New Antibiotics

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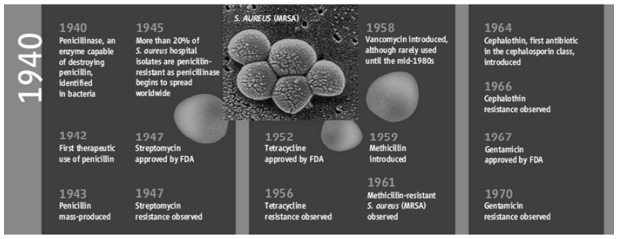
http://www.who.int/world-health-day/2011/en/index.html

Critical impact of antimicrobial resistance

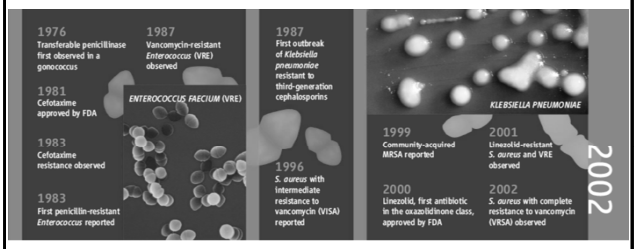
"If we do not act to address the problem of AR, we may lose quick and reliable treatment of infections that have been a manageable problem in the United States since the 1940s. Drug choices for the treatment of common infections will become increasingly limited and expensive - and, in some cases, nonexistent."

-A Public Health Action Plan to Combat Antimicrobial Resistance
CDC

Underline added



Science 2008;321:356-361



Science 2008;321:356-361

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**

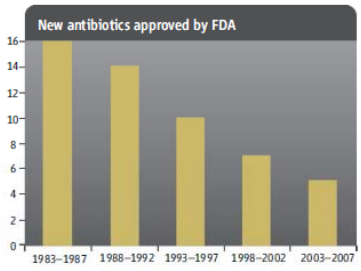
ESKAPE pathogens

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

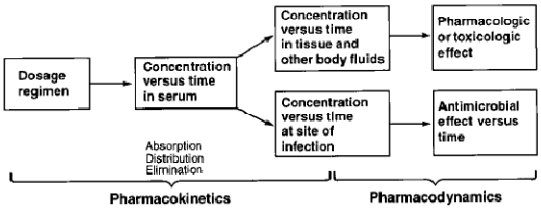
Rice LB. *J Infect Dis* 2008;197:1079-81

Emerging Antimicrobial Resistance

- **Epidemic strains of *C. difficile***
- **Vancomycin-resistant *Enterococcus ssp.* (VRE)**
- **Vancomycin-intermediate *Staphylococcus aureus* (VISA)**
- **Vancomycin-resistant *Staphylococcus aureus* (VRSA)**



Science 2008;321:356-361



Clin Infect Dis 1998;16:1-12

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."**

Clin Infect Dis 2007;44:159-177

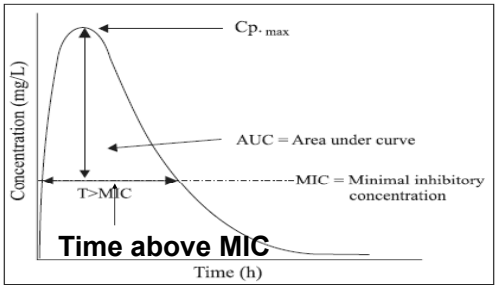
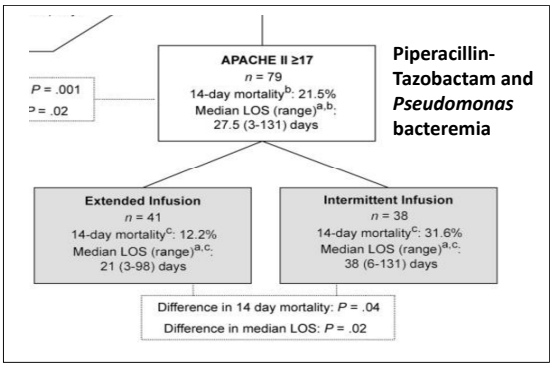


