How active are antibiotics when directed towards bacteria hiding intracellularly? Do accumulation and subcellular disposition matter?

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Work made in collaboration with Françoise Van Bambeke and many doctoral and postdoctoral fellows (see last slide)
Why intracellular bacteria?

**S. aureus in THP-1 macrophages**

Van Bambeke & Tulkens unpublished

**S. aureus in human osteoblasts**


**S. aureus in and released from neutrophils in a mouse osteomyelitis model**


Intracellular S. aureus
And more ...

*Fig. 1.* Electron micrographs of different types of infected host cells. Adherence and uptake of *S. aureus* in epithelial A549 cells (A). Intracellular location of *S. aureus* after infection of primary osteoblasts (B). Dividing figure of *S. aureus* within an intracellular phagosome (C) and intracellular bacterial degradation (D) 24 h after infection of endothelial cells (HUVEC).
Why do we wish to look at intracellular activity of antibiotics?

- Beyond truly obligate intracellular parasites (e.g., *Legionella*, *Chlamydia*, *Mycobacteria*, …many more "common" bacteria are facultative (e.g. *Listeria*) or occasional (e.g. *Staphylococci*, *Pseudomonas*) intracellular parasites …

- These bacteria form a reservoir from where bacteria may escape causing relapses and recurrences of the infection…

- Natural defenses often restrict their growth and decrease their persistence, but not always…

- You may need to help host defenses with antibiotics
Are antibiotics active at all in cells? ¹

Control (no antibiotic) ²

Oxacillin 63 mg/L  
(= $C_{\text{max}}$ and 500 x MIC)

Oritavancin 25 mg/L  
(= $C_{\text{max}}$ and 100 x MIC)

² gentamicin added at 1 x MIC to prevent extracellular growth
Intracellular activity of antibiotics

• What has been known for long about pharmacokinetics…

• What has surprised us …

• Adding pharmacodynamics …

• A renewed model ?
Intracellular activity of antibiotics

• What has been know for long about pharmacokinetics…

• What has surprised us …

• Adding pharmacodynamics …

• A renewed model ?
A simple view in 1991

Which antibiotics accumulate in cells?

- beta-lactams: ≤ 1x
- aminoglycosides: <1 to 2 x
- ansamycins: 2-3 x
- tetracyclines: 2-4 x
- fluoroquinolones: 5 - 20 x
- macrolides: 4 to > 100 x *
- glycopeptides: 1 to 400 x !! **

* azithromycin, ketolides
** oritavancin
How do antibiotics penetrate in cells?

1. diffusion

- macrolides
- fluoroquinolones
- tetracyclines
- ansamycines
- $\beta$-lactams,
- ...

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3rd Global Microbiologists Annual, Portland, OR
How do antibiotics penetrate in cells?

2. carrier-mediated influx

- specific structure
- (some energy-dependent)
- saturable
- competition by analogues

highly variable from cell type to another
How do antibiotics penetrate in cells?

3. pinocytosis

- aminoglycosides
- glycopeptides
How do antibiotics penetrate in cells?

**receptor-mediated pinocytosis in kidney cortex**

**Binding to megalin and acidic phospholipids**

Silverblatt & Kuehn C. Kidney Int. 1979;15:335-45 - PMID: 5134933
Sastrasinh et al. J Pharmacol Exp Ther 1982;222:350-8 - PMID: 2097208

**In vivo accumulation of gentamicin in rat renal cortex**

- V\(_{\text{max}}\) = 149.83 ± 9.08 µg/g per h
- K\(_{\text{m}}\) = 15.01 ± 1.55 µg/ml

**Giuliano et al. J Pharmacol Exp Ther 1986;236:470-5 - PMID: 3944766**
How do antibiotics penetrate in cells?

membrane binding and uptake of lipoglycopeptides

But once in cells, where are the drugs?
Subcellular localization: a quick answer?

- cytosol
  - fluoroquinolones
  - beta-lactams
  - ansamycins
  - macrolides (1/3)

- lysosomosomes
  - macrolides (2/3)
  - aminoglycosides

- endosomes

- phagolysosomes

- phagosomes
So, what we know in a nutshell ...

