The Great ID Debates of One-Eight

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Disclosures

• **Monica V. Mahoney**: CutisPharma: Advisory Board; Melinta Therapeutics: Advisory Board; Roche Diagnostics: Advisory Board; Tetraphase Pharmaceuticals, Inc.: Advisory Board

• All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Vancomycin vs Linezolid for Empiric Coverage of MRSA in Nosocomial Pneumonia

Vancomycin  Brandon Dionne  @BWDionne
Linezolid  Meghan N. Jeffres  @PharmerMeg
In a patient with nosocomial (HAP/VAP) pneumonia, which medication should be used first line as empiric therapy?

A. Vancomycin
B. Linezolid
Empiric Anti-MRSA Agent: Vancomycin

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MRSA in Nosocomial Pneumonia

- *Staphylococcus aureus* was responsible for 31.9-36.5% of HAP/VAP in SENTRY surveillance program
  - ~50% were methicillin-resistant

- MRSA colonization
  - MRSA nasal swabs have 99% negative predictive value for MRSA pneumonia
  - Positive predictive value only around 37%

2016 IDSA/ATS HAP/VAP Guidelines

• Recommend vancomycin or linezolid if:
  – Previous IV antibiotics within 90 days
  – Septic shock or ventilatory support required due to pneumonia
  – MRSA prevalence >10-20% in unit/institution
  – ARDS preceding VAP
  – Acute renal replacement therapy preceding VAP

• Recommended duration of 7 days

# Vancomycin vs Linezolid Pneumonia RCTs

<table>
<thead>
<tr>
<th></th>
<th>Rubinstein et al.</th>
<th>Wunderink et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Clinical Cure</td>
<td>68.1%</td>
<td>66.4%</td>
</tr>
<tr>
<td>Microbiologic Cure</td>
<td>71.8%</td>
<td>67.9%</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>33.7%</td>
<td>31.0%</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Linezolid non-inferior to vancomycin</td>
<td>Linezolid non-inferior to vancomycin</td>
</tr>
</tbody>
</table>

Vancomycin vs. Linezolid Meta-analysis

- Includes 9 randomized trials with direct comparison in nosocomial pneumonia
- 99.9% power to detect a difference in clinical cure and mortality
- Most trials used a fixed dose of vancomycin 1 g IV q12h
- Many did not allow monitoring and dose adjustment of vancomycin

# Vancomycin Dosing in RCTs

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose of Vancomycin</th>
<th>Adjustment allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubinstein (2001)</td>
<td>1 g q12h</td>
<td>? (for renal function)</td>
</tr>
<tr>
<td>Stevens (2002)</td>
<td>1 g q12h</td>
<td>X</td>
</tr>
<tr>
<td>Kaplan (2003)</td>
<td>10-15 mg/kg q6-24h (pediatric)</td>
<td>X</td>
</tr>
<tr>
<td>Wunderink (2003)</td>
<td>1 g q12h</td>
<td>X</td>
</tr>
<tr>
<td>Jaksic (2006)</td>
<td>1 g q12h</td>
<td>✔ (no details)</td>
</tr>
<tr>
<td>Kohno (2007)</td>
<td>1 g q12h</td>
<td>✔ (no details)</td>
</tr>
<tr>
<td>Wunderink (2008)</td>
<td>1 g q12h</td>
<td>X</td>
</tr>
<tr>
<td>Lin (2008)</td>
<td>1 g or 750 mg (&gt;60 yo) q12h</td>
<td>X</td>
</tr>
<tr>
<td>Wunderink (2012)</td>
<td>15 mg/kg q12h</td>
<td>✔</td>
</tr>
</tbody>
</table>
# Meta-analysis – Clinical Cure

## Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study Name</th>
<th>Statistics for each study</th>
<th>Mortality / Total</th>
<th>Risk difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk difference</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Rubinstein E 2001</td>
<td>0.029</td>
<td>-0.064</td>
<td>0.121</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink R 2003</td>
<td>-0.012</td>
<td>-0.068</td>
<td>0.063</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Jaksic B 2006</td>
<td>0.019</td>
<td>-0.016</td>
<td>0.055</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Lin D 2008</td>
<td>0.014</td>
<td>-0.130</td>
<td>0.158</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink R 2012</td>
<td>0.021</td>
<td>-0.019</td>
<td>0.062</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Stevens D 2002</td>
<td>0.017</td>
<td>-0.007</td>
<td>0.041</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Kaplan S 2003</td>
<td>-0.057</td>
<td>-0.121</td>
<td>0.007</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Kohno S 2007</td>
<td>-0.008</td>
<td>-0.115</td>
<td>0.100</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink R 2008</td>
<td>0.052</td>
<td>-0.062</td>
<td>0.165</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.009</td>
<td>-0.012</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I²=0%*
Meta-analysis – Mortality

Problems with Linezolid

- Outbreaks of linezolid-resistant *S. aureus* have been reported
- Higher drug costs
- Drug interactions
- Bacteriostatic
- Adverse effects

Linezolid Adverse Effects

- Neurotoxicity - peripheral neuropathy is potentially irreversible
- Serotonin syndrome
- Gastrointestinal symptoms - higher incidence in linezolid group in the meta-analysis
- Thrombocytopenia

### Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Thrombocytopenia

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study name</th>
<th>Risk difference</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>p-Value</th>
<th>Thrombocytopenia / Total</th>
<th>Risk difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Double-blind</td>
<td>Rubinstein E 2001</td>
<td>0.000</td>
<td>-0.010</td>
<td>0.010</td>
<td>1.000</td>
<td>0 / 203</td>
<td>-0.25 (-0.010 to 0.193)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink R 2003</td>
<td>0.004</td>
<td>-0.025</td>
<td>0.033</td>
<td>0.752</td>
<td>12 / 321</td>
<td>0.13 (0.025 to 0.248)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Lh 2008</td>
<td>0.025</td>
<td>-0.018</td>
<td>0.075</td>
<td>0.234</td>
<td>2 / 71</td>
<td>0.000 (-0.250 to 0.250)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink 2012</td>
<td>0.032</td>
<td>-0.008</td>
<td>0.072</td>
<td>0.122</td>
<td>97 / 597</td>
<td>0.13 (0.032 to 0.250)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink 2012</td>
<td>0.005</td>
<td>-0.007</td>
<td>0.017</td>
<td>0.403</td>
<td>111 / 1192</td>
<td>0.13 (0.005 to 0.208)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Stevens D 2002</td>
<td>0.069</td>
<td>0.026</td>
<td>0.112</td>
<td>0.002</td>
<td>23 / 240</td>
<td>0.13 (0.069 to 0.219)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Kaplan S 2003</td>
<td>0.019</td>
<td>-0.005</td>
<td>0.042</td>
<td>0.119</td>
<td>4 / 215</td>
<td>0.000 (-0.019 to 0.048)</td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Konnos S 2007</td>
<td>0.170</td>
<td>0.085</td>
<td>0.256</td>
<td>0.000</td>
<td>19 / 100</td>
<td>0.13 (0.170 to 0.250)</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink 2008</td>
<td>0.013</td>
<td>-0.003</td>
<td>0.060</td>
<td>0.471</td>
<td>1 / 75</td>
<td>0.000 (-0.013 to 0.049)</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink 2008</td>
<td>0.053</td>
<td>0.008</td>
<td>0.099</td>
<td>0.021</td>
<td>47 / 630</td>
<td>0.13 (0.053 to 0.186)</td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink 2008</td>
<td>0.008</td>
<td>-0.003</td>
<td>0.020</td>
<td>0.161</td>
<td>158 / 1822</td>
<td>0.13 (0.008 to 0.188)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Intention-to-Treat Population. Z=1.402; P=0.161; Heterogeneity: Q=26.861; P=0.001; I²=74%
Why Should Vancomycin Be Preferred?

- "Vancomycin is considered the gold standard for treatment of MRSA infections" – Meghan Jeffres
- Years of experience and still very little resistance
- Preserve activity of alternative agents
- Significantly lower drug cost
- Fewer drug interactions
- Potentially lower incidence of neurotoxicity and thrombocytopenia
Empiric Anti-MRSA Agent: Linezolid

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University of Colorado Hospital
Aurora, CO

@PharmerMeg
Microbiology

VAP, n=8474

HAP, n=2585


### Meta-analysis – Clinical Cure

#### Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response*

<table>
<thead>
<tr>
<th>Group by Study Design</th>
<th>Study name</th>
<th>Risk difference</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>Mortality / Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Double-blind</td>
<td>Rubinstein E 2001</td>
<td>0.029</td>
<td>-0.064</td>
<td>0.121</td>
<td>0.548</td>
<td>71 / 203</td>
<td>62 / 193</td>
<td></td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink R 2003</td>
<td>-0.012</td>
<td>-0.068</td>
<td>0.063</td>
<td>0.747</td>
<td>114 / 321</td>
<td>111 / 302</td>
<td></td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Jaksic B 2006</td>
<td>0.019</td>
<td>-0.016</td>
<td>0.055</td>
<td>0.288</td>
<td>19 / 304</td>
<td>13 / 301</td>
<td></td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Lin D 2008</td>
<td>0.014</td>
<td>-0.130</td>
<td>0.158</td>
<td>0.848</td>
<td>19 / 71</td>
<td>18 / 71</td>
<td></td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Wunderink R 2012</td>
<td>0.021</td>
<td>-0.019</td>
<td>0.062</td>
<td>0.306</td>
<td>95 / 597</td>
<td>81 / 587</td>
<td></td>
</tr>
<tr>
<td>Randomized Double-blind</td>
<td>Stevens D 2002</td>
<td>0.017</td>
<td>-0.007</td>
<td>0.041</td>
<td>0.159</td>
<td>318 / 1496</td>
<td>285 / 1454</td>
<td></td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Kaplan S 2003</td>
<td>0.013</td>
<td>-0.221</td>
<td>0.247</td>
<td>0.914</td>
<td>20 / 39</td>
<td>16 / 32</td>
<td></td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Kohn S 2007</td>
<td>-0.008</td>
<td>-0.115</td>
<td>0.100</td>
<td>0.889</td>
<td>11 / 100</td>
<td>6 / 51</td>
<td></td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink R 2008</td>
<td>0.052</td>
<td>-0.062</td>
<td>0.165</td>
<td>0.372</td>
<td>13 / 75</td>
<td>9 / 74</td>
<td></td>
</tr>
<tr>
<td>Randomized Open-label</td>
<td>Wunderink R 2012</td>
<td>-0.024</td>
<td>-0.073</td>
<td>0.024</td>
<td>0.327</td>
<td>53 / 429</td>
<td>41 / 258</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.009</td>
<td>-0.012</td>
<td>0.031</td>
<td>0.409</td>
<td>371 / 1925</td>
<td>326 / 1712</td>
<td></td>
</tr>
</tbody>
</table>