Figure 1. Depiction of pharmacodynamic parameters over a concentration time profile

http://www.scielo.br/img/revistas/bjm/v38n2/n2a01fig02.gif

Clinical implications

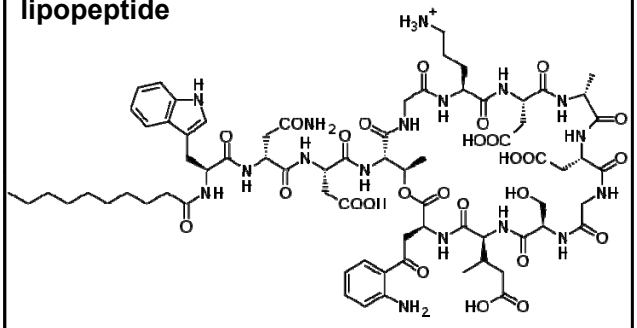


Piperacillin-Tazobactam and *Pseudomonas* bacteremia

Clin Infect Dis 2007;44:357-363

Daptomycin

lipopeptide



Time dependent killing; 24 hr AUC/MIC; Peak/MIC

http:/www.wikipedia.org

Newer antibiotics

- **Daptomycin**
- **Linezolid**
- **Tigecycline**
- **Ceftaroline**
- **Telavancin and dalbavancin: will not discuss**
- **Colisitin**
- **Fidaxomicin**

Daptomycin

- **Active against Gram-positive bacteria**
- **Binds to bacterial membrane with rapid depolorization 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**

Curr Opin Chem Biol 13:144-151; Antimicrob Agents Chemother 54:707-717; www.micromedixsolutions.com

Daptomycin-FDA indications

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

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220282.htm

METHODS

We randomly assigned 124 patients with *S. aureus* bacteremia with or without endocarditis to receive 6 mg of daptomycin intravenously per kilogram of body weight daily and 122 to receive initial low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin. The primary efficacy end point was treatment success 42 days after the end of therapy.

RESULTS

Forty-two days after the end of therapy in the modified intention-to-treat analysis, a successful outcome was documented for 53 of 120 patients who received daptomycin as compared with 48 of 115 patients who received standard therapy (44.2 percent vs. 41.7 percent; absolute difference, 2.4 percent; 95 percent confidence interval, −10.2 to 15.1 percent). Our results met prespecified criteria for the noninferiority of daptomycin. The success rates were similar in subgroups of patients with complicated bacteremia, right-sided endocarditis, and methicillin-resistant *S. aureus*. Daptomycin therapy was associated with a higher rate of microbiologic failure than was standard therapy (19 vs. 11 patients, P=0.17). In 6 of the 19 patients with microbiologic failure in the daptomycin group, isolates with reduced susceptibility to daptomycin emerged; similarly, a reduced susceptibility to vancomycin was noted in isolates from patients treated with vancomycin. As compared 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 (17 vs. 8, P=0.06). Clinically significant renal dysfunction occurred in 11.0 percent of patients who received daptomycin and in 26.3 percent of patients who received standard therapy (P=0.004).

***New Engl J Med* 2006;355:653-665**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

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

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., Henry F. Chambers, M.D., Francis P. Tally, M.D., Gloria A. Vigliani, M.D., Christopher H. Cabell, M.D., M.H.S., Arthur Stanley Link, M.D., Ignace DeMeyer, M.D., Scott G. Filler, M.D., Marcus Zervos, M.D., Paul Cook, M.D., Jeffrey Parsonnet, M.D., Jack M. Bernstein, M.D., Connie Savor Price, M.D., Graeme N. Forrest, M.D., Gerd Fätkenheuer, M.D., Marcelo Gareca, M.D., Susan J. Rehm, M.D., Hans Reinhardt Brodt, M.D., Alan Tice, M.D., and Sara E. Cosgrove, M.D., for the *S. aureus* Endocarditis and Bacteremia Study Group

***New Engl J Med* 2006;355:653-665**

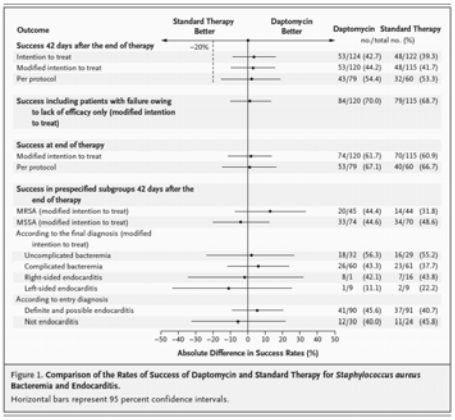
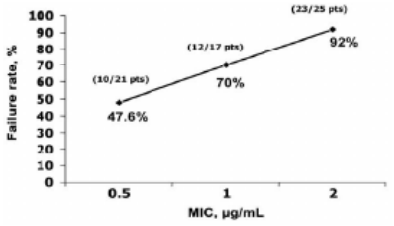


Figure 1. **Comparison of the Rates of Success of Daptomycin and Standard Therapy for *Staphylococcus aureus* Bacteremia and Endocarditis.**
Horizontal bars represent 95 percent confidence intervals.

