Educational Workshop

EW19: Basic concepts of pharmacokinetics and pharmacodynamics

Arranged with EPASG

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Marked in red = no handouts available
Basic Concepts of PK/PD
-pharmacodynamic indices-

Johan W. Mouton MD PhD FIDSA
Professor pharmacokinetics and pharmacodynamics

This patient needs antibiotics. But which ones?

Intensive care patient

Which of the following dosing regimens is best?

A. 1000 mg q12h
B. 500 mg q6h
C. 2000 mg q12h
D. 1000 mg q8h
Dosing should be such that the level of antimicrobial activity is associated with a high likelihood of therapeutic success.

Dose Finding - The Past

Efficacy of the drug

Potency of a drug (MIC)  Exposure to the bug *in vivo* (PK)
ACTIVITY in vitro (MIC) → CONCENTRATIONS in vivo (PK) → DOSSING regimen

ANTIMICROBIAL EFFICACY (Microbiological Cure)

CLINICAL EFFICACY (Clinical Cure)

- Thus, we have to:
  - Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
  - Determine which dosing regimens are optimal for Treatment in relation to the MIC
Any idea where we are today?

No idea...
may be a mouse?

Might be a human,... though...

An elephant....
Today it is an elephant!

Neutropenic Mouse Model
Example with q6h dosing

Cyclophosphamide i.p.
100 mg/kg 100 mg/kg

Antimicrobial therapy s.c.

Time h
-96 -24 -20 6 12 18 24

5.10^5 cfu

Thigh model
2 strains/mouse, 1/thigh

Infection

Homogenization thigh
CPU counts
**PK/PD dose fractionation studies**

- Neutropenic mouse thigh model
- Various doses and dosing regimens (q1 to q24)
- Outcome parameter: cfu counts after 24 h
- Plot PK parameter and/or PK/PD index (AUC, Peak %fT>MIC) to effect

**General Diagram Dose fractionation studies**

- Cyclophosphamide i.p.
- Antibacterial therapy s.c.
- Treatment:
  - -96, -24, 0, 3, 6, 9, 12, 18, 21, 24
  - q24, q12, q6, q3
- Time h
- 5.10^6 cfu
- Infection
- Thigh model 2 strains/mouse, 1/thigh
- Homogenization thigh CFU counts

**Pharmacokinetic parameters: Measures of Exposure**

- Area under the concentration-time curve
- Integrated concentration over time

- AUC
- Concentration
- Time
**Pharmacokinetic parameters:** Measures of Exposure

AUC is *usually* linearly related to Dose

- Dose $\times 2 = \text{AUC} \times 2$
- Dose $\times 4 = \text{AUC} \times 4$

**K. pneumoniae**, imipenem

Every point = one mouse thigh

$\text{dlogcfu} = \text{logcfu (t=24h)} - \text{logcfu (t=0h in controls)}$ = net effect of treatment

*Based on data from Craig WA*
For *K. pneumoniae*, there is no clear relation between AUC (or total daily dose) of imipenem and efficacy in an in vivo model of infection.

AUC and Peak are *usually* linearly related to Dose.

Time > MIC dependent on dose frequency.
For beta-lactams, there is a direct relation between Time > MIC and efficacy.

Levofloxacin in *S. pneumoniae* infection in mice

- Relationship between T > MIC, Peak, AUC
- Each dot represents one mouse/dosing regimen.

PK/PD relationship is Class Dependent

3 Possible Outcomes of Dose fractionation (in general)

- Efficacy Q3 > Q6 > Q12 > Q24: Primarily Time dependent (f)
- Efficacy Q3 < Q6 < Q12 < Q24: Primarily Cmax (D) dependent
- Efficacy Q3 = Q6 = Q12 = Q24: Primarily AUC (TDD) dependent

Relationship PkPd and Effect

<table>
<thead>
<tr>
<th>T&gt;MIC</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Monobactams</td>
<td>Lipopeptides</td>
</tr>
<tr>
<td>Tribactams</td>
<td>Ketolides</td>
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<tr>
<td></td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td>Streptogramins</td>
</tr>
<tr>
<td></td>
<td>Glycopeptides</td>
</tr>
<tr>
<td></td>
<td>Glycylcyclines</td>
</tr>
<tr>
<td></td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Azoles</td>
</tr>
</tbody>
</table>
Relationship AUC and effect

- What has the MIC to do with this?