*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I²=0%
#1 – Superior Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success EOT</td>
<td>150/180 (83%)</td>
<td>130/186 (70%)</td>
<td>15% (4.9-22.0)</td>
</tr>
<tr>
<td>Success EOS</td>
<td>95/165 (58%)</td>
<td>81/174 (47%)</td>
<td>11% (0.5-21.6)</td>
</tr>
</tbody>
</table>

VA cohort

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n=265</th>
<th>n=946</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>12%</td>
<td>26%</td>
<td>2.6 (1.7-4.0)</td>
</tr>
<tr>
<td>60 day mortality</td>
<td>18%</td>
<td>36%</td>
<td>2.6 (1.8-3.8)</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>22%</td>
<td>42%</td>
<td>2.7 (1.9-3.9)</td>
</tr>
</tbody>
</table>

PP = per protocol
EOT = end of therapy
EOS = end of study (7-30 days after EOT)
AOR = adjusted odds ratio

#2 – Less Toxicity

- 7 randomized controlled trials
  - 6: linezolid vs. vancomycin
  - 1: ceftaroline vs. vancomycin
- n=4033
- Acute kidney injury
  - Relative Risk = 2.42
  - Attributable risk 59%

#3 – No Monitoring (aka Massive Time Suck)

**EOS success and day 3 troughs**
*Linezolid vs. Vancomycin*

- <8 mcg/mL: 50%
- 8-12 mcg/mL: 40%
- 13-17 mcg/mL: 30%
- >17 mcg/mL: 20%

**Cure and median troughs**
*Telavancin vs. Vancomycin*

- <10 mcg/mL: 80%
- 10-15 mcg/mL: 60%
- >15 mcg/mL: 40%

EOS = end of study
#4 - Cost

<table>
<thead>
<tr>
<th>Direct Costs</th>
<th>Vancomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication cost</td>
<td>$30 x 7 = $210</td>
<td>$100 x 7 = $700</td>
</tr>
<tr>
<td>Vancomycin assay</td>
<td>$20 x 2 = $60</td>
<td>$0</td>
</tr>
<tr>
<td>Total</td>
<td>$270</td>
<td>$700</td>
</tr>
</tbody>
</table>

Indirect costs
- Cost of treatment failure
- Cost of toxicity

Opportunity cost, loss of potential gain from an alternative choice

Time spent monitoring vancomycin
Nursing, lab, pharmacy

Time spent on antimicrobial stewardship, transitions of care, patient education
Empiric Anti-MRSA Agent: Vancomycin Rebuttal

Brandon Dionne, Pharm.D., AAHIVP, BCPS-AQ ID

@BWDionne
ZEPHyr Trial – Patients

• 1184 patients randomized (ITT population)
  – 484 (41%) had confirmed MRSA pneumonia (mITT population)
  – 339 (28%) included in per-protocol analysis

• Vancomycin patients had higher rates of:
  – Mechanical ventilation – 73.9% vs 66.9% (p=0.15)
  – Bacteremia – 10.8% vs 5.2% (p=0.039)
  – Chronic kidney disease – 36.9% vs 27.9% (p=0.07)
• Vancomycin levels may not have been optimized
  – Median on day 3 was 12.3 mg/L (IQR 7.6-17 mg/L)
  – Median on day 6 was 14.7 mg/L (IQR 9.5-19.9 mg/L)
  – Outcomes analyzed by trough quartile?

• Pfizer had the ability to override clinical outcome decisions

• No differences in 60-day mortality
  – 15.7% for linezolid and 17.0% for vancomycin in ITT analysis
  – 28.1% for linezolid and 26.3% for vancomycin in mITT analysis

VA Cohort Study

• Population was patients age >65 years with “HCAP” from 2002-2007

• Higher proportion of vancomycin patients had VA priority score of 1 (24.8% vs 17.0%, p=0.019)

• Only 18.6% of patients were culture positive
  – More *Staphylococcus aureus* in vancomycin group (8.8% vs 1.5%, p=0.019)
  – More MRSA in vancomycin group (5.0% vs 1.9%, p=0.004)

Vancomycin AUC Monitoring

- Trough levels do not always correspond with AUC

- AUC-based dosing resulted in
  - ~50% reduction in nephrotoxicity (aOR 0.52; 95% CI, 0.34 to 0.80)
  - Fewer levels required (3.6 vs 2.4, p=0.003)
  - Similar clinical efficacy

Continuous Infusion Vancomycin

- Continuous infusion vancomycin
  - Fewer levels required for monitoring (7.7 vs 11.8, p<0.0001)
  - Less nephrotoxicity than intermittent infusion (RR 0.61; 95% CI, 0.47-0.80) with similar outcomes

Linezolid Monitoring?

- Significant inter- and intra-patient variability in linezolid exposure
  - Optimal AUC not achieved in 63% of patients
  - Optimal T>MIC not achieved in 50% of patients

- Strong correlation between renal clearance and linezolid clearance (r=0.933, p<0.001)
  - Renal dysfunction associated with elevated serum concentrations
  - Elevated serum concentrations associated with thrombocytopenia

Empiric Anti-MRSA Agent: Linezolid Rebuttal

Meghan N. Jeffres, Pharm.D.

