

New Drugs For Old Bugs: What To Do When Vancomycin Fails You

Denise Sprague, BScPharm, ACPR, PharmD
Clinical Pharmacy Specialist – ID
Kelowna General Hospital
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Disclosure Statement

- I have no conflicts of interest to disclose.

Objectives

- To highlight the important differences between linezolid, daptomycin, tigecycline and ceftobiprole (e.g. antimicrobial spectrum and toxicity).
- To review the clinical evidence supporting the use of linezolid, daptomycin, tigecycline and ceftobiprole.
- To illustrate the place in therapy for linezolid, daptomycin, tigecycline and ceftobiprole using a case-based approach.

When Vancomycin Fails...

- Allergy/intolerable adverse reaction
 - Interstitial nephritis
 - Desquamating rash
 - Neutropenia/thrombocytopenia
- Resistance
 - VISA, VRE
- Clinical failure
 - PK/PD issues – e.g. dosing, penetration

Case One

DS is a 30 yo IVDU admitted to KGH with haMRSA pneumonia. Blood cultures and TEE negative. On day 5 of vancomycin therapy, she continues to be febrile, O2 requirements have not changed.

- Has vancomycin failed you?
- If so, which therapy do you choose?

Linezolid vs Vancomycin*

Analysis of Two Double-Blind Studies of Patients With Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

*Richard G. Wunderink, MD, FCCP; Jordi Rello, MD, PhD;
Sue K. Cammarata, MD, FCCP; Rodney V. Croos-Dabrera, PhD; and
Marin H. Kollef, MD, FCCP*

Conclusions: In this retrospective analysis, initial therapy with linezolid was associated with significantly better survival and clinical cure rates than was vancomycin in patients with nosocomial pneumonia due to MRSA. (CHEST 2003; 124:1789-1797)

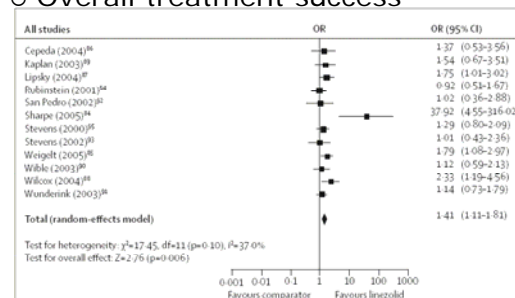
Linezolid - Overview

Class	Oxazolidinone
Mechanism	Protein synthesis inhibition (50S/70S)
Spectrum	Staph, Strep, Enterococcus, ? anaerobes
Cidal vs static?	Bacteriostatic (cidal vs Strep)
ADRs	H/A, N/V/D, rash Late- blood dyscrasias, peripheral neuropathy, optic neuropathy, lactic acidosis
Drug Interactions	Potential for serotonin syndrome with serotonergic drugs/foods
Dose	600 mg PO/IV Q12H 10 mg/kg PO/IV Q8H (peds)

Drug Safety 2008; 31: 753-68

Linezolid – The Evidence

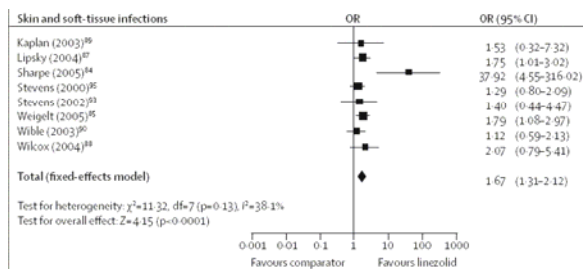
- o Meta-analysis of 12 trials
 - No difference in overall mortality (not shown)
- o Overall treatment success