<table>
<thead>
<tr>
<th>Pharmacological class</th>
<th>Antibiotic</th>
<th>Accumulation level at equilibrium ($C_d/C_e)^a$</th>
<th>Cellular concentration at equilibrium (mg/l)$^b$</th>
<th>Time to equilibrium</th>
<th>Predominant subcellular localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>All</td>
<td>&lt; 1</td>
<td>~ 20 to 50</td>
<td>Fast</td>
<td>Cytosol</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin</td>
<td>4 to 10</td>
<td>~ 40 to 150</td>
<td>Moderate (a few hours)</td>
<td>2/3 Lysosomes 1/3 Cytosol</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>10 to 50</td>
<td>~ 20 to 400</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Roxithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>40 to 300</td>
<td>~ 16 to 120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin</td>
<td>4 to 10</td>
<td>~ 16 to 40</td>
<td>Fast (&lt; 1 h) to very fast (&lt; 5 min)</td>
<td>Cytosol</td>
</tr>
<tr>
<td></td>
<td>Levofoxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grepafloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>10 to 20</td>
<td>~ 40 to 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Garenoxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gemifloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>All</td>
<td>2 to 4 (after several days)</td>
<td>~ 40 to 80</td>
<td>Slow (several days)</td>
<td>Lysosomes</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Clindamycin</td>
<td>5 to 20</td>
<td>~ 50 to 200</td>
<td>Fast</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>Lincomycin</td>
<td>1 to 20</td>
<td>~ 15 to 60</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Probably all</td>
<td>1 to 4</td>
<td>~ 2 to 12</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td>Ansamycins (rifamycins)</td>
<td>Rifampin</td>
<td>2 to 10</td>
<td>~ 36 to 180</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Rifapentine</td>
<td>60 to 80</td>
<td>~ 1200 to 1600</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>8 (after 24 h)</td>
<td>~ 400</td>
<td>Slow (several hours)</td>
<td>Lysosomes (in kidney)</td>
</tr>
<tr>
<td></td>
<td>Teicoplanin</td>
<td>60</td>
<td>~ 6000</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Oritavancin</td>
<td>150 to 300 (after 24 h)</td>
<td>~ 3750 to 7500</td>
<td></td>
<td>Lysosomes</td>
</tr>
<tr>
<td></td>
<td>Telavancin</td>
<td>50 (after 24 h)</td>
<td>~ 4500</td>
<td></td>
<td>Lysosomes</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>~ 1</td>
<td>~ 20</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Adapted from Van Bambeke et al., Curr Opin Drug Discov Devel 2006;9:216-230 – PMID: 16566292
But where does this lead us for activity?

* taken from a slide presented at ECCMID in 2002

Ph. Geluck, with permission
Intracellular activity of antibiotics

- What has been know for long about pharmacokinetics…

- What has surprised us …

- Adding pharmacodynamics …

- A renewed model?
Intracellular activity is not directly correlated to accumulation

**Adapted from Van Bambeke et al., Curr Opin Drug Discov Devel 2006;9:218-230 – PMID: 16566292**
Intracellular activity is not directly correlated to accumulation

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Intracellular activity is not directly correlated to accumulation

Adapted from Van Bambeke et al., Curr Opin Drug Discov Devel 2006;9:218-230 – PMID: 16566292

AMP=ampicillin; AZM=azithromycin; CIP=ciprofloxacin; ETP=ertapenem; GEN=gentamicin; GRN=garenoxacin; LNZ=linezolid; LVX=levofloxacin; MEM=meropenem; MXF=moxifloxacin; NAF=nafcillin; ORI=oritavancin; OXA=oxacillin; PEN V=penicillin V; RIF=rifampicin; TEC=teicoplanin; TEL=telithromycin; VAN=vancomycin
Thus, there is now an obvious conclusion

"Accumulation only" may not be the key property

One size does not fill all

Each class of antibiotic / bacteria combination may need to be examined separately
Subcellular bioavailability of antibiotics?

- High
- Fair
- Nil

FQ / oxazolidinones / β-lactams

ML / AG
Subcellular bioavailability of antibiotics?