@PharmerMeg
LEADER = linezolid experience and accurate determination of resistance
Linezolid Adverse Events

**Long-term use (>28 days)**
- Anemia
- Peripheral and optic neuropathy

**Short-term use**
- Thrombocytopenia
- Serotonin syndrome

**Unpredictable**
- Lactic acidosis

Linezolid-induced Thrombocytopenia

Linezolid and Serotonin Syndrome

Incidence of Serotonin Syndrome

- **Linezolid, n=3218**
- **Comparator, n=3001**

Common Ground

- Reduction in the use of anti-MRSA agents
- MRSA Nasal swabs meta-analysis = NPV 97%

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCR, n=27</th>
<th>PCR, n=30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of vancomycin therapy</td>
<td>4 days ± 2</td>
<td>2 days ± 1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with vancomycin assays</td>
<td>13 (48%)</td>
<td>5 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>7 (26%)</td>
<td>1 (3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (15%)</td>
<td>2 (7%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

In a patient with nosocomial (HAP/VAP) pneumonia, which medication should be used first line as empiric therapy?

A. Vancomycin
B. Linezolid
Vancomycin vs Linezolid for Empiric Coverage of MRSA in Nosocomial Pneumonia

Vancomycin
Brandon Dionne
@BWDionne

Linezolid
Meghan N. Jeffres
@PharmerMeg
Vancomycin vs Fidaxomicin for *Clostridioides difficile* Infection

Fidaxomicin  Tristan Timbrook  @TimbrookTT
Vancomycin  Julie Ann Justo  @julie_justo
In a patient with *C. difficile* infection, which medication should be used first line?

A. Vancomycin
B. Fidaxomicin
The Great ID Debates of One-Eight: Fidaxomicin treatment of Clostridium (Clostridioides) difficile infection

Tristan T. Timbrook, Pharm.D., M.B.A., BCPS
Antimicrobial Stewardship Pharmacist
University of Utah Health
Salt Lake City, UT

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Learning Objectives

- Recognize the guideline recommended first-line treatments for *Clostridium (Clostridioides) difficile* infection (CDI)
- Evaluate the clinical efficacy of fidaxomicin (FID) compared to vancomycin (VAN) in randomized controlled trials (RCTs) for CDI
- Appraise the clinical effectiveness of FID among real world studies
- Examine the cost-effectiveness of FID
Major Points – FID

• Decreased recurrence compared to VAN in RCTs, overall increase in global clinical cure (cure without recurrence)

• Among real world studies, FID effectiveness optimal (even in SOT, cancer, and critically ill) for decreased recurrence

• Cost-effectiveness supports first-line use
# Previous 2010 Guideline Treatment Recommendations

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>WBC &lt; 15k and SCr &lt; 1.5x baseline</td>
<td>Metronidazole</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC ≥ 15k and SCr ≥ 1.5x baseline</td>
<td>VAN</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension, shock, ileus, megacolon</td>
<td>VAN AND metronidazole*</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>First recurrence</td>
<td>---</td>
<td>Same as initial episode</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>---</td>
<td>VAN taper or pulse</td>
<td>B</td>
<td>III</td>
</tr>
</tbody>
</table>

*If complete ileus, consider PR vancomycin; Cohen, SH et al. ICHE 2010.
## Current 2018 Guideline Treatment Recommendations

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC &lt; 15k and SCr &lt; 1.5x baseline</td>
<td>VAN OR FID</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC ≥ 15k and SCr ≥ 1.5x baseline</td>
<td>VAN OR FID</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension, shock, ileus, megacolon</td>
<td>VAN AND metronidazole*</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>First recurrence</td>
<td>---</td>
<td>VAN with taper if used initially</td>
<td>Weak</td>
<td>Low</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>---</td>
<td>Several regimens</td>
<td>Weak except FMT (Strong)</td>
<td>Low except FMT (Moderate)</td>
</tr>
</tbody>
</table>

FMT: Fecal Microbiota Transplantation; *If complete ileus, consider PR vancomycin; McDonald LC. Clin Infect Dis. 2018.
Where in therapy do the 2018 IDSA CDI guidelines place FID?

A. Strong rec, high quality evidence for initial episode, non-severe disease
B. Strong rec, high quality evidence for initial episode, severe disease
C. Equal recommendation to VAN for first recurrence but higher quality evidence for FID
D. All of the above
FID: Efficacy
Phase 3 Studies

• Louie TJ et al, NEJM 2011
  – Population – Patients with initial CDI episode diagnosed by ≥3 diarrhea episode in 24h period and a positive CDI test
    • Excluded severe, severe complicated (toxic megacolon, etc)
  – Randomized to FID 200 mg BID or VAN 125mg QID for 10 days
  – N = 629
  – Rates of clinical cure mITT FID 88.2% vs 85.5% VAN, 92.1% and 89.9% in PP
  – Lower rates of recurrence with FID than VAN (mITT 15.4% vs 25.3%, p=.005; PP 13.3% vs 24.0%, p=.004)
  – Notably, recurrence not different among NAP1/BI/027 strains
    • Though subgroup analysis violates randomization and therefore could relate to confounding

mITT: modified intention-to-treat analysis; PP: per protocol
Other Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Treatment</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornely OA, et al. 2012. <em>Lancet Infect Dis.</em></td>
<td>Multicenter EU and USA</td>
<td>≥ 16 yo, toxin positive CDI</td>
<td>FID 200mg BID vs. VAN 125 QID x 10d</td>
<td>Clinical cure</td>
<td>FID 221/252 (87.7%) vs. VAN 223/257(86.8%) (p=ns)</td>
<td>Among patients on concomitant antibiotics, 90.2% achieved cure with FID vs 73.3% with VAN (p=.031)</td>
</tr>
</tbody>
</table>
| Cornely OA, et al. 2013. *J Clin Oncol.*   | Posthoc analysis of two RCTs in US and Canada | Comparisons of patients with solid tumors or hematologic malignancies to those without (≥ 16y o, toxin positive CDI, ≥ 3 diarrheal events/24h) | FID 200mg BID vs. VAN 125 QID x 10d | Clinical cure | Among cancer patients, FID associated with higher global clinical cure 64/87 (73.6%) vs VAN 50/96 (52.1%) (OR = 2.56, p=0.003) | Among cancer patients, decreased recurrence with fidaxomicin (OR 0.37, p=0.018)  
MV analysis, VAN associated with increased recurrence |
Plausibility of Decreased Recurrence with FID?

