Approaches to Current and Future Treatment Options in Gram-positive Infections

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With approval of the Common Belgian Medical Ethical platform - visa no. 13/V1/5871/054190
Disclosures

• Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), and Walloon and Brussels Regions

• Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

• Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)
Objectives

• Recognize the benefits, risks and gaps of currently available therapies for infections due to MRSA

• Review the current pipeline of evolving products for the management of infections due to MRSA and identify potential benefits and risks and how they may impact the current treatment paradigm
## Currently Used Therapy for MRSA

<table>
<thead>
<tr>
<th>FDA-approved agent</th>
<th>cSSSI</th>
<th>Evidence</th>
<th>Nosocomial Pneumonia</th>
<th>Evidence</th>
<th>Bacteremia</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline (IV)</td>
<td>✔</td>
<td>AI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin (IV)</td>
<td>✔</td>
<td>AI</td>
<td></td>
<td></td>
<td>✔</td>
<td>AI</td>
</tr>
<tr>
<td>Linezolid (IV/PO)</td>
<td>✔</td>
<td>AI</td>
<td></td>
<td>✔</td>
<td></td>
<td>AI</td>
</tr>
<tr>
<td>Telavancin (IV)</td>
<td>✔</td>
<td>AI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline (IV)</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (IV)</td>
<td>✔</td>
<td>AI</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>AI</td>
</tr>
</tbody>
</table>

### Oral Generics (no FDA-approved indication)
- Tetracyclines
  - Doxycycline, minocycline
- Trimethoprim/sulfamethoxazole
- Clindamycin

1960: introduction of methicillin …

1961: emergence of resistance to methicillin in 1961

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 40 to 50 times on Celbenin* ditch 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, coagulase 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.
From penicillin to vancomycin (VISA)

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

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

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* Vancomycin was first described in 1955-57 (Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

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**Correspondence**

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


K. Hiramatsu\(^a\)*, H. Hanaki\(^b\), T. Ino\(^b\), K. Yabuta\(^b\), T. Oguri\(^c\) and F. C. Tenover\(^d\)

\(^a\)Department of Bacteriology; \(^b\)Department of Pediatrics, Juntendo University, Tokyo; \(^c\)Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; \(^d\)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

![Graph showing concentration of VAN at different times after a dose.](image)
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

For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (e.g., necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 mg/mL are recommended (B-II).
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**

- **MIC = 1.5 mg/L**
- **25-30 mg/L**
- **400**

**Toxicity**

- **C_{ss} vancomycin > 28 mg/L:**
  - Increased nephrotoxicity risk
  - [OR 21.236; P = 0.004]

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Linezolid

1996:
First description of linezolid


Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

Steven J. Brickner,* Douglas K. Hutchinson, Michael R. Barbachyn, Peter R. Manninen, Debra A. Ulanowicz, Stuart A. Garmon, Kevin C. Grega, Susan K. Herdges, Dana S. Toops, Charles W. Ford, and Gary E. Zurenko

Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 22, 1995

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

2007:
Resistance to linezolid by methylation (cfr) (plasmid mediated)

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>ATCC 29213</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.

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): may decrease 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

MAO-A

Serotonin
Noradrenaline
Adrenaline
Octopamine

Dopamine
Tyramine\(^a\)
Tryptamine
Kynuramine
3-methoxytyramine

Consequences of MAO-A Inhibition
- Serotonin Syndrome
- Hypertensive crisis

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 & Bertoni. Expert Opin Pharmacother. 2008;9:2759-2772)
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

LINEZOLID and Haematological Toxicity


Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with Gram-positive infections