Fluconazole efficacy in mice
Dose vs MIC

Pharmacokinetic parameters:
Measures of Exposure

AUC and Peak are usually linearly related to Dose
Fluconazole Pharmacodynamics Against Isogenic Strain Pairs of Susceptible and Resistant C. albicans

In vitro effect at fixed concentrations

In vivo CT profile dynamic concentrations

Response Curve
Treatment with fluconazole
Doses 50 – 800 mg

Individually
Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome

Why is the term PK/PD index used instead of PK/PD parameter?

- A ratio (e.g.) of two independent parameters, not a parameter by itself

Rodriquez-Tudela et al, AAC 2007
Thus, 2 factors influence the value of the pk/pd index:

MIC and its Errors/variation
Pharmacokinetics and its variation

Growth and/or kill rate dependent:
- strain, species
- medium composition, brand
- MH, supplements, ISO
- number of bacteria
- inoculum
- $5.10^5$ (CLSI) vs $10^5$ (BSAC)
- temperature (35$^\circ$ vs 37$^\circ$)
- growth phase
- CO$_2$
- etc.
The reference method

- Microdilution, 0.1 ml
- Mueller Hinton (1941, Corn starch)
- Inoculum 5 (2-8) 10^5 cfu/ml
- 36 ± 1°C
- 18 ± 2 h incubation

The reproducibility of the MIC test is within 2 2-fold dilutions. The variation introduced in the AUC/MIC and Peak/MIC values by the MIC is there for at least 0.5 to 2 x the pk/pd index value!
Mouton - Introduction to PK/PD

Why is outcome of beta-lactams %T>MIC related? And aminoglycosides AUC related?

In vitro activity of ceftazidime – exposure-response relationship

- Incubate inoculum at increasing concentrations
- Sample every two h

Modelling Kill Kinetics

\[ E = E_{max} \cdot \frac{C^\gamma}{(C^\gamma + E_{IC}^\gamma)} \]
Mouton - Introduction to PK/PD

Patterns of activity: Kill curves of *P. aeruginosa*

ceftazidime  
![Graph showing ceftazidime kill curves.]

tobramycin  
![Graph showing tobramycin kill curves.]

**Figure 47**

<table>
<thead>
<tr>
<th>Concentration (mg/l)</th>
<th>Kill Rate (h⁻¹)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.59</td>
</tr>
<tr>
<td>10</td>
<td>13.4</td>
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</table>

Steep: high concentration independent  
Shallow: low concentration dependent

Conclusions

- The overall effect of antimicrobial therapy is dependent on exposure AND MIC.
- The effect differs by antibiotic class:
  - Beta-lactams: %T>MIC related
  - Most others: AUC related
- Exposure response relationship can be explained by the pd characteristics:
  - Fast vs slow kill (speed of killing)
  - Maximum kill rate (extent of killing)
  - Concentration effect (hill slope)
- Adjust dosing regimens based on pkpd!
  - For beta-lactams: adjust dose; frequency matters!
  - For most others: adjust frequency.
PHARMACOKINETIC parameters

**Definition**: The Area under the Concentration-time curve over 24 hours.

*Note*: It should be stated how the AUC is determined: based on (log) linear trapezoidal rule, based on clearance, or based on microconstants.

**Dimensions**: Concentration x time e.g. mg.h/L or µg.h/mL

Mouton et al., J Antimicrob Chemother 2005. Available from ISAP site

AUC

- AUC 0-24 = 3033
- AUC inf = 5100
- AUC 0-24 sd = 1361
- AUC inf sd = 1700

AUC 0-24 = 3033
AUC inf = 5100
AUC 0-24 sd = 1361
AUC inf sd = 1700

Mg.h/L
WHICH AUC?

