



New Antibacterials

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Reasons for New Antimicrobials

- Emerging Resistance to Current Drugs
 - MRSA – increasing incidence and appearance in the community
 - VISA-VRSA – minimal emergence of resistance to multiple drugs
 - DRSP – high incidence with multidrug resistance; incidence may be decreasing with pneumococcal vaccine
 - VRE – increasing incidence
 - GNB – increasing resistance to multiple drugs
- Improved dosing (long half-life, sustained release, new formulations)

DRSP = drug-resistant *Streptococcus pneumoniae*; VISA = vancomycin–intermediate [-resistant] *Staphylococcus aureus*; VRSA = vancomycin-resistant *S. aureus*; MRSA = methicillin-resistant *S. aureus*; VRE = vancomycin-resistant enterococci; GNB = gram-negative bacilli.

Incidence of MRSA

- TSN data (300 microbiology labs across US)

<i>S. aureus</i> Strains That Are MRSA (%)	
Non-ICU	59.2
ICU	55.0
Outpatient	47.9

- Many community isolates are the same clone (US300), with *mec* type IV and PVL genes

PVL = Panton-Valentine leukocidin; TSN = The Surveillance Network.

Styers D, et al. *Ann Clin Microbiol Antimicrob.* 2006;5:2.

New Antibacterials

- Directed against MRSA (and *Enterococcus*)
 - Tigecycline
 - Dalbavancin
 - Telavancin
 - MRSA beta-lactams
 - Iclaprim
 - Daptomycin
- Directed against respiratory pathogens
 - Faropenem
 - New formulations
- Directed against gram-negative pathogens
 - Tigecycline
 - Doripenem

Tigecycline (Glycylcyclines)

- 9-*t*-butylglycylamido derivative of minocycline



- Blocks tetracycline-specific efflux
- Binds tighter to ribosome and overcomes ribosomal protection

In Vitro Activity Against Gram-Positive Pathogens

Organism	MIC ₉₀ (µg/mL)		
	Tigecycline	Minocycline	Vancomycin
<i>S. aureus</i> (MSSA)	0.25	0.12	1
<i>S. aureus</i> (MRSA)	0.5	8	2
<i>S. aureus</i> (GISA)	0.5	ND	8
<i>S. pneumoniae</i> (PSSP)	0.12	0.12	0.5
<i>S. pneumoniae</i> (PRSP)	0.12	16	0.5
<i>Enterococcus faecium</i> (Van-S)	0.25	4	2
<i>E. faecium</i> (Van-R)	0.12	8	>128

GISA = glycopeptide-intermediate [-resistant] *S. aureus*; MIC = minimum inhibitory concentration; MSSA = methicillin-susceptible *S. aureus*; PSSP = penicillin-susceptible *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; VAN-S = vancomycin-susceptible; VAN-R = vancomycin-resistant.

Milatovic D, et al. *Antimicrob Agents Chemother.* 2003;47:400-404; Betriu C, et al. *Antimicrob Agents Chemother.* 2002;46:892-895.

In Vitro Activity of Tigecycline Against Enterobacteriaceae and Other GNB

Organism	MIC ₉₀ (µg/mL)		
	Tigecycline	Minocycline	Imipenem
<i>Escherichia coli</i>	0.5	16	0.25
<i>Klebsiella pneumoniae</i>	2	32	32
<i>Citrobacter freundii</i>	2	32	4
<i>Enterobacter cloacae</i>	4	128	1
<i>Acinetobacter</i>	4	32	25
<i>Pseudomonas aeruginosa</i>	32	128	325

- MICs >1 mg/L usually associated with multidrug efflux pumps

Pharmacokinetics of Tigecycline

- Oral bioavailability Poor
- C_{\max} 0.62-0.91 mg/L
- $AUC_{0-12\text{ h}}$ 3.07 mg•h/L
- Half-life 37-38 h
- Protein binding 69%-87%
- Urinary excretion 8%-11% as unchanged drug in 48 h
- ELF levels 32% higher than serum AUC
- Blister fluid levels 74% of serum AUC

ELF = epithelial lining fluid.

Stein GE, Craig WA. *Clin Infect Dis*. August 2006. In press.

