Updates on treatment of
*Staphylococcus aureus* / MRSA

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Why do we need new antimicrobials?
Easy resistance …

![Diagram showing resistance levels with MIC50 and MIC90 markers.](chart)

- **Susceptible** range: 0.015 to 0.06
- **Resistant** range: 0.12 to 256

- **MIC50** indicates 50% susceptibility
- **MIC90** indicates 90% susceptibility

- **1945** to **1995** trend in resistance levels

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**Legend**:
- **50%** threshold
- **90%** threshold
- **Susceptible** region
- **Resistant** region

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5/9/2009

SSAC, Tromsoe
A more difficult situation …

Multiplicity of mechanisms

50% 90%

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32

MIC_{50} MIC_{90} 2009
Populations of decreased susceptibility

- Well known for *S. pneumoniae* (and, more recently with *S. aureus* [VISA])
- Rediscovered under the acronym "MPC" (*Mutation Prevention Concentration*) for fluoroquinolones with *Mycobacteria* (and since then, with several other microorganisms)

![Graph showing survival vs. concentration with MIC<sub>99</sub> = 0.8 and MPC<sub>10</sub> = 9]
MIC creep

- Suggested to take place with vancomycin
- Viable according to reports (local or technique variations?)
- Significance to be established, but …

Ampe et al. ECCMID 2009

This where we start seeing failures…
The concept of "Resistance/Selection/Induction Window"

Modified to introduce the notion of selection/induction
New antibiotics … a risky business…

- Registered in the EU (EMEA) and the U.S.A. (FDA)

- Registration pending in the US but EMEA status uncertain
  - Telavancin (Theravance / Astellas; may become available in the U.S.A.)

- Registration postponed in the US and EMEA status uncertain
  - Ceftobiprole (Basilea / Johnson & Johnson; available in Canada, Switzerland and Ukraine)

- Withdrawn from both FDA and EMEA
  - Oritavancin (The Medicines Company; uncertain status)

- Rejected by EMEA
  - Gemifloxacin (Oscient Pharm. In the US; but under chapter 11)

- Rejected by the FDA
  - Iclaprim

- Development on hold…
  - Dalbavancin (Pfizer)

"Consistent with Basilea’s earlier press releases, an FDA "Warning Letter" issued in August 20008 asserts that there was a failure to ensure proper monitoring of the studies as well as deficiencies in study conduct…”

(Basilea Press Release August 18th, 2009)
Daptomycin: historical landmarks....

1987
Discovery of daptomycin as a novel anti-Gram + lipopeptide
In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.

1993
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”

1997
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 ...
PK/PD of daptomycin - animal models

Mouse thigh - *S. aureus*

Efficacy for
- Peak/MIC > 60-100
- AUC/MIC > 400-550 (total concentr.)

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 (registered dose)</td>
<td>serum</td>
<td>417</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td>inflam. exsudate</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
Dvorchik 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:
- pneumonia (neutralization by the surfactant)
- VISA strains (no access to target)

Only available as intravenous form!

Carpenter & Chambers CID (2004) 38: 994-1000
Daptomycin: where are we in EU?

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.
Daptomycin: where are we going to?

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.

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.

Tigecycline: historical landmarks …

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-butylglycylamide derivative of minocycline (GAR-936).
Tigecycline: chemical structure
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>E. coli</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>S. aureus</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>

E. coli and S. aureus data are from Petersen et al., AAC (1999) 43:738-44.
### Tigecycline: pharmacokinetics

<table>
<thead>
<tr>
<th>Single dose: 100 mg</th>
<th>tissue</th>
<th>AUC$_{24h}$ (mg.h/L)</th>
<th>serum/tissue AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bile</td>
<td>2815</td>
<td>537</td>
</tr>
<tr>
<td></td>
<td>bladder</td>
<td>120</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>colon</td>
<td>17.3</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>lung</td>
<td>9.19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>bone</td>
<td>2.05</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>synovial fluid</td>
<td>1.68</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>CSF</td>
<td>0.46</td>
<td>0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>100 mg + 6x50 mg q12h</th>
<th>ELF</th>
<th>4.54</th>
<th>1.31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>alveolar МΦ</td>
<td>268</td>
<td>77.5</td>
</tr>
</tbody>
</table>