Lancet Infect Dis 2008; 8: 53-66

Linezolid – The Evidence

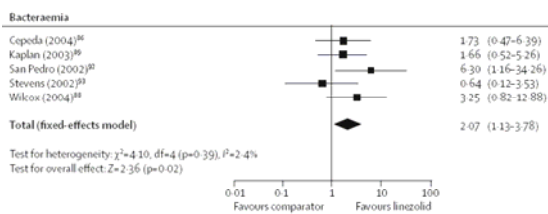
- o Treatment success: SSTIs



Lancet Infect Dis 2008; 8: 53-66

Linezolid – The Evidence

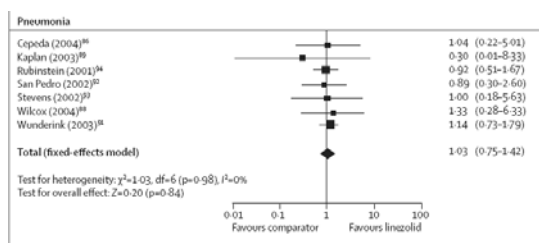
- o Treatment success: bacteremia



Lancet Infect Dis 2008; 8: 53-66

Linezolid – The Evidence

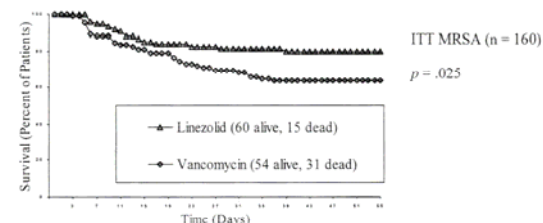
- o Treatment success: pneumonia



Lancet Infect Dis 2008; 8: 53-66

Linezolid – The Controversy

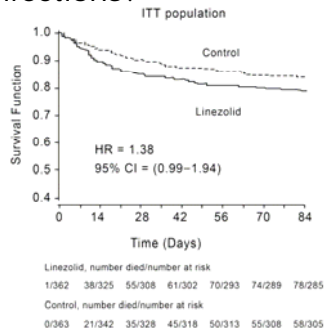
- o Superior, inferior or non-inferior to vanco for pneumonia?
 - Retrospective pooled analysis of 2 RCTs



Chest 2003; 124: 1789-97

Linezolid – The Controversy

- o Not optimal for catheter-related infections?



Clin Infect Dis 2009;
48: 203-12

Case Two

RP is a 31 yo IVDU admitted to VGH with MRSA bacteremia and TV endocarditis. Blood cultures –ve at day 8. By day 12 of appropriately dosed vancomycin therapy, SCr has doubled and she develops a rash. Urine eos +ve.

- o Has vancomycin failed you?
- o If so, which therapy do you choose?

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

CONCLUSIONS

Daptomycin (6 mg per kilogram daily) is not inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis. (ClinicalTrials.gov number, NCT00093067.)

Daptomycin - Overview

Class	Cyclic lipopeptide
Mechanism	Inhibits DNA, RNA, protein synthesis via depolarization of cell membrane, K efflux
Spectrum	Staph, Strep, Enterococcus, ?anaerobes
Cidal vs static?	Bactericidal
ADRs	CK elevation/myopathy (interval-related), renal failure, hepatitis, peripheral neuropathy
Drug Ixns	?Statins
Dose	4 mg/kg (cSSTI) or 6 mg/kg IV daily (Q48H if < 30 mL/min)

Clin Infect Dis 2004; 38: 994-1000

Daptomycin – The Evidence

- o RCT bacteremia & right sided endocarditis

Table 2. Outcomes 42 Days after the End of Therapy, According to Prespecified Diagnostic Categories.

Criteria	no. of patients/total no. (%)		Absolute Difference in Success Rates % (95% CI)*
	Daptomycin	Standard Therapy	
Overall success (intention to treat)	53/124 (42.7)	48/122 (39.3)	3.4 (-8.9 to 15.7)
Overall success (modified intention to treat)	53/120 (44.2)	48/115 (41.7)†	2.4 (-10.2 to 15.1)
Success according to methicillin susceptibility of <i>Staphylococcus aureus</i> ‡			
MSSA	33/74 (44.6)	34/70 (48.6)	-4.0 (-20.3 to 12.3)
MRSA	20/45 (44.4)	14/44 (31.8)	12.6 (-7.4 to 32.6)

NEJM 2006; 191: 355; 653-65

Daptomycin – The Controversy

- o Not optimal for pneumonia
 - Successful for hematogenous pneumonia in animals
 - 4 mg/kg daily didn't meet non-inferiority criteria vs ceftriaxone in RCT
 - in vitro modeling revealed inactivation by surfactant

J Infect Dis 2005; 191: 2149-52

Clin Infect Dis 2008; 46: 1142-51

Daptomycin – The Controversy

- o Resistance on therapy
- o Cross-resistance with vancomycin?

