Therapeutic options for MRSA: what next beyond vancomycin and linezolid?

Paul M. Tulkens, MD, PhD *

Cellular and Molecular Pharmacology
& Center of Clinical Pharmacy
Louvain Drug Research Institute

Université catholique de Louvain
http://www.facm.ucl.ac.be

* with several slides borrowed from Françoise Van Bambeke, PharmD, PhD

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With approval of the Common Belgian Medical Ethical platform - visa no. 13/V1/4806/053906
The Staphylococcus aureus saga: 60 first years …

1881:
First observation of staphylococci in pus by Alexander Ogston

1884:
First distinction between S. aureus and S. albus by Friedrich Rosenbach

"Micrococci so deleterious when injected are seemingly harmless on the surface of wounds and ulcers". Br Med J 1881;1:369-375

1914-1918:
Half of the casualties in the trenches of the First World War were due to septic wound infections with S. aureus.

1940-45:
The production process for penicillin (then still universally active against the bacterium*) was a military secret

* the original observation of Fleming (1928) was made on S. aureus
The *Staphylococcus aureus* saga: the next 17 years ...

1944:
First description of a β-lactamase in *S. aureus* *

1950-70:
almost all strains of *S. aureus* produce a β-lactamase

1960:
introduction of methicillin ... and emergence of resistance to methicillin in 1961

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* The first description of a β-lactamase was made in 1940 in *E. coli* (Nature 146, 837 (28 December 1940))

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**Methicillin-resistant staphylococci**

**MARY BARBER**

From the Department of Bacteriology, Postgraduate Medical School of London

**SYNOPSIS** Eighteen strains of *Staph. pyogenes* (nine penicillin-sensitive and nine penicillin-destroying) were passed for 40 to 50 times on Celbenin*®* plates.

All strains developed an increase in resistance to Celbenin and eight strains (four penicillin-sensitive and four penicillin-destroying) were able to grow in 100 µg/mL or more Celbenin. Resistance was of the drug-tolerant type and none of the cultures inactivated Celbenin. There was an associated increase in tolerance to benzyl penicillin.

The highly Celbenin-resistant cultures isolated from penicillin-destroying staphylococci were in sharp contrast to those from penicillin-sensitive strains, as well as to penicillin G-tolerant staphylococci isolated in vitro, because they retained the cultural characteristics, coagulate and haemolytic activity, and mouse virulence of the parent strains, and the degree of resistance remained stable after repeated passage in the absence of Celbenin.

Three naturally occurring Celbenin-resistant strains of *Staph. pyogenes* isolated from infective processes were also studied. All three strains grew luxuriantly in concentrations of Celbenin up to 12.5 µg/mL, but very poorly in higher concentrations.

The possible significance of these findings is discussed.
The *Staphylococcus aureus* saga: from 1961 onwards...

**1970's:**
Spreading of methicillin resistance
In hospitals

**1980's:**
Large scale re-introduction of vancomycin *

**1997:**
Strains with reduced susceptibility to vancomycin

FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.


* Vancomycin was described in 1955-57

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**1980's:**
Large scale re-introduction of vancomycin *

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**Correspondence**

Methicillin-resistant *Staphylococcus aureus*
clinical strain with reduced vancomycin susceptibility


K. Hiramatsu*, H. Hanaki*, T. Ino*, K. Yabuta*, T. Oguri* and F. C. Tenover*

*Department of Bacteriology; †Department of Pediatrics, Juntendo University, Tokyo; ‡Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; ‡Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA
Vancomycin (in the good old time)

- Peak level: 30-40 mg/L 2 h after the end of infusion
- Trough level: 5-10 mg/L just before the next dose

Conc. (mg/L) at 3th VAN dose

(VAN BID 1g q12h)

Time (h)

0 6 12
Vancomycin in 2011

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,1 Arnold Bayer,1,2 Sara E. Cosgrove,5 Robert S. Daum,1 Scott K. Fridkin,3 Rachel J. Gorwitz,9 Sheldon L. Kaplan,10 Adolf W. Karchmer,11 Donald P. Levine,12 Barbara E. Murray,14 Michael J. Rybak,12,13 David A. Talan,4,5,6 and Henry F. Chambers1,2


63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (B-II).
Vancomycin in 2013

Nephrotoxicity occurred in 78 patients (23%), occurring in 56%, 11%, and 33% of patients at Hospitals A, B, and C, respectively. The median (interquartile range) increase from baseline to peak serum creatinine was 0.0 mg/dL (0.0, 0.2) for patients who did not develop nephrotoxicity versus 1.0 mg/dL (0.6, 2.1) for patients who developed nephrotoxicity. Fifteen percent of patients had a vancomycin trough concentration greater than 20 mcg/ml. Concurrent nephrotoxins included contrast dye (34%), aminoglycosides (19%), and vasopressors (12%). Concomitant antimicrobials active against MRSA were used in 23% of patients.
Vancomycin: will continuous infusion help?

