Contribution of new antibiotics to current and future challenges of main Gram-positive infections

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ECCMID MSD Integrated Symposium
Are Gram-positive infections still a major concern to patients and Healthcare system?
Saturday 23 April 2018 – 16:00 – 18:00
Disclosures

Research grants and Speaker's honoraria from
- Cempra Pharmaceuticals ¹
- Cerexa
- GSK
- Melinta Therapeutics ²
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics ³
- Merck
- Bayer

Influenced by my participation to the
- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

¹ merged in 2017 with and renamed as Melinta Therapeutics
² formerly RibX Pharmaceuticals
³ acquired by Cubist (2014), which was then acquired by Merck (2016)
Learning objectives

• Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed

• Current duration of hospitalization: when could the patient go home?

• Contribution of new therapeutic options:
  – review of some key available data
  – my personal views on specific/appropriate contribution of the new therapeutic options to both short and long term use and infection management
Common challenges when managing Gram positive infections

• Clinical management challenges with various:
  – clinical entities,
  – site of infections,
  – involved Gram positive pathogens
  – antibiotic therapeutic options and duration

• Resistance challenges

• BJI and Biofilms challenges to antibiotic treatment

• intracellular forms / persisters / small colony variants
Resistance challenges (in *S. aureus*)

<table>
<thead>
<tr>
<th>Category</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td><strong>PBP2a</strong>, penicillinase, thick cell wall, gyrA mutations, cfr, erm, mprF, fusA, dfrA, dpsA</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>van A, van H, norA, mrsA (efflux)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones (linezolid)</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Lincosamides (daptomycin)</td>
<td></td>
</tr>
<tr>
<td>Lipopeptides</td>
<td></td>
</tr>
<tr>
<td>Fusidic acid</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td></td>
</tr>
</tbody>
</table>

This has considerably reduced our potential arsenal, with full or partial demise of:
- conventional β-lactams (except the recent anti-MRSA cephalosporins [ceftaroline, …])
- most currently EU-approved fluoroquinolones
- currently approved macrolides and lincosamides
- fusidic acid (in Europe) and sulfamethoxazole/trimethoprim
- even menacing
- vancomycin (for isolates with MIC > 1.5 mg/L (EUCAST "R" breakpoint is > 2 mg/L)
- linezolid -

**Alternatives treatments** include:
- quinupristin/dalfopristin (*availability ?*)
- tigecycline (*efficacy ?*)
- and newly EU-approved drugs
  - oritavancin, dalbavancin
  - tedizolid
  - ceftarolline….
Are MRSA still of concern?

<table>
<thead>
<tr>
<th>Region</th>
<th>S. aureus (N)</th>
<th>MSSA (%)</th>
<th>MRSA (%)</th>
<th>Testing period</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>43,331</td>
<td>53.6</td>
<td>46.4</td>
<td>2011–2014</td>
<td>57</td>
</tr>
<tr>
<td>Canada</td>
<td>2539</td>
<td>80.2</td>
<td>19.8</td>
<td>2010–2012</td>
<td>58</td>
</tr>
<tr>
<td>Europe</td>
<td>40,414</td>
<td>82.6</td>
<td>17.4</td>
<td>2013</td>
<td>59</td>
</tr>
<tr>
<td>China</td>
<td>6656</td>
<td>51.1</td>
<td>48.9</td>
<td>2004–2011</td>
<td>60</td>
</tr>
<tr>
<td>Asia</td>
<td>4117</td>
<td>47.5</td>
<td>52.5</td>
<td>2004–2006</td>
<td>61</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>1971</td>
<td>38.1</td>
<td>61.9</td>
<td>2012</td>
<td>62</td>
</tr>
<tr>
<td>Latin America</td>
<td>1066</td>
<td>41.7</td>
<td>58.3</td>
<td>2012</td>
<td>63</td>
</tr>
<tr>
<td>Middle East/</td>
<td>NR</td>
<td>NR</td>
<td>42.1</td>
<td>Before 2014</td>
<td>25</td>
</tr>
<tr>
<td>North Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NR, not reported.