Dario Cattaneo\textsuperscript{a,\dagger}, Giovanna Orlando\textsuperscript{b}, Valeria Cozzi\textsuperscript{a}, Laura Cordier\textsuperscript{b}, Sara Baldelli\textsuperscript{a}, Stefania Merli\textsuperscript{b}, Serena Fucile\textsuperscript{a}, Cecilia Gulisano\textsuperscript{b}, Giuliano Rizzardini\textsuperscript{b}, Emilio Clementi\textsuperscript{c,d}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Time of linezolid assessment} & \textbf{LNZ $C_{\text{min}}$ (mg/L)} & \textbf{mean ± S.D.} \\
\hline
\hline
Patients with toxicity ($n = 9$) & & \\
1st evaluation & Day 3 & 9.0 ± 6.4 \\
2nd evaluation & Day 9 & 10.7 ± 5.3 \\
3rd evaluation & Day 12\textsuperscript{a} & 10.7 ± 5.8 \\
4th evaluation ($n = 5$)\textsuperscript{b} & Day 16 & 4.0 ± 1.4 \\
\hline
Patients without toxicity ($n = 41$) & & \\
1st evaluation & Day 3 & 4.9 ± 3.7 \\
2nd evaluation & Day 10 & 4.8 ± 3.3 \\
3rd evaluation & Day 15 & 5.0 ± 1.9 \\
4th evaluation & Day 24 & 4.9 ± 4.6 \\
\hline
\end{tabular}
\caption{Daily linezolid (LNZ) plasma trough concentrations ($C_{\text{min}}$) measured in patients who did or did not develop drug-related hematological toxicity.}
\end{table}

\textsuperscript{a} Median duration of LNZ treatment to development of haematological toxicity.

\textsuperscript{b} Four patients withdrew from LNZ after the adverse events, whilst the five remaining patients received a reduced drug dose.

Fig. 1. Box plot of linezolid plasma trough concentrations measured in 50 patients ($n = 210$ evaluations). Each circle identifies a single concentration assessment.
High Frequency of Linezolid-Associated Thrombocytopenia and Anemia among Patients with End-Stage Renal Disease

Vin-Cont Wu,1 Yu-Ting Wang,2 Cheng-Yi Wang,3 I.-Jung Tsai,2 Kwan-Dun Wu,2 Juey-Jen Hwang,3,4 and Po-Ren Hsueh1,4

1Department of Internal Medicine, Yun-Lin Branch, and Departments of Internal Medicine, Pediatrics, and Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

Figure 1. Kaplan-Meier survival estimates for patients receiving linezolid treatment who had end-stage renal disease (ESRD) or non-end-stage renal disease (NESRD) (P<.001, by the log-rank test).
So, what are our possibilities?

"Scientist" by Ben Shahn
New Jersey State Museum, Trenton, N.J.
New Drugs Approved for MRSA Since 2003

- Daptomycin (approved in 2003)
- Tigecyclin (approved in 2005)
- Telavancin (approved in 2009 – 2012)
- Ceftaroline (approved in 2012)
Daptomycin: Historical Landmarks of a drug with totally novel mode of action....

1987 1993 1997 2003-2006 2009- ...

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

Approval at 4 mg/kg (skin) and 6 mg/kg (bacteremia, endocarditis) by FDA and EMA

• dose increase needed
• emergence of resistance
• safety concerns
DAPTOMYCIN: Was the Dosage Correct?

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: high Doses?

Safety and efficacy of high-dose daptomycin as salvage therapy for severe gram-positive bacterial sepsis in hospitalized adult patients

Chung-Chih Lai, Wang-Huei Sheng, Jann-Tay Wang, Aristine Cheng, Yu-Chung Chuang, Yee-Chun Chen and Shan-Chwen Chang

Table 3 Outcomes and adverse events of patients with high-dose daptomycin therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 67)</th>
<th>Daptomycin dose (mg/kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤ 8 (n = 41)</td>
<td>&gt; 8 (n = 26)</td>
</tr>
<tr>
<td>14-day mortality</td>
<td>11 (16.4%)</td>
<td>6 (14.6%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>24 (35.8%)</td>
<td>13 (31.7%)</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>Vancomycin MIC ≥ 2 µg/mL</td>
<td>19 (79.2%)</td>
<td>13/14 (92.9%)</td>
<td>6/10 (60%)</td>
</tr>
</tbody>
</table>