- *In vitro*, FID inhibits spore production more than VAN\(^1\)
- *In vivo* among first episode patients, FID associated with at least \(2\log_{10}\) colony-forming units/g greater reduction in spores as compared to VAN\(^2\)
- FID associated with greater preservation of normal microbiome (*Bacteroides/Prevotella spp.*) than patients treated with VAN\(^3\)
- Whole genome sequencing of isolates for the RCTs reflects both decrease relapse with same clonal isolate and reinfection with FID as compared with VAN (p<0.05)\(^4\)
- *Important* as 17% of CDI patients have a 1st recurrence and 35% of those patients have a second recurrence\(^5\)

---

### Pooled Effects of RCTs

- **FID higher** global clinical cure (cure w/o recurrence)\(^1\) than VAN\(^2\)
  - **mITT**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fidaxomicin Events</th>
<th>Total</th>
<th>Vancomycin Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comely 2012</td>
<td>193</td>
<td>252</td>
<td>163</td>
<td>257</td>
<td>45.8%</td>
<td>1.21 [1.08, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Louie 2011</td>
<td>214</td>
<td>287</td>
<td>198</td>
<td>309</td>
<td>54.2%</td>
<td>1.16 [1.05, 1.30]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>539</strong></td>
<td><strong>566</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.18 [1.09, 1.28]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>407</td>
<td>381</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- **Per Protocol**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fidaxomicin Events</th>
<th>Total</th>
<th>Vancomycin Events</th>
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<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comely 2012</td>
<td>172</td>
<td>216</td>
<td>154</td>
<td>235</td>
<td>44.5%</td>
<td>1.22 [1.08, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Louie 2011</td>
<td>204</td>
<td>265</td>
<td>190</td>
<td>283</td>
<td>55.5%</td>
<td>1.15 [1.03, 1.27]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>481</strong></td>
<td><strong>518</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.18 [1.09, 1.27]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>376</td>
<td>344</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Pooled Effects of RCTs

Consistent with findings and interpretation from:

  RR 1.17 (95% CI 1.07 to 1.27)
  – “Moderate quality evidence suggests FID is superior to VAN”

• Beinortas T, et al. Lancet Infect Dis. 2017’s Systematic Review and Network Meta-analysis of RCTs
  – “(for initial CDI) the highest quality evidence indicated FID provides sustained symptomatic clinical cure most frequently...is a better treatment option than VAN...”
How does the clinical efficacy of FID and VAN compare in RCTs?

A. FID associated with decreased recurrence and spore burden
B. FID associated with increased global clinical cure
C. FID associated with increased cure among patients on concomitant antibiotics for other infections
D. All of the above
FID: Real World Effectiveness
## Real-world Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting / Study type</th>
<th>Population</th>
<th>Comparison</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clutter AAC 2013</td>
<td>Multicenter EU and USA</td>
<td>SOT and HSCT patients</td>
<td>FID vs conventional therapies (VAN, metro)</td>
<td>Clinical cure</td>
<td>10/15 (67%) vs 41/44 (89%) (p=NS)</td>
<td>VRE colonization only occurred among patients on conventional therapies</td>
</tr>
<tr>
<td>Penziner AAC 2015</td>
<td>Single center retrospective</td>
<td>ICU or wards patients</td>
<td>FID among ward vs ICU</td>
<td>Clinical cure</td>
<td>67% vs 60% (p=0.9)</td>
<td>Similar recurrence rates 10% vs 8%</td>
</tr>
<tr>
<td>Esmaily-Fard et al, Pharmacotherapy 2014</td>
<td>Single center retrospective academic cancer hospital</td>
<td>Cancer patients with CDI treatment failure or recurrence</td>
<td>Descriptive results of FID use</td>
<td>Clinical cure</td>
<td>91% cure, with 82% sustained clinical cure</td>
<td>86% of patients were on concomitant antibiotics</td>
</tr>
<tr>
<td>Eiland et al. Infect Dis Clin Pract. 2015</td>
<td>Single center retrospective</td>
<td>Admitted patients with CDI</td>
<td>Descriptive results of FID use</td>
<td>Clinical success</td>
<td>58/60 (96.7%) clinical success</td>
<td>6/58 (10.3%) 90d recurrence</td>
</tr>
<tr>
<td>Spiceland et al. J Clin Gastroenterol. 2016.</td>
<td>Multicenter retrospective</td>
<td>CDI FID treated patients with at least 8 weeks followup</td>
<td>Descriptive results</td>
<td>Clinical response</td>
<td>100% among initial, 96% for 1st recurrence, 82% ≥2 recurrence</td>
<td>Recurrence was 0% after 1st episode, 23% after 1 prior episode, 29% after 2 or more</td>
</tr>
</tbody>
</table>
VRE RISK with VAN Treatment

Stevens V, et al. ECCMID 2018

- National Veterans Affairs cohort from 2006-2016 of patients with CDI and no history of VRE infection or colonization in last year

- Patients with oral VAN propensity score matched to other CDI therapies
  - Balanced on important patient characteristics, including CDI severity, comorbidities, and prior IV or oral VAN exposure

- Followed for VRE bloodstream infection or any clinical culture within 3 months

- Of 82,405 patients meeting inclusion criteria, 16,402 patients treated with oral VAN were matched 1:2 to patients who were not

- VAN treated patients were more likely to develop VRE than patients who were treated with other therapies, Relative Risk 1.48 (95% CI 1.26 – 1.75)
How does the clinical efficacy of VAN and FID compare in real world studies?