**efficacy**

- VAN serum conc. (mg/L)
  - 25-30 mg/L

**toxicity**

- C<sub>ss</sub> vancomycin > 28 mg/L en increased nephrotoxicity risk
  - [OR 21.236; P = 0.004]

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Staphylococcus aureus and linezolid

1996:
First description of linezolid

1998-2002:
Resistance to linezolid by target mutation (remains rate)

2007:
Resistance to linezolid by methylation (cfr)

Table 1. In Vitro Antibacterial Activity. Minimum Inhibitory Concentration (µg/mL)

<table>
<thead>
<tr>
<th>organism</th>
<th>strain number</th>
<th>U-100592</th>
<th>U-100766</th>
<th>vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>UC#9213</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>UC 12673</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>ATCC29213</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>UC 30031</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>ATCC 29212</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>UC 12712</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>UC 9912</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>UC 152</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>ATCC 25285</td>
<td>1</td>
<td>1</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>ATCC 13124</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>H37Rv</td>
<td>≤0.125</td>
<td>≤0.125</td>
<td>f</td>
</tr>
</tbody>
</table>

a Upjohn Culture (registered trademark of The Upjohn Co.).
b American Type Culture Collection.
c MRSA.
d Comparative control value for clindamycin was 0.5 µg/mL.
e Comparative control value for clindamycin was 0.06 µg/mL.
f Comparative control value for isontazid was 0.20 µg/mL.

Linezolid breakpoint

Linezolid / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database 2013-08-11

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

MIC Epidemiological cut-off: WT ≤ 4 mg/L
Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L

we are very close
Toxicological limitations of linezolid

• Drug interactions:
  – cytochrome P450: no special effect
  – antibiotics: rifampin causes a 21 % decrease in LZD serum levels
  – Monoamine Oxidase Inhibition (reversible, nonselective inhibitor):
    adrenergic and serotonergic agents (PRECAUTIONS)

• Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)

• Hypoglycemia

• Lactic acidosis (PRECAUTION – Immediate medical attention)

• Peripheral and Optic Neuropathy (> 28 days)

• Convulsions
LINEZOLID and Monoamine Oxidase A

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis

MAO-A

**Serotonin**
Noradrenaline
Adrenaline
Octopamine

Dopamine
Tryptamine
Kynuramine
3-methoxytyramine

MAO-B

Benzylamine
Phenylethylamine
N-phenylamine
Octylamine
N-acetylputrescine
Milacemide
N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

\[ a \] MAO-A is the predominate form for oxidation of tyramine. Elmer and Bertoni. *Expert Opin Pharmacother.* 2008;9:2759-2772
This is what we tell the pharmacists in Belgium ....

Interactions linezolid - médicaments

Anti-migraineux
- triptans
dihydroergotamine

Anti-Parkinsoniens
- L-Dopa
bromocryptine
selegiline

Sympathomimétiques
- bronchodilatateurs
pseudoéphérine

Analgésiques
- dextropropoxyphène
fentanyl
tramadol

Anti-psychothiques
- clozapine
olanzapine
risperidone
lithium

Anti-psychotiques
- dextromethorphan
codéine

Anti-dépresseurs
- tricycliques
IMAO
ISRS

Anxiolytiques
- buspironé

Vasopresseurs
- (nor)adrénaline

Anti-émétiques
- setrons
metoclopramide

Lawrence et al., CID (2006) 42:1578-83
LINEZOLID and myelosuppression: treatment discontinuation
So, what are our possibilities?

"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.
Main drugs approved for MRSA before 2008

- **Daptomycin** (approved in 2003)
- **Tigecyclin** (approved in 2005)
- Cotrimoxazole, clindamycin, doxycyclin/minocyclin (CA-MRSA) (also old guys)
Daptomycin: historical landmarks....

1987 1993 1997

Discovery of daptomycin as a novel anti-Gram + lipopeptide

In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.

Development halted
- lack of efficacy
- toxicity

“Lilly was not satisfied with the overall clinical results observed with the twice-daily dosing regimen utilized in these studies”

Taking over by CUBIST
or “pharmacodynamics in action .....”

Once-daily dosing in dogs optimizes daptomycin safety.

Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha et al, 2003, AAC 47:1598-603
Daptomycin ...


Ca++

J. Silverman, 45th ICAAC, 2005
**PK/PD of daptomycin - application to humans**

<table>
<thead>
<tr>
<th>dose and route of administration</th>
<th>compartment</th>
<th>AUC</th>
<th>AUC/MIC (1 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mg/kg iv</td>
<td>serum</td>
<td>417</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td>inflamm. exudate</td>
<td>318</td>
<td>318</td>
</tr>
<tr>
<td>6 mg/kg iv</td>
<td>serum</td>
<td>747</td>
<td>747</td>
</tr>
</tbody>
</table>

Dose adjustment if creatinine clearance < 30 ml/min

**EUCAST breakpoint:**

1 mg/L

Wise et al., AAC (2002) 46:31-3

Dvorichik et al., AAC (2003) 47:1318-23
Launching daptomycin…

Registration
- FDA: 2003
- Europe: 2006

Indications in Europe
- Complicated skin and soft tissues infections with Gram (+)
- Bacteremia
- Endocarditis
- Complicated urinary tract infections

Efficacy up to an MIC of 1 mg/L
- Pneumonia (neutralization by the surfactant)
- VISA strains (no access to target)

Lack of efficacy:
- Only available as intravenous form!

Carpenter & Chambers CID (2004) 38: 994-1000
4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to Staphylococcus aureus. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- Staphylococcus aureus bacteraemia (SAB) when associated with RIE or with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.\(^{32}\)

To minimize the risk, three steps are advised:

first to explore the potential for higher dosage, guaranteeing levels above a ‘mutant prevention concentration’;

secondly, to recognize patients where surgical debridement is warranted;

and thirdly, to prevent cross-infection with resistant organisms.

Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

DAPTOMYCIN

Warnings and Precautions

- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN and treat signs/symptoms. (5.1)
- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN and consider treatment with systemic steroids. (5.3)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.5)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.6)
- Decreased efficacy was observed in patients with moderate baseline renal impairment. (5.7)

Adverse Reactions

The most clinically significant adverse reactions observed with CUBICIN 4 mg/kg (cSSSI trials) and 6 mg/kg (*S. aureus* bacteremia/endocarditis trial) were abnormal liver function tests, elevated CPK, and dyspnea. (6.1)
DAPTOMYCIN: is the dosage correct?

JAC

Future directions with daptomycin

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Daptomycin is the first new natural-product antibiotic launched in a generation. It was licensed first for skin and soft tissue infections (SSTIs) and, more recently, for staphylococcal bacteraemia and endocarditis. Further clinical trials are in progress, some investigating performance in subsets of SSTIs while others, more interestingly, are evaluating efficacy in enterococcal endocarditis and neutropenic fevers—settings where the compound’s bactericidal activity is potentially advantageous. There is a need for further trials in bone and joint infections. On the negative side, there are several reports of mutational resistance emerging during the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections, mostly in settings with a heavy bacterial load, and there is a need to determine whether higher dosages or combination regimens will reduce this risk. A few patients have already been treated with doses of up to 12 mg/kg. Lastly, daptomycin is entering a market increasingly crowded with new anti-Gram-positive agents. More work is required to establish those settings where daptomycin and other new compounds offer real advantages over established glycopeptides and over each other. There is presently a paradox whereby vancomycin is agreed to be less than ideal, with outcomes impaired against MRSA with modestly raised MICs, but where new agents have yet to demonstrate unequivocal superiority.

Keywords: Gram-positive infections, MRSA, enterococci, Staphylococcus aureus
Daptomycin: pros and cons

- rapidly bactericidal
- highly potent, including against MDR strains

- not usable for pneumonia
- not active against VISA
- risk of side effects if dosage is increased
Discovery of glycylcyclines as a novel class of antibiotics

In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.

Demonstration of the spectrum of activity and candidate selection

In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).

and then, Pfizer bought Wyeth…
Tigecycline: chemical structure

Tigecycline

minocycline

glycyl-
t-butyl
Mode of action of tigecycline

- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to - ribosomal protection - Tet efflux pumps;
- But remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in P. aeruginosa)

Olson et al., AAC (2006) 50:2156-66
### Tetra- and glycyl-cyclines: activity and resistance

<table>
<thead>
<tr>
<th>species</th>
<th>phenotype</th>
<th>tetracycline</th>
<th>minocycline</th>
<th>tigecycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td>susceptible</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Efflux (Tet)</td>
<td>&gt; 32</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Ribosomal protection</td>
<td>&gt; 32</td>
<td>&gt; 32</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td>susceptible</td>
<td>0.12</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Efflux (Tet)</td>
<td>&gt; 32</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Ribosomal protection</td>
<td>&gt; 32</td>
<td>4</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Petersen et al., AAC (1999) 43:738-44
# Tigecycline: Pharmacokinetics

<table>
<thead>
<tr>
<th>Tissue</th>
<th>AUC$_{24h}$ (mg.h/L)</th>
<th>Serum/tissue AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose: 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bile</td>
<td>2815</td>
<td>537</td>
</tr>
<tr>
<td>bladder</td>
<td>120</td>
<td>23</td>
</tr>
<tr>
<td>colon</td>
<td>17.3</td>
<td>2.6</td>
</tr>
<tr>
<td>lung</td>
<td>9.19</td>
<td>2</td>
</tr>
<tr>
<td>bone</td>
<td>2.05</td>
<td>0.4</td>
</tr>
<tr>
<td>synovial fluid</td>
<td>1.68</td>
<td>0.31</td>
</tr>
<tr>
<td>CSF</td>
<td>0.46</td>
<td>0.11</td>
</tr>
<tr>
<td>100 mg + 6x50 mg q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELF</td>
<td>4.54</td>
<td>1.31</td>
</tr>
<tr>
<td>alveolar МΦ</td>
<td>268</td>
<td>77.5</td>
</tr>
</tbody>
</table>

*Conte et al., Int J Antimicrob Agents (2005) 25:523-9*
Tigecycline EUCAST breakpoints

Tetracyclines - EUCAST clinical MIC breakpoints
2008-06-19 (v 2.2)

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>Species-related breakpoints (S/I/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RD</td>
</tr>
</tbody>
</table>

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.

But will this last?
(T.E.S.T. will tell but TK reports MIC\textsubscript{90} at 0.75
In 2008)

Denis et al., AAC (2006) 50:2680-5
4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

**Paediatric patients**

Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

* pediatric studies are ongoing and/or proposed to Regulatory Authorities
# Tigecycline: side effects

**Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥ 2% of Patients Treated in Clinical Studies**

<table>
<thead>
<tr>
<th>Body System</th>
<th>TYGACIL (N=2514)</th>
<th>Comparators (N=2307)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Abscess</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td><strong>Hemic and Lymphatic System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
## Tigecycline: clinical failures

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>TYGACIL</th>
<th>Comparator</th>
<th>Risk Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td>cSSSI</td>
<td>12/834</td>
<td>1.4</td>
<td>6/813</td>
</tr>
<tr>
<td>cIAI</td>
<td>42/1382</td>
<td>3.0</td>
<td>31/1393</td>
</tr>
<tr>
<td>CAP</td>
<td>12/424</td>
<td>2.8</td>
<td>11/422</td>
</tr>
<tr>
<td>HAP</td>
<td>66/467</td>
<td>14.1</td>
<td>57/467</td>
</tr>
<tr>
<td>Non-VAP*</td>
<td>41/336</td>
<td>12.2</td>
<td>42/345</td>
</tr>
<tr>
<td>VAP*</td>
<td>25/131</td>
<td>19.1</td>
<td>15/122</td>
</tr>
<tr>
<td>RP</td>
<td>11/128</td>
<td>8.6</td>
<td>2/43</td>
</tr>
<tr>
<td>DFI</td>
<td>7/553</td>
<td>1.3</td>
<td>3/508</td>
</tr>
<tr>
<td>Overall Adjusted</td>
<td>150/3788</td>
<td>4.0</td>
<td>110/3646</td>
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</tbody>
</table>

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.

* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

** Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

* These are subgroups of the HAP population.

Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).
Tigecycline: pros and cons

- Active against MRSA resistant to other antibiotics
- Good cellular penetration

- Bacteriostatic
- MIC's very close to breakpoint
- Side effects limit dose increase
The newcomers (approved for MRSA after 2008)

- **Telavancin** (approved in 2009 for cSSSI and later for VAP)
- **Ceftaroline** (approved in 2010 [AbSSSI and non-MRSA CAP])
  - Iclaprim, oritavancin, ceftobiprole, cethromycin were not accepted
New (lipo)glycopeptides: structure-activity relationships

Lipophilic side chain (TEC, ORI, TEL, DAL)
- membrane anchoring
- prolonged half-life
- increased activity (enterococci)

Sugar (ORI)
- dimerization

Basic amide (DAL)
- increased activity (staphylococci)

Polar group (TEL)
- decreased half-life

CI (VAN, TEC, ORI, TEL)
- dimerization

Telavancin and Oritavancin

Van Bambeke et al., TIPS (2008) 29:124-34
### Telavancin: In vitro activity

<table>
<thead>
<tr>
<th>species</th>
<th>phenotype</th>
<th>ORI</th>
<th>TLV</th>
<th>VAN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. aureus</strong></td>
<td>MSSA</td>
<td>0.25/0.5</td>
<td>0.25/0.5</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>0.25/0.5</td>
<td>0.25/0.25</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>VISA</td>
<td>1/1</td>
<td>0.5-1</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>VRSA</td>
<td>0.5*</td>
<td>2-4</td>
<td>16*</td>
</tr>
<tr>
<td><strong>S. pneumo</strong></td>
<td>PenS</td>
<td>≤0.002/0.004</td>
<td>≤0.06/0.06</td>
<td>≤0.25 ≤0.25</td>
</tr>
<tr>
<td></td>
<td>Pen nonS</td>
<td>≤0.002/0.004</td>
<td>≤0.06/0.06</td>
<td>≤0.25 ≤0.5</td>
</tr>
<tr>
<td><strong>Enterococci</strong></td>
<td>VanS</td>
<td>0.12/0.5</td>
<td>0.12/0.5</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>VanR</td>
<td>0.03*</td>
<td>4-16</td>
<td>16*</td>
</tr>
</tbody>
</table>

* Median value

---

*Draghi et al., AAC (2008) 52:2383-2388*
*ICAAC (2008) C1-146,150,151*
Telavancin: In vitro activity and breakpoint

Telavancin / Staphylococcus aureus MRSA
EUCAST MIC Distribution - Reference Database 2013-08-11

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC: Epidemiological cut off WT ≥ 1 mg/L

3280 observations (10 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 1 mg/L

we are (also) very close
Telavancin clinical studies: safety

Adverse events and laboratory abnormalities for pooled cSSTIs and HAP studies

<table>
<thead>
<tr>
<th>AE, n/N (%)</th>
<th>Telavancin</th>
<th>Vancomycin</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AE</td>
<td>1454/1864</td>
<td>1393/1868</td>
<td>1.20 (0.97–1.49)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>314/1864</td>
<td>251/1868</td>
<td>1.38 (0.90–2.13)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>144/1864</td>
<td>100/1868</td>
<td>1.48 (1.14–1.93)</td>
</tr>
<tr>
<td>Nausea</td>
<td>318/1864</td>
<td>190/1868</td>
<td>1.88 (1.54–2.29)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>143/1113</td>
<td>78/1116</td>
<td>1.97 (1.47–2.63)</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>325/1029 (31.6)</td>
<td>62/1033 (6)</td>
<td>7.37 (5.52–9.85)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>73/1029</td>
<td>81/1033</td>
<td>0.90 (0.65–1.25)</td>
</tr>
<tr>
<td>Constipation</td>
<td>174/1864</td>
<td>144/1868</td>
<td>1.12 (0.72–1.74)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>137/1780</td>
<td>136/1785</td>
<td>1.14 (0.62–2.11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>34/1029</td>
<td>68/1033</td>
<td>0.48 (0.32–0.74)</td>
</tr>
<tr>
<td>Headache</td>
<td>147/1113</td>
<td>132/1116</td>
<td>1.14 (0.89–1.47)</td>
</tr>
<tr>
<td>Chills</td>
<td>47/1029</td>
<td>23/1033</td>
<td>2.10 (1.27–3.48)</td>
</tr>
<tr>
<td>Cr elevation</td>
<td>166/1638</td>
<td>88/1674</td>
<td>2.22 (1.38–3.57)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>73/1528</td>
<td>44/1521</td>
<td>1.91 (0.91–4.00)</td>
</tr>
<tr>
<td>AST increase</td>
<td>36/1045</td>
<td>39/1084</td>
<td>0.93 (0.43–2.04)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>38/1101</td>
<td>61/1165</td>
<td>0.64 (0.42–0.97)</td>
</tr>
<tr>
<td>QTcF increaseb</td>
<td>59/1560 (3.8)</td>
<td>49/1578 (3.1)</td>
<td>1.24 (0.84–1.83)</td>
</tr>
<tr>
<td>Anemia</td>
<td>66/1052</td>
<td>65/1058</td>
<td>1.01 (0.71–1.46)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>12/1006</td>
<td>19/989</td>
<td>0.62 (0.30–1.28)</td>
</tr>
<tr>
<td>Platelet decreasec</td>
<td>8/1064 (0.8)</td>
<td>10/1110 (0.9)</td>
<td>0.87 (0.35–2.17)</td>
</tr>
</tbody>
</table>