Table 1. Effect of increasing vancomycin MICs on daptomycin susceptibility for *Staphylococcus aureus* isolates.

Vancomycin MIC, µg/mL	No. (%) of isolates	
	Daptomycin MIC ≤1 µg/mL	Daptomycin MIC ≥2 µg/mL
≤2	812 (97)	30 (3)
4	11 (20)	43 (80)
8–16	1 (7)	15 (93)
≥32	5 ^a (100)	0 (0)

NOTE. *P* < .0001; χ^2 test for trend.
^a Five *S. aureus* isolates with *vanA*-mediated resistance. Clin Infect Dis 2006; 42: 1652

NEJM 2006; 355: 653-65
 Clin Infect Dis 2007; 45: 601-8

Case Three

DM is a 50 yo poorly controlled diabetic with chronic renal impairment admitted with left leg cellulitis and a diabetic foot ulcer. Blood and wound cultures are pending. He has unspecified vancomycin and penicillin allergies, previous diabetic foot infections were polymicrobial, incl. MRSA and Pseudomonas. The dispensary pages you because tigecycline has been ordered and it's currently out of stock.

- o Has vancomycin failed you?
- o If so, is tigecycline an appropriate alternative?

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2005, p. 4658-4666
 0066-834X/05/50(06):4658-09. doi:10.1128/AAC.49.11.4658-4666.2005
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Safety and Efficacy of Tigecycline in Treatment of Skin and Skin Structure Infections: Results of a Double-Blind Phase 3 Comparison Study with Vancomycin-Aztreonam

Johannes Breedt,^{1*} Jüri Teras,² Janis Gardovskis,³ Frans Jacobus Maritz,⁴ Tjit Vaasna,⁵
 Douglas Patrick Ross,⁶ Martine Gioud-Paquet,⁷ Nathalie Dartois,⁷
 Evelyn J. Ellis-Grosse,⁸ and Evan Loh⁹ for the Tigecycline 305 cSSSI Study Group

*Eugene Marais Hospital, Lev Marais, Pretoria, Republic of South Africa*¹; *North Estonian Regional Hospital, Clinic of Surgery, Tallinn, Estonia*²; *P. Stradina Clinical University Hospital, Medical Academy of Latvia, Riga, Latvia*³; *Tiger Trial Centre, Karl Bremer and University of Stellenbosch, Bellville, Republic of South Africa*⁴; *Tartu University Clinics, Tartu, Estonia*⁵; *St. Mary's Hospital, Darban, Republic of South Africa*⁶; *Clinical Research and Development, Wyeth Research, Paris, France*⁷; *and Clinical Research and Development, Wyeth Research, Collegeville, Pennsylvania*⁸

Tigecycline -Overview

Class	Glycylcycline
Mechanism	Protein synthesis inhibition (30S)
Spectrum	Broad spectrum, but not Pseudomonas or Proteus
Cidal vs static?	Bacteriostatic
ADRs	Most common - N/V/D Other - photosensitivity, pancreatitis
Drug Interactions	? Warfarin
Dose	100 mg IV load; 50 mg IV Q12H (100 mg, then 25 mg IV Q12H if severe hepatic disease)

AJHP 2006; 63: 1235-43

Tigecycline – The Evidence

Pooled analysis of 2 IAI studies

Table 2. Clinical cure rates, by study population, at the test-of-cure visit.