***New Engl J Med* 2006;355:653-665**

Vancomycin MIC creep

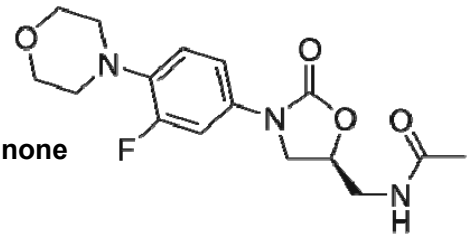


Daptomycin for vancomycin failure and infections due to VISA or VRSA

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

J Antimicrobial Chemotherapy 51 (Suppl 2):1145-1153;
Expert Opinion on Drug Safety 2009;8:485-491

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)

www.fda.gov; www.micromedixsolutions.com

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*

www.fda.gov; www.micromedixsolutions.com

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.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085249.htm

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.**

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085249.htm

Background. Catheter-related bloodstream infection (CRBSI) causes substantial morbidity and mortality, 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 complicated skin and skin structure infection (cSSSI) 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 cSSSI (microbiologic success rate for linezolid recipients, 89.6% [146 for 163 patients]; for the control group, 89.9% [134 of 149]; 95% CI, −7.1 to 6.4) and CRBSI (for linezolid recipients, 86.3% [82 of 95]; for the control group, 90.5% [67 of 74]; 95% CI, −13.8 to 5.4). The frequency and severity of adverse events were similar between groups. Mortality rates were 10.4% for linezolid recipients (28 of 269 patients) and 10.1% for control subjects (26 of 257) in the modified intent-to-treat population (i.e., all patients with gram-positive baseline culture) through test of cure, and they were 21.5% for linezolid recipients (78 of 363) and 16.0% for the control group (58 of 363; 95% CI, −0.2 to 11.2) for all treated patients through poststudy treatment day 84.

Conclusions. Linezolid demonstrated microbiologic success rates noninferior to those for vancomycin in patients with cSSSIs 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.

Clin Infect Dis **2009;48:203-212**

Complicated Skin and Skin-Structure Infections and Catheter-Related Bloodstream Infections: Noninferiority of Linezolid in a Phase 3 Study

Mark H. Wilcox,[1] Kenneth J. Tack,[4]* Emilio Bouza,[2] Daniel L. Herr,[5] Bernhard R. Ruf,[3] M. Marian Ijzerman,[4]* Rodney V. Croos-Dabrera,[4] Mark J. Kunkel,[6] and Charles Knirsch[7]

[1]Department of Microbiology, Leeds General Infirmary and University of Leeds Teaching Hospitals, Leeds, England; [2]Hospital General Gregorio Maranon, Madrid, Spain; [3]Hospital Center St. Georg, University of Leipzig Teaching Hospital, Leipzig, Germany; [4]Pfizer Global Research and Development, Ann Arbor, Michigan, [5]Surgical Critical Care Department, Washington Hospital Center, Washington, D.C., and [6]Pfizer Global Medical and [7]Pfizer Global Research and Development, New York, New York

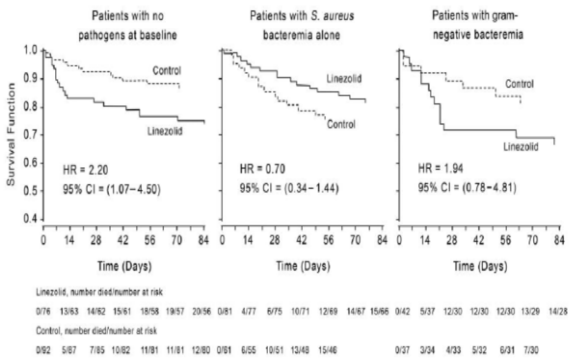
Clin Infect Dis **2009;48:203-212**

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

Population	Linezolid group	Control group	95% CI
Complicated SSSI			
End of treatment	129/154 (83.8)	122/142 (85.9)	−10.3 to 6.0
Staphylococcus aureus	66/81 (81.5)	52/66 (78.8)	−10.3 to 15.7
Methicillin-resistant *S. aureus*	42/46 (91.3)	33/39 (84.6)	−7.3 to 20.6
Test of cure	123/158 (77.8)	113/145 (77.9)	−9.4 to 9.3
S. aureus	63/84 (75.0)	49/67 (73.1)	−12.2 to 16.0
Methicillin-resistant *S. aureus*	39/45 (86.7)	31/39 (79.5)	−8.9 to 23.3
Bloodstream infection			
End of treatment	73/89 (82.0)	61/74 (82.4)	−12.2 to 11.4
S. aureus	39/52 (75.0)	29/42 (69.0)	−12.3 to 24.2
Methicillin-resistant *S. aureus*	22/25 (88.0)	16/21 (76.2)	−10.4 to 34.0
Test of cure	70/93 (75.3)	59/73 (80.8)	−18.1 to 7.0
S. aureus	36/54 (66.7)	28/42 (66.7)	−19.0 to 19.0
Methicillin-resistant *S. aureus*	19/24 (79.2)	16/21 (76.2)	−21.4 to 27.4

NOTE. Data are no. (%) of successes or no. (%) of patients assessed, unless otherwise indicated. Percentages were based on number of patients assessed and excluded patients with indeterminate or missing outcomes.