Biofilms are associated to 65\textsuperscript{a}–80\textsuperscript{b} \% of human infections and can colonize virtually all organs …


\textsuperscript{a}CDC 1999; \textsuperscript{b}Lewis et al., Nat Rev Microbiol. 2007; 5:48-56
Biofilms are recalcitrant to antibiotics once formed and mature

MSSA
24 h incubation
- biomass (crystal violet [CV])
- viability (resorufin [RF])

vancomycin vs. young biofilms

vancomycin vs. mature biofilm

Biofilms: possible strategies

• select highly bactericidal antibiotics
• disrupt the matrix
• combine both approaches

Live/dead staining (antibiotics at 32 X MIC) – ATCC MRSA

• select highly bactericidal antibiotics
• disrupt the matrix
• combine both approaches

Disruption of *Staphylococcus aureus* biofilms using rhamnolipid biosurfactants

S. S. e Silva,* J. W. P. Carvalho,† C. P. Aires,‡ and M. Nitschke*†

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†Faculdade de Arquitetura e Engenharia, State University of Mato Grosso, Rua A, 3, Carabão São Raimundo, Campus Petrolina 92, CEP 78930-4
‡Faculty of Medical Sciences, São Paulo University, Avenida do Céu, 151, São Paulo, SP, Brazil

†Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Avenida do Céu, 151, Ribeirão Preto, SP, Brazil


**Figure 2.** Scanning electron microscopy pictures of *Staphylococcus aureus* biofilms grown in nutrient broth and skim milk before (A and C) and after (B and D) treatment with 0.1% rhamnolipids at 25°C.
Biofilms: possible strategies

- select highly bactericidal antibiotics
- disrupt the matrix
- combine both approaches

Activity (dose response) of delafloxacin alone or combined with caspofungin on S. aureus biofilms in vivo: (mouse subcutaneous biofilm model). Animals were treated for 7 days with caspofungin (CAS; 4 mg/kg of body weight) once daily, delafloxacin twice daily (at 10, 20, or 40 mg/kg), or with delafloxacin at each of these doses combined with caspofungin. Statistical analysis (one-way ANOVA; Tukey post-hoc test): groups with different letters are significantly different from one another (P<0.05).
Other challenges: Intracellular forms – Persisters – Small colony Variants

S. aureus in human osteoblasts

Recalcitrant to eradication....

Not all bacteria are killed!

Eradication necessitates prolonged antibiotic therapy including drug combinations


Figure 1: Small colony variants. Columbia blood-agar plates that show the normal (a) and the small colony variant (b) phenotype of Staphylococcus aureus are shown.
Learning objectives

• Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed

• **Current duration of hospitalization: when could the patient go home?**

• Contribution of new therapeutic options:
  - review of some key available data
  - my personal views on specific/appropriate contributions to both short and long term use and infection management
Treatment duration for MRSA infections: the classical way (IDSA guidelines)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Antibiotics</th>
<th>Recommended treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTI</td>
<td>VAN/DAP/LZD/TLV/CLI</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Uncomplicated bacteremia</td>
<td>VAN/DAP</td>
<td>&gt; 2 weeks</td>
</tr>
<tr>
<td>Complicated bacteremia</td>
<td>VAN/DAP</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>VAN/DAP</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>VAN/LZD/CLI</td>
<td>7-21 days</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>VAN/DAP/LZD/CLIN/SMX-TMP+RIF</td>
<td>&gt; 8 weeks</td>
</tr>
<tr>
<td>Arthritis</td>
<td>idem</td>
<td>3-4 weeks</td>
</tr>
<tr>
<td>Meningitis</td>
<td>VAN(+RIF)/LZD/SMX-TMP</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

