"Treatment of Gram-Positive Infections by using PK / PD: focusing on Teicoplanin"

Henri A. Verbrugh MD PhD
Erasmus MC
Rotterdam
<table>
<thead>
<tr>
<th>Species</th>
<th>Resistance phenotype</th>
<th>Mechanism(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>β-Lactam</td>
<td>Low-affinity penicillin-binding proteins</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>Mutant topoisomerases</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>Penicillin</td>
<td>β-Lactamase</td>
</tr>
<tr>
<td></td>
<td>Oxacillin</td>
<td>Low-affinity penicillin binding proteins</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>Constitutive erm expression</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Mechanism unclear</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>Ampicillin</td>
<td>Low-affinity penicillin-binding proteins</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Altered peptidoglycan precursor</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Mutant ribosomal RNA genes</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>Mechanism unclear</td>
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</tbody>
</table>
teicoplanin

• teicoplanin is widely used outside the United States for the treatment of infections cause by Gram-positive bacteria. This antibiotic demonstrates bactericidal activity against a broad spectrum of Gram-positive organisms including MRSA and methicillin-resistant coagulase-negative *Staphylococcus epidermidis*. It has a longer half-life, higher protein binding, higher bone uptake, and less potential for nephrotoxicity compared with vancomycin. Selection of resistance may be a problem.
### Cochrane analysis 2010

#### Teicoplanin versus vancomycin for proven or suspected infection

**Patient or population:** patients with proven or suspected infection  
**Settings:**  
**Intervention:** Teicoplanin versus vancomycin

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nephrotoxicity</strong></td>
<td></td>
<td>RR 0.66</td>
<td>2596 (23 studies)</td>
<td>⬤⬤⬤⬤ moderate¹</td>
</tr>
<tr>
<td>Medium risk population</td>
<td>Medium risk population</td>
<td>RR 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92 per 1000</td>
<td>61 per 1000</td>
<td>RR 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(44 to 83)</td>
<td></td>
<td>RR 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure or improve-</td>
<td></td>
<td>RR 1.03</td>
<td>1703 (20 studies)</td>
<td>⬤⬤⬤⬤ moderate¹</td>
</tr>
<tr>
<td>ment</td>
<td>Medium risk population</td>
<td>RR 1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>730 per 1000</td>
<td>752 per 1000</td>
<td>RR 1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(715 to 788)</td>
<td></td>
<td>RR 1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiological cure</td>
<td>Medium risk population</td>
<td>RR 0.98</td>
<td>914 (16 studies)</td>
<td>⬤⬤⬤⬤ moderate¹</td>
</tr>
<tr>
<td>850 per 1000</td>
<td>833 per 1000</td>
<td>RR 0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(790 to 875)</td>
<td></td>
<td>RR 0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure needing</td>
<td>See comment</td>
<td>Not estimable²</td>
<td>606 (3)</td>
<td>See comment</td>
</tr>
<tr>
<td>dialysis²</td>
<td>See comment</td>
<td>Not estimable²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Medium risk population</td>
<td>RR 1.02</td>
<td>1565 (16 studies)</td>
<td>⬤⬤⬤ low³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 1.02</td>
<td></td>
<td></td>
</tr>
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</table>
Teicoplanin / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database 2013-04-13

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC
Epidemiological cut-off: WT ≤ 2 mg/L

Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

56561 observations (19 data sources)
pharmacokinetics

host defense/virulence

antibiotic

pharmacodynamics

susceptible/resistant

pathogen/commensal
definitions

- **Pharmacokinetics** is what the body does to the drug: absorption, distribution, metabolism, interactions, elimination

- **Pharmacodynamics** is what the drug does to the bug in the body: growth inhibition, bacterial killing
which is a pharmacodynamic parameter?

- MIC
- Cmax
- Cmax/MIC
- T1/2
- Vd
- % bioavailability
- $C_{\text{blood}}/C_{\text{tissue}}$
which is a pharmacodynamic parameter?