Clin Infect Dis **2009;48:203-212**



Clin Infect Dis **2009;48:203-212**

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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Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Richard G. Wunderink,[1] Michael S. Niederman,[2] Marin H. Kollef,[3] Andrew F. Shorr,[4] Mark J. Kunkel,[5] Alice Baruch,[5,a] William T. McGee,[6] Arlene Reisman,[5] and Jean Chastre[7]

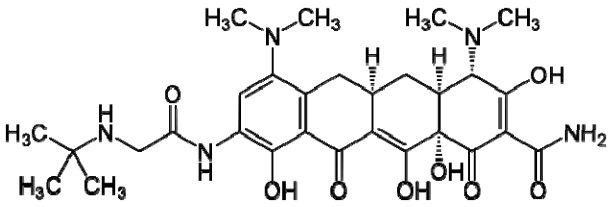
[1]Department of Pulmonary and Critical Care, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [2]Department of Medicine, Winthrop-University Hospital, Mineola, New York; [3]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri; [4]Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, D.C.; [5]Specialty Care, Pfizer, New York, New York; [6]Baystate Medical Center, Springfield, Massachusetts; and [7]Service de Réanimation Médicale, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France

Results. Of 1184 patients treated, 448 (linezolid, n = 224; vancomycin, n = 224) were included in the mITT and 348 (linezolid, n = 172; vancomycin, *n* = 176) in the PP population. In the PP population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at EOS (95% confidence interval for difference, 0.5%–21.6%; *P* = .042). All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

Conclusions. For the treatment of MRSA nosocomial pneumonia, clinical response at EOS in the PP population was significantly higher with linezolid than with vancomycin, although 60-day mortality was similar.

Clinical Infect Dis **2012;54:621-629**

Tigecycline



Glycylcycline—structurally related to tetracyclines

Time dependent killing; 24 hr AUC/MIC

http:/www.wikipedia.org

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***

http://www.pfizerpro.com/hcp/tygacil/indications?source=google&HBX_PK=s_indication++tigecycline&o=47364352|223603648|0&skwid=43700003785225796

Tigecycline-Adverse Effects

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

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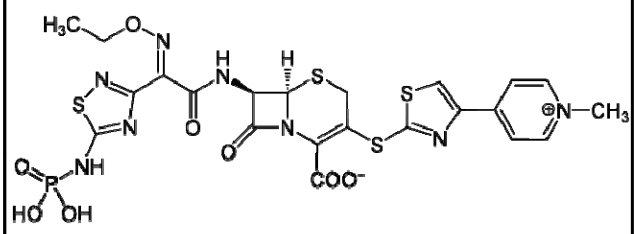
FDA Safety Communication

- **[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 infections. 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.**

http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm

Ceftaroline



Advanced generation cephalosporin

Time above MIC; time-dependent killing

http:/www.wikipedia.org

Ceftraoline

- **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***

www.fda.gov; www,micromedixsolutions.com

Comparative in vitro MIC_{90}s

Table 1. Comparative in vitro MIC 90s of Ceftaroline and Other Comparators against Gram-Positive Bacteria

Organism (no. of isolates tested)	Ceftaroline[a]	Vancomycin	Daptomycin	Ceftriaxone	Linezolid	Erythomycin
Staphaylococcus aureus						
MSSA (348)	0.25	1	0.5	NA	2	NA
MRSA (92)	1	1	1	NA	2	NA
VISA (20)	1	8	4	NA	2	NA
VRSA (10)	0.5	. 64	1	NA	2	NA
Coagulase-negative staphylococci						
Methicillin susceptible (201)	0.12	2	4	NA	2	NA
Methicillin resistant (299)	0.5	2	. 32	NA	2	NA
Enterococcus faecalis						
Vancomycin susceptible (157)	4	2	1	NA	2	NA
Vancomycin resistant(25)	4	. 16	1	NA	2	NA
Enterococcus faecium (157)	. 16	. 16	4	NA	2	NA
Streptococcus pyogenes						
Erythromycin susceptible(91)	, .008	0.5	NA	, .008	1	0.06
Erythromycin resistant (10)	, .015	0.5	NA	0.12	1	. 16
Streptococcus agalactiae (59)	0.015	0.5	NA	0.12	1	0.06
Streptococcus pneumoniae						
Penicillin sensitive (202)	0.015	0.5	NA	0.06	1	0.5
Penicillin intermediate (103)	0.06	0.5	NA	0.5	1	. 16
Penicillin resistant (296)	0.12	0.5	NA	0.12	1	. 16