\(^a\)The FAST 1 study is included in the analysis.
\(^b\)>60 ms.
\(^c\)<75×10^9/L.

Polysos et al., PLoSone (2012) 7: e41870
Telavancin: current indications

**EMA approved indication (2011):**

treatment of adults with nosocomial pneumonia, including ventilator associated pneumonia,
  - known or suspected to be caused by MRSA;
  - only in situations where it is known or suspected that other alternatives are not suitable.

**FDA approved indication (2009):**

treatment of adult patients with complicated skin and skin structure infections
  - caused by susceptible Gram-positive bacteria,
  - including *Staphylococcus aureus*, both MRSA and MSSA

Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*, when alternative treatments are not suitable.
Telavancin: pros and cons

- Rapidly bactericidal
- Once-a-day
- Active on VISA to some extent

- No oral route
- Not active on VRSA
- Renal toxicity?
- EMA and FDA warnings
Ceftaroline

Gram-neg

β-lactamases

Prodrug (fosamyl) TAK-599

Ceftaroline and MRSA

Ceftaroline / Staphylococcus aureus MRSA
EUCAST MIC Distribution - Reference Database 2013-08-11

MIC distributions include collected data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

% microorganisms

MIC (mg/L)

< 0.002 0.004 0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32 64 128 256 512

MIC Epidemiological cut-off: WT ≤ 0.5 mg/L
Clinical breakpoints: S ≤ 1 mg/L, R > 1 mg/L

6041 observations (2 data sources)

we are perhaps too close
Ceftaroline: current indications

**EMA approved indications (2012):**

- treatment of adults
  - with community acquired pneumonia
  - complicated skin and soft tissue infection

**FDA approved indications (2010):**

- community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.

- acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*
### Ceftaroline Safety profile (Phase III)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teflaro (N=1300)</td>
<td>Pooled Comparators(^a) (N=1297)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>2%</td>
</tr>
</tbody>
</table>

\(^a\) Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials.
Ceftaroline: pros and cons

- Broad spectrum
- Safety profile

- Broad spectrum
- No oral route
- Indications are "minimal"
- Anti-MRSA activity borderline?
The "soon" to be registered

- Fluoroquinolones
  - Delafloxacin
  - JNJ-Q2
- Oxazolidinones
  - Tedizolid
- Ketolides
  - Solithromycin
- Lipoglycopeptides
  - Dalbavancin
  - Oritavancin
- Anti-MRSA β-lactams
  - Ceftobiprole
DELAFLOXACIN

**FIG. 2.** Comparative susceptibilities of various *S. aureus* isolates to moxifloxacin (circles) or delafloxacin (squares). MICs were measured at pH 7.4, and strains are ranked based on their susceptibility to moxifloxacin. Resistance phenotypes and/or strain source are designated by lowercase letters along the x axis: a, animal MRSA; c, CA-MRSA; e, efflux (NorA); h, HA-MRSA; l, linezolid-resistant; m, characterized mutations in fluoroquinolone targets; s, MSSA.

Activity still improved at acidic pH due to increased penetration inside bacteria!

Delafloxacin: pros and cons

- rapidly bactericidal
- highly potent, including against MDR strains
- highly active on intracellular bacteria

- side effects of FQ
Randomized, Double-Blind, Phase II, Multicenter Study Evaluating the Safety/Tolerability and Efficacy of JNJ-Q2, a Novel Fluoroquinolone, Compared with Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infection

Paul Covington,1‡, J. Michael Davenport,1 David Andrae,1 William O’Riordan,2 Lisa Liverman,1 Gail McIntyre,1 and June Almenoff†

Furiex Pharmaceuticals, Morrisville, North Carolina,1 and eStudySite, San Diego, California2

Received 8 June 2011/Returned for modification 15 August 2011/Accepted 15 September 2011
### TABLE 10. Summary of adverse events

<table>
<thead>
<tr>
<th>Adverse event category</th>
<th>No. (%) patients with indicated no. and type of adverse event&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JNJ-Q2</td>
</tr>
<tr>
<td></td>
<td>(n = 83)</td>
</tr>
<tr>
<td>Total no. of adverse events</td>
<td>111</td>
</tr>
<tr>
<td>No. of unique patients with at least 1 adverse event</td>
<td>50 (60.2)</td>
</tr>
<tr>
<td>Adverse events that occurred in &gt;5% of either group</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (14.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (12.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Elevated ALT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (8.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Percentages are based on the total number of patients in each treatment group.