Fluoroquinolones, β-lactams, oxazolidinones, … may move easily across membranes
Conversely, poorly diffusible antibiotics (aminoglycosides, oritavancin, e.g.) or subjected to proton-trapping sequestration (macrolides, e.g.), may remained confined where they are ...
Intracellular activity of antibiotics

• What has been known for long about pharmacokinetics…

• What has surprised us …

• Adding pharmacodynamics …

• A renewed model ?
24h pharmacodynamic dose-effect model

1. Cell exposure to a wide range of extracellular concentrations of the antibiotic

- **Opsonization** (45°, 37°C)
  - 9 mL RPMI +
  - 1 mL human serum

- **Phagocytosis** (1 h)
  - 4 cfu/cell (MOI = 4)
  - 500,000 THP-1 cells/mL

- **Extracellular Wash**
  - GEN 50 µg/mL
  - (45 min)

- Typical post-phagocytosis inoculum:
  - 5 to 7x10^5 CFU/mg prot.

- **Incubation (with ATB)**
  - (T0, T24 h)

- **Cell washing, collection, and lysis**
- **Cell-associated CFUs counting**
- **Cell Protein content determination**

This example is for *S. aureus*.

Similar design for other bacteria

Interpretation of the results of the 24h dose-effect model

2. Analysis of the response

$E_{\text{min}}$: cfu increase (in $\log_{10}$ units) at 24 h from the corresponding initial inoculum as extrapolated for an infinitely low antibiotic concentration

Static concentration ($C_{\text{stat}}$): extracellular concentration resulting in no apparent bacterial growth (number of cfu identical to the initial inoculum)

$E_{\text{max}}$: cfu decrease (in $\log_{10}$ units) at 24 h from the corresponding initial inoculum as extrapolated from infinitely large antibiotic concentration

Interpretation of the results of the 24h dose-effect model

2. the analysis of the response

\[ E_{\min} \]: cfu increase (in log_{10} units) at 24h from the corresponding initial inoculum as extrapolated for an infinitely low antibiotic concentration

\[ E_{\max} \]: cfu decrease (in log_{10} units) at 24h from the corresponding initial inoculum as extrapolated from infinitely large antibiotic concentration

Static concentration (\( C_{\text{stat}} \)): extracellular concentration resulting in no apparent bacterial growth (number of cfu identical to the initial inoculum)

Are intracellular and extracellular activities equal?

S. aureus model (ATCC25223)


Compare the extracellular and the intracellular E_{max}.
Antibiotics have a much lower intracellular $E_{\text{max}}$...
Antibiotics have a much lower intracellular $E_{\text{max}}$ ... but also often a similar $C_s$ than in broth

Van Bambeke & Tulkens, ASM Microbe 2016 – poster SARTURDAY 571 – Session 188
### Numerical values...

<table>
<thead>
<tr>
<th>antibiotic</th>
<th>strain</th>
<th>$E_{\text{max}}$ (log$_{10}$ CFU decr.)</th>
<th>$C_s$ (multiple of MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>broth</td>
<td>intracellular</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftaroline</td>
<td>ATCC33591</td>
<td>-5.3</td>
<td>-0.56</td>
</tr>
<tr>
<td></td>
<td>multiple strains</td>
<td>-5.1</td>
<td>-0.58</td>
</tr>
<tr>
<td>daptomycin</td>
<td>ATCC33591</td>
<td>-5.1</td>
<td>-0.99</td>
</tr>
<tr>
<td>GSK1322322</td>
<td>ATCC25923</td>
<td>-5.5</td>
<td>-0.48</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>ATCC25923</td>
<td>-4.3</td>
<td>-2.7</td>
</tr>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftazidime</td>
<td>PAO1</td>
<td>-5.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>meropenem</td>
<td>PAO1</td>
<td>-6.0</td>
<td>-3.0</td>
</tr>
<tr>
<td>colistin</td>
<td>PAO1</td>
<td>-5.4</td>
<td>-1.0</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>PAO1</td>
<td>-5.2</td>
<td>-2.6</td>
</tr>
<tr>
<td>RX-P853</td>
<td>multiple strains</td>
<td>-5.1</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

*a* a novel peptide deformylase inhibitor with activity against multi-resistant *S. aureus*

*b* a novel inhibitor of bacterial protein synthesis acting at the translation step with broad spectrum activity