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PK/PD of tigecycline – animal models

Mouse thigh - *S. pneumoniae*

**Efficacy for AUC\textsubscript{24h}/MIC of**
- 1-5 (free fraction)
- $\sim$ 10-50 (total conc.)

van Ogtrop *et al.*, AAC (2000) 44:943-9
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&lt;R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>RD 1/2E</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<sub>90</sub> at 0.75
In 2008)

Denis et al., AAC (2006) 50:2680-5
Launching tigecycline in EU

1993  2005-6

European Medicines Agency

4.1 Therapeutic indications

Tigacil 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

Tigacil 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
Other novel antibiotics (pipeline…[with leaks…])

- **Ceftobiprole** (Basilea / Johnson & Johnson)
  - first cephalosporin with anti-MRSA action (is also active against *P. aeruginosa*)
  - 2 x 750 mg ou 3 x 500 mg … (limited because of toxicity ?)
  - "target attainment rate" : MIC of 4 mg/L (EUCAST breakpoint)
  - submitted for "complicated skin and soft tissue infections" in EU and in the USA but no decision expected before end of 2009 or even later …
  - failure in nosocomial pneumonia (reason still unclear ?)

- **Telavancin** (Theravance / Astellas)
  - first lipoglycopeptide with FDA "near approval"; status uncertain in EU (safety issues)
  - very bactericidal (but Gram + ONLY); once-daily dosing
  - trend towards superiority in "complicated skin and soft tissue"
  - success in nosocomial pneumonia (S. aureus)

- **Oritavancin** (The Medicines Company)
  - lipopeptide very active against Gram +, with activity against SCV [incl. cystic fibrosis] and biofilm
  - very long half-life and large cellular accumulation
  - uncertain future (new phase 3 study requested by the FDA plus additional safety studies; withdrawn from EMEA)
### MIC of novel anti-Gram (+) antibiotics and EUCAST breakpoints

<table>
<thead>
<tr>
<th>organism</th>
<th>ceftobiprole (4/4)</th>
<th>telavancin (1/1)**</th>
<th>oritavancin (0.125/0.25)**</th>
<th>vancomycin (2/2)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>0.12-1</td>
<td>0.25/0.5</td>
<td>0.25/0.5</td>
<td>1/1</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.25-4</td>
<td>0.25/0.25</td>
<td>0.25/0.5</td>
<td>1/1</td>
</tr>
<tr>
<td>VISA</td>
<td>0.5-2</td>
<td>0.5-1</td>
<td>1/1</td>
<td>4/4</td>
</tr>
<tr>
<td>VRSA</td>
<td>1-2</td>
<td>2-4</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td><em>S. pneumo</em> Pen non-S</td>
<td>0.25-1 *</td>
<td>≤ 0.06/≤ 0.06</td>
<td>≤0.002/0.004</td>
<td>≤ 0.25/≤ 0.5</td>
</tr>
<tr>
<td><em>Enteroc. Van S</em></td>
<td>0.064-16 *</td>
<td>0.12/0.5</td>
<td>0.12/0.5</td>
<td>1/2</td>
</tr>
<tr>
<td><em>Enteroc. Van R</em></td>
<td>*</td>
<td>4-16</td>
<td>0.03</td>
<td>16</td>
</tr>
</tbody>
</table>

* no EUCAST breakpoint set (insufficient evidence)
** draft (submitted for consultation)

Ceftobiprole: mode of action

Lovering et al. ECCMID 2006, Abstract P1586.

Figure 5. Loss of secondary structure accompanies acylation.