NOTE. Adapted from [7, 8]. MIC_{90} values are given as l g/mL. MIC_{90},90% minimum inhibitory concentration; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus; NA, not applicable.; VISA, vancomycin-intermediate S. aureus; VRSA, vancomycin-resistant S. aureus.

[a] Ceftaroline MIC breakpoints areas follows: S. aureus < 1 for skin isolates only, S. pneumoniae < 0.25 l g/mL for community-acquired bacterial pneumonia isolates only, Streptococcus pyogenes < 0.015 for skin isolates only, and Streptococcus agalactiae < 0 .03 l g/mL for skin isolates only.

Saravolatz LD, Stein GE, Johnson LB. *Clin Infect Dis* 2011;52:1157-1163.

Supporting Studies

- ***Corey GR, Wilcox M, Talbot GH, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infections. Clin Infect Dis* 2010; 51:641-650.**
  - **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).**
- ***Integrated analysis of FOCUS 1 and FOCUS 2: randomized, double-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis* 2011; 51:1395-1405.**
  - **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 ceftriaxone (1 gram IV over 30 minutes every 24 hours).**

The CANVAS 1 study

JAC

Table 7. Clinical cure rates by study population, geographical region, infection type and important subgroups in CANVAS 1

	Ceftaroline fosamil, n/N (%)	Vancomycin plus aztreonam, n/N (%)	Difference in response rates, % (95% CI)
Population			
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (−4.2, 6.2)
CE	288/316 (91.1)	280/300 (93.3)	−2.2 (−6.6, 2.1)
ME	225/244 (92.2)	215/227 (94.7)	−2.5 (−7.2, 2.1)
Subgroup (CE population)			
region of enrolment			
USA	111/133 (83.5)	96/131 (73.3)	10.2 (0.2, 20.1)
outside USA	193/218 (88.5)	201/216 (93.1)	−4.5 (−10.2, 1.0)
EU	65/79 (82.3)	73/79 (92.4)	−10.1 (−21.1, 0.3)
non-EU Europe	102/108 (94.4)	103/109 (94.5)	−0.1 (−6.8, 6.7)
Latin America	26/31 (83.9)	25/28 (89.3)	−5.4 (−24.1, 13.8)
patients with bacteraemia (ME population)	14/17 (82.4)	10/10 (100.0)	−17.6 (−41.5, 12.9)
patients with diabetes mellitus	49/56 (87.5)	57/61 (93.4)	−5.9 (−18.1, 5.1)
lower-extremity infection in patients with diabetes mellitus or PVD	19/19 (100)	18/19 (94.7)	5.3 (−12.4, 25.0)
patients with PVD	41/45 (91.1)	41/45 (91.1)	0.0 (−13.3, 13.3)
Infection type			
cellulitis	101/111 (91.0)	98/107 (91.6)	−0.6 (−8.5, 7.4)
major abscess	78/88 (88.6)	74/78 (94.9)	−6.2 (−15.3, 2.6)
infected wound	40/45 (88.9)	34/38 (89.5)	−0.6 (−14.9, 14.7)
infected burn	24/24 (100)	17/17 (100)	0.0 (−14.1, 18.8)
infected ulcer	20/22 (90.9)	28/30 (93.3)	−2.4 (−22.4, 14.1)

PVD, peripheral vascular disease.

JAC 2010;65(Suppl4):iv41-51

Table 5. Clinical cure rates in select patient subgroups (CE population)