- AUC \(_{0-24h}\) or AUC \(_{\infty}\)
- Steady State?
- (log) trapezoidal rule?
- Derived? \((A/\alpha + B/\beta\) or other)

Definition: The area under the concentration-time curve over 24 hours in steady state divided by the MIC.

Note: For unbound fraction of the drug, use \(fAUC/MIC\).

Dimensions: no dimensions

AUC/MIC

Definition: The area under the concentration-time curve over 24 hours in steady state divided by the MIC.

Note: For unbound fraction of the drug, use \(fAUC/MIC\).

Dimensions: no dimensions

AUIC

Definition: The Area under the inhibitory curve over 24 hours.

Note: The AUIC should be reserved for those cases where actual inhibitory titers have been measured and used in the calculations. The AUIC is not equal to the AUC/MIC. See also Flaherty et al, AAC 1988;32(12):1825-29; Hyatt JM et al AAC 1994;38(12):2730-7; Occhipinti DJ et al, AAC 1997;41(11):2511-7.

Dimensions: none
Peak/MIC

*Definition*: the peak level divided by the MIC.

*Dimensions*: no dimensions.

Mouton et al., J Antimicrob Chemother 2005
Available from ISAP site

**WHICH PEAKLEVEL?**

- After the 1st, 2nd or later dose?
- If more than one compartment, the peak level in compartment 1, 2 or even 3?

Scaglione et al., AAC 2003

Fig 1
**Time > MIC**

**Definition**: the % of time above the MIC over a period of 24 hours.

**Note**: if the period is other than 24 h, this should be stated explicitly.

**Dimensions**: %.

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**Variation in methods, definitions**

Variation in estimation

Variation in population

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**For all indices**:

how are they determined

how are they calculated

what is the error?

Only when these questions have been answered do we know the true impact and value of the index.
Translating PK-PD Concepts to the Clinic

William Hope
Antimicrobial Pharmacodynamics & Therapeutics
University of Liverpool
ECCMID
April 2015

Pharmacokinetics-Pharmacodynamics

<table>
<thead>
<tr>
<th>DOSE</th>
<th>OUTCOME OF CLINICAL INTEREST/IMPORTANCE</th>
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<tbody>
<tr>
<td>0.01</td>
<td>• Survival</td>
</tr>
<tr>
<td>0.1</td>
<td>• Resolution of clinical syndrome</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>100</td>
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</tr>
<tr>
<td>1000</td>
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</tr>
</tbody>
</table>

Effect (log_{10} CFU/g)
Hope - Translating PK/PD concepts into the clinics

Three Questions

• What is required for translation (bridging)?
• What problems can be solved by translation (bridging)?
• What are the threats to the validity of the process?

Let’s assume the first part is done, and done well

• The PK-PD of Drug x against pathogen y has been established
  – Good idea of the PD index that best links drug exposure with the observed effect
    • e.g. AUC:MIC, Peak:MIC, T>MIC
  • Good idea of the magnitude of the PD index that is required to generate an effect
    – e.g. relationship between AUC:MIC and orders of logarithmic killing

To enable statements like...

(1) Drug x is AUC:MIC driven
(2) An AUC:MIC of 250.46 is associated with a 1-log kill
(3) An AUC:MIC of 356.8 is associated with a 2-log kill etc. etc.

Or some variant of this...
What is the purpose of bridging?
There are two:
• Identification of dosages and schedules of drug administration that are likely to be safe and effective for patients
  • Nontoxic and associated with near maximal antimicrobial activity
• Setting/Establishing/Verifying in vitro susceptibility breakpoints

What then is required for the translation (bridge) to the clinic?