A. FID has not been shown to be associated with VRE while VAN has
B. FID has shown to be effective in SOT, HSCT, cancer patients, critically ill
C. FID has shown similar safety and efficacy to VAN
D. A and B
FID: Cost Effectiveness
Cost Effectiveness Analyses (Simulation Studies)

Systematic reviews

• Le P, et al. *ICHE*. 2018
  – 5 databases from inception to August 2016
  – 14 studies included, decision tree model or Markov models
  – Initial CDI, FID more cost effective than VAN in 2 of 3 studies
  – For severe initial, FID most cost effective
  – For recurrent CDI, cost-effective in 3/5 studies

• Burton HE, et al. *Pharmacoeconomics*. 2017
  – OVID search through Aug 2016
  – 27 studies included
  – Fidaxomicin was cost effective vs. VAN or metro 14/24 studies (58.3%)
Real World Cost-effectiveness

• 2-year clinical and economic impact study of academic medical center use of protocol encouraging FID first line

• Compared patients on VAN or FID for CDI
  – Age ≥65, concomitant antibiotics, immunocompromised, or severe CDI

• Primary outcome: 90 day CDI readmission

• Economic evaluation based on hospital charges and insurance reimbursement for readmission, also cost of CDI therapy

• Recurrence 10/49 (20.4%) FID v.s 19/46 (41.3%) vancomycin (p=0.027)
  – Confirmed in multivariate regression (FID aOR 0.33, 95% CI 0.12 to 0.93)

• Hospital costs on average of $3,286 with FID vs $6,333 with VAN
  – Cost savings of $3,047 with FID

How does the cost effectiveness of VAN and FID compare?

A. Cost-effectiveness analysis (simulation studies) overwhelmingly favor VAN
B. Cost-effectiveness analysis (simulation studies) overwhelmingly favor FID
C. Real world implementation cost effectiveness studies favor FID, the majority of cost-effectiveness analysis studies favor FID
D. None of the above
1) Overall, fidaxomicin is a more efficacious therapy than VAN as it is associated with increased global clinical cure and decreased recurrence.

2) Special populations (cancer, SOT) and severe CDI also benefit from FID therapy over alternatives.

3) Institutions should adopt FID as first line therapy based on clinical outcomes in addition to economic data which support its cost-effectiveness.
The Great ID Debates of One-Eight: Vancomycin treatment of *Clostridium (Clostridioides) difficile* infection

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Learning Objectives

• Recognize the recommended first-line treatments for *Clostridium (Clostridioides) difficile infection* (CDI)

• Evaluate the clinical efficacy of vancomycin compared to fidaxomicin in randomized controlled trials (RCTs) for CDI

• Evaluate the real-world implications of replacing vancomycin with fidaxomicin in the treatment of CDI
Major Points – Pro Vancomycin

• Vancomycin (VAN) now the gold standard therapy for CDI treatment

• Patient accessibility to vancomycin >>> fidaxomicin (FDX)

• Differences in CDI recurrence rates between VAN & FDX can be mitigated by other factors
### IDSA/SHEA 2017 Guideline Update for CDI

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment</th>
<th>Strength of Recommendation/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC ≤ 15k and SCr &lt; 1.5x baseline</td>
<td>VAN 125 mg PO QID x10 days OR FDX 200 mg PO BID x10 days</td>
<td>Strong/High</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC &gt; 15k or SCr ≥ 1.5x baseline</td>
<td>VAN 125 mg PO QID x10 days OR FDX 200 mg PO BID x10 days</td>
<td>Strong/High</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>VAN 500 mg PO QID (+ Rectal VAN if ileus) + Metronidazole 500 mg IV Q8h</td>
<td>Strong/Moderate, except Weak/Low for rectal VAN</td>
</tr>
<tr>
<td>First recurrence</td>
<td>---</td>
<td>VAN PO, with taper/pulse if VAN initially OR FDX 200mg PO BID x 10 days, if VAN initially</td>
<td>Weak/Low</td>
</tr>
<tr>
<td>Second or subsequent recurrence</td>
<td>---</td>
<td>Several regimens, e.g. VAN PO taper/pulse, FDX PO, FMT</td>
<td>Weak/Low, except Strong/Moderate for FMT</td>
</tr>
</tbody>
</table>

FDX = Fidaxomicin, FMT = Fecal microbiota transplant, RCT = Randomized controlled trial, SCr = Serum creatinine, VAN = Vancomycin, WBC = White blood cell count

Where in therapy do the IDSA/SHEA 2017 updated CDI guidelines place vancomycin?