Adverse events

<table>
<thead>
<tr>
<th>CPK elevations</th>
<th>Total (n = 67)</th>
<th>Daptomycin dose (mg/kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>16 (29.2%)</td>
<td>7/37 (18.9%)</td>
<td>9/24 (37.5%)</td>
</tr>
<tr>
<td>By definition</td>
<td>4/61 (6.6%)</td>
<td>0/37 (0%)</td>
<td>4/24 (16.7%)</td>
</tr>
</tbody>
</table>

(1) CPK values ≥ 3 times the upper limit of normal (ULN) based on two serial measurements during therapy, and one of two levels ≥ 5 times the ULN or CPK levels ≥ 5 times the ULN on two serial measurements if abnormal CPK levels at baseline [26]. The ULN of CPK value at NTUH is 160 IU/L.
Daptomycin: Pros and Cons

- rapidly bactericidal
- highly potent, including against MDR strains

- not for pneumonia
- not active against VISA
- risk of emergence of resistance at low doses
- need to increase the dose in difficult-to-treat infections with toxicity risk
Tigecycline: Historical Landmarks of a resurrection of tetracyclines ....

1993

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.

1999

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).

2005-6

approval BY FDA and EMA

2009

and then, Pfizer bought Wyeth...
Table 2. Patients with Outcome of Death by Infection Type

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>TYGACIL n/N</th>
<th>TYGACIL %</th>
<th>Comparator n/N</th>
<th>Comparator %</th>
<th>Risk Difference* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSSSI</td>
<td>12/834</td>
<td>1.4</td>
<td>6/813</td>
<td>0.7</td>
<td>0.7 (-0.3, 1.7)</td>
</tr>
<tr>
<td>cIAI</td>
<td>42/1382</td>
<td>3.0</td>
<td>31/1393</td>
<td>2.2</td>
<td>0.8 (-0.4, 2.0)</td>
</tr>
<tr>
<td>CAP</td>
<td>12/424</td>
<td>2.8</td>
<td>11/422</td>
<td>2.6</td>
<td>0.2 (-2.0, 2.4)</td>
</tr>
<tr>
<td>HAP</td>
<td>66/467</td>
<td>14.1</td>
<td>57/467</td>
<td>12.2</td>
<td>1.9 (-2.4, 6.3)</td>
</tr>
<tr>
<td>Non-VAP(^a)</td>
<td>41/336</td>
<td>12.2</td>
<td>42/345</td>
<td>12.2</td>
<td>0.0 (-4.9, 4.9)</td>
</tr>
<tr>
<td>VAP(^a)</td>
<td>25/131</td>
<td>19.1</td>
<td>15/122</td>
<td>12.3</td>
<td>6.8 (-2.1, 15.7)</td>
</tr>
<tr>
<td>RP</td>
<td>11/128</td>
<td>8.6</td>
<td>2/43</td>
<td>4.7</td>
<td>3.9 (-4.0, 11.9)</td>
</tr>
<tr>
<td>DFI</td>
<td>7/553</td>
<td>1.3</td>
<td>3/508</td>
<td>0.6</td>
<td>0.7 (-0.5, 1.8)</td>
</tr>
<tr>
<td>Overall Adjusted</td>
<td>150/3788</td>
<td>4.0</td>
<td>110/3646</td>
<td>3.0</td>
<td>0.6 (0.1, 1.2)**</td>
</tr>
</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.

