Integrated Symposium

THE EVOLVING CONCEPT OF BACTERIAL SKIN INFECTIONS IN COMPPLICATED PATIENTS

Industry chair: Prof. Matteo Bassetti, Udine, Italy
ESCMID appointed chair: Prof. Pierre Tattevin, Rennes, France
Various treatment approaches and pre-clinical profiles

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**ECCMID Menarini Integrated Symposium**
*The evolving concept of bacterial skin infections in complicated patients*
April 21st, 2018 - 13:30 - 15:30

With approval of the Belgian Common Ethical Health Platform – visa no. 18/V1/10743/097270
Disclosures

Research grants for work on investigational compounds discussed in this presentation from:

- Cempra Pharmaceuticals
- Cerexa
- GSK
- Melinta Therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics

Influenced by my participation in:

- 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)

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1. merged in 2017 with and renamed as Melinta Therapeutics
2. formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
3. antibiotic portfolio acquired by Melinta Therapeutics in 2018
4. acquired by Cubist (2014), which was then acquired by Merck (2016)
What is your view of the new antibiotics pipeline?
Here are the possibilities …

The pipeline

1. is empty
2. has only me-too's (no interest for the clinician)
3. contains compounds with useful properties compared to old friends…
4. contains truly novel compounds

Please, think about what YOU would choose!
Newly registered anti-Gram(+) antibiotics in 2008-2012

Approvals of systemic antibiotics

16
14
10
7
4
2

1983-1987
1988-1992
1993-1997
1998-2002
2003-2007
2008-2012

DECLINING ANTIBACTERIAL APPROVALS (PAST 25 YEARS)

telavancin
ceftaroline
Newly registered anti-Gram (+) antibiotics since 2013

Approvals of systemic antibiotics

- ceftobiprole *
- oritavancin
- dalbavancin
- tedizolid
- delafloxacin **
- telavancin
- ceftaroline

* EU only (currently)
** US only (currently)
Lipoglycopeptides

- prolonged half-life
- membrane anchoring
- dimerization

- decreased half-life

Dual mode of action of lipoglycopeptides

Oritavancin (lipoglycopeptide)

Van Bambeke et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com/
# Pharmacokinetics of vancomycin vs lipoglycopeptides

<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>$C_{\text{max}}$</td>
<td>20-50</td>
<td>93</td>
<td>138</td>
<td>287</td>
</tr>
<tr>
<td>(mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>260</td>
<td>668</td>
<td>1110 (24h)</td>
<td>3185 (24h)</td>
</tr>
<tr>
<td>(mg.h/L)</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>$t_{\frac{1}{2}}$</td>
<td>1 (β)</td>
<td>8</td>
<td>14 (β)</td>
<td>346 (γ)</td>
</tr>
<tr>
<td>(h)</td>
<td>3-9 (γ)</td>
<td></td>
<td>245 (γ)</td>
<td></td>
</tr>
</tbody>
</table>

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

**common approved dosage / schedule for ABSSSI** (FDA/EMA)

- 1 g q12h 7-14 days
- 10 mg/kg qD 7-14 days
Tedizolid is an improved linezolid …

Substantial differences that DO impact on:
- **intrinsic activity** (4-8 x more potent)
- activity against *cfr*+ LZDR strains
- **half-life** (~2 x longer)
Key PK/PD parameters and breakpoints for tedizolid

- excellent oral bioavailability (IV ~ oral)
- long half-life (~ 12 h)
  (with concentrations > 0.5 mg/L for ~18 h)
- activity dependent from the AUC$_{24h}$ (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)

✓ ONCE daily dosing (oral or IV) @ 200 mg
✓ breakpoint: $S \leq 0.5$ mg/L – $R > 0.5$ (EUCAST) or $\geq 2$ (FDA)

- elimination mainly by the faeces

✓ no need of dose adjustment in patients with renal impairment or in hemodialysis
Ceftobiprole and ceftaroline

<table>
<thead>
<tr>
<th>Structural modifications of β-lactams antibiotics in order to overcome methicillin-resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples)</th>
</tr>
</thead>
</table>

[Chemical structures of Ceftobiprole and Ceftaroline]

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Fig. 130.4 Structural modifications of β-lactam antibiotics in order to overcome methicillin resistance, as applied to cephalosporins (with ceftobiprole and ceftaroline as examples). The bulky hydrophobic moieties (dotted-lined ellipse) added to the molecules forces a conformational change in PBP2a resulting in the opening of the active site and allowing acylation (inactivation) by the antibiotic. Although activity is largely restored towards methicillin-resistant organisms, MICs remain still typically one to four dilutions higher than for susceptible ones. The increase in lipophilicity also makes it necessary to administer the molecules as prodrugs – medocaril for ceftobiprole and fosamyl for ceftaroline (not shown).