	n/N (%)		
Patient subgroup	ceftaroline fosamil	ceftriaxone	Difference, % (95% CI)
Age, years			
<65	89/105 (84.8)	86/118 (72.9)	11.9 (1.1, 22.4)
≥65	105/119 (88.2)	97/116 (83.6)	4.6 (−4.4, 13.8)
Sex			
male	122/141 (86.5)	115/153 (75.2)	11.4 (2.3, 20.3)
female	72/83 (86.7)	68/81 (84.0)	2.8 (−8.3, 14.1)
PORT risk class			
III	136/150 (90.7)	113/142 (79.6)	11.1 (3.0, 19.5)
IV	58/74 (78.4)	70/92 (76.1)	2.3 (−10.9, 15.0)
Receipt of prior antibiotic treatment			
yes[a]	85/105 (81.0)	87/106 (82.1)	−1.1 (−11.8, 9.5)
no	109/119 (91.6)	96/128 (75.0)	16.6 (7.5, 25.8)
Renal impairment			
mild (CL_{CR}=51–80 mL/min)	58/69 (84.1)	57/73 (78.1)	6.0 (−7.2, 19.0)
moderate (CL_{CR}=31–50 mL/min)	36/41 (87.8)	27/35 (77.1)	10.7 (−6.7, 28.9)
Bacteraemia	6/8 (75.0)	4/7 (57.1)	NA
Mixed typical pathogen and atypical pathogen infection[b]	5/5 (100)	5/8 (62.5)	NA
Typical pathogen infection	57/64 (89.1)	49/63 (77.8)	11.3 (−1.8, 24.6)

JAC 2011;66 (Suppl3):iii19-iii32

Table 6. Clinical cure rates by study population, geographical region, infection type and important subgroups in CANVAS 2

	Ceftaroline fosamil, n/N (%)	Vancomycin plus aztreonam, n/N (%)	Difference in response rates, % (95% CI)
Population			
MITT	291/342 (85.1)	289/338 (85.5)	−0.4 (−5.8, 5.0)
CE	271/294 (92.2)	269/292 (92.1)	0.1 (−4.4, 4.5)
ME	209/224 (93.3)	206/219 (94.1)	−0.8 (−5.5, 4.0)
Subgroup (CE population)			
region of enrolment			
USA	133/170 (78.2)	132/168 (78.6)	−0.3 (−9.2, 8.5)
outside USA	158/172 (91.9)	157/170 (92.4)	−0.5 (−6.5, 5.5)
EU	60/68 (88.2)	61/66 (92.4)	−4.2 (−15.1, 6.5)
non-EU Europe	77/79 (97.5)	77/79 (97.5)	0.0 (−6.6, 6.6)
Latin America	21/25 (84.0)	19/25 (76.0)	8.0 (−15.1, 30.8)
patients with bacteraemia (ME population)	8/9 (88.9)	11/11 (100.0)	−11.1 (−44.4, 17.6)
patients with diabetes mellitus	47/54 (87.0)	43/49 (87.8)	−0.7 (−14.2, 13.2)
lower-extremity infection in patients with diabetes mellitus or PVD	8/8 (100.0)	9/11 (81.8)	
patients with PVD	39/45 (86.7)	34/39 (87.2)	−0.5 (−15.7, 15.4)
Infection type			
major abscess	106/114 (93.0)	103/110 (93.6)	−0.7 (−7.8, 6.5)
deep/extensive cellulitis	88/94 (93.6)	99/108 (91.7)	2.0 (−6.0, 9.7)
wound	33/39 (84.6)	31/35 (88.6)	−4.0 (−20.4, 13.0)

JAC 2010;65(Suppl 4):iv53-65

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**

Pharmacotherapy 2010;30:375-389

Treatment of bacteremia?

J Antimicrob Chemother
doi:10.1093/jac/dks006

Journal of Antimicrobial Chemotherapy

Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy

Tony T. Ho[1], Jose Cadena[1,2], Lindsey M. Childs[2,3], Miguel Gonzalez-Velez[1] and James S. Lewis II[1,3,4]*

Ho TT, Cadena J, Childs LM, et al. *J Antimicrob Chemother* 2012;1-4.

Ceftaroline-Adverse Effects

- **Diarrhea, nausea, uriticaria, rash**
- **Increased transaminases, hypokalemia, phlebitis, fever**
- **Anemia, neutropenia, thrombocytopenia**
- **Anaphylaxis, positive Direct Coomb's test**
- **Dizziness, seizures**
- **bradyarrythimias**

