New Antibiotics

Kurt B. Stevenson, MD, MPH
Professor of Medicine and Epidemiology
Division of Infectious Diseases
Department of Internal Medicine
The Ohio State University College of Medicine

Critical impact of antimicrobial resistance

“However we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive - and, in some cases, nonexistent.”

-A Public Health Action Plan to Combat Antimicrobial Resistance

CDC

Underline added


Science 2008;321:356-361
**ESKAPE pathogens**

- *Enterococcus faecium* (VRE)
- *Staphylococcus aureus* (MRSA)
- *Klebsiella pneumonia* (ESBL-producing)
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter* species

**Emerging Antimicrobial Resistance**

- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- Multi-drug resistant gram-negative bacilli
  - “SPACE” organisms (Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter)
  - Ciprofloxacin resistance
  - AmpC/inducible beta-lactamases
  - Extended spectrum beta-lactamases (ESBLs)
  - Carbapenem-resistance (KPC, NDM-1)
  - Colistin resistance

**Rice LB. J Infect Dis 2008;197:1079-81**
Role of Antimicrobial Stewardship

- “Antimicrobial stewardship includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.”
Clinical implications

Piperacillin-Tazobactam and Pseudomonas bacteremia

Newer antibiotics

• Daptomycin
• Linezolid
• Tigecycline
• Ceftaroline
• Telavancin and dalbavancin: will not discuss
• Colistin
• Fidaxomicin

Daptomycin

• Active against Gram-positive bacteria
• Binds to bacterial membrane with rapid depolarization of membrane potential
• Proven activity in vitro against enterococci (including VRE) and Staphylococcus aureus (including MRSA)
• Binds avidly to pulmonary surfactant and thus, it cannot be used in pneumonia

http://www.wikipedia.org

Daptomycin-FDA indications

- Complicated skin and skin structure infections (cSSSI)
- Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infection endocarditis.


Methods
We randomly assigned 134 patients with S. aureus bacteremia with or without embolic events to receive 6 mg of daptomycin intravenously per kilogram of body weight daily and 1.2 to receive intravenous daptomycin plus either an antifungal or vancomycin. The primary efficacy end point was treatment success 45 days after the end of therapy.

Results
Every two days after the end of therapy in the modified intention-to-treat analysis, a successful outcome was documented for 51 of 68 patients who received daptomycin compared with 39 of 66 patients who received standard therapy (46.2 percent absolute difference, 24 percent confidence interval, 9.5 to 40.0 percent). The results were preserved even after the exclusion of patients with right-sided infection endocarditis. Daptomycin was more successful in patients with methicillin-resistant S. aureus and those with endocarditis than in patients with methicillin-sensitive S. aureus (bacteremia) and methicillin-resistant S. aureus. Daptomycin therapy was associated with a higher rate of microbiologic failure than was standard therapy (39 vs. 47 patients, P=0.03). In 6 of the 10 patients with microbiologic failure in the daptomycin group, isolates with reduced susceptibility to daptomycin were identified. Similar results were noted in patients with vancomycin. In comparison with daptomycin therapy, standard therapy was associated with a nonsignificantly higher rate of adverse events that led to treatment failure due to the discontinuation of therapy (27 vs. 8, P=0.16). Clinically significant renal dysfunction occurred in 13.4 percent of patients who received daptomycin and in 26.3 percent of patients who received standard therapy (P=0.04).


The NEW ENGLAND JOURNAL OF MEDICINE

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by Staphylococcus aureus


Figure 1. Comparison of the Rates of Success of Daptomycin and Standard Therapy for Staphylococcus aureus Bacteremia and Endocarditis.*
Vancomycin MIC creep

Daptomycin for vancomycin failure and infections due to VISA or VRSA

Moise-Broder PA. Clin Infect Dis 2004;38:1700-1705

Linezolid

oxazolidinone

Time dependent killing; 24 hr AUC/MIC

http://www.wikipedia.org

Daptomycin-Adverse Effects

- Diarrhea (5.2-11.7%), vomiting (3.2-11.7%)
- Pain in throat (8.3%)
- Rhabdomyolysis—need to always monitor CPK level
- Renal failure (2.2-3.3%)
- Asthmatic pulmonary eosinophilia