Bridging Experimental Data: Population PK
• Population PK provides an estimate of central tendency and variability of drug behaviour within a population
• Or, put differently, Pop PK enables a description of the distribution of drug exposures (AUC:MIC, trough concentration, T>MIC etc. etc.) that develop when a population of patients is administered a given dosage
• And, since drug exposure is linked to effect, the impact of inherent PK variability on the antimicrobial effect can be estimated
Hope - Translating PK/PD concepts into the clinics

**Bridging Experimental Data**

**Monte Carlo simulation**

- The initial idea of simulation was used to solve nuclear shielding problems
  - Problems too expensive or dangerous for experimentation
  - Problems too complicated for an analytical solution
- For PK, a computer generates virtual patients
  - Each with an individual set of PK parameters (Vc, SCL etc.)
  - Based on the population PK parameter means and covariance matrix given by the population PK model
- Each virtual patient receives a drug and the resultant drug exposure is calculated (e.g. AUC:MIC)
- The drug exposure is then linked to the response via the drug exposure response relationship

**An Example**
Hope - Translating PK/PD concepts into the clinics

Micafungin exhibits a dose-dependant fungicidal effect

The transform: drug exposure is now quantified in terms of the common invading pathogen

\[
\log_{10} \text{CFU/g} = 3.20 - \left(2.81 \times \frac{\text{AUC:MIC}}{2499^{1.12} + \text{AUC:MIC}^{1.12}}\right)
\]

\[r^2 = 0.61; p < 0.01\]

Assume that the pharmacodynamics in the experimental system and babies are the same
The simulated effect in 9,999 neonates with HCME receiving micafungin

- A: 3 mg/kg
  - mean: 1.79
  - median: 1.55
  - SD: 0.12

- B: 6 mg/kg
  - mean: 2.33
  - median: 1.26
  - SD: 0.14

- C: 9 mg/kg
  - mean: 1.11
  - median: 1.01
  - SD: 0.08

- D: 12 mg/kg
  - mean: 8.87
  - median: 3.30
  - SD: 0.20

- E: 15 mg/kg
  - mean: 0.87
  - median: 3.70
  - SD: 0.22

Hope et al. J Infect Dis 2008

Once you have figured out how to use a simulator, bridging is pretty easy...the real question is whether you are right!

What are the threats to validity of bridging...a personal opinion
1. Is the preclinical PK-PD giving the right answers?

- The most important thing here is the experimental model
  - Is it a faithful mimic of human disease and pathogenesis?
  - Has it been characterized at a pathological level?
  - What about background immunosuppression?
  - What about the delay in administration of antimicrobial therapy?
  - Are the strains "real" rather than pet laboratory strains?
  - What about the severity of the model?

“I don’t treat Hollow Fibre Infection Models…I treat patients”

How could HFIM ever be predictive?

How to convince yourself conclusions from a HFIM (or any model) are real

- There isn’t any rule about this
- No need to take anyone’s word
  - Make your own mind up
- Consider carefully what you effect site is being modeled
  - Different tissue beds have different exposure-response relationships
  - e.g. a HFIM may not be appropriate to model meningitis unless CSF concentrations are mimicked
  - or ELF concentrations are modeled for pneumonia
- Use some form of triangulation
  - Different experimental model (lab animal model)
  - Other published studies
  - Altered experimental conditions
- Be critical, stay cautious and play conservatively
2. What is the magnitude of the “best” endpoint that is associated with an outcome of interest?

- $E_{50}$
- 1 log drop in CFU/g
- 2 log drop in CFU/g
- Stasis

[these endpoints not absolute or divine!!]

One way to do this is not make a decision about log drop, but just show a histogram of effect

Study Endpoints (cont.)

- I recently heard George Drusano talk about reducing burden to < 6 logs to enable neutrophils to kill in an optimal manner
  - That’s OK if it also makes clinical sense like it does in VAP
  - But may not be applicable to every situation
  - Sometimes you have to admit you don’t know (that’s OK!!)
  - Sometimes you can define a lower margin that is unlikely to be effective- that defines a minimum effect that is acceptable
  - Sometimes it may be appropriate to take as much effect as you can get given what you know about toxicity

- Can consider trying to triangulate other study endpoints
  - Survival
  - Histopathological findings
  - Clinical data if available
3. Beware of the following++

- Protein binding
  - Free drug generally modeled in HFIMs
  - Total drug generally measured in animals
  - I still don’t quite know what to do about all of this, and beware of anyone that says they do know!
- “Invisible” immune effect (next slide)
- Emergence of drug resistance (next slide)
- Loading dosages (next slide)
  - Which AUC do you bridge?
  - The early one with the loading dose or at steady state?
- Duration (next slide)

“Invisible” Immune Effects...even with proper controls

Drug holds the organism early on until there immune effectors become active- it is then possible to attribute ALL the antimicrobial effect to the drug (trust me, have made this mistake before!)

