New antistaphylococcal agents: Hopes and limitations

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Why do we need new antistaphylococcal agents?

- rising resistance ... reaching the limits of what we can give to patients ...

- intrinsic PK/PD limitations of conventional glycopeptides towards *S. aureus* is severe infections

- intracellular development of *S. aureus* ... causing recurrence, relapses, and perhaps also resistance ...
The (sad) story of the *S. aureus*

- **Penicillin** → **Penicillin-resistant S. aureus** [1950s]
- **Methicillin** → **Methicillin-resistant S. aureus (MRSA)** [1980s]
- **Vancomycin** → **Vancomycin-resistant enterococcus (VRE)** [1985]
- **Vancomycin intermediate resistant S. aureus (VISA)** → **Vancomycin-Resistant S. aureus (VRSA)** 2004
- **CA-MRSA** 2002
Intrinsic limitations of glycopeptides …

• only slowly bactericidal …

• require higher dosages than originally thought to be effective … \(\text{AUC/MIC} \geq 400\) …

\(\text{the classical dose of 2 x 15 mg/kg per day gives an AUC of 520, which will cover organisms up to a MIC of } 1-2 \text{ mg/L only}\)

• most often require the co-administration of another antibiotic because of too narrow spectrum

• yet, may cause severe surinfections …

Intracellular infection and recurrence/relapses

In vivo importance assumed based on in vitro data


Intracellular Staphylococcus aureus. A mechanism for the indolence of osteomyelitis.

Ellington JK, Harris M, Webb L, Smith B, Smith T, Tan K, Hudson M.


Intracellular persistence of Staphylococcus aureus small-colony variants within keratinocytes: a cause for antibiotic treatment failure in a patient with dipher’s disease.

von Eiff C, Becker K, Metze D, Lubritz G, Hockmann J, Schwarz T, Peters G.

Institute of Medical Microbiology, Westfalische Wilhelms-Universitat Münster, Münster, Germany.


Phagocytosis of Staphylococcus aureus by cultured bovine aortic endothelial cells: model for postadherence events in endovascular infections.

Hamill RJ, Vann JM, Proctor RA.
Intracellular infection and recurrence/relapses

Phagocytic and non phagocytic cells in mastitis

A real pipeline?
### In vitro susceptibility of new agents against *Staphylococcus aureus*.

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Development status</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam</td>
<td>Ceftobiprole (BAL9141/5788, Ro 63-9141)</td>
<td>Clinical</td>
<td>0.5–1 M&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2–4 M&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-Lactam</td>
<td>TAK-599</td>
<td>Preclinical</td>
<td>0.25 M&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 M&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quinolone</td>
<td>WCK-771</td>
<td>Clinical</td>
<td>0.015 Q&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 Q&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quinolone</td>
<td>WCK-919/1153</td>
<td>Pre-clinical</td>
<td>0.03 Q&lt;sup&gt;S&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 Q&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quinolone</td>
<td>DX-619</td>
<td>Pre-clinical</td>
<td>0.06 M&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 M&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 Q&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Linezolid</td>
<td>Approved</td>
<td>4</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Ranbezolid (RBX 7544)</td>
<td>Pre-clinical</td>
<td>2</td>
</tr>
<tr>
<td>Ketolide</td>
<td>Telithromycin</td>
<td>Approved</td>
<td>0.12 E&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.25 E&lt;sup&gt;R-ind&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td>&gt;128 E&lt;sup&gt;R-const&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.12 E&lt;sup&gt;R-msr&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lincosamide</td>
<td>VIC-10555</td>
<td>Pre-clinical</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptogramin</td>
<td>Quinupristin–dalfopristin</td>
<td>Approved</td>
<td>0.5</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Teicoplanin</td>
<td>Approved</td>
<td>1–2</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Oritavancin (LY333328)</td>
<td>Clinical</td>
<td>1–2</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Dalbavancin (BI397)</td>
<td>Clinical</td>
<td>0.06–0.25</td>
</tr>
<tr>
<td>Lipopeptide</td>
<td>Daptomycin</td>
<td>Approved</td>
<td>0.5</td>
</tr>
<tr>
<td>Diaminopyrimidine</td>
<td>Iclaprim (AR-100)</td>
<td>Clinical</td>
<td>0.5</td>
</tr>
<tr>
<td>Glycylcycline</td>
<td>Tigecycline</td>
<td>Clinical</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>PDF-inhibitor</td>
<td>LBM415 (NVP PDF-713)</td>
<td>Pre-clinical</td>
<td>2–4</td>
</tr>
</tbody>
</table>