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Linezolid

- Works on the initiation of protein synthesis; binds to 50S ribosome
- This disruption occurs earlier in the process than other protein synthesis inhibitors (chloramphenicol, clindamycin, aminoglycosides, and macrolides)
- Effective against gram positives: enterococcus (VRE), staphylococcus (MRSA)
- Some anaerobic activity
- No gram negative activity
- Excellent lung penetration

Antimicrobial Agents Chemotherapy 1998;42:3251-3255
### Linezolid
- Excellent bioavailability
- Predictable thrombocytopenia typically >14 days
- Neuropathy when given longer time periods (typically >6-12 weeks)
  - Optic: usually reversible
  - Peripheral: may persist; painful sensory
- Mitochondrial toxicity: lactic acidosis

### FDA Indications-2
- Uncomplicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible strains only) or *S. pyogenes*
- Community-acquired pneumonia caused by *S. pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or *S. aureus* (methicillin-susceptible strains only)

### FDA Indications
- Vancomycin-resistant *Enterococcus faecium* (VRE), including cases with or without concurrent bacteremia
- Pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible strains only)
- Complicated skin and skin structure infections caused by *S. aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*

### FDA Alert
- FDA ALERT [3/16/2007]: FDA is issuing this alert to advise you of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. In this study, patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study.

FDA Alert

• Linezolid is not approved for the treatment of catheter-related bloodstream infections, catheter-site infections, or for the treatment of infections caused by Gram negative bacteria. If infection with Gram negative bacteria is known or suspected, appropriate therapy should be started immediately. FDA is currently evaluating the new study along with other information about linezolid.


Background. Catheter-related bloodstream infection (CRBSI) causes substantial mortality and morbidity, but few randomized, controlled studies have been conducted to guide therapeutic interventions.

Methods. To determine whether linezolid would be noninferior to vancomycin in patients with CRBSI, we conducted an open-label, multicenter, comparative study. Patients with suspected CRBSI were randomized to receive linezolid or vancomycin (control group). The primary end point was microbiologic outcome at test of cure 1–2 weeks after treatment, as assessed by step-down procedure. The first analysis population was complications skin and skin structure infection (cSSI) in patients with suspected CRBSI: patients with CRBSI were analyzed if noninferiority criteria (lower bound of the 95% confidence interval [CI] not outside -15%) were met.

Results. Noninferiority criteria were met for cSSI (microbiologic success rate for linezolid recipients, 89.6%; 146 of 163 patients) and for the control group, 89.9% (141 of 158; 95% CI, 79–to 96.6) and CRBSI (linezolid recipients, 86.3% [82 of 95]; for the control group, 85.5% [67 of 79]; 95% CI, 73–to 97). The frequency and severity of adverse events were similar between groups. Mortality rates were 10.4% for linezolid recipients (2 of 20 patients) and 10.3% for control subjects (2 of 27) in the modified intent-to-treat population (i.e., all patients with gram-positive baseline culture) through test of cure, and they were 33.3% for linezolid recipients (7 of 35) and 45.8% for the control group (5 of 36; 95% CI, 13 to 112) for all treated patients through poststudy treatment day 84.

Conclusion. Linezolid demonstrated microbiologic success rates noninferior to those for vancomycin in patients with CRBSI and CRBSIs caused by gram-positive organisms. Patients with catheter-related infections must be carefully investigated for the heterogeneous underlying causes of high morbidity and mortality, particularly for infections with gram-negative organisms.

Table 4. Clinical outcome analysis of patient subtests with complicated skin and skin-structure infection (cSSI) and bloodstream infections.