Current FDA Indications

- Complicated skin and skin structure infections
- Complicated intra-abdominal infections
- Currently being studied in community-acquired and nosocomial pneumonia
- Dose: 100 mg IV over 30-60 minutes, followed by 50 mg IV over 30-60 minutes q12h × 5-14 days
- No modification in renal disease or mild hepatic failure
- 100 mg + 25 mg q12h in moderate hepatic failure

Tigecycline in Complicated Skin and Skin Structure Infections (Pooled Clinical Trial Data)

Regimen	Clinical Response	Microbiologic Response
Tigecycline (100 mg/50 mg q12h)	365/422 (86.5%)	229/279 (82.1%)
Vancomycin/Aztreonam (1 g/2 g q12h)	364/411 (88.6%)	225/261 (86.2%)
95% CI	-6.8% to 2.7%	-10.6% to 2.4%

CI = confidence interval.

Ellis-Grosse EJ, et al. *Clin Infect Dis*. 2005;41:S341-S353.

Tigecycline in Complicated Intra-abdominal Infections (Pooled Clinical Trial Data)

Regimen	Clinical Response	Microbiologic Response
Tigecycline (100 mg/50 mg q12h)	594/685 (86.7%)	441/512 (86.1%)
Imipenem/Cilastin (500 mg q6h)	607/697 (87.1%)	442/513 (86.2%)
95% CI	-4.1% to 3.3%	-4.5% to 4.4%

- Majority had complicated appendicitis; all had operation or drainage procedure

Adverse Effects

- Nausea (24%-34%) and vomiting (20%) most common AEs in clinical trials – (more than twice the rates for comparators in complicated skin and soft-tissue infections)
- However, most gastrointestinal AEs were mild or controlled by antiemetics; discontinuation rates similar to comparators
- Low incidence of other AEs
- No significant drug-drug interactions

Dalbavancin

- Semisynthetic glycopeptide – similar to teicoplanin, with a very prolonged half-life of 8.5 days
- Highly protein bound (93%-97%), with 42% excreted unchanged in urine; rest eliminated in stool
- Very high potency; MICs for MRSA are about 16-fold lower than MICs for vancomycin
- 1 g dose provides free drug levels above 1 mg/L for >7 days
- Effective in STIs and catheter-related bacteremia at a dose of 1 g, followed by a dose of 0.5 g 1 week later
- Very low incidence of AEs

Comparative Activity vs Staphylococci

Organism (n)	MIC ₉₀ (mg/L)			
	MSSA (2834)	MRSA (1119)	MS-CoNS (353)	MR-CoNS (1129)
Dalbavancin	0.06	0.06	0.06	0.12
Teicoplanin	1	4	4	4
Vancomycin	1	2	2	2
Levofloxacin	0.5	>4	>4	>4
Quin/Dalfo	0.5	1	0.5	0.5
Linezolid	2	2	1	1
Daptomycin	0.5	0.5	0.5	0.5

CoNS = coagulase-negative staphylococci.