Van Bambeke & Tulkens, ASM Microbe 2016 – poster SARTURDAY 571 – Session 188
### A few more comparisons of $E_{\text{max}}\ldots$ a

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Molecule *</th>
<th>Extracellular **</th>
<th>intracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>beta-lactams</strong></td>
<td>oxacillin $^1$</td>
<td>-3.1</td>
<td>-1.6</td>
</tr>
<tr>
<td></td>
<td>ceftaroline $^2$</td>
<td>-5.4</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipopeptides</strong></td>
<td>daptomycin $^2$</td>
<td>-5.1</td>
<td>-1.0</td>
</tr>
<tr>
<td><strong>fluoroquinolones</strong></td>
<td>moxifloxacin $^4$</td>
<td>-4.8</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin $^5$</td>
<td>-4.9</td>
<td>-1.6</td>
</tr>
<tr>
<td><strong>pyrrolocytosines</strong></td>
<td>RX-P873 $^6$</td>
<td>-4.2</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>peptides (defensins)</strong></td>
<td>NZ2114 $^7$</td>
<td>-4.1</td>
<td>-1.5</td>
</tr>
<tr>
<td><strong>deformylase inhibitors</strong></td>
<td>GSK1322322 $^3$</td>
<td>-4.8</td>
<td>-0.4</td>
</tr>
<tr>
<td><strong>glycopeptides</strong></td>
<td>vancomycin $^2$</td>
<td>-5.1</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipoglycopeptides</strong></td>
<td>oritavancin $^1$</td>
<td>-5.5</td>
<td>-3.1</td>
</tr>
<tr>
<td><strong>oxazolidinones</strong></td>
<td>linezolid $^2$</td>
<td>-2.9</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

* all molecules but linezolid are highly bactericidal by conventional MBC/MIC measurements
** limit of detection: $-5.5 \log_{10}$ units

---

*a Reminder: $E_{\text{max}}$ is the maximal reduction of the initial inoculum for an infinitely large drug concentration*
**A few more comparisons of $E_{\text{max}}$...**

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Molecule</th>
<th>Extracellular $\Delta \log_{10}$CFU at 24h</th>
<th>Intracellular $\Delta \log_{10}$CFU at 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>beta-lactams</strong></td>
<td>oxacillin $^1$</td>
<td>-3.1</td>
<td>-1.6</td>
</tr>
<tr>
<td></td>
<td>ceftaroline $^2$</td>
<td>-5.4</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipopeptides</strong></td>
<td>daptomycin $^2$</td>
<td>-5.1</td>
<td>-1.0</td>
</tr>
<tr>
<td></td>
<td>vancomycin</td>
<td>-4.1</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>fluoroquinolones</strong></td>
<td>moxifloxacin</td>
<td>-4.8</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>ciprofloxacin</td>
<td>-4.9</td>
<td>-1.6</td>
</tr>
<tr>
<td><strong>pyrrolocytosines</strong></td>
<td>RX-P873</td>
<td>-4.2</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>peptides (defensins)</strong></td>
<td>NZ2114</td>
<td>-4.1</td>
<td>-1.5</td>
</tr>
<tr>
<td><strong>deformylase inhibitors</strong></td>
<td>GSK1322322</td>
<td>-4.8</td>
<td>-0.4</td>
</tr>
<tr>
<td><strong>glycopeptides</strong></td>
<td>vancomycin</td>
<td>-5.1</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipoglycopeptides</strong></td>
<td>oritavancin</td>
<td>-5.5</td>
<td>-3.1</td>
</tr>
<tr>
<td><strong>oxazolidinones</strong></td>
<td>linezolid</td>
<td>-2.9</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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$a$ Reminder: $E_{\text{max}}$ is the maximal reduction of the initial inoculum for an infinitely large drug concentration.
## Some antibiotics are better…