CLI: clindamycin  
DAP: daptomycin  
LZD: linezolid  
RIF: rifampicin  
SMX: sulfamethoxazole  
TLV: televancin  
TMP: trimethprim  
VAN: vancomycin

→ Treatment duration not always well defined but depends on infection type

Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey

Matthew Dryden a, *, Arjana Tambic Andrasevic a, Matteo Bassetti a, Emilio Bouza a, Jean Chastre a,*,
Mo Baguneid a, Silvano Esposito a, Helen Giamarello b, Inge Gydesen c, Andreas Voss c, Mark Wilcox a

Fig. 9. What are the top health economic factors that most influence your antibiotic choice for the management of MRSA infections?
Do we need to shorten hospital stay duration?


Mean 18% reduction in acute care beds

EU, all European Member states plus Switzerland; EU12, countries that joined the EU in 2004 and 2007 (Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia).

Key results: country-specific patterns

<table>
<thead>
<tr>
<th>Country</th>
<th>IV Days</th>
<th>LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N=1,502)</td>
<td>14.0</td>
<td>20.6</td>
</tr>
<tr>
<td>UK (N=169)</td>
<td>10.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Czech Republic (N=41)</td>
<td>11.7</td>
<td>12.1</td>
</tr>
<tr>
<td>Italy (N=190)</td>
<td>12.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Slovakia (N=50)</td>
<td>12.7</td>
<td>18.3</td>
</tr>
<tr>
<td>Austria (N=54)</td>
<td>13.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Spain (N=183)</td>
<td>13.9</td>
<td>21.8</td>
</tr>
<tr>
<td>Greece (N=151)</td>
<td>14.8</td>
<td>19.4</td>
</tr>
<tr>
<td>Germany (N=217)</td>
<td>15.0</td>
<td>22.1</td>
</tr>
<tr>
<td>France (N=261)</td>
<td>15.2</td>
<td>22.0</td>
</tr>
<tr>
<td>Portugal (N=141)</td>
<td>16.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Poland (N=43)</td>
<td>18.6</td>
<td>23.1</td>
</tr>
</tbody>
</table>

Early switch and early discharge – potential days saved

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Hypothetical</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV line days saved in ES eligible patients</td>
<td>15.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Bed days saved in ED eligible patients</td>
<td>20.8</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Potential to save 6 IV days on average due to ES eligibility
Potential to save 6.2 bed days on average due to ED eligibility

ES Eligible: Patient met literature-based criteria for early switch ≥1 day before their IV antibiotic treatment was discontinued.
ED Eligible: Patient met literature-based criteria for early discharge ≥1 day before they were discharged.

Short(er) treatments (early switch [ES] / early discharge [ED]): we have simple criteria!

- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study, inclusive of Desai\(^1\) and Parodi\(^2\) criteria
- The key (essential) criteria were selected by key opinion leaders and were used to estimate ES/ED hypothetical opportunities

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## New Anti Gram-positive approved drugs

<table>
<thead>
<tr>
<th>Company in Europe</th>
<th>Drug</th>
<th>Pharmacol. class</th>
<th>Approved indications</th>
<th>Useful activity against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theravance</td>
<td>telavancin</td>
<td>lipoglycopeptides</td>
<td>cSSSI (US only)</td>
<td>MRSA: ✓, MDRSP: ✓, VRE: VanB only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HABP/VABP</td>
<td></td>
</tr>
<tr>
<td>Allergan</td>
<td>dalbavancin</td>
<td></td>
<td>ABSSSI</td>
<td>MRSA: ✓, MDRSP: ✓, VRE: VanB only</td>
</tr>
<tr>
<td>The MedCo²</td>
<td>oritavancin</td>
<td></td>
<td>ABSSSI</td>
<td>✓, ✓, ✓</td>
</tr>
<tr>
<td>MSD / Bayer</td>
<td>tedizolid</td>
<td>oxazolidinone</td>
<td>ABSSSI</td>
<td>✓, ✓, ✓</td>
</tr>
<tr>
<td>Pfizer</td>
<td>ceftaroline</td>
<td>β-lactams</td>
<td>ABSSSI / CABP</td>
<td>✓, ✓, ✓</td>
</tr>
<tr>
<td>Basilea³</td>
<td>ceftobiprole</td>
<td></td>
<td>CAP / HAP</td>
<td>✓, ✓, ✓</td>
</tr>
<tr>
<td>Menarini⁵</td>
<td>delafloxacin⁵</td>
<td>fluoroquinolone⁶</td>
<td>ABSSSI (US only / EMA submitted)</td>
<td>✓, ✓, E. faecalis only</td>
</tr>
</tbody>
</table>