<sup>b</sup> Although not recorded by investigators as adverse events, patients with elevated ALT levels were included in the chart if they demonstrated the combination of at least 1.5× the ULN and at least a 1.5-fold increase above baseline for ALT. No subject had a simultaneous elevation of ALT and bilirubin. One subject included in the JNJ-Q2 group experienced an asymptomatic ALT elevation to 875, but without concomitant elevation of bilirubin, and the ALT elevation resolved by day 30.
JNJ-Q2

- rapidly bactericidal
- highly potent, including against MDR strains

- side effects of FQ
- why did J&J gave it away?
Tedizolid - Radezolid

<table>
<thead>
<tr>
<th>strain</th>
<th>Phenotype</th>
<th>Linezolid</th>
<th>Tedizolid</th>
<th>Radezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 25923</td>
<td>MSSA</td>
<td>2</td>
<td>0.25</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>ATCC 33591</td>
<td>HA-MRSA</td>
<td>1</td>
<td>0.125-0.25</td>
<td>0.5-1</td>
</tr>
<tr>
<td>SA 238</td>
<td>HA-MRSA</td>
<td>2</td>
<td>0.25-0.5</td>
<td>0.5-1</td>
</tr>
<tr>
<td>SA 238L</td>
<td>HA-MRSA, LZD&lt;sup&gt;R&lt;/sup&gt;</td>
<td>16</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NRS 192</td>
<td>CA-MRSA</td>
<td>2</td>
<td>0.125-0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>NRS 384</td>
<td>CA-MRSA</td>
<td>2</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>NRS 52</td>
<td>VISA</td>
<td>2</td>
<td>0.125</td>
<td>2</td>
</tr>
<tr>
<td>VRS 1</td>
<td>VRSA</td>
<td>1-2</td>
<td>0.125-0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>VRS 2</td>
<td>VRSA</td>
<td>1-2</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGD</td>
<td>1-2</td>
<td>0.125</td>
<td>0.03-0.06</td>
<td></td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153</td>
<td></td>
<td>4-8</td>
<td>0.25-0.5</td>
<td>0.5-1</td>
</tr>
</tbody>
</table>

Tedizolid and activity against cfr+ strains

Binding of tedizolid to methylated ribosomes

Tedizolid and MAO inhibition

In Vitro, In Vivo, and Clinical Studies of Tedizolid To Assess the Potential for Peripheral or Central Monoamine Oxidase Interactions

S. Flanagan,* K. Bartizal,* S. L. Minassian,† E. Fang,* P. Prokocimer†
Trius Therapeutics, Inc., San Diego, California, USA; Minassian Biostatistics, Inc., San Diego, California, USA

FIG 3 Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, P < 0.05 versus the control group.
Tedizolid Phase III

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections
The ESTABLISH-1 Randomized Trial

Trial Registration clinicaltrials.gov Identifier: NCT01170221
JAMA. 2013;309(6):559-569

Official Title: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections
### Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid Phosphate (n = 331)</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>135 (40.8)</td>
</tr>
<tr>
<td>≥1 Serious TEAE</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Discontinuation due to TEAE</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Most commonly reported TEAE</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (8.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (6.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (4.5)</td>
</tr>
<tr>
<td>Abscess</td>
<td>14 (4.2)</td>
</tr>
<tr>
<td>Abscess limb</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

---

**a** Patients reporting a particular adverse event more than once are counted only once by preferred term.  
**b** Percentages were calculated as 100 × (number of patients/total number).  
**c** In either treatment group, 2% or more reported 1 of these adverse events.
TEDIZOLID Phase III

Table 6. Patients With Treatment-Emergent Adverse Events (TEAEs) in the Safety Analysis Set

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Tedizolid Phosphate (n = 331)</th>
<th>Linezolid (n = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 TEAE</td>
<td>135 (40.8)</td>
<td>145 (43.3)</td>
</tr>
<tr>
<td>≥1 Serious TEAE</td>
<td>5 (1.5)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Low platelet counts were less than half as frequent in the tedizolid phosphate group as in the linezolid group, but the study was not Adequately powered to make conclusions about the risk of Myelosuppression with tedizolid phosphate.
New oxazolidinones: pros and cons

- active on LZD-resistant strains
- more potent against intracellular bacteria
- possibly less toxic than LZD
- rather bacteriostatic
CETHROMYCIN-SOLITHROMYCIN

- Cethromycin: binding to domain II of ribosomes; activity on methylated ribosomes; poor recognition by S. pneumo efflux pumps; pharmacokinetics: cellular accumulation, half-life; tolerance.
- Solithromycin: acid stability; absence of inducibility of MLSB resistance; poor recognition by S. pneumo efflux pumps; carbamate increase in activity; improvement of pharmacokinetics; vinyl pharmacokinetics: prolonged half-life, high tissue penetration.

**Heteroarylalkylgroup**: (in 6, 11, or on 6,11-bridge)

- **Cethromycin**: carbamate increase in activity
- **Solithromycin**: carbonyl

Solithromycin: in vitro activity

Activity against *S. pneumoniae* (Belgian-German strains, including MDR)
New ketolides: pros and cons

- active on ML-resistant strains
- more bactericidal than conventional macrolides
- possibly less toxic than telithromycin

- drug interactions?
Dalbavancin

- VERY long half life (1 g followed by 500 mg 1 week later)
- skin and skin structure infections
- catheter-related bloodstream infections (Phase II)
- ➔ priority review status by the FDA for the treatment of MRSA complicated skin and soft tissue infections