\(^a\) 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
New (lipo)glycopeptides: Structure-activity Relationships for a new mode of action

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

## Telavancin and Oritavancin: 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><em>S. aureus</em></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><em>S. pneumo</em></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>Enterococci</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 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 (78)</td>
<td>1393/1868 (74.6)</td>
<td>1.20 (0.97–1.49)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>314/1864 (16.8)</td>
<td>251/1868 (13.4)</td>
<td>1.38 (0.90–2.13)</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>144/1864 (7.7)</td>
<td>100/1868 (5.4)</td>
<td>1.48 (1.14–1.93)</td>
</tr>
<tr>
<td>Nausea</td>
<td>318/1864 (17.1)</td>
<td>190/1868 (10.2)</td>
<td>1.88 (1.54–2.29)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>143/1113 (12.8)</td>
<td>78/1116 (7)</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 (7.1)</td>
<td>81/1033 (7.8)</td>
<td>0.90 (0.65–1.25)</td>
</tr>
<tr>
<td>Constipation</td>
<td>174/1864 (9.3)</td>
<td>144/1868 (7.7)</td>
<td>1.12 (0.72–1.74)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>137/1780 (7.7)</td>
<td>136/1785 (7.6)</td>
<td>1.14 (0.62–2.11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>34/1029 (3.3)</td>
<td>68/1033 (6.6)</td>
<td>0.48 (0.32–0.74)</td>
</tr>
<tr>
<td>Headache</td>
<td>147/1113 (13.2)</td>
<td>132/1116 (11.8)</td>
<td>1.14 (0.89–1.47)</td>
</tr>
<tr>
<td>Chills</td>
<td>47/1029 (4.6)</td>
<td>23/1033 (2.2)</td>
<td>2.10 (1.27–3.48)</td>
</tr>
<tr>
<td>Cr elevation</td>
<td>166/1638 (10.1)</td>
<td>88/1674 (5.3)</td>
<td>2.22 (1.38–3.57)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>73/1528 (4.8)</td>
<td>44/1521 (2.9)</td>
<td>1.91 (0.91–4.00)</td>
</tr>
<tr>
<td>AST increase</td>
<td>36/1045 (3.4)</td>
<td>39/1084 (3.6)</td>
<td>0.93 (0.43–2.04)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>38/1101 (3.5)</td>
<td>61/1165 (5.2)</td>
<td>0.64 (0.42–0.97)</td>
</tr>
<tr>
<td>QTcF increase&lt;sup&gt;a&lt;/sup&gt;</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 (6.3)</td>
<td>65/1058 (6.1)</td>
<td>1.01 (0.71–1.46)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>12/1006 (1.2)</td>
<td>19/989 (1.9)</td>
<td>0.62 (0.30–1.28)</td>
</tr>
<tr>
<td>Platelet decrease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8/1064 (0.8)</td>
<td>10/1110 (0.9)</td>
<td>0.87 (0.35–2.17)</td>
</tr>
</tbody>
</table>

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

doi:10.1371/journal.pone.0041870.t003

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 - 2011):**

- 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

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: Pros and Cons

- Broad spectrum
- Safety profile

- Broad spectrum
- No oral route
- Indications are "minimal"
- Anti-MRSA activity border-line?
# Anti Gram-positive Agents in the Pipeline