Population	Tigecycline		Imipenem-cilastatin		Difference (tigecycline – imipenem-cilastatin), % (95% CI)	Test for noninferiority, <i>P</i>	Test for differences
	No. of patients/total	Percentage of patients (95% CI)	No. of patients/total	Percentage of patients (95% CI)			
Clinically evaluable	694/695	80.7 (83.9–89.2)	607/697	87.1 (84.4–89.5)	-0.4 (-4.1 to 3.3)	<.0001	0.9003
Overall					-0.3 (-3.8 to 3.3) ^a		0.2851
c-mITT	629/601	79.8 (76.8–82.5)	656/600	92.0 (79.2–84.6)	-2.2 (-0.2 to 1.8)	<.0001	1.0000
Overall					-2.0 (-5.9 to 1.8)		0.6167
Microbiologically evaluable	441/512	86.1 (82.8–89.0)	442/513	86.2 (82.9–89.0)	0.0 (-4.5 to 4.4)	<.0001	1.0000
Monomicrobial	166/180	92.2 (87.3–95.7)	175/194	90.2 (85.1–94.0)	2.0 (-4.3 to 8.3)		0.6167
Polymicrobial	275/332	82.8 (78.3–86.7)	267/319	83.7 (79.2–87.6)	-0.9 (-6.8 to 5.1)		0.6167
Overall					0.6 (-3.5 to 4.6) ^a		0.6167
m-mITT	506/631	80.2 (76.9–83.2)	514/631	81.5 (78.2–84.4)	-1.3 (-5.8 to 3.2)	<.0001	0.6167
Monomicrobial	204/241	84.6 (79.5–89.0)	211/247	85.4 (80.4–89.6)	-0.8 (-7.5 to 5.9)		0.6167
Polymicrobial	302/390	77.4 (73.0–81.5)	303/384	78.9 (74.5–82.2)	-1.5 (-7.5 to 4.5)		0.6167
Overall					-1.2 (-5.4 to 3.1) ^a		0.6167

NOTE. c-mITT, clinical modified intent-to-treat population; m-mITT, microbiological modified intent-to-treat population.
^a Adjusted difference and its 95% CI were calculated from a generalized linear model with a binomial probability function and an identity link.

Clin Infect Dis 2005; 41: S354-67

Tigecycline – The Evidence

RCT cSSTI

TABLE 2. Clinical success rates by study population at test-of-cure visit

Population	Tigecycline		V/A		% (95% CI) for difference (tigecycline – V/A)	<i>P</i> value for test for noninferiority	Test for differences
	No. of patients in population/ total no.	% (95% CI)	No. of patients in population/ total no.	% (95% CI)			
CE	200/223	89.7 (84.9, 93.3)	201/213	94.4 (90.4, 97.1)	-4.7 (-10.2, 0.8)	<0.001	0.1015
c-mITT	220/261	84.3 (79.3, 88.5)	225/259	86.9 (82.1, 90.7)	-2.6 (-9.0, 3.8)	<0.001	0.4755
ME	148/164	90.2 (84.6, 94.3)	143/148	96.6 (92.3, 98.9)	-6.4 (-12.4, -0.3)	0.0019	0.0372
Monomicrobial	83/90	92.2 (84.6, 96.8)	78/81	96.3 (89.6, 99.2)	-4.1 (-12.6, 4.6)		
Polymicrobial	65/74	87.8 (78.2, 94.3)	65/67	97.0 (89.6, 99.6)	-9.2 (-19.6, 1.2)		-6.2 (-11.7, -0.7) ^a
m-mITT	180/204	88.2 (83.0, 92.3)	177/196	90.3 (85.3, 94.1)	-2.1 (-8.6, 4.5)	<0.001	0.6114
Monomicrobial	104/114	91.2 (84.5, 95.7)	99/111	89.2 (81.9, 94.3)	2.0 (-6.6, 10.8)		
Polymicrobial	76/90	84.4 (75.3, 91.2)	78/85	91.8 (83.8, 96.6)	-7.3 (-17.9, 3.4)		-1.7 (-7.9, 4.5) ^a

Antimicro Agents Chemother 2005; 49:4658-66

Tigecycline – The Controversy

- Resistance
 - Retrospective analysis of 18 patients with serious MDR gm –ve infections
 - 5/9 Acinetobacter intermediate (4 deaths), 1/9 developed resistance
 - Persistent bacteremia in other susc. Isolates (deep seated infections)

Clin Infect Dis 2007; 46: 567-70

Tigecycline – The Controversy

- New indication for CAP?
 - 2 MC RCTs
 - Non-inferior to IV levofloxacin 500 mg daily and Q12H
 - One study allowed switch to OL PO levofloxacin

Diag Microbiol Infect Dis 2008; 61: 329-38

Case Four

ID is a 50 yo patient with HAP & bacteremia secondary to MRSA on day 2 of vancomycin therapy. Further investigations pending. The physician requests a switch to ceftobiprole because the vancomycin MIC is 1.5 mg/L, and she prefers a cidal agent.