Withdrawn (by Pfizer) in Sep 2008

- Re-developed by DURATA since 2009
- No clinical data published since then but the web site says "Dalbavancin has completed a total of fifteen Phase 3, Phase 2 and Phase 1 clinical trials, over approximately ten years, in which more than 1,000 patients have been dosed with dalbavancin"
Oritavancin

- Also a VERY long half life (5-10 mg/kg 1x day ~ 10 days)
- skin and soft tissue infection
- bloodstream infections (Phase II)

Rejected by FDA in 2008 and withdrawn from EMA

- Re-developed by the Medicines Company since 2009 as single and infrequent dosing of intravenous (i.v.) for the treatment of cSSSI caused by Gram-positive pathogens
Comparison of the Efficacy and Safety of Oritavancin Front-Loaded Dosing Regimens to Daily Dosing: an Analysis of the SIMPLIFI Trial

Lala M. Dunbar, Joe Milata, Ty McClure, Margaret M. Wasilewski, and the SIMPLIFI Study Team

LSU Health Sciences Center, School of Medicine at New Orleans, New Orleans, Louisiana; Eli Lilly and Company, Indianapolis, Indiana; Infinity Pharmaceuticals, Inc., Cambridge, Massachusetts; and ID Remedies, LLC, Arlington, Massachusetts

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Oritavancin is a novel lipoglycopeptide with demonstrated effectiveness against complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens, including those caused by methicillin-resistant Staphylococcus aureus (MRSA). The pharmacokinetic and pharmacodynamic profile of oritavancin is favorable for single or infrequent dosing. A phase 2, multicenter, randomized, double-blind, parallel, active-comparator study (ClinicalTrials.gov identifier, NCT00514527) of single and infrequent dosing of intravenous (i.v.) oritavancin for the treatment of cSSSI caused by Gram-positive pathogens (wound infections, major abscess, and cellulitis) was undertaken to evaluate the noninferiority of front-loaded dosing regimens compared to a daily-dosing regimen. A total of 302 patients ≥18 years of age were randomized equally to one of three oritavancin treatment groups, receiving either a daily dose (200 mg) administered for 3 to 7 days, a single dose (1,200 mg), or an infrequent dose (800-mg dose with the option for an additional 400 mg on day 5). The primary efficacy was defined as a clinical response in clinically evaluable (CE) patients assessed at days 21 to 29 (test of cure [TOC]). The cure rates in the CE population were 72.4% (55/76) in the daily-dose group, 81.5% (66/81) in the 1,200-mg-single-dose group, and 77.5% (55/71) in the infrequent-dose group. In patients with MRSA at baseline, the cure rates were 78.3% (18/23), 73.0% (27/37), and 87.0% (20/23) in the daily-, 1,200-mg-single-, and infrequent-dose groups, respectively; however, the study was not powered to assess outcomes in the MRSA subpopulation, and given the heterogeneity of the types of infection and the small sample size, these do not suggest any true differences in efficacy rates for these pathogens. The frequencies of adverse events were similar among treatment groups. The results of this study show that single- and infrequent-dosing schedules of oritavancin were as efficacious as daily administration and had a similar safety profile in treating cSSSI caused by Gram-positive pathogens, including MRSA.
Dalbavancin/Oritavancin: pros and cons

- Rapidly bactericidal
- Once / once a-week
- Active on VRSA and VISA to some extent
- Safety

- No oral route
- Once-a-week?
- Prolonged retention in the organism?
Ceftobiprole

Rates of hydrolysis by purified β-lactamases

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus PC 1</td>
<td></td>
</tr>
<tr>
<td>Ro 63-9141</td>
<td>0.93</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>19</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>200</td>
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<tr>
<td>Penicillin G</td>
<td>10,000</td>
</tr>
</tbody>
</table>

Affinity for PBPs

IC₅₀ for competition with fluorescein-labeled ampicillin (µM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Staphylococcus epidermidis PBP 2'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ro 63-9141</td>
<td>0.386</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>115</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;500</td>
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<tr>
<td>Methicillin</td>
<td>&gt;500</td>
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</table>

Model of the active site of SaPBP2' complexed with ceftobiprole.

Lovering et al., ECCMID (2006) P1586
Hebeisen et al., AAC (2001) 45:825-31
Ceftobiprole

- broad spectrum?
  (polymicrobial infections)
- bactericidal
- synergistic with AG
- tissue penetration
- efficient in cSSTI, CAP

- broad spectrum?
- trend to MIC increase
- IV only
- 2-3 x/day
- dysgeusia, nausea
- inefficient in VAP
Conclusions

• Contrary to what is often said, the pipeline for anti-Gram-positive organisms (incl. *S. aureus*) is far from being empty…

• As there is a definite need for improvement over vancomycin and linezolid, emphasis for development and registration should be given to compounds with
  – Improved microbiological properties
  – clear clinical equivalence against vancomycin-susceptible strains AND superiority against vancomycin-insusceptible and linezolid-resistant strains
  – improved safety profile
  – easier mode of treatment

• A premium price may need to be awarded as otherwise development will be limited…
Back-up
VANCOMYCIN

------------------------WARNINGS / PRECAUTIONS------------------------

- Vancomycin must be given orally for treatment of staphylococcal enterocolitis and \textit{C. difficile}-associated diarrhea. Orally administered Vancomycin capsules are not effective for other types of infections. (5.1)

- Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active \textit{C. difficile}-associated diarrhea. Monitoring of serum concentrations may be appropriate in some instances. (5.2)

- Nephrotoxicity has occurred following oral vancomycin therapy and can occur either during or after completion of therapy. The risk is increased in geriatric patients (5.3) Monitor renal function.