<table>
<thead>
<tr>
<th>Population</th>
<th>Linezolid group</th>
<th>Control group</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Companied SSSI</td>
<td>129/154 (83.8)</td>
<td>122/142 (85.9)</td>
<td>10.3 to 60</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>66/61 (91.0)</td>
<td>62/71 (87.6)</td>
<td>5.7 to 15.7</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>42/46 (91.3)</td>
<td>32/39 (82.1)</td>
<td>7.3 to 23.6</td>
</tr>
<tr>
<td>Test of cure</td>
<td>123/156 (77.6)</td>
<td>113/145 (77.6)</td>
<td>9.4 to 93</td>
</tr>
<tr>
<td>S. aureus</td>
<td>36/44 (81.8)</td>
<td>48/77 (62.3)</td>
<td>12.2 to 16.0</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>36/48 (74.1)</td>
<td>38/50 (76.0)</td>
<td>19.7 to 24.3</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>7/8 (87.5)</td>
<td>6/7 (85.7)</td>
<td>12.2 to 11.4</td>
</tr>
<tr>
<td>Test of cure</td>
<td>7/8 (87.5)</td>
<td>6/7 (85.7)</td>
<td>18.0 to 17.0</td>
</tr>
<tr>
<td>S. aureus</td>
<td>3/4 (75.0)</td>
<td>3/4 (75.0)</td>
<td>0.0 to 19.0</td>
</tr>
<tr>
<td>Methicillin-resistant S. aureus</td>
<td>3/4 (75.0)</td>
<td>3/4 (75.0)</td>
<td>21.4 to 27.4</td>
</tr>
</tbody>
</table>

Note: Data are no. of failures or no. of patients assessed, unless otherwise indicated. Percentages were based on number of patients assessed and excluded patients with indeterminate outcomes.
Linezolid-Adverse Effects

- Rash (0.4-7%)
- Diarrhea (2.8-11%); nausea (1.4-9.6%); vomiting (0.9-9.4%)
- Headache (0.5-11.3%)
- Fever (1.6-14.1%)
- Serious: lactic acidosis, myelosuppression and thrombocytopenia, neuropathy, optic nerve disorders

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Tigecycline

- Active against many gram positives (including MRSA), gram negative bacilli, and anaerobes; no activity against Pseudomonas or Proteus
- Licensed against skin and soft tissue infections, intra-abdominal infections, and community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, Haemophilus influenzae (beta-lactamase negative isolates), and Legionella pneumophila

Tigecycline-Adverse Effects

- Abdominal pain, diarrhea, nausea, vomiting
- Headache
- Serious: septic shock, pancreatitis, elevated liver ALT, anaphylaxis

FDA Safety Communication

- [09-01-2010] The U.S. Food and Drug Administration (FDA) is reminding healthcare professionals of an increased mortality risk associated with the use of the intravenous antibacterial Tygacil (tigecycline) compared to that of other drugs used to treat a variety of serious infections. The increased risk was determined using a pooled analysis of clinical trials. The cause of the excess death in these trials is often uncertain, but it is likely that most deaths in patients with these severe infections were related to progression of the infection.
- The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infection. Tygacil is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia) or diabetic foot infection. Tygacil is approved by FDA for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia.

Ceftaroline

Advanced generation cephalosporin
Time above MIC; time-dependent killing


http://www.wikipedia.org
Ceftriaxone

- Broad-spectrum oxyimino-cephalosporin
- Activity against Gram-positive organisms including MRSA and drug-resistant S pneumoniae and a variety of Gram-negative organisms
- Antimicrobial activity correlates with T>MIC

**FDA Indications**

- Acute bacterial skin and skin structure infections
  - *Staphylococcus aureus* (MSSA and MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*
- Community-acquired bacterial pneumonia
  - *Streptococcus pneumoniae* (with or without bacteremia), *S. aureus* (MSSA only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, *E. coli*

**Comparative in vitro MIC<sub>90</sub>s**

<table>
<thead>
<tr>
<th>Organism (no. of isolates tested)</th>
<th>Ceftaroline</th>
<th>Vancomycin</th>
<th>Daptomycin</th>
<th>Ceftriaxone</th>
<th>Linezolid</th>
<th>Erythromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (MSSA) 348</td>
<td>0.25</td>
<td>8</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (MRSA) 92</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>*Vancomycin-resistant (VISA) 20</td>
<td>1</td>
<td>32</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>*Vancomycin-resistant (VRSA) 10</td>
<td>0.5</td>
<td>32</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> (MSSA) 201</td>
<td>0.12</td>
<td>2</td>
<td>4</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> (MRSA) 299</td>
<td>0.5</td>
<td>32</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (Erythromycin susceptible) 157</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (Erythromycin resistant) 10</td>
<td>1.5</td>
<td>0.5</td>
<td>NA</td>
<td>0.12</td>
<td>1</td>
<td>0.16</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (Erythromycin susceptible) 59</td>
<td>0.015</td>
<td>0.5</td>
<td>NA</td>
<td>0.12</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (Erythromycin resistant) 25</td>
<td>4</td>
<td>16</td>
<td>1</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em> (Erythromycin susceptible) 157</td>
<td>0.012</td>
<td>0.5</td>
<td>NA</td>
<td>0.06</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em> (Erythromycin resistant) 157</td>
<td>0.012</td>
<td>0.5</td>
<td>NA</td>
<td>0.06</td>
<td>1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Supporting Studies**