- Has vancomycin failed you?
- If so, is ceftobiprole an appropriate alternative?

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

- 2 Terminated **A Study of Ceftobiprole in Patients Who Have a Fever and Have Abnormally Low Numbers of the White Blood Cells Called Neutrophils in the Blood Stream (Neutropenia).**
 Conditions: Neutropenia; Pseudomonas; Gram-Positive Bacterial Infections; Fever
 Interventions: Drug: Ceftobiprole Medocaril; Drug: Cefepime w/ or w/o vancomycin
- 3 Withdrawn **Ceftobiprole in the Treatment of Hospitalized Patients With Staphylococcus Aureus Bacteremia**
 Condition: Bacteremia
 Intervention: Drug: ceftobiprole medocaril

Ceftobiprole - Overview

Class	Cephalosporin
Mechanism	Cell wall synthesis inhibition
Spectrum	Broad spectrum, including MRSA and Enterococcus (not VRE. faecium)
Cidal vs static?	Bactericidal
ADRs	Most common - N/V/D, caramel taste Other – H/A, hepatitis, hyponatremia, renal failure, phlebitis
Drug Interactions	? Warfarin
Dose	500 mg IV Q12H (gram +ve) 500 mg IV Q8H (gram -ve)

Ann Pharmacother 2008; 42: 806-16

Ceftobiprole – The evidence

	Trial 1	Trial 2
Target pathogens	Gram +	Gram +/Gram –
Randomization ratio	1:1	2:1
No. of patients	784	828
No. of patients, ceftobiprole/comparator	397/387	547/281
Ceftobiprole dose	500 mg bid	500 mg tid
Comparator regimen	Vancomycin	Vancomycin ceftazidime
Vancomycin dose	1 g bid	1 g bid
Ceftazidime dose		1g tid
Cure rate, no. of cured/total (%)		
At TOC visit in CE population		
Ceftobiprole	263/282 (93.3)	439/485 (90.5)
Comparator	259/277 (93.5)	220/244 (90.2)
<i>S. aureus</i> infection		
Ceftobiprole	177/187 (94.6)	228/247 (92.3)
Comparator	162/172 (94.2)	117/128 (91.4)
MRSA infection		
Ceftobiprole	56/61 (91.8)	78/87 (89.7)
Comparator	54/60 (90.0)	31/36 (86.1)
<i>P. aeruginosa</i> infection	Not applicable	
Ceftobiprole		26/30 (86.7)
Comparator		9/9 (100.0)
Diabetic foot infection	Excluded	
Ceftobiprole		125/145 (86.2)
Comparator		63/77 (81.8)

○ SSTIs

Diag Microbiol Infect Dis 2008; 61: 103-9

Ceftobiprole – The Controversy

- CAP/HAP
 - Studies completed in 2007, awaiting publication
 - Noninferior to ceftazidime & linezolid for HAP?
 - Similar to ceftriaxone ± linezolid for CAP?
- Limited clinical experience
 - Not approved in US – questionable data integrity?

www.reuters.com

Place in therapy

- Linezolid
 - alternative for resistant gram positive infections (esp. pneumonia)
 - Not for catheter related infections?
- Daptomycin
 - alternative for resistant gram positive infections (esp. endocarditis/bacteremia) if susceptibility confirmed
 - Not for pneumonia
- Tigecycline
 - alternative for polymicrobial IAI, cSSTI, ?HAP/VAP
 - Not when Pseudomonas, Proteus or MDR Acinetobacter is a concern
- Ceftobiprole
 - to be determined
 - alternative for polymicrobial cSSTIs, ?pneumonia

Considerations

- When vancomycin fails you...
 - Why did it fail?
 - Is it truly a “failure?”
- When choosing newer alternatives...
 - What is the underlying infection?
 - What are the patient’s comorbid conditions, and concomitant meds?
 - Do I really need a new agent now? Can I reserve it to prevent resistance? Do we have sufficient clinical experience with it?