1. FDA (US Food and Drug Administration) and/or EMA (European Medicines Agency) unless indicated otherwise.
3. Distributed by Cardiome (end of 2017).
4. Approved in 13 EU countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK.
5. Licensee of Melinta; delafloxacin is presently approved only in the US (FDA) and not in EU.
6. Activity also demonstrated against several Gram-negative organisms but with documentation.

**Useful activity against**
- MRSA: Methicillin-resistant Staphylococcus aureus
- MDRSP: Multidrug resistant Streptococcus pneumoniae
- VRE: Vancomycin resistant Enterococci

- cSSSI: Complicated skin and skin structures infections
- ABSSSI: Acute bacterial skin and skin structures infections
- CABP: Community-acquired bacterial pneumonia
- CAP: Community-acquired pneumonia
- HAP: Hospital-acquired pneumonia (nosocomial)

**Abbreviations:**
- cSSSi: Complicated skin and skin structures infections
- ABSSSI: Acute bacterial skin and skin structures infections
- CABP: Community-acquired bacterial pneumonia
- HAP: Hospital-acquired pneumonia (nosocomial)
- MRSA: Methicillin-resistant Staphylococcus aureus
- MDRSP: Multidrug resistant Streptococcus pneumoniae
- VRE: Vancomycin resistant Enterococci
- VanB only: Vancomycin-resistant strain B of Enterococcus faecium
### Susceptibility breakpoints

#### Breakpoints vs. susceptibility of current MRSA isolates

<table>
<thead>
<tr>
<th>antibiotic</th>
<th>breakpoint</th>
<th>susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>EUCAST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>telavancin</td>
<td>$\leq 0.125$</td>
<td>$&gt; 0.125$</td>
</tr>
<tr>
<td>dalbavancin</td>
<td>$\leq 0.125$</td>
<td>$&gt; 0.125$</td>
</tr>
<tr>
<td>oritavancin</td>
<td>$\leq 0.125$</td>
<td>$&gt; 0.125$</td>
</tr>
<tr>
<td>ceftobiprole</td>
<td>$\leq 2$</td>
<td>$&gt; 2$</td>
</tr>
<tr>
<td>ceftaroline</td>
<td>$\leq 1$</td>
<td>$&gt; 1$</td>
</tr>
<tr>
<td>tedizolid</td>
<td>$\leq 0.5$</td>
<td>$&gt; 0.5$</td>
</tr>
<tr>
<td>FDA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>delafloxacin*</td>
<td>$\leq 0.25$</td>
<td>$\geq 1$</td>
</tr>
</tbody>
</table>

* not currently approved in Europe

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**Most current isolates are susceptible BUT surveillance is essential!**
Lipoglycopeptides

- prolonged half-life
- membrane anchoring
- dimerization
- decreased half-life

Lipoglycopeptides: dual mode of action

Oritavancin has a dual mode of action!