The main classes…

Those already approved …
- tigecycline (the tetracyclines are back…)
- daptomycin (an old but really new drug…)
- moxifloxacin (quinolones do not give up…)

Those in late phase III …
- new quinolones …
- ceftobiprole (the first new anti-MRSA cephalosporins)
- the new lipoglycopeptides:
  - the real new one: telavancin,…
  - a not so novel but with unusual PK properties: dalbavancin

Those which will probably fail …
- new oxazolidinones …

And those which were approved and forgotten but may come back…
- SYNERCID ?
- arbekacin …
Tigecycline...

- truly made to resist efflux-mediated resistance in Gram(-) bacteria
- broad spectrum including MRSA (MIC < 2 mg/L) and VISA
- tet(M) [ribosomal protection] or tet(K) [efflux] have no discernible effect on MICs (AAC 2006 Feb;50(2):505-10).
- large tissue accumulation (Vd=7-9L/kg) ➞ low $C_{\text{max}}$ (1.5 mg/L; 70-80% protein-bound).

- approved by the FDA in June 2005 for
  - complicated skin infections, skin-structure infections;
  - intra-abdominal infections
    both at 100 mg IV (initial) followed by 50 mg/12h IV
  - bkpt for S. aureus (FDA): $S \leq 0.5$ mg/L
Tigecycline in Europe...

- approval by the EMEA in April 2006 for
  - Complicated skin and soft tissue infections
  - Complicated intra-abdominal infections
    both at 100 mg IV (initial) followed by 50 mg/12 h
    for 5 to 14 days.
  - bkpt for S. aureus (EUCAST): S ≤ 0.5 mg/L
    with the following comments:
    - Strains with MIC values above the breakpoint
      are very rare or not yet reported. The
      identification and antimicrobial susceptibility
      tests on any such isolate must be repeated
      and if the result is confirmed the isolate sent to
      a reference laboratory.
    - The S/I breakpoint was increased to avoid
      dividing wild type distributions of relevant
      species.
Tigecycline... why a breakpoint $\leq 0.5$ mg/L?

Distributions of MIC as submitted to EUCAST

Probability of target attainment of an suitable AUC/MIC ratio ($\geq 7$) for the recommended dosage

http://217.70.33.99/Eucast2/SearchController/regShow.jsp?Id=7563

Wyeth: data on file
Tigecycline… why a breakpoint $\leq 0.5$ mg/L?

Putting all together …. ➔ you will be effective as long as the MIC remain $\leq 0.5$ mg/L.
Tigecycline… why a breakpoint ≤ 0.5 mg/L?

Probability of target attainment of an suitable AUC/MIC ratio (≥ 7) for the recommended dosage
Tigecycline and intracellular S. aureus:

accumulation in PMN: about 20-30 fold


activity in PMN: about $1 \log_{10}$ at 1 mg/L
S. aureus ATCC 29213 (MIC = 0.25 mg/L)
Daptomycin ...

- very bactericidal towards Gram (+) organisms through membrane destabilization (no need of proteinaceous receptor!)
- BUT intrinsically inactive against Gram(-) due to LPS protection
- spare mammalian cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes

- got a fast track registration in the US because of activity against vancomycin-resistant enterococci (VRE)
Setting Daptomycin breakpoint …

Figure 1: Daptomycin MIC distribution and probability of target attainment for S. aureus

- Setting Daptomycin breakpoint …

358 is the minimal value for efficacy based on animal and human data.
Is there a place for daptomycin (in Europe)?

- breakpoint (as per EUCAST): 1 mg/L
- now registered in Europe for complicated skin and soft tissue infections (4 mg/kg administered once every 24 hours for 7-14 days)
- potential issues:
  - limited no. of clinical studies submitted in Europe so far (only equivalence to vancomycin!);
  - VISA strains tend to have MIC > 1 mg/L
  - safety (myopathy);
  - lack of Gram(-) coverage (no empiric treatment possible);
  - price (about 3-4 x vancomycin …)
- potential future: registration for bacteremia

\begin{quote}
\textit{Staphylococcus aureus} bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

The efficacy of CUBICIN in patients with left-sided infective endocarditis due to \emph{S. aureus} has not been demonstrated. The clinical trial of CUBICIN in patients with \emph{S. aureus} bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see \textbf{CLINICAL STUDIES}). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis.
\end{quote}
Moxifloxacin

![Moxifloxacin structure](image)

Lowest MIC amongst currently available quinolones, but resistance does exist!