Van Bambeke et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com
Why does ceftaroline act on PBP2a? The new (and probably correct) mechanism

Fig. 1. Domains of PBP2a and key ligands. (A) The chemical structures of a synthetic NAG-NAM(pentapeptide) (1) and ceftaroline (2). The R1 and R2 groups of 2 are labeled. (B) Ribbon representation of PBP2a acylated by ceftaroline. The N-terminal extension is colored in green, the remaining allostERIC domain is colored in gold, and the transpeptidase (TP) domain is colored in blue. These domain colors are retained in all other figures. Two molecules of ceftaroline (capped sticks in red) are found in complex with protein: one covalently bound as an acyl-enzyme in the TP domain (CFT1) and one intact at the allosteric domain (CFT2). A muramic acid saccharide (capped sticks in magenta) is found at the center of the allosteric domain. The arrow indicates the point of attachment of the membrane anchor. (C) The solvent-accessible surface representation for PBP2a is shown. The distance between the two ceftaroline molecules is 60 Å. (D) Ribbon representation of PBP2a in complex with 1 (black sticks). This view is rotated ~45° on the y axis compared with the view of C.

Ceftaroline for MSSA and MRSA (Belgium) *

- 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)

** EUCAST "S" breakpoint **

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

* Tulkens et al, 26th ICC, 2013 and unpublished
Ceftaroline for MSSA and MRSA (EUCAST) *

** EUCAST MIC distributions ([https://mic.eucast.org/Eucast2/](https://mic.eucast.org/Eucast2/) [last visited: 31 Jan 2018])
Pharmacocchemistry of delafloxacin

1. An heteroaromatic group in N1
   ➔ the molecular surface

2. A chlorine in C8
   ➔ activity

3. No basic group in C7
   ➔ Anionic character

Delafloxacin is currently not approved in Europe
Delafloxacin microspecies distribution and MICs at neutral pH


Delafloxacin is currently not approved in Europe
Delafloxacin microspecies distribution and MICs at acid pH


Delafloxacin is currently not approved in Europe
Figure 3 | Reactions of topoisomerases. a) In eubacteria, DNA gyrase imparts negative supercoils into closed circular DNA by the concerted breaking and rejoicing of double strands. Both DNA gyrase and topoisomerase IV can remove super coils. b) Supercoiled DNA is catenated by DNA gyrase and decatenated by both DNA gyrase and topoisomerase IV.


Delafloxacin is currently not approved in Europe
Double targeting…

Table 5. Formation of cleavable complexes with bacterial and human topoisomerases

<table>
<thead>
<tr>
<th>Species</th>
<th>DNA topoisomerase</th>
<th>Conc (µg/ml) for inhibition of cleavable complex formationa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABT-492</td>
<td>Trovafloxacin</td>
</tr>
<tr>
<td>E. coli</td>
<td>DNA gyrase</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Topoisomerase IV</td>
<td>1.1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>DNA gyrase</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Topoisomerase IV</td>
<td>1.7</td>
</tr>
<tr>
<td>Human</td>
<td>Topoisomerase II</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

For bacterial topoisomerases, the results are reported as the drug concentration causing half-maximal DNA cleavage. For human topoisomerase II, the results are reported as the drug concentration causing 7% more DNA cleavage than that seen without drug treatment.


ABT-495 = delafloxacin

Delafloxacin is currently not approved in Europe

Fluoroquinolones and bacterial killing in biofilms

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

Delafloxacin is currently not approved in Europe

The antifungal caspofungin increases fluoroquinolone activity against Staphylococcus aureus biofilms by inhibiting N-acetylglucosamine transferase

Caspofungin and fluoroquinolone cooperation

The antifungal caspofungin increases fluoroquinolone activity against Staphylococcus aureus biofilms by inhibiting N-acetylglucosamine transferase

Wafi Siala1, Sofia Kucharikova2-3, Annabel Braem4, Jed Vleugels3, Paul M. Tulkens1, Marie-Paule Mingot-Leclercq1, Patrick Van Dijck 2-3 & Françoise Van Bambeke1

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).

Delafloxacin is currently not approved in Europe

Let us see what the clinicians tell us

From clinical trial results of latest antibiotics to the real life practice
Prof. James A. McKinnell (USA)