A. Strong rec, high quality evidence for initial episode, non-severe disease
B. Strong rec, high quality evidence for initial episode, severe disease
C. Recommended for fulminant CDI and/or any recurrences
D. All of the above
Proven Track Record

• No studies show superiority over vancomycin

• Vancomycin DOES show superiority over other therapies
Vancomycin vs. Metronidazole

**Zar et al 2007**

<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort (N=150)</th>
<th>Severe CDI (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>90%</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Clinical Cure**

P = 0.02

**Johnson et al 2014**

<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort (N=1071)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>81%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>73%</td>
</tr>
<tr>
<td>Tolevamer</td>
<td>44%</td>
</tr>
</tbody>
</table>

**Clinical Success**

P = 0.020

Vancomycin vs. Fidaxomicin

Louie et al 2011
N=596

Cornely et al 2012
N=509

Which of the following is true regarding the clinical efficacy of vancomycin in RCTs?

A. VAN associated with decreased **clinical cure** vs. metronidazole  
B. FDX associated with increased **clinical cure** vs. VAN  
C. VAN associated with decreased **sustained response** vs. FDX  
D. All of the above
Vancomycin Plays Well With Others

- **Accessibility**: On formulary & stocked in most pharmacies
- **Availability**: New & improved RECONSTITUTED oral vancomycin solution
  - Removes need for “compounding”
- **Administratibility**: Capsule and liquid formulations
  - Any oral entry = drug delivery
- **Affordability**: Covered by most/all major payors
  - Generic product!
## Price Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Average Wholesale Price(^1)</th>
<th>Estimated Cost for 10-day Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>125 mg PO QID x 10 days</td>
<td><strong>Firvanq® 50mg/mL reconstituted solution:</strong> $1.00 per mL (150 mL, 300 mL)</td>
<td>$1 x 150 mL = <strong>$150</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin HCl 125 mg: $31.33 per capsule</td>
<td>$31 x 40 caps = <strong>$1,240</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancocin® 125 mg: $94.38 per capsule</td>
<td>$94 x 40 caps = <strong>$3,760</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin compounded oral solution</td>
<td>~$60 (varies)(^2)</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>200 mg PO BID x 10 days</td>
<td><strong>Dificid® 200 mg:</strong> $220.90 per tablet</td>
<td>$220 x 20 tabs = <strong>$4,400</strong></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg PO TID x 10 days</td>
<td>Metronidazole 500 mg PO: $0.26-$0.93 per tablet</td>
<td>$0.60 x 30 caps = <strong>$18</strong></td>
</tr>
<tr>
<td></td>
<td>500 mg IV Q8h</td>
<td>Metronidazole 5 mg/mL IV: $0.01-$0.06 per mL</td>
<td>$0.03 x 3,000 mL = <strong>$90</strong></td>
</tr>
</tbody>
</table>

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2. Personal communication with Palmetto Health Richland Hospital Pharmacy on October 1, 2018.
Deployability of First-Line Fidaxomicin?

• Difficult to determine those at highest risk for CDI recurrence
  → Give fidaxomicin to everyone?

• Real-life hurdles of payment for fidaxomicin ($$$)

• Time needed to secure access, e.g. prior authorization, also costly to healthcare system
Preventing CDI Recurrence

• Benefit of fidaxomicin is compared to vancomycin x 10 days

• Why not extend, taper, and/or pulse vancomycin?
  – Vancomycin taper/pulse is an accepted option for first recurrence\textsuperscript{1,2}
    • Option for those at high risk of first recurrence too?
  – More vancomycin is still cheaper than a course of fidaxomicin

• Why not give vancomycin in combination with more economical (& likely more effective) non-antibiotic therapies?

Early Fecal Microbiota Transplant (FMT)?

- Observational cohort of CDI (N=111) in France
- Evaluated all-cause 3-month mortality with early FMT vs. no FMT
  - Adjusted OR 0.13 (95% CI 0.04-0.44, p=0.001)
- Limitations:
  - Elderly cohort (median age 81-83 years)
  - Unblinded investigators

Number needed to treat to save 1 life at 3 months in severe CDI cases:

2

Early Kefir?

• Case series of recurrent CDI (N=25)\textsuperscript{1}

• 8-week course of staggered and tapered antibiotic withdrawal (STAW) regimen with metronidazole (N=4) or VAN (N=21) + Probiotic liquid kefir 150 mL PO TID with meals

• 84% (21/25) remained free of diarrheal symptoms at 9 months
  – 16% (4/25) patients relapsed, but were successfully treated with VAN x 14 days, followed by rifaximin x 14 days

• Counseling point for all CDI?

Multiple CDI Recurrences

• Let’s be real...just give me the poop, please.
Fear Mongering

• Concern for emergence of vancomycin-resistant enterococci (VRE)?

Brief pause for Dr. Timbrook to indicate where the IDSA/SHEA CDI guidelines state that oral vancomycin is a risk factor for VRE acquisition
Fidaxomicin for Everyone?
Does It Pass the Mentor “Sniff” Test?
KEY TAKEAWAYS

• Vancomycin now the gold standard therapy for CDI treatment
  – Including non-severe, severe, fulminant disease and/or recurrence

• Patient accessibility to vancomycin >>> fidaxomicin
  – Oral vancomycin now available as reconstituted oral solution or generic capsules (or compounded product if still available locally)
  – Fidaxomicin remains exceedingly expensive for many patients/payers

• We should explore more economical options to ↓ the CDI recurrence rate
  – Vancomycin taper/pulse, adjunctive FMT or kefir, etc.
ReBUTTal: FID For Your Father, VAN For Your Father-in-law

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Why Not FID for Everyone?