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of strains with indicated MIC (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.25</td>
</tr>
<tr>
<td>NFLX</td>
<td>0</td>
</tr>
<tr>
<td>ENX</td>
<td>0</td>
</tr>
<tr>
<td>CPFX</td>
<td>1</td>
</tr>
<tr>
<td>TFLX</td>
<td>4</td>
</tr>
<tr>
<td>FLRX</td>
<td>0</td>
</tr>
<tr>
<td>SPFX</td>
<td>4</td>
</tr>
<tr>
<td>LVFX</td>
<td>3</td>
</tr>
<tr>
<td>GFLX</td>
<td>4</td>
</tr>
<tr>
<td>MFLX</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviation: NFLX, norfloxacin; ENX, enoxacin; CPFX, ciprofloxacin; TFLX, tosufloxacin; FLRX, fleroxacin; SPFX, sparfloxacin; LVFX, levofloxacin; GFLX, gatifloxacin; MFLX, moxifloxacin.

* The positions of breakpoints for resistance interpreted by the NCCLS are underlined. Breakpoints of MFLX and TFLX have not been established by the NCCLS.

b MIC: ≥64 mg/l.

c Not determined.

Moxifloxacin is very active against intracellular MSSA …

\[ \text{log extracellular concentration (X MIC)} \]

\[ C_{\text{max}} \]

2.5 log decrease at \( C_{\text{max}} \) (4.5 mg/L)

Moxifloxacin is very active against intracellular MSSA...

2.5 log decrease at $C_{\text{max}}$ (4.5 mg/L)

which is much better than oxacillin or gentamicin

Moxifloxacin is also active against intracellular HA-MRSA and VISA ...

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006
The main classes...

Those already approved …
- tigecycline
- daptomycin
- moxifloxacin

Those in late phase III …
- new quinolones …
- ceftobiprole (or the new anti-MRSA cephalosporins)
- the new lipoglycopeptides: the real one (telavancin,…)
  and the not so novel (dalbavancin)

Those which will probably fail …
- new oxazolidinones …

And those which were approved and forgotten but may come back…
- SYNERCID ?
- arbekacin …
**New quinolones: can we still do better?**

<table>
<thead>
<tr>
<th>Quinolone</th>
<th>Range of MIC of MRSA</th>
<th>MIC 50</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>0.03-32</td>
<td>1-2</td>
<td>4-16</td>
</tr>
<tr>
<td>WCK 771</td>
<td>0.015-4</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>DX 619</td>
<td>0.008-2</td>
<td>0.125</td>
<td>1</td>
</tr>
</tbody>
</table>

WCK 771, a new quinolone in clinical trials  

DK 619, a new desquinolone in preclinical trials

*Patel et al., AAC (2004) 48:4754-4761*  
*Bogdanovich et al., AAC. (2005) 49:3325-33.*
Anti-MRSA cephalosporins (ceftobiprole)…

- Highly resistant to beta-lactamases
- High affinity for PBP2a

- developed through Basilea Pharmaceutica Ltd. and Cilag AG International
- will be marketed by Ortho-McNeil Pharmaceutical, Inc. in the U.S. and by Janssen-Cilag in Europe, Japan and China.

Anti-MRSA cephalosporins (ceftobiprole)...

- MIC range: 0.25-0.5 mg/L for MSSA
  0.25-2 mg/L for MRSA
  0.5-2 for SCV
- bactericidal
- synergistic with aminoglycosides

- FDA fast track designation for
  - the treatment of complicated skin and skin structure infections due to MRSA
  - a second indication in the treatment of hospital-acquired (nosocomial) pneumonia, including ventilator-associated pneumonia due to suspected or proven MRSA

- Excellent tissue penetration and powerful activity in models of
  - osteomyelitis
  - foreign-body infection
  - aortic valve endocarditis
new glycopeptides (dalbavancin-telavancin)…

Hemi-synthetic derivatives derived from

vancomycin

Phase III,
Theravance → Astellas

teicoplanin

Marketeted,
Vicuron → Pfizer

Telavancin…

lipophilic side chain

polar group

this causes increase in bacterial membrane permeability

New pharmacodynamic profile due to new mode of action …

⇒ strong concentration-dependent bactericidal effect

extracellular

![Graphs showing the effect of vancomycin and telavancin on the log CFU from time 0 over time (h).](image-url)
Telavancin…

Cellular accumulation (and distribution in pahgolysosomes) …

lığın intracellular activity

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006
Microbiology, pharmacokinetics and clinical indications under investigation for the new glycopeptides (dalbavancin-telavancin)...