Van Bambeke et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com/
Lipoglycopeptides: the key is their pharmacokinetics

<table>
<thead>
<tr>
<th>parameter</th>
<th>vancomycin</th>
<th>telavancin</th>
<th>oritavancin</th>
<th>dalbavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>15 mg/kg</td>
<td>10 mg/kg</td>
<td>1200 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>20-50</td>
<td>93</td>
<td>138</td>
<td>287</td>
</tr>
<tr>
<td>AUC (mg.h/L)</td>
<td>260</td>
<td>668</td>
<td>1110 (24h)</td>
<td>3185 (24h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2800 (tot)</td>
<td>23443 (tot)</td>
</tr>
<tr>
<td>(%) prot. binding</td>
<td>55</td>
<td>95</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>1 ($\beta$)</td>
<td>8</td>
<td>14 ($\beta$)</td>
<td>346 ($\gamma$)</td>
</tr>
<tr>
<td></td>
<td>3-9 ($\gamma$)</td>
<td></td>
<td>245 ($\gamma$)</td>
<td></td>
</tr>
</tbody>
</table>

1.2 g single dose
1.5 g single dose
or 1000 mg + 500 mg at day 7

1 g q12h 7-14 days
10 mg/kg qD 7-14 days

common approved dosage / schedule for ABSSSI (FDA/EMA)
Tedizolid: structure changes vs. linezolid and implications

Substantial differences that DO impact on

- **intrinsic activity** *(4-8 x more potent)*
- activity against *cfr*+ LZDR strains
- **half-life** *(~2 x longer)*
Oxazolidinones: the cfr+ mechanism of resistance

- both chromosome and plasmid-mediated
- First identified in animals and then in clinical isolates
- acting through C-8 methylation of the a ribosomal adenine (A2503)
- causes cross-resistance to linezolid and 5 drug classes (phenicols, lincosamides, pleuromutilins, streptogramins and 16-membered macrolides)
- present now in Europe and in China
Oxazolidinones: the cfr+ mechanism of resistance

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• causes cross-resistance to linezolid and 5 drug classes (phenicols, lincosamides, pleuromutilins, streptogramins and 16-membered macrolides)

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1 Toh et al. Mol Microbiol 2007;64:1506-14 - PMID 17555436
5 Giessing et al. RNA 2009;15:327-36 - PMID 19144912
7 Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405
8 Inkster et al. J Hosp Infect. 2017;97:397-402. - PMID 28698020
10 Bi et al. J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082
Tedizolid: key PK/PD parameters and breakpoints

- long half-life (∼12 h)
  (with concentrations > 0.5 mg/L for ∼18 h)
- activity dependent from the \( \text{AUC}_{24h} \) (total daily dose/clearance)
  irrespective of the dosing scheme (Q8, Q12, Q24)
  - ONCE daily dosing (oral or IV) @ 200 mg
  - breakpoint: \( S \leq 0.5 \text{ mg/L} - R > 0.5 \) (EUCAST) or ≥ 2 (FDA)
- almost complete bioavailability of the oral form (por-drug)
  - early oral switch possible
Tedizolid safety: Platelet counts – Pooled Phase 3 Studies

At any post-baseline assessment through last dose of study drug $^a$

![Graph showing patients with TEAEs (%) below LLN or substantially abnormal (<75% of LLN) over time.](image)

$P = 0.0002$ for 6-Day TZP 200 mg once daily vs. 10-Day LZD 600 mg twice daily ($P = 0.0175$).

6-Day TZP 200 mg once daily
- Below LLN: 6.4%
- Substantially Abnormal (<75% of LLN): 12.6%

10-Day LZD 600 mg twice daily
- Below LLN: 2.1%
- Substantially Abnormal (<75% of LLN): 4.5%

TEAE=treatment-emergent adverse events; LLN=lower limit of normal; TZP=tedizolid; LZD=linezolid.

$^a$Platelet counts were collected on Study Day 7-9, Study Day 11-13, and after last dose of study drug.