• Obviously FID is a better drug for global clinical cure and decreased recurrence

• Economic analysis reflects better overall impact

• Possible proposed problem:
  – May not be able to justify FID first line for everyone

• The **REAL** problems:
  – Over diagnosis of CDI with molecular testing
  – Risk of recurrence *not reliably predictable*
Overdiagnosis of CDI: Fix Your Testing

Issue:
• Most labs performing PCR for CDI detection
  – Does not detect toxin production and therefore may reflect colonization
  – CDI rates often reported to double after switching to PCR

Solutions:
• Increase pre-test probability of disease with EHR modifications
  – Discourage testing if
    • Recent laxatives, tube feeds
    • Insufficient stooling criteria
  – ESCMID recommends and IDSA acknowledges multistep testing algorithms with different technologies can help to mitigate inappropriate diagnosis
Risk Scores: Better Than Guessing but Perfect?

- Possible solution?: CDI initial episode recurrence risk score\(^1\)
  - Low risk (8.9%; 0-2 pts)
  - Medium risk (20.2%; 3-5 pts)
  - High-risk (35%; 6-8 pts)

- Caution overestimation of prediction reliability from risk scores
  - MRSA nasal colonization outperforms risk scores for predicting MRSA BSIs and wound infections\(^2,3\)
  - Genotypic detection outperforms multiple risk scores for ceftriaxone non-susceptibility in *Enterobacteriaceae* bloodstream infections\(^4\)
    - AUC 92.3% vs 68.7-71.1% (86-89% original studies)
  - In general, risk models suffer in performance in other populations due to “overfitting” in source cohort\(^5\)


<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior 3(^{rd}) or 4(^{th}) generation Cephalosporins</td>
<td>1</td>
</tr>
<tr>
<td>PPI</td>
<td>1</td>
</tr>
<tr>
<td>Prior anti-diarrheals</td>
<td>1</td>
</tr>
<tr>
<td>Non-severe CDI</td>
<td>2</td>
</tr>
<tr>
<td>Community-onset CDI</td>
<td>3</td>
</tr>
</tbody>
</table>

*During 90 days prior
Risk Factors: Can You Tell Who Is At High Risk Of Recurrence?

• Seven hospitals in UK started using FID

• Methods
  – Include patients with positive CDI test, ≥ 3 diarrheal episodes/24h, excluded patients with CDI in last 3 months
  – Hospitals had different use protocols
  – At the two hospitals (A&B) using FID first line for everyone while others (C-G) used only in select patients

• Results
  – At hospitals A&B recurrence for initial fell from 10.6-16.3% to 3.1%, mortality dropped significantly as well (p<0.05)
  – Hospital C-G had overall minimal changes and in one hospital recurrence increased

In Closing: CDI Treatment For Your Favorite Colleague

Julie,
Would you give your friend and beloved coworker, Brandon Bookstaver vancomycin for CDI?

*Adapted from MADID 2017 Sheetz vs Lodise debate*
ReBUTTal: Pro Vancomycin

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Cost-Effectiveness Data

• For 1st recurrence of CDI, compared FDX, VAN, or VAN + bezlotoxumab

• Outcome: Incremental cost-effectiveness ratio (ICER)
  – Payer’s perspective
  – Willingness-to-pay (WTP) threshold of $100,000

  - VAN has 68.4% probability of being the most cost-effective
    • Only 29.2% for FDX and 2.4% for VAN + bezlotoxumab

Expanding Fidaxomicin Use in the Real-World

- 7 hospitals in the United Kingdom included FDX in their clinical protocols between 2012-2014

Expanding Fidaxomicin Use in the Real-World

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Expanding Fidaxomicin Use in the Real-World

### Table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI recurrence rates</td>
<td>Absolute ↓ of ~10% with FDX for all (Hospital A, B) ✅</td>
</tr>
<tr>
<td>Length of stay</td>
<td>↑ or stayed the same ✗</td>
</tr>
<tr>
<td>Time to resolution of diarrhea</td>
<td>↑ or stayed the same ✗</td>
</tr>
</tbody>
</table>

- **Discrepancies:**
  - Hospitals E & F actually had 49%-66% FDX use in post period
    - Yet had comparable outcomes in recurrence and mortality??
  - Hospital D had only 7% (4/56) FDX use in post period
    - Yet still managed to significantly ↓ recurrence rate and mortality??

- **Lesson:** Difficult to predict the impact of expanding your local FDX use

In a patient with *C. difficile* infection, which medication should be used first line?

A. Vancomycin  
B. Fidaxomicin
Vancomycin treatment of Clostridium (Clostridioides) difficile infection

Fidaxomicin
Vancomycin
Tristan Timbrook
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KEY TAKEAWAYS

1) VANCOMYCIN IS THE GOLD STANDARD – PRO VANCOMYCIN
We have used vancomycin for 50 years with vancomycin with very little resistance. Increasing linezolid use had been shown to cause spikes in resistance.

2) OPPORTUNITY COST OF VANCOMYCIN – PRO LINEZOLID
Time spent monitoring vancomycin can and should be reallocated to activities proven to improve patient care, outcomes, and institutional costs.

3) FIDAXOMICIN IS MULTIFACETED – PRO FIDAXOMICIN
Higher upfront cost results in increased global cure, decreased recurrence, & proven cost-effectiveness.

4) VANCOMYCIN IS THE GOLD STANDARD – PRO VANCOMYCIN
Recommended for ALL types of CDI. Fidaxomicin isn’t the answer – call for research for more economical solutions.
The Great ID Debates of One-Eight

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