<table>
<thead>
<tr>
<th></th>
<th>telavancin</th>
<th>dalbavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC MRSA</td>
<td>&lt; 0.06-2</td>
<td>0.06-1</td>
</tr>
<tr>
<td>VISA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>VRSA</td>
<td>2</td>
<td>inactive</td>
</tr>
<tr>
<td>Half-life</td>
<td>7 h → once-a-day</td>
<td>149 h → once-a-week !!</td>
</tr>
<tr>
<td>Tissular and cellular distribution</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>skin &amp; soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAP</td>
<td></td>
<td>skin and soft tissue</td>
</tr>
<tr>
<td>models of endocarditis</td>
<td></td>
<td>HAP catheter-related bloodstream infections</td>
</tr>
</tbody>
</table>
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• daptomycin
• moxifloxacin

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• ceftobiprole (or the new anti-MRSA cephalosporins)
• the new lipoglycopeptides: the real one (telavancin,…) and the not so novel (dalbavancin)

Those which will probably fail …
• new oxazolidinones …

And those which were approved and forgotten but may come back…
• SYNERCID ?
• arbekacin …
Oxazolidinones (linezolid…)

- **Linezolid:**
  - resistance increases… and will continue because of increased use of LNZ against MRSA…
  - lower MIC desirable for PK/PD reasons…
  - neuropathy: limits therapy duration…
  - myelosuppression, MOA inhibition…

- **Present patent situation for oxazolidinones:** marked rise in 2002-2005 (Pfizer, AstraZeneca/Syngenta, Bayer, DuPont, J&J, others…), BUT …
  - various analogues tested …
  - modest to fair improvements in MIC (0.12 mg/L for VIC104203)
  - only marginal safety improvements obtained
  - no clinical candidate so far …
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• SYNERCID ?
• arbekacin …
SYNERCID® = quinupristin + dalfopristin

SYNERCID®

- originally discovered and developed by Rhône-Poulenc (France)
- European (mutual recognition) and FDA approval in the late 90's for:
  - complicated skin and soft tissues infections by MSSA/strepto
  - bacteremia due to VR *E. faecium* (fast track at FDA)
  - efficacy also demonstrated in nosocomial pneumonia (= vanco; lower success if MRSA in both groups)
- abandoned in early 2000's because of
  - side effects (rash; infusion-site inflammation; pain and edema; thrombophlebitis …) and inhibition of cytochrome P450 3A4
  - difficulties of production in large quantities
  - loss of interest after the merge of Rhône-Poulenc with Hoechst-Marion-Roussel to form AVENTIS…
- presently commercialized at a low scale by
  - Nordic Pharma in Europe
  - King Pharmaceuticals in the US
SYNERCID® does not behave too badly for intracellular S. aureus…

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006
and why not an aminoglycoside?

Arbekacin remains active against most MRSA producing inactivating-enzymes (including bi-functional).

TABLE 3. AME and aminoglycoside resistance

<table>
<thead>
<tr>
<th>AME gene present</th>
<th>Total no. of strains</th>
<th>% of isolates resistant (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{aac}(6')-\text{aph}(2''))</td>
<td>(\text{ant}(4')-\text{I})</td>
<td>(\text{aph}(3')-\text{III})</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>+</td>
<td>+</td>
<td>–</td>
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<td>+</td>
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<tr>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>381</td>
<td>61.7</td>
</tr>
</tbody>
</table>

\(^a\) Gm, gentamicin; Tob, tobramycin; Lvcm, lividomycin; Sm, streptomycin; Km, kanamycin; Abb, arbekacin; the cutoff MIC (in micrograms per milliliter) is given in parentheses.
Will this be successful?

MSSA: Easy

VISA: Difficult

HA-MRSA: Not so easy

and VRSA?
Where can you find more information?


These slides will be available on http://www.facm.ucl.ac.be