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Molecule</th>
<th>Emax ($\Delta \log_{10}$CFU at 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Extracellular **</td>
</tr>
<tr>
<td><strong>beta-lactams</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxacillin 1</td>
<td>-3.1</td>
<td>-1.6</td>
</tr>
<tr>
<td>ceftaroline 2</td>
<td>-5.4</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipopeptides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin 2</td>
<td>-5.1</td>
<td>-1.0</td>
</tr>
<tr>
<td><strong>fluoroquinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxifloxacin 4</td>
<td>-4.8</td>
<td>-2.0</td>
</tr>
<tr>
<td>ciprofloxacin 5</td>
<td>-4.9</td>
<td>-1.6</td>
</tr>
<tr>
<td><strong>pyrrolocytosines</strong></td>
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<td></td>
</tr>
<tr>
<td>RX-P873 6</td>
<td>-4.2</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>peptides (defensins)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ2114 7</td>
<td>-4.1</td>
<td>-1.5</td>
</tr>
<tr>
<td><strong>deformylase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK1322322 3</td>
<td>-4.8</td>
<td>-0.4</td>
</tr>
<tr>
<td><strong>glycopeptides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin 2</td>
<td>-5.1</td>
<td>-0.6</td>
</tr>
<tr>
<td><strong>lipoglycopeptides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>oritavancin 1</td>
<td>-5.5</td>
<td>-3.1</td>
</tr>
<tr>
<td><strong>oxazolidinones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>linezolid 2</td>
<td>-2.9</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

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** limit of detection: -5.5 log10 units

References:  

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*Reminder: $E_{\text{max}}$ is the maximal reduction of the initial inoculum for an infinitely large drug concentration*
Intracellular activity of antibiotics

• What has been known for long about pharmacokinetics…

• What has surprised us …

• Adding pharmacodynamics …

• A renewed model?
The seven pillars of intracellular activity?

1. Penetration

This is obvious:
no penetration = no activity
ex.: aminoglycosides in short term exposures
The seven pillars of intracellular activity?

1. Penetration
2. No efflux

Also obvious:
Efflux decreases the intracellular concentration. Ex: fluoroquinolones (MRP4), macrolides (Pg-p)
The seven pillars of intracellular activity?

1. Penetration
2. No efflux
3. Accumulation

Much less obvious …
no simple correlation accumulation-activity
ex.: fluoroquinolones, macrolides, β-lactams…
The seven pillars of intracellular activity?

1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability

This is probably the most critical property
ex.: fluoroquinolones, oxazolidinones vs macrolides and aminoglycosides
The seven pillars of intracellular activity?

1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability
5. Expression of activity

Interesting aspect but could vary for drugs and bugs …
• one + example: intracellular MRSA and conventional β-lactams… (not shown in this lecture)
The seven pillars of intracellular activity?

1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability
5. Expression of activity
6. Bacterial responsiveness (population)

Probably critical to explain the non-eradication or part of the intracellular inoculum... → future therapeutic targets?
The seven pillars of intracellular activity?

1. Penetration
2. No efflux
3. Accumulation
4. Subcell. bioavailability
5. Expression of activity
6. Bacterial responsiveness and pharmacodynamics
7. Cooper. with host def.

Not addressed here but probably very important
But what can we do NOW?

• All tested antibiotics fail to eradicate intracellular *S. aureus* (and many other bacteria) in the THP-1 model (and in other models)…

• Some antibiotics, however, fare better (moxifloxacin, oritavancin, e.g.) and could be our drugs of (desperate) choice…

• We must now try to understand the reasons for this global failure … and/or screen for better compounds *(follow us…)*

• In the meantime, intracellular organisms will remain a cause of concern and may (unfortunately) justify large doses and prolonged treatments… which is what we most often do…
But this work would not have been possible without

The drugs…

• **β-lactams**: penicillin V, oxacillin, cloxacillin, ceftaroline*, ceftobiprole* (+ avibactam*)
• **aminoglycosides**: gentamicin, amikacin
• **lincosamides**: clindamycin, pirlimycin
• **fluoroquinolones**: ciprofloxacin, pefloxacin, lomefloxacin, sparfloxacin, moxifloxacin, garenoxacin*, gemifloxacin, finafloxacin*, delafloxacin*
• **oxazolidinones**: linezolid, radezolid*, tedizolid*
• **glycopeptides**: vancomycin, telavancin*, oritavancin*,
• **macrolides**: clarithromycin, azithromycin, solithromycin*,
• **other classes**: daptomycin, GSK 1322322*, gepoditacin*, Debio1452*
• etc…

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* new molecules studied at preclinical level

The people…

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