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Initial Case Series

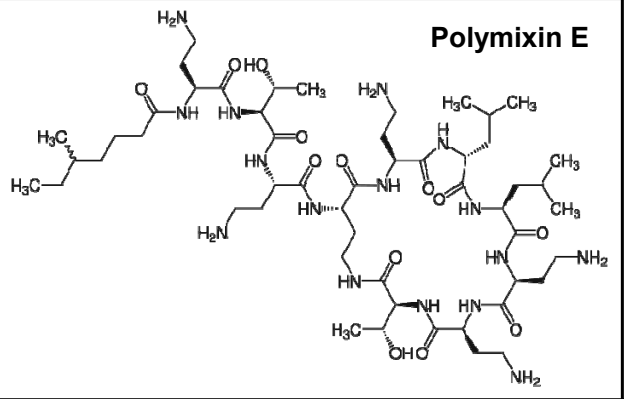
Table 1. Summary of cases and outcomes

Case	Source of MRSA bacteraemia	Duration of bacteraemia (days)	Prior therapy (days)	VAN MIC (mg/L)[a]	DAP MIC (mg/L)[a]	Linezolid MIC (mg/L)[a]	Ceftaroline MIC (mg/L)[a], dose/duration[b]	Complications	Clinical outcome
1	endocarditis	13 days, cleared and relapsed day 17, cleared on day 18 (start of ceftaroline therapy)	13 (VAN), then 4 (DAP)	day 17: 4	2	NA	0.5—VISA isolate, 600 mg iv q8h for 42 days	mitral valve replacement, ESBL *Klebsiella pneumonia* bacteraemia; responded to 10 days of meropenem	resolution
2	endocarditis	15	15 (VAN)	1.5	0.5	1	0.5, 600 mg iv q8h ×3 weeks, then linezolid 600 bid ×3 weeks	none	resolution
3	skin and soft tissue, uveitis, endocarditis	2[c]	22 (VAN)	2	NA	NA	0.5, 600 mg q8h ×3 weeks, then linezolid 600 mg orally bid ×3 weeks	none	resolution
4	urinary tract infection	11	11 (VAN)	2	2	0.5	0.5, 600 mg q12h for 10 days	GI bleeding	death
5	uveitis, ethmoid osteomyelitis	13	12 (VAN)	2	1	2	0.5, 600 mg q8h for 2 weeks, then VAN for 4 weeks	none	resolution
6	prostatitis, septic thrombophlebitis	13	8 (VAN)	1.5	1	2	0.5, 600 mg q8h for 22 days, then VAN to finish 6 weeks	none	resolution

bid, twice daily; DAP, daptomycin; ESBL, extended-spectrum β-lactamase; GI, gastrointestinal; iv, intravenously; NA, not available; q8h, every 8 h; q12h, every 12 h; VAN, vancomycin; VISA, vancomycin-intermediate *S. aureus*.
[a]All MICs determined using Etest.
[b]All ceftaroline infusions administered over 1 h. No ceftaroline therapeutic drug monitoring was performed.
[c]Progression of ocular lesions while on therapy with vancomycin and appearance of new pulmonary nodules/lesions consistent with embolization.

Ho TT, Cadena J, Childs LM, et al. *J Antimicrob Chemother* 2012;1-4.

Colistin



http:/www.wikipedia.org

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

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

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

Anna S. Levin, Antonio A. Barone, Juliana Penço, Marcio V. Santos, Ivan S. Marinho, Erico A. G. Arruda, Edison I. Manrique, and Silvia F. Costa

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Sixty nosocomial infections caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem were treated with colistin (one patient had two infections that are included as two different cases). The infections were pneumonia (33% of patients), urinary tract infection (20%), primary bloodstream infection (15%), central nervous system infection (8%), peritonitis (7%), catheter-related infection (7%), and otitis media (2%). A good outcome occurred for 35 patients (58%), and three patients died within the first 48 hours of treatment. The poorest results were observed in cases of pneumonia: only five (25%) of 20 had a good outcome. A good outcome occurred for four of five patients with central nervous system infections, although no intrathecal treatment was given. The main adverse effect of treatment was renal failure; 27% of patients with initially normal renal function had renal failure, and renal function worsened in 58% of patients with abnormal baseline creatinine levels. Colistin may be a good therapeutic option for the treatment of severe infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii*.

Clin Infect Dis 1999;28:1008-1011

Journal of Antimicrobial Chemotherapy (2007) 60, 1163–1167
doi:10.1093/jac/dkm305
Advance Access publication 29 August 2007

JAC

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

Kwan Soo Ko[1,2], Ji Yeun Suh[2], Ki Tae Kwon[3], Sook-In Jung[4], Kyong-Hwa Park[4], Cheol In Kang[5], Doo Ryeon Chung[6], Kyong Ran Peck[5] and Jae-Hoon Song[2,5]*

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Objectives: To investigate antimicrobial resistance in clinical isolates of *Acinetobacter* spp. from two Korean hospitals.

Methods: Two hundred and sixty-five isolates of *Acinetobacter* spp. from two Korean hospitals were collected and were identified to species level using partial *rpoB* gene sequences. Antimicrobial susceptibility testing was performed using a broth microdilution method.