- MIC
- $C_{\text{max}}$
- $C_{\text{max}}/\text{MIC}$
- $T_{1/2}$
- $V_d$
- % bioavailability
- $C_{\text{blood}}/C_{\text{tissue}}$
The graph shows the plasma concentration over time for a drug. Key parameters include:

- **$C_{\text{max}}$**: Maximum plasma concentration.
- **$T_{\text{max}}$**: Time at which the maximum concentration is reached.
- **$AUC$**: Area Under the Curve, representing the total exposure to the drug.
- **$C_{\text{min}}$**: Minimum plasma concentration.
- **$C_{\text{max}}/\text{MIC}$**: The ratio of maximum plasma concentration to the minimum inhibitory concentration.

The graph is divided into two phases:

1. **Absorption Phase**: The period during which the drug is absorbed from the bloodstream into the body tissues, peaking at $C_{\text{max}}$ at $T_{\text{max}}$.
2. **Elimination Phase**: The period during which the drug is metabolized and excreted from the body, characterized by the decline in plasma concentration over time, eventually reaching $C_{\text{min}}$. The half-life ($T_{1/2}$) is a measure of the rate of elimination.
Vancomycin/teicoplanin response in *S. pneumoniae* infected mice

![Graph a](image1.png)

![Graph b](image2.png)
• target AUC:MIC ratio for vancomycin is > 400
• difficult to attain and maintain in patients infected with *S. aureus* strains with MIC >1.0 mg/l (VISA)
Predicted outcome of S.aureus/VISA infection among ICU patients with varying renal function/ages

Br J Clin Pharmacol 2010
V Hal et al., Clinical Significance of Vancomycin MIC (1.5). CID 2012;54; 755
Vancomycin / Staphylococcus aureus
EUCAST MIC Distribution - Reference Database 2013-04-13

MIC distributions include collated data from multiple sources, geographical areas, and time periods and can never be used to infer rates of resistance.

MIC
Epidemiological cut-off: WT = 2 mg/L
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

87764 observations (33 data sources)
**Figure 1.** Pharmacodynamic depiction of the mutant selection window. A hypothetical pharmacokinetic profile is shown in which MIC and MPC are arbitrarily indicated. Double-headed arrow indicates the mutant selection window.
Figure 1. Pharmacodynamic depiction of the mutant selection window. A hypothetical pharmacokinetic profile is shown in which MIC and MPC are arbitrarily indicated. Double-headed arrow indicates the mutant selection window.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class (mechanism of action)</th>
<th>Route of administration</th>
<th>Activity against</th>
<th>Common toxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide (cell wall synthesis inhibitor)</td>
<td>IV only</td>
<td>MRSA All</td>
<td>VRE No</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Lipoglycopeptide (cell membrane disruption, probably also acts at cell wall)</td>
<td>IV only</td>
<td>SSSI, BSI, SARIE, not pneumonia</td>
<td>VRE Yes (Enterococcus faecium only)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Oxazolidonone (protein synthesis inhibitor)</td>
<td>IV or oral</td>
<td>SSSI, pneumonia, not BSI</td>
<td>VRE Yes</td>
</tr>
<tr>
<td>Quinupristin-dalfupristin</td>
<td>Streptogramin (protein synthesis inhibitor)</td>
<td>IV only</td>
<td>Salvage</td>
<td>E faecium</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Lipoglycopeptide (cell wall synthesis inhibitor)</td>
<td>IV only</td>
<td>SSSI, CAP</td>
<td>VRE Yes</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Glycylcycline (protein synthesis inhibitor)</td>
<td>IV only</td>
<td>SSSI, CAP, not HAP/VAP or BSI</td>
<td>VRE Yes</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>Cephalosporin (cell wall synthesis inhibitor)</td>
<td>IV only</td>
<td>SSSI, CAP</td>
<td>VRE No</td>
</tr>
</tbody>
</table>

BSI = bloodstream infection; CAP = community-acquired pneumonia; HAP/VAP = hospital-acquired pneumonia/ventilator-associated pneumonia; IV = intravenous; MRSA = methicillin-resistant Staphylococcus aureus; SARIE = Staphylococcus aureus right-sided endocarditis; SSSI = skin and skin structure infection; VRE = vancomycin-resistant enterococci.
volume of distribution of drug is expressed in:

• Liters
• Kilograms
• volume % (ml/100 ml)
• weight % (grams/100 ml)
• C-blood/C-tissue ratio
# Pharmacodynamics of resistance

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>% time &gt; MIC</th>
<th>resistance rate</th>
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<tr>
<td>None</td>
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*Experimental *Pseudomonas endocarditis*

Fantin, JAC 1994
volume of distribution of drug is expressed in:

- Liters
- Kilograms
- volume % (ml/100 ml)
- weight % (grams/100 ml)
- C-blood/C-tissue ratio
which class has highest Vd?