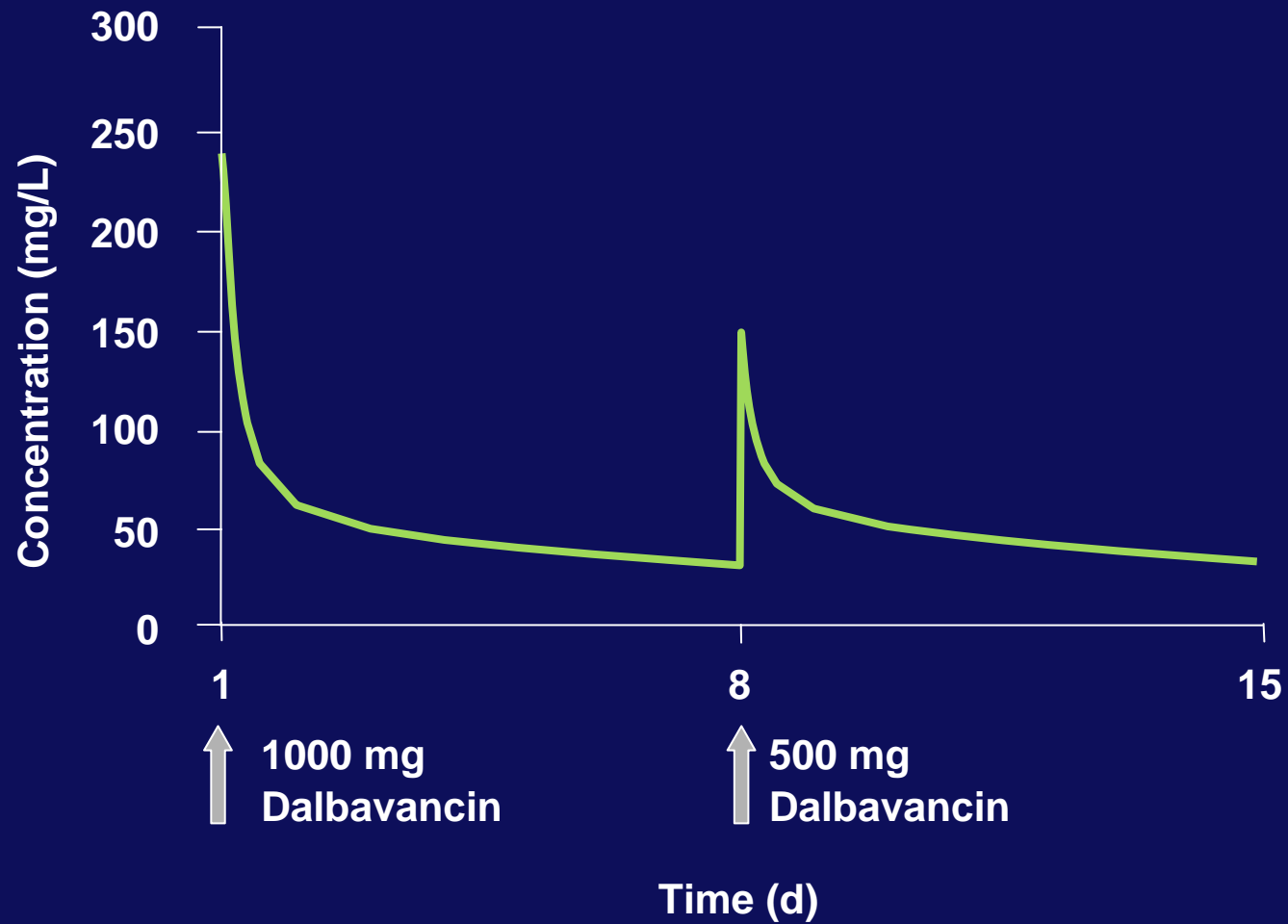
Jones, 2004. Data on file.

Comparative Activity vs Enterococci

Organism (n)	MIC ₉₀ (mg/L)		
	Van-S <i>E. faecalis</i> (1324)	Van-S <i>E. faecium</i> (189)	Other <i>Enterococcus</i> spp. (76)
Dalbavancin	0.06	0.12	0.12
Vancomycin	2	2	>16
Penicillin	8	>32	>32
Quin/Dalfo	>2	2	>2
Linezolid	2	2	2
Daptomycin	1	-	4