- Ototoxicity has occurred in patients receiving vancomycin (5.4) Assessment of auditory function may be appropriate in some instances.

- Prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria. (5.6)

--------------------------ADVERSE REACTIONS--------------------------

The most common adverse reactions ($\geq 10\%$) were nausea (17%), abdominal pain (15%), and hypokalemia (13%). (6.1)
VANCOMYCIN

Nephrotoxicity (e.g., reports of renal failure, renal impairment, blood creatinine increased) occurred in 5% of subjects treated with vancomycin hydrochloride. Nephrotoxicity following Vancomycin typically first occurred within one week after completion of treatment (median day of onset was Day 16). Nephrotoxicity following vancomycin hydrochloride occurred in 6% of subjects >65 years of age and 3% of subjects ≤65 years of age (see WARNINGS AND PRECAUTIONS, Nephrotoxicity [5.3]).
Adverse events observed in all enrolled patients (n = 94).


- at least 1 adverse event: 13.8%
- nephrotoxicity ‘possible’ ADE multiple RF
- treatment discontinuation in only 2 cases

*IDSA consensus statement def. of vancomycin nephrotoxicity (Rybak et al. Am J Health-Syst Pharm 2009): 2 or 3 documented increases in serum creatinine level; increase of 0.5 mg/dL OR ≥ 50% increase from baseline after several days of vancomycin therapy.
TEDIZOLID Phase I: platelets (21 days)
RADEZOLID

combines the most important interactions defined by sparsomycin and linezolid into a single molecular design.

Skripkin et al. AAC (2008) 52:3350-57
# Anti Gram-positive agents in the pipeline

<table>
<thead>
<tr>
<th>Company</th>
<th>Class</th>
<th>Drug</th>
<th>Status (clinical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib-X</td>
<td>fluoroquinolones</td>
<td>delafloxacin</td>
<td>III (ABSSSI) II (CAP)</td>
</tr>
<tr>
<td>TaiGen</td>
<td>nemonoxacin</td>
<td></td>
<td>II (CAP/diabetic foot)</td>
</tr>
<tr>
<td>Furiex</td>
<td>JNJ-Q2</td>
<td></td>
<td>III CAP/ABSSSI</td>
</tr>
<tr>
<td>Trius</td>
<td>oxazolidinones</td>
<td>tedizolid</td>
<td>III (ABSSSI)</td>
</tr>
<tr>
<td>Rib-X</td>
<td>radezolid</td>
<td></td>
<td>II ABSSSI/CAP</td>
</tr>
<tr>
<td>Adv. Life Sci.</td>
<td>ketolides</td>
<td>cethromycin</td>
<td>III (CAP) / anthrax</td>
</tr>
<tr>
<td>Cempra</td>
<td>solithromycin</td>
<td></td>
<td>III (CAP)</td>
</tr>
<tr>
<td>Durata</td>
<td>Lipogycopptides (*)</td>
<td>dalbavancin</td>
<td>III ABSSSI</td>
</tr>
<tr>
<td>The MedCo</td>
<td>oritavancin</td>
<td></td>
<td>III (ABSSSI)</td>
</tr>
<tr>
<td>Nabriva</td>
<td>Pleuromotulin (*)</td>
<td>BC-3781</td>
<td>II (ABSSSI)</td>
</tr>
<tr>
<td>Polymedics</td>
<td>Peptidomimetic (**)</td>
<td>PMX-30063</td>
<td>II (ABSSSI)</td>
</tr>
<tr>
<td>Affinium</td>
<td>Fab inhibitor (**)</td>
<td>AFN-1252</td>
<td>II (ABSSSI)</td>
</tr>
<tr>
<td>GSK</td>
<td>deformylase inhibitor (**)</td>
<td>GSK1322322</td>
<td>II (ABSSSI/CAP)</td>
</tr>
</tbody>
</table>

* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine
Ketolides and neuronal toxicity

Molecular Characterization of Off-Target Activities of Telithromycin: a Potential Role for Nicotinic Acetylcholine Receptors$

Daniel Bertrand,1,* Sonia Bertrand,1 Estelle Neveu,1 and Prabhavathi Fernandes2

HiQScreen Sàrl, 15 rue de l’Athénée, 1206 Geneva, Switzerland,1 and Cempra Pharmaceuticals Inc., Chapel Hill, North Carolina 275142

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Adverse effects have limited the clinical use of telithromycin. Preferential inhibition of the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction (α3β2 and NMJ), the ciliary ganglion of the eye (α3β4 and α7), and the vagus nerve innervating the liver (α7) could account for the exacerbation of myasthenia gravis, the visual disturbance, and the liver failure seen with telithromycin use. The studies presented here enable the prediction of expected side effects of macrolides in development, such as solithromycin (CEM-101).
Ketolides and neuronal toxicity

FIG. 5. Inhibition of ganglionic and central nAChRs by four macrolides. (A to C) Concentration-inhibition curves for α3β4, α7, and α4β2 with telithromycin (closed circles) and the novel ketolide CEM-101 (open circles). (D to F) Concentration-inhibition curves for α3β4, α7, and α4β2 with azithromycin (open triangles) and clarithromycin (open squares). Responses obtained from three to seven cells were normalized versus the ACh-evoked current measured as a control and plotted as a function of the logarithm of the macrolide concentration. Bars indicate the standard errors of means. Continuous curves through the data points are the best fits obtained with the empirical Hill equation.