  - Total of 1396 adults with clinically documented complicated skin and skin structure infection were enrolled in two identical, randomized, multi-center, multinational, double-blind, non-inferiority trials comparing ceftaroline (600 mg IV over 1 hour every 12 hours) to vancomycin plus aztreonam (1 g administered over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours).
  - A total of 1231 adults with a diagnosis of CABP with enrolled in two randomized, multi-center, multinational, double-blind, non-inferiority trials comparing ceftaroline (600 mg administered IV over 1 hour every 12 hours) with ceftiraxone (1 gram IV over 30 minutes every 24 hours).
Potential off label uses

- Refractory MRSA bacteremia
  - Rabbit endocarditis model
- MRSA pneumonia
  - Murine MRSA pneumonia model with ceftaroline performing better than vancomycin or linezolid
- MRSA meningitis
Treatment of bacteremia?

Initial Case Series


Ceftaroline-Adverse Effects

- Diarrhea, nausea, urticaria, rash
- Increased transaminases, hypokalemia, phlebitis, fever
- Anemia, neutropenia, thrombocytopenia
- Anaphylaxis, positive Direct Coomb’s test
- Dizziness, seizures
- Bradycardia

Colistin

Polymixin E

**Colisitin**

- Mixture of cyclic polypeptides (polymixin A and B); polycationic with both hydrophilic and lipophilic moieties
- Disrupts cell membrane
- Active against gram negative bacteria *esp* *Pseudomonas* and *Acinetobacter*
- Previous concerns for neurotoxicity and nephrotoxicity
- Resistance currently is rare

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**Colistin resistance**

- 265 isolates of *Acinetobacter* from 2 Korean hospitals
- Categorized into 3 subgroups:
  - Subgroup I (142 isolates [53.6%])
  - Subgroup II (54 [20.4%])
  - Subgroup III (18 [6.8%])
- Forty-eight isolates (18.1%) and 74 isolates (27.9%) were resistant to polymyxin B and colistin, respectively.

*J. Antimicrob Chemother.* 2007; 60:1163-1167

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**Intravenous Colistin as Therapy for Nosocomial Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanii***

Anna S. Levis, Janaina A. Barone, Juliane Pompei,
Marcio V. Santos, Renato M. Murtinho, Enzo A. G. Arambay,
Eduardo M. Venturim, and Silvia F. Costa

J Clin Infect Dis 1999;28:1008-1011

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*Advances in Anti-infective Chemotherapy* 29 August 2007

High rates of resistance to colistin and polymyxin B in subgroups of *Acinetobacter baumanii* isolates from Korea

Koore Su Ha1, Ji Young Suh, Ki Seol Kim, Seok-Jin Jung, Kyung-Ho Park, Chul Ho Kang, Doo Byon Chun, Kyung-Ran Park and Joo-Heon Song

1Department of Medical Microbiology, Kangnung University School of Medicine, Gangneung, Korea
2Kangnung Research Foundation for Infectious Disease (KaRFD), Gangneung, Korea
3Division of Infectious Diseases, Kangnung National University Medical School, Gangneung, Korea
4Division of Infectious Diseases, Kangnung University School of Medicine, Gangneung, Korea

Clin Infect Dis 1999:28:1008-1011
Objective: To investigate antimicrobial resistance in clinical isolates of Achromobacter spp. from two Korean hospitals.

Methods: Two hundred and sixty-five isolates of Achromobacter spp. from two Korean hospitals were screened and were identified in species level using partial 16S rRNA gene sequences. Antimicrobial susceptibility testing was performed using an broth microdilution method.