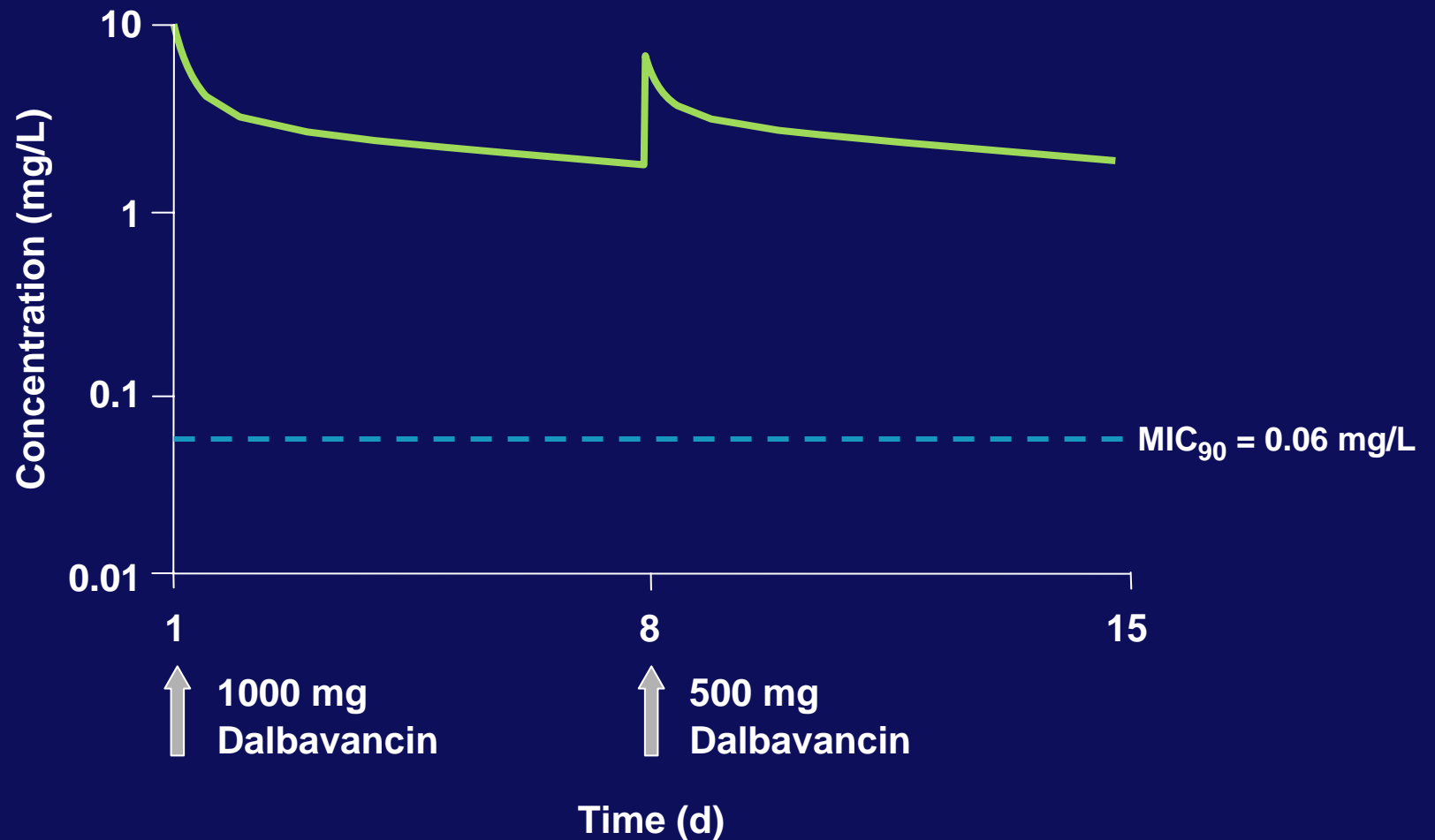
Jones, et al. Presented at: 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); October 30-November 2, 2004; Washington, DC. Poster E-2009.

Dalbavancin Pharmacokinetic Profile



Data on file. Pfizer Inc.

Free-Drug Dalbavancin Pharmacokinetic Profile



Data on file. Pfizer Inc.

Dalbavancin vs Linezolid: Complicated Skin and Soft-Tissue Infections

Regimen	Clinical Response	Microbiologic Response
Dalbavancin (1 g/0.5 g q7d)	386/434 (88.9%)	320/358 (89.5%)
Linezolid (600 mg q12h)	206/226 (91.2%)	168/192 (87.5%)
Lower limit of 95% CI	-7.3%	

- 51% of patients had MRSA

Telavancin

- Semisynthetic glycopeptide with dual action (inhibition of cell wall synthesis + membrane effect)
- MIC₉₀ for MSSA and MRSA is 0.5 mg/L, for both
- Modest activity against VRE (MIC, 0.5-8 mg/L)
- Exhibits concentration-dependent killing
- Adequate penetration into ELF and no inactivation by surfactant
- Once-daily dosing (half-life, 7-9 h)
- Good efficacy against MRSA in initial clinical trials in STI and nosocomial pneumonia (dose, 7.5-15 mg/kg)

VRE = vancomycin-resistant enterococci.

Telavancin vs Antistaphylococcal Penicillin or Vancomycin: Complicated Skin and Soft-Tissue Infections

Regimen	Clinical Response (No. of Patients)	Microbiologic Response (No. of Patients)
Telavancin (7.5 mg/kg qd)	61/66 (92.4%)	52/56 (92.9%)
Vanco 1 g q12h or Naf, Oxa, Clox 1 g q6h	63/66 (95.5%)	53/56 (94.6%)
95% CI	-13% to 5%	-13% to 9%

- 36% were MRSA: 82% telavancin and 69% vancomycin; decreased platelet count and increased creatinine in 7% with telavancin

MRSA–Active Cephalosporins and Carbapenems

- Bind to PBP 2A and resist hydrolysis by penicillinase
- Multiple compounds
 - Ceftobiprole (BAL9141, RO 63-9141) – similar to cefepime for gram-negative activity
 - Ceftaroline (PPI-0903, TAK-599)
 - RO 4908463 (CS-023) – slightly more active than meropenem for *P. aeruginosa*
- Parenteral drugs