- Fluoroquinolones
- aminoglycosides
- glycopeptides
- penicillins
- carbapenems
- sulfonamides
which class has highest Vd?

- Fluoroquinolones
- aminoglycosides
- glycopeptides
- penicillins
- carbapenems
- sulfonamides
which drug class penetrates well into eukaryotic cells?

• fluoroquinolones
• macrolides
• rifamycins
• tetracyclines
• none of the above
• all of the above
which parameter best predicts efficacy of: macrolides

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of:
aminoglycosides

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of: cephalosporins

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of:
aminopenicillins

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of: glycopeptides

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of: 
fluoroquinolones

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
drugs with a high volume of distribution

- have high molecular weight
- have low molecular weight
- are hydrophilic
- are hydrophobic
- have low isoelectric point
- have high isoelectric point
which drug class penetrates well into eukaryotic cells?

- fluoroquinolones
- macrolides
- rifamycins
- tetracyclines
- none of the above
- all of the above
which of the following is a pharmacodynamic parameter

- Cmax
- Cmax/MIC
- T1/2
- Vd
- % bioavailability
Cmax/MIC, AUC/MIC and T>MIC are

1] pharmacodynamic parameters

2] pharmacokinetic parameters
the mutant protection concentration (MPC) is:

1] lower than the MIC

2] similar to the MIC

3] higher than the MIC
which drug class has highest volume of distribution?

- fluoroquinolones
- aminoglycosides
- penicillins
- carbapenems
- sulfonamides
The mutant selection window is the time during a dosing interval that the serum concentration is

1] < MIC
2] < MPC
3] < MIC but > MPC
4] < MPC but > MIC
which parameter best predicts efficacy of:

aminopenicillins

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2] AUC/MIC

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2] AUC/MIC

3] time > MIC
The mutant selection window of azithromycin versus erythromycin is

1] longer
2] same
3] shorter
antibiotics with a high volume of distribution

- have high molecular weight
- have low molecular weight
- are hydrophilic
- are hydrophobic
- have low isoelectric point
- have high isoelectric point
which class has highest Vd?

- aminoglycosides
- penicillins
- carbapenems
- sulfonamides
which class has highest Vd?

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• carbapenems
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• rifamycins
• tetracyclines
which drug class penetrates well into eukaryotic cells?

- fluoroquinolones
- macrolides
- rifamycins
- tetracyclines
which is a pharmacodynamic parameter

- Cmax
- Cmax/MIC
- T1/2
- Vd
- % bioavailability
- AUC
which is a pharmacodynamic parameter

- Cmax
- Cmax/MIC
- T1/2
- Vd
- % bioavailability
- AUC
- AUC/MIC
- % T>MIC
The diagram illustrates the relationship between plasma concentration and time. It shows the Absorption Phase, which is marked by a peak in plasma concentration ($C_{\text{max}}$) at $T_{\text{max}}$. Following the Absorption Phase is the Elimination Phase, characterized by a decrease in plasma concentration over time. The Area Under the Curve (AUC) is a measure of the total exposure to the drug. The MIC (Minimum Inhibitory Concentration) is shown as the minimum concentration at which the drug inhibits the growth of the microorganism.
which PD parameter best predicts efficacy of:

macrolides

1] Cmax/MIC

2] AUC/MIC
which PD parameter best predicts efficacy of: macrolides

1] Cmax/MIC

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of:

aminoglycosides

2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of: 
aminoglycosides

1] Cmax/MIC 

2] AUC/MIC 

3] time > MIC
which parameter best predicts efficacy of: cephalosporins

1] Cmax/MIC

2] AUC/MIC
which parameter best predicts efficacy of:
cephalosporins

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2] AUC/MIC

3] time > MIC
which parameter best predicts efficacy of:

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3] time > MIC
which parameter best predicts efficacy of:
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2] AUC/MIC

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which parameter best predicts efficacy of: glycopeptides

1] Cmax/MIC

3] time > MIC
which parameter best predicts efficacy of:
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The mutant selection window of azithromycin versus erythromycin is

2] same
3] shorter
The mutant selection window of azithromycin versus erythromycin is

1] longer
2] same
3] shorter
Zeckel ML.
Source
Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, USA.
zeckelvmichaelvl@lilly.com
Abstract

The worldwide increase in the incidence of resistant Gram-positive infections has renewed interest in the glycopeptide class of antimicrobial agents. Two glycopeptides are available in many parts of the world--vancomycin and teicoplanin. These two agents appear to differ in several respects, including: potential for selecting microbial resistance, dosing convenience, safety, and efficacy in severe infection. Teicoplanin appears to have lower toxicity and greater convenience; however, its widespread acceptance has been plagued by concerns over antimicrobial resistance, efficacy, and appropriate dosing. A review of available studies suggests that teicoplanin, when dosed at 6 mg/kg/day, is better tolerated than vancomycin 15 mg/kg/q12h; however, at these doses, it appears to be somewhat less effective than vancomycin in serious Staphylococcus aureus infection, such as endocarditis. Although higher doses of teicoplanin, 12 mg/kg/day to 30 mg/kg/day, have been associated with efficacy comparable to that of vancomycin in serious S. aureus infections, such doses may eliminate some of the safety advantages conferred by lower teicoplanin doses. Teicoplanin has been associated with resistance among coagulase-negative staphylococci and the selection of resistance in S. aureus. There is some evidence that widespread use of teicoplanin might accelerate the development of S. aureus resistance to both teicoplanin and vancomycin. The selection of an appropriate glycopeptide in an individual patient should be based not only on convenience, but also on a determination of optimal efficacy, safety at an efficacious dose, and
The pyramid of infectious diseases.
## Pharmacodynamics of resistance

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*Experimental *Pseudomonas endocarditis*

Fantin, JAC 1994
The pyramid of infectious diseases.

- Therapy
- Activity
- Resistance
- Colonization resistance
- Host resistance
- Virulence
- Pharmacokinetics
- Toxicity

Host
Pathogens
Commensals
antibiotics with a high volume of distribution

- have high molecular weight
- have low molecular weight
- are hydrophilic
- are hydrophobic
- have low isoelectric point
- have high isoelectric point
Cmax/MIC, AUC/MIC and T>MIC are

1] pharmacodynamic parameters

2] pharmacokinetic parameters
Teicoplanin is a glycopeptide antibiotic used for the treatment of infection due to beta-lactam resistant Gram-positive microorganisms (e.g. MRSA). An initial loading dose of 400 mg every 12 hours for three doses is the standard dosing regimen. The area under the unbound drug concentration-time curve \( [fAUC]/MIC \) is thought to be the best predictor of efficacy for many classes of antimicrobial agents including the glycopeptides. However, some authors argue for glycopeptide dosing regimens where the serum free-drug concentrations never go below the MIC during the whole treatment period. This fact becomes clinically relevant when choosing dosing regimens for glycopeptides, especially for teicoplanin, where MICs’ may vary significantly. Also, the \( fAUC/MIC \) index was shown to be sensitive to differences in PK in subpopulations, uncertainty in MICs, and dosing intervals. A model-based approach, where the full time course of effect can be predicted, has a lower sensitivity to study design and allows for PK differences in subpopulations to be considered directly. Simulations provide useful information regarding the initial assessment of glycopeptide dosing, the conventional dosing regimen probably being suboptimal in many adult patients, especially those on intensive care. An extended loading regimen (400 mg every 12 hours for the first 5 doses) would be a treatment option to maximize the therapeutic effects of teicoplanin in patients with systemic Gram-positive infection.