<table>
<thead>
<tr>
<th>Class</th>
<th>Company</th>
<th>Drug</th>
<th>Status (clinical)</th>
<th>Timing</th>
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<td>fluoroquinolones</td>
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<td>delafloxacin</td>
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<td>TaiGen</td>
<td>nemonoxacin</td>
<td>II (CAP/dfi)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Furiex</td>
<td>JNJ-Q2</td>
<td>III CAP/ABSSSI</td>
<td>Entering PIII</td>
</tr>
<tr>
<td>oxazolidinones</td>
<td>Trius</td>
<td>tedizolid</td>
<td>III (ABSSSI)</td>
<td>Two PIII trials completed; NDA filing projected 2H13</td>
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<td>radezolid</td>
<td>II ABSSSI/CAP</td>
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</tr>
<tr>
<td>ketolides</td>
<td>Adv. Life Sci.</td>
<td>cethromycin</td>
<td>III (CAP) / anthrax</td>
<td>Additional data requested by FDA / operations suspended</td>
</tr>
<tr>
<td></td>
<td>Cempra</td>
<td>solithromycin</td>
<td>III (CAP)</td>
<td>4Q13 Initiation of PIII trial in CABP</td>
</tr>
<tr>
<td>Lipogyclopeptides (*)</td>
<td>Durata</td>
<td>dalbavancin</td>
<td>III ABSSSI</td>
<td>NDA late September/projected launch 2H14</td>
</tr>
<tr>
<td></td>
<td>The MedCo</td>
<td>oritavancin</td>
<td>III (ABSSSI)</td>
<td>PIII completed – projected filing 4Q13 in US; 2014 European filing</td>
</tr>
<tr>
<td>Pleuromotulin (*)</td>
<td>Nabriva</td>
<td>BC-3781</td>
<td>II (ABSSSI)</td>
<td></td>
</tr>
<tr>
<td>Peptidomimetic (**)</td>
<td>Polymedics</td>
<td>PMX-30063</td>
<td>II (ABSSSI)</td>
<td></td>
</tr>
<tr>
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<td>Affinium</td>
<td>AFN-1252</td>
<td>II (ABSSSI)</td>
<td></td>
</tr>
<tr>
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<td>GSK</td>
<td>GSK1322322</td>
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<td></td>
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* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine
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<td>tedizolid</td>
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<td>Rib-X</td>
<td>radezolid</td>
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<td>cethromycin</td>
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</tr>
<tr>
<td><strong>Lipogycopptides (</strong>)**</td>
<td>Durata</td>
<td>dalbavancin</td>
<td>III ABSSSI</td>
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</table>

* new target (not yet exploited) – dual site of action for oritavancin
** old target but not exploited in human systemic medicine
### Tedizolid – Radezolid and LZD-resistant Strains

**Structures:**
- **Linezolid**
- **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><em>Staphylococcus aureus</em></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><em>Listeria monocytogenes</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGD</td>
<td></td>
<td>1-2</td>
<td>0.125</td>
<td>0.03-0.06</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></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

wild-type and methylated ribosomes

linezolid

tedizolid

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.
Gastrointestinal AEs include: diarrhea, nausea, vomiting, and dyspepsia

** Statistically significant ($p=0.004$)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tedizolid (200 mg QD 6 Days)</th>
<th>Linezolid (600 mg BID 10 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment Emergent Adverse Event (TEAE)</td>
<td>40.8%</td>
<td>43.3%</td>
</tr>
<tr>
<td>Any Drug-Related TEAE</td>
<td>24.2%</td>
<td>31.0%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders*</td>
<td>16.3%**</td>
<td>25.4%**</td>
</tr>
</tbody>
</table>

Tedizolid Had Significantly Lower Impact on Platelets than Linezolid

<table>
<thead>
<tr>
<th>Hematology Parameter</th>
<th>Percent of Patients with Value below the Lower Limit of Normal (LLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid (200mg QD 6 days)</td>
</tr>
<tr>
<td>Platelets Below LLN</td>
<td>9.2%*</td>
</tr>
<tr>
<td>Platelets – Substantially Abnormal Value (&lt;75% LLN)</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

* Statistically significant ($p=0.035$)

Fang E, et al. Safety Profile of Tedizolid Phosphate Compared to Linezolid in a Phase 3 ABSSSI Study. ICAAC 2012; Poster L1-1664.
New oxazolidinones: Pros and Cons

- active on LZD-resistant strains (cfr+)
- more potent against intracellular bacteria
- possibly less toxic than LZD

- rather bacteriostatic
## More anti Gram-positive Agents in the Pipeline

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

I'm afraid, it's getting late… Please ask questions for what I have not covered
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
From penicillin to vancomycin (and VISA)