MIC for MRSA Cephalosporins

Organism	MIC ₅₀ /MIC ₉₀ (mg/L)	
	Ceftobiprole	Ceftaroline
MRSA	1/2	1/2
MSSA	0.5/0.5	0.25/0.25
MRSE	1/2	0.25/0.5
MSSE	0.12/0.25	0.06/0.25
<i>S. pneumoniae</i>	0.015/0.25	0.015/0.25
<i>E. faecalis</i>	0.5/8	0.5/4

MRSE = methicillin-resistant *Staphylococcus epidermidis*; MSSE = methicillin-susceptible *S. epidermidis*.

Deshpande LM, et al. Presented at: 41st ICAAC; December 16-19, 2001; Chicago, Ill; Sader HS, et al. Presented at: 44th ICAAC; October 30-November 2, 2004; Washington, DC.

MRSA–Active Cephalosporins and Carbapenems

- Low-to-moderate protein binding
- Excellent efficacy in experimental endocarditis caused by MRSA and *E. faecalis*
- Initial pharmacokinetic data in humans suggest q8h or q12h dosing

Iclaprim

- New diamino pyrimidine with increased activity over trimethoprim
- MIC₉₀ levels for MSSA and MRSA are 0.06 mg/L and 0.12 mg/L, respectively; at least 32-fold lower than those for trimethoprim
- Peak serum concentrations 1-2 mg/L with 93% protein binding
- Half-life of 1.6-2 h
- ELF levels 20-fold higher than in serum
- Good efficacy in phase II clinical trials in complicated skin and skin structure infections
- Currently being studied in phase III clinical trials

Daptomycin

- A parenteral lipopeptide antibiotic that disrupts the cell membrane potential; FDA approved since 2003 at 4 mg/kg qd for complicated skin and skin structure infections
- Low incidence of AEs
- Frequently used off label for treatment of complicated staphylococcal bacteremia at similar or higher dose
- Recently received FDA approval at 6 mg/kg qd for complicated staphylococcal bacteremia with or without right-sided endocarditis (compared with antistaphylococcal penicillin/vancomycin + low-dose gentamicin)

Daptomycin vs Standard Therapy: Treatment for Staphylococcal Bacteremia With Known or Suspected Infective Endocarditis (IE)

ITT Population	Daptomycin (Patient Response)	Comparator (Patient Response)
All cases	53/120 (44.2%)	48/115 (41.7%)
	▲ 2.4% (95% CI, -10.2 to 15.1)	
MRSA	20/45 (44.4%)	14/43 (32.6%)
	▲ 11.9% (95% CI, -8.3 to 32.1)	
IE	9/28 (32.1%)	9/25 (36.0%)
	▲ 3.9%	

ITT = intent to treat.

Fowler V, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC.

Daptomycin vs Standard Therapy: Treatment for Staphylococcal Bacteremia With Known or Suspected IE (CONT'D)

- Six failures with daptomycin (five with MRSA) had increase in MIC from 0.25-0.5 mg/L to 2-4 mg/L
- More failures in comparator group because of development of renal impairment
- CPK increase >500 in six (5%) – only one had weakness, possibly related to daptomycin

CPK = creatinine phosphokinase.

Fowler V, et al. Presented at: 45th ICAAC; December 16-19, 2005; Washington, DC.

Faropenem and New Formulations

- Faropenem daloxate
 - Oral carbapenem
 - Good activity against respiratory pathogens
 - High protein binding (93%-95%)
 - Twice-daily dosing
 - Comparative efficacy in CAP and sinusitis

- Azithromycin extended-release
 - Single oral suspension of 2 g
 - Minimal nausea, moderate diarrhea
 - Comparative efficacy in CAP and sinusitis

CAP = community-acquired pneumonia.

New Carbapenems

- Doripenem

- Parenteral carbapenem similar to meropenem
- Increased activity against some imipenem-resistant strains of *P. aeruginosa* and *Acinetobacter*
- Currently in phase III clinical trials
- Will be studied in intensive care units as 3-hour infusion to increase T>MIC against more resistant gram-negative pathogens

Other Antibacterials in Development

- Fluoroquinolones
- Oxazolidinones
- Macrolides/ketolides
- Pleuromutilins
- Deformylase inhibitors
- MRSA cephalosporins
- Beta-lactamase inhibitors
- Lysostaphin
- Lipopeptides
- Peptide antimicrobials