Results: *rpoB* gene sequences indicated that 214 isolates (80.8%) were *Acinetobacter baumannii*, and allowed these to be classified into three subgroups (I, II and III); 142 isolates (53.6%) belonged to subgroup I, 54 (20.4%) to subgroup II and 18 (6.8%) to subgroup III. Forty-eight isolates (18.1%) and 74 isolates (27.9%) were resistant to polymyxin B and colistin, respectively. However, antimicrobial resistance rates varied markedly between subgroups. While *A. baumannii* subgroup I showed low resistance rates to polymyxin B and colistin (2.1% and 7.0%, respectively), subgroups II and III showed high resistance rates to these antibiotics (38.9% and 64.8% in subgroup II and 72.2% and 88.9%, in subgroup III, respectively). Multidrug resistance was also significantly more frequent in subgroup I (45.1%) than in subgroups II and III (13.0% and 16.7%, respectively).

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

Journal of Antimicrobial Chemotherapy (2007) 60, 1163–1167
doi:10.1093/jac/dkm305
Advance Access publication 29 August 2007

JAC

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 effectiveness and considerably less toxicity than was reported in old studies. The frequency of nephrotoxicity and severity of neurotoxicity seem to be substantially less than previously believed. Recently, a significant increase in the data gathered on colistin has focused on its chemistry, antibacterial activity, mechanism of action and resistance, pharmacokinetics, pharmacodynamics, and new clinical application. Colistin has attracted more 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 mentioned that no well-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.

Crit Care Clin 24 (2008) 377–391

ELSEVIER SAUNDERS

CRITICAL CARE CLINICS

Crit Care Clin 24 (2008) 377–391

Colistin and Polymyxin B in Critical Care

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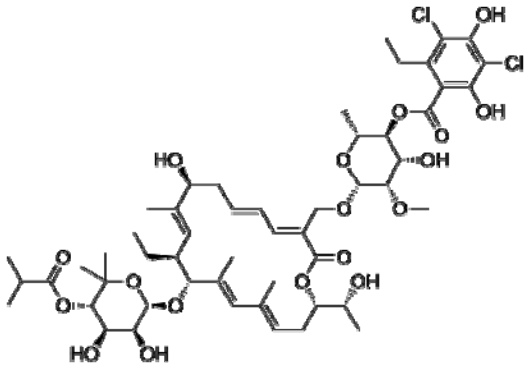
Crit Care Clin 24 (2008) 377–391

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 548 (87.1%) 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 (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% 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. 24.0%, 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.

NEJM 2011;364:422-431

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

NEJM 2011;364:422-431

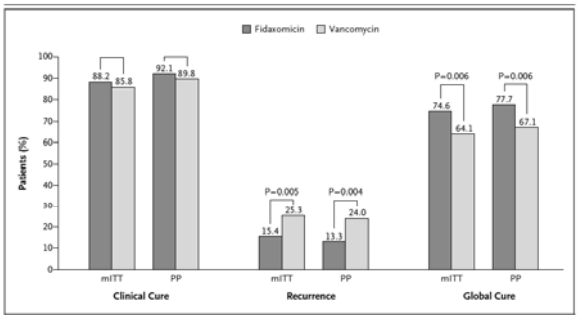


Figure 2. **Rates of Primary and Secondary End Points.**
For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was −3.1 percentage points in the modified intention-to-treat (mITT) analysis and −2.6 percentage points in the per-protocol (PP) analysis.

NEJM 2011;364:422-431

Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Kathleen M. Mullane,[1] Mark A. Miller,[2] Karl Weiss,[3] Arnold Lentnek,[4] Yoav Golan,[5] Pamela S. Sears,[6] Youe-Kong Shue,[6] Thomas J. Louie,[7] and Sherwood L. Gorbach[5,6]

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Results. CAs were prescribed for 27.5% of subjects during study participation. The use of CAs concurrent with CDI treatment was associated with a lower cure rate (84.4% vs 92.6%; $P < .001$) and an extended time to resolution of diarrhea (97 vs 54 hours; $P < .001$). CA use during the follow-up was associated with more recurrences (24.8% vs 17.7%; not significant), and CA administration at any time was associated with a lower global cure rate (65.8% vs 74.7%; $P = .005$). When subjects received CAs concurrent with CDI treatment, the cure rate was 90.0% for fidaxomicin and 79.4% for vancomycin ($P = .04$). In subjects receiving CAs during treatment and/or follow-up, treatment with fidaxomicin compared with vancomycin was associated with 12.3% fewer recurrences (16.9% vs 29.2%; $P = .048$).

Clinical Infect Dis 2011;53:440-447

Fidaxomicin-Adverse Effects

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

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