1928: Fleming observes the killing effect of a mould against S. aureus

1940-45: Mass production of penicillin universally active against S. aureus

1944: First description of a $\beta$-lactamase in S. aureus

1950-70: almost all strains of S. aureus produce a $\beta$-lactamase

Article number 122.
Daptomycin Mode of Action


J. Silverman, 45th ICAAC, 2005
Eosinophilic pneumonia associated with daptomycin: a case report and a review of the literature

Andreas S Kalogeropoulos\textsuperscript{1}, Sotirios Tsiodras\textsuperscript{2}, Dionysis Loverdos\textsuperscript{3}, Panagiotis Fanourgakis\textsuperscript{1}, Athanasios Skoutelis\textsuperscript{1}

Abstract

Introduction: Although several studies did not demonstrate that daptomycin may cause significantly higher rates of pulmonary adverse effects when compared with vancomycin or penicillinase-resistant penicillins, there have been a few case reports of severe pulmonary complications associated with daptomycin administration.

Case presentation: A rare case of eosinophilic pneumonia occurring 10 days after daptomycin administration in a 78-year-old Caucasian man with possible infectious endocarditis is described. He developed new onset fever, up to 38.5°C, with bilateral pulmonary crackles on physical examination and with no signs of severe respiratory failure. A chest computed tomography-scan showed bilateral nodular consolidations with air bronchograms and pleural effusions. Immediate discontinuation of daptomycin was followed by vigorous improvement of clinical signs and symptoms with progressive resolution of pulmonary consolidations a month later.

Conclusion: Physicians should be aware of this rare but serious complication during daptomycin treatment, and prompt discontinuation of the offending agent, with or without additional supportive treatment, must occur immediately.
Tigecycline: Chemical Structure

minocycline

t-butyl
glycyl-

H₃C
H₃C
NH
C
O
O
OH
H₃C
H₃C
NH
C
O
O
OH
H₃C
H₃C
NH
C
O
O
OH
H₃C
H₃C
NH₂
## Tigecycline In vitro Activity

<table>
<thead>
<tr>
<th>species</th>
<th>phenotype</th>
<th>tetracycline</th>
<th>minocycline</th>
<th>tigecycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></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><em>S. aureus</em></td>
<td>susceptible</td>
<td>0.12</td>
<td>0.06</td>
<td>0.25</td>
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<td>Ribosomal protection</td>
<td>&gt; 32</td>
<td>4</td>
<td>0.25</td>
</tr>
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Petersen et al., AAC (1999) 43:738-44
Telavancin and Oritavancin
**Tigecycline and Breakpoints in 2013**

**Table 2**
Regional and global activity of tigecycline and comparator antimicrobial agents when tested against resistant subsets (2011).

<table>
<thead>
<tr>
<th>Antimicrobial agent/organism (no. tested/frequency)</th>
<th>North America</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLSI&lt;sup&gt;a&lt;/sup&gt; %S/%R</td>
<td>EUCAST&lt;sup&gt;a&lt;/sup&gt; %S/%R</td>
</tr>
<tr>
<td>MRSA (1538/49.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline&lt;sup&gt;b&lt;/sup&gt;</td>
<td>100.0/-</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>100.0/-</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10.4/88.1</td>
<td>10.5/89.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>31.2/65.2</td>
<td>31.2/65.2</td>
</tr>
<tr>
<td>Linezolid</td>
<td>99.8/0.2</td>
<td>99.8/0.2</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>100.0/0.0</td>
<td>99.9/0.1</td>
</tr>
<tr>
<td>Trimethoprim/ sulfamethoxazole</td>
<td>97.7/2.3</td>
<td>97.7/2.2</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100.0/0.0</td>
<td>100.0/0.0</td>
</tr>
</tbody>
</table>

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EUCAST breakpoints: S $\leq$ 0.5 - R > 0.5
FDA breakpoint: S $\leq$ 0.5