Imipenem (▲) causes increased ellipticity between 198 and 206 nm

More random coil
More disorder in acyl-enzyme

Ceftobiprole (●) has a largely unperturbed spectrum between 198 and 206 nm

Loss of α-helix with all β-lactams
Ceftobiprole: susceptibility in Belgium

Comparison of 96 MRSA isolates from wound and skin-structure infections

Lemaire et al., submitted
Telavancin: mode of action

Telavancin and MSSA, MRSA, VISA, VRSA

3 h kill curves

Telavancin: clinical trials in cSSI caused by MRSA

Therapeutic regimens
- Telavancin - 10 mg/kg IV q 24hr; or
- Vancomycin - 1 gm IV q 12 hr
  (adjusted per site SOP)


Telavancin data presented at the FDA (public hearing – November 2008)
- comparable to standard therapy for the cSSI
- Trials finalized for S. aureus pneumonia and bacteremia
- adverse effects: taste disturbance, foamy urine, headache, procedural site pain, nausea, renal toxicity (3 %), QTc prolongation without clinical effect, potentially teratogenic
Oritavancin and SCV

Perhaps due to membrane-detabilization effect …
- Domenech et al. Biochim Biophys Acta. 2009 May 18. [Epub]
- Baudoux et al. ICAAC 2009 [C1-1354]

it's hard to exceed 2 log drop intracellularly
Drugs with a (still) more uncertain future?

- **anti MRSA β-lactams**
  - **ceftaroline**: low MICs but still from 0.25 to 2 mg/L
  - less favorable pharmacokinetics than ceftobiprole ($t_{1/2} = 2.6h$ vs. 3-4h)
  - what will be the dose (presently 600mg q12h) and the breakpoint?

- **glycopeptides**
  - **dalbavancin**: very long half life ($t_{1/2} \sim 7$ days); no useful activity against VRSA and doubtful against VISA development on hold…

- **trimethoprim derivatives**
  - **iclpram**: "impossible" pharmacokinetics; inferior to linezolid in phase 3 trials; further development uncertain…and lively discussions about the future of the compound at the last General Assembly of investors (August 19th, 2009)
As conclusion…

• Many molecules in development over the last years …
• But …
  – only narrow low margins between acceptable levels of drug exposure (safety) and what is needed to really stay above EUCAST breakpoints (aka = PK/PD plus clinical trials)…
  – difficulties in demonstrating superiority with the clinical trials as they are performed now for registration purposes, and, therefore, in substantiating clinically the superiority properties anticipated from the microbiological and pre-clinical studies
  – toxicity concerns has stopped several products…
  – We see faster than anticipated emergence of resistance…
• So far, only daptomycin and tigecycline are available as new anti-MRSA agents…
• I'm afraid vancomycin has still a lot of work to do … if you have MRSA …
I did not find this by my-self…

It is always difficult to see important things without help

But when someone knowing comes along, you get the picture

It is all a team work…
And here is the team...

The drug companies making the compounds about which I talked
A few papers to help …


• Lemaire S et al. Activity of ceftobiprole and other cephalosporins against extracellular and intracellular (THP-1 macrophages, keratinocytes) forms of Methicillin-Sensitive (MSSA) and Methicillin-Resistant Staphylococcus aureus (MRSA) * Antimicrobial Agents and Chemotherapy (2009) 53:2289-2297


• Appelbaum PC. MRSA--the tip of the iceberg. Clin Microbiol Infect. 2006; Suppl 2:3-10.


* papers available on www.facm.ucl.ac.be
Disclosures

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• the Public Federal Service "Public Health" for "Appropriate antibiotic use" studies in General Practice

• Pharmaceutical Industry for specific drug-related studies

Note:

• all work, irrespective the source of funding, is published in peer-reviewed journals and is available from our web site *

• P.M. Tulkens is member of the Committee organising public campaigns for appropriate use of antibiotics in Belgium since 2000 ** and member of the steering committee of EUCAST***

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* [http://www.facm.ucl.ac.be/publicat_facm.htm](http://www.facm.ucl.ac.be/publicat_facm.htm)

** [http://www.antibiotiques.org](http://www.antibiotiques.org)

*** [http://www.eucaest.org](http://www.eucaest.org)

"Was auch als Wahrheit oder Fabel In tausend Büchern dir erscheint, Das alles ist ein Turm zu Babel, Wenn es die Liebe nicht vereint."

J.W. von Goethe