A way to handle the bridging when a loading dose is used
4. Is the population PK right?

- Have an “adequate” number of patients been studied?
  - May under or over estimate variance with small numbers (both bad!)
  - 40 is a good number, but not always possible
- Has the right population group been studied (e.g. healthy volunteers, versus ICU patients)?
  - PK will change...especially estimates of variance
- Is the population PK concordant with other published studies?
  - If not, why not?
- If using studies from the literature, how sure are you that you are simulating the right parameters?
  - Has caused confusion for me in the past (especially NONMEM papers)
  - Can ask authors just to give you their data, offer co-authorship and re-solve the problem...that’s safe and everyone wins
When all said and done...

- PK-PD bridging informs and derisks clinical development
  - It isn't the definitive answer that can be used to write treatment guidelines...it is a step on the path
- Now a critical part of the regulatory framework
- Is a fantastic way to learn about drugs and diseases!
Therapeutic Drug Level Monitoring (TDM)

Goal:
To Find an Individualized Dosing Regimen (Personalized Medicine)

- Define Target Concentration Range
- Determine Initial Dosing Regimen Based on Population Average
- Monitor Drug Concentration
- Re-adjust Dosing Regimen
- Repeat Monitoring

Aminoglycosides

- Gentamicin
- Tobramycin
- Amikacin

Concentration dependent killing
Bactericidal
Low resistance development
Low cost
**Distribution**

- Extracellular Fluid Space
- 25% Fluid in Body
- <10% Protein Bound

**Body Weight**

Gentamicin

Group I (average weight 55 kg)
Vd = 13 L or 0.24 L/kg

Group II (average weight 104 kg)
Vd = 19 L or 0.19 L/kg

Uptake into excess body mass is about 40% of uptake into lean body mass

Schwartz et al., 1976

**Dosing Weight**

Aminoglycosides

\[
ABW = IBW + 0.4 \times (TBW - IBW)
\]

Use TBW if TBW is less than 120% of IBW
Use ABW if TBW is more than 120% of IBW

IBW  Ideal Body Weight
TBW  Total Body Weight
ABW  Adjusted Body Weight
Gentamicin

Volume of Distribution

![Gentamicin Distribution Volume](image)

- Number of Patients
- Normal Distribution Function
- Mean ± 2.5 SD
- Mean ± 1.96 ± 2 SD

Gentamicin

Triphasic Disposition

- α-phase, \( t_{1/2} = 10 \text{ min} \)
- β-phase, \( t_{1/2} = 1-2 \text{ h} \)
- γ-phase, \( t_{1/2} = 100-150 \text{ h} \)

Gentamicin

Half-Life

![Gentamicin Half-Life](image)
Derendorf - Drug level monitoring and dosing recommendations - facts and myths

### Peak Concentrations

<table>
<thead>
<tr>
<th>Peak</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 ug/ml</td>
<td>53%</td>
</tr>
<tr>
<td>&gt; 4 ug/ml</td>
<td>67%</td>
</tr>
<tr>
<td>&gt; 8 ug/ml</td>
<td>80%</td>
</tr>
</tbody>
</table>

### Toxicity

- **Nephrotoxicity**
  - **Incidence**
    - 6-25%
    - Increase in Serum Creatinine >0.5
  - **Mechanism**
    - Active Transport into Proximal Tubule
    - Cell Death
    - Decrease Creatinine Clearance

### Troughs < 2 ug/ml