
<td>1998</td>
<td>50</td>
<td>0.125</td>
<td>0.25</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>Betriu et al</td>
<td>Spain</td>
<td>2001</td>
<td>55</td>
<td>0.5</td>
<td>1</td>
<td>≤0.06–1</td>
</tr>
<tr>
<td>Citron et al</td>
<td>USA</td>
<td>2003</td>
<td>18</td>
<td>0.5</td>
<td>1</td>
<td>0.25–1</td>
</tr>
<tr>
<td>Finegold et al</td>
<td>USA (CA)</td>
<td>2003</td>
<td>72</td>
<td>0.5</td>
<td>1</td>
<td>0.25–2</td>
</tr>
<tr>
<td>Karlowsky et al</td>
<td>Canada</td>
<td>2007</td>
<td>208</td>
<td>0.5</td>
<td>1</td>
<td>0.25–4</td>
</tr>
<tr>
<td></td>
<td>(Manitoba)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>398</td>
<td>0.25</td>
<td>0.5</td>
<td>&lt;0.06-2</td>
</tr>
<tr>
<td>Reigadas et al</td>
<td>Spain</td>
<td>2013</td>
<td>100</td>
<td>0.25</td>
<td>0.5</td>
<td>0.06-1</td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011-12</td>
<td>925</td>
<td>1</td>
<td>2</td>
<td>&lt;0.06-4</td>
</tr>
<tr>
<td>BI/027/Nap1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citron et al</td>
<td>USA</td>
<td>2004–2005</td>
<td>NR</td>
<td></td>
<td>2</td>
<td>0.5–2</td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>0.5</td>
<td>1</td>
<td>0.5-1</td>
<td></td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011-12</td>
<td>2</td>
<td>2</td>
<td>&lt;0.06-4</td>
<td></td>
</tr>
</tbody>
</table>
Bottom line: this may simply be a PK/PD problem

- Mean concentrations of metronidazole in stool: \(<0.25-9.5 \text{ ug/g}\)
- MIC\(_{50}\): 1 \text{ ug/ml} \quad \text{MIC}\(_{90}\): 2 \text{ ug/ml}
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Bolton et al. Gut 1986
Explosion in treatment possibilities for CDI minus 1

**Current:** Probiotics
- FMT
- Vancomycin
- Fidaxomicin
- IVIG

**Future:**
- 2nd generation FMT
- non-tox C diff M3
- Ecobiotics
- Surotomycin
- Cadazolid
- SMT-19969
- Monoclonal antibodies vs. C diff toxins
- Toxoid vaccines
Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence

The second phase III study showed similar results (Crook et al. Lancet ID)
However, this drug is quite costly: Fidaxomicin Use By Region

- **Midwest**
  - 2011 – 0.1%
  - 2012 – 2.3%
  - 2013 – 2.4%

- **South**
  - 2011 – 0.1%
  - 2012 – 2.2%
  - 2013 – 3.5%

- **West**
  - 2011 – 0.3%
  - 2012 – 2.4%
  - 2013 – 4.6%

- **Northeast**
  - 2011 – 0%
  - 2012 – 2.3%
  - 2013 – 2.8%

Shah, Chan, Garey. Springer Plus 2016
Appropriate use of fidaxomicin

• Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population almost always in combination with other C diff or other antibiotics

• Remember: fidaxomicin’s primary MOA is its narrow spectrum of activity preserving host microbiota

• Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?
How do we decide who to give fidaxomicin to?

• As far as I can tell, 100% of the money we have used on fidaxomicin has been a waste of money (only kind of kidding).

• Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?
Recurrent CDI is costly: Healthcare utilization for recurrent CDI

* Of disease-attributable readmission, 85% returned to the initial hospital for care

Aitken, DuPont, Garey. PLOS One 2014 July 24;9(7)
Increased healthcare utilization = increased healthcare costs

**Table:**

<table>
<thead>
<tr>
<th>Cost in US dollars; median (IQR)</th>
<th>Without recurrent CDI</th>
<th>With recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI pharmacologic treatment*</td>
<td>$60 (23 - 200)</td>
<td>$140 (30 - 260)</td>
</tr>
<tr>
<td>CDI-attributable hospitalization^</td>
<td>$13,168 (7,525 - 24,455)</td>
<td>$28,218 (15,049 – 47,030)</td>
</tr>
<tr>
<td>Total hospitalization^</td>
<td>$20,693 (11,287 - 41,386)</td>
<td>$45,148 (20,693 - 82,772)</td>
</tr>
</tbody>
</table>

Shah et al. ICAAC 2014 Poster #K-356, Sat, Sept 6, 2014
Any evidence that fidaxomicin may reduce these costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%
Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals

![Bar chart showing 90-day hospital recurrence rate before and after fidaxomicin (Fidaxo) treatment.](chart.png)

- **A (n=98)**: First line, all episodes, Before Fidaxo 10.6, After fidaxo 3.1
- **B (n=162)**: First line, R-CDI, Before Fidaxo 16.3, After fidaxo 3.1
- **D (n=127)**: First line, R-CDI, Before Fidaxo 21.1, After fidaxo 12.5
- **C (n=511)**: Select episodes only, Before Fidaxo 7.7, After fidaxo 8.3
- **E (n=209)**: Select episodes only, Before Fidaxo 12.9, After fidaxo 11.8
- **F (n=178)**: Select episodes only, Before Fidaxo 16.9, After fidaxo 9
- **G (n=278)**: Select episodes only, Before Fidaxo 5.4, After fidaxo 5.8

Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)

Before Fidaxo  After fidaxo

Re-admission within 30 days or primary CDI

A (n=98) B (n=162) D (n=127) C (n=511) E (n=209) F (n=178) G (n=278)

First line, all episodes First line, R-CDI Select episodes only

P<0.05

I do also wonder if we are missing the most important endpoints?

Aitken et al. ICAAC 2014 Poster #K-360, Sat, Sept 6, 2014
Final thoughts on antibiotic treatment

• Limit use of metronidazole as alternative agent
• Consider a certain budget that you can afford to prove the worth of fidaxomicin and then use it for that purpose (first recurrence?).
• As more narrow-spectrum branded drugs become available, may have to prove themselves in other pharmacologic niches (decreased toxin expression).
  – This assumes similar phase III results
Conclusion

• As long as we live in a world of elderly, hospitalized patients given broad spectrum antibiotics, CDI is here to stay
• With a coordinated effort and contemporary epidemiologic techniques, we can likely control and respond to future changes in the pathogenesis of CDI
• With a little luck and good science, we may also be able to discover new insights into strategies to prevent and control CDI.
Cost-effective Treatment of *Clostridium difficile* Infection in the ICU

Kevin W. Garey, PharmD, MS. Professor and Chair
University of Houston College of Pharmacy

Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

Lessa CF et al. NEJM 2015;372:825-34.