Results: rpoC gene sequences indicated that 214 isolates (80.8%) were Achromobacter baumannii, and allowed these to be classified into three subgroups: I, II, and III. 153 isolates (57.4%) belonged to subgroup I, 54 (20.4%) to subgroup II, and 14 (5.3%) to subgroup III. Forty-eight isolates (18.1%) and 74 isolates (27.8%) were resistant to polymyxin B and colistin, respectively. However, antimicrobial resistance rates varied markedly between subgroups. While A. baumannii of subgroup I showed low resistance rates to polymyxin B and colistin (7.7% and 7.1%, respectively), subgroups II and III showed high resistance rates to these antibiotics (38.9% and 64.6% in subgroup II and 72.2% and 88.6%, in subgroup III, respectively). Multilocus resistance was also significantly more frequent in subgroups II (63.1%) than in subgroups I and III (15.0% and 16.7%, respectively).

Conclusion: Our data indicate that subgroup identification of A. baumannii may aid selection of appropriate antimicrobial agents for the treatment of Achromobacter infections.

Journal of Antimicrobial Chemotherapy (2017) 72, 1863–1871
doi:10.1093/jac/dkw695
Advance Access publication 2 August 2017

Summary

Recent studies in critically ill patients who received intravenous polymyxins for the treatment of serious P. aeruginosa and A. baumannii infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable efficacies and considerably less toxicity than was reported in old studies. The frequency of nephrotoxicity and severity of neurotoxicity seems to be substantially less than previously believed. Recently, a significant increase in the data gathered on colistin has focused on its chemistry, antimicrobial activity, mechanism of action and resistance, pharmacokinetics, pharmacodynamics, and new clinical applications. Colistin has attracted much interest during the last years because of its significant activity against MDR P. aeruginosa, A. baumannii, and K. pneumoniae strains responsible for ICU-acquired infections in critically ill patients. It is likely that colistin will be an important antimicrobial option against MDR gram-negative bacteria for at least several years (32). It should be terminated that no self-designed, randomized controlled studies have been conducted to evaluate the effectiveness and safety of polymyxins for the treatment of life-threatening, ICU-acquired infections caused by MDR gram-negative pathogens, such as P. aeruginosa, A. baumannii, and K. pneumoniae. For this reason, such trials are urgently needed.


Fidaxomicin

http://www.wikipedia.org
Fidaxomicin

- Inhibits bacterial RNS polymerase resulting in the death of *C. difficile*
- FDA indications: treatment of *C. difficile* infections

Current Opinion Microbiology 2011; 14:532-543

**METHODS**

Adults with acute symptoms of *C. difficile* infection and a positive result on a stool toxin test were eligible for study entry. We randomly assigned patients to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The primary end point was clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy). The secondary end points were recurrence of *C. difficile* infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure (i.e., cure with no recurrence).

**RESULTS**

A total of 629 patients were enrolled, of whom 546 (86.1%) could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.3% with fidaxomicin and 85.6% with vancomycin) and the per-protocol analysis (93.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%; P=0.005) and the per-protocol analysis (13.3% vs. 24.1%; P=0.004). The lower rate of recurrence was seen in patients with non-North American Pulsed Field Type 1 strains. The adverse-event profile was similar for the two therapies.

Original Article

**Fidaxomicin versus Vancomycin for Clostridium difficile Infection**

Thomas J. Louis, M.D., Mark A. Miller, M.D., Kathleen M. Mullen, D.O., Karl Weiss, M.D., Arnold Lennox, M.D., Yossi Golan, M.D., Sherwood Gerbach, M.D., Pamela Sears, Ph.D., and Yoon-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

NEJM 2011;364:422-431

Figure 1: Rates of Primary and Secondary End Points.

For the primary outcome of clinical cure, the lower boundary of the 95% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was >3 percentage points in the modified intention-to-treat (MITT) analysis and >2.6 percentage points in the per-protocol (PP) analysis.
Fidaxomicin-Adverse Effects

- Abdominal pain, nausea, vomiting
- Anemia, neutropenia
- Bowel obstruction (<2%), GI bleeding (4%)

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