DeAnda et al. Integrated results from 2 phase 3 studies comparing tedizolid phosphate 6 days vs. linezolid 10 days in patients with ABSSSI. Poster presented at: 53rd Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. (L-203).
Anti-MRSA cephalosporins

Resistance to β-lactamases

Binding to PBP2a

ceftaroline

ceftobiprole

ceftaroline & PBP2a

catalytic site

allosteric site

Ceftaroline vs MSSA and MRSA *

MSSA / MRSA (n = 83 / 157)

** Isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013 and unpublished

** The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour)
In a nutshell

1. An heteroaromatic group in N1 → the molecular surface
2. A chlorine in C8 → activity
3. No basic group in C7 → anionic character

Hanselmann et al. PCT Int. Appl. (2010), WO 2010036329 A2 20100401 (and other patents)
Duffy et al. 50th ICAAC 2010: Abstract E183
Delafloxacin: recent MICs…

In Vitro Activity of Delafloxacin against Contemporary Bacterial Pathogens from the United States and Europe, 2014

M. A. Pfaller,*H. S. Sader,* P. R. Rhomberg,* R. K. Flamm*
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FDA breakpoints
S ≤ 0.25
R ≥ 1


S. aureus / MRSA (EU isolates) (n = 250 / 64)
Learning objectives

• Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed

• Current duration of hospitalization: when could the patient go home?

• Contribution of new therapeutic options:
  - review of some key available data
  - my personal views on specific/appropriate contribution of the new therapeutic options to both short and long term use and infection management
What do new drugs bring to our arsenal?

### Empirical therapy?

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Spectrum</th>
</tr>
</thead>
<tbody>
<tr>
<td>telavancin</td>
<td>G+</td>
</tr>
<tr>
<td>dalbavancin</td>
<td>G+</td>
</tr>
<tr>
<td>oritavancin</td>
<td>G+</td>
</tr>
<tr>
<td>ceftobiprole</td>
<td>G+ G- b</td>
</tr>
<tr>
<td>ceftaroline</td>
<td>G+ G- b</td>
</tr>
<tr>
<td>tedizolid</td>
<td>G+</td>
</tr>
<tr>
<td>delafloxacin</td>
<td>G+ G- d</td>
</tr>
</tbody>
</table>

### Short treatment?

<table>
<thead>
<tr>
<th>Treatment (duration /doses)</th>
<th>Oral bioavailability</th>
<th>Main risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-14 days (q24h) *</td>
<td>No</td>
<td>nephrotoxicity</td>
</tr>
<tr>
<td>2 doses (at days 1 &amp; 7)</td>
<td>No but 2 doses only</td>
<td>drug retention</td>
</tr>
<tr>
<td>1 dose (a day 1)</td>
<td>No but 1 dose only</td>
<td>drug retention / interactions</td>
</tr>
<tr>
<td>not specified</td>
<td>No</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>5-14 days (BID/TID)*</td>
<td>No</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>6 days q24h*</td>
<td>almost full (90%)</td>
<td>linezolid-like *</td>
</tr>
<tr>
<td>5-14 days q12h*</td>
<td>partial (~ 60%)</td>
<td>quinolones-like **</td>
</tr>
</tbody>
</table>

* q24h: every 24h  
q12h: every 12h  
q8h: every 8h

### Switch to oral?

<table>
<thead>
<tr>
<th>Oral bioavailability</th>
<th>Main risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>nephrotoxicity</td>
</tr>
<tr>
<td>No but 2 doses only</td>
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* milder in clinical trials and in case reports  
** as per the US (FDA) label

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Based on analysis of the corresponding Summary of Product Characteristics (SmPC [EMA; MHRA for ceftobiprole]) or of US (FDA) label for delafloxacin, and recent literature data.

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*a* not approved in EU for skin and skin structures infections  
*b* but NOT ESBL producers  
*c* not currently approved in EU  
*d* documentation needed
While it became generally accepted after Vespucci that Columbus's discoveries were not Asia but a "New World", the geographic relationship between the two continents was still unclear…


Like Spain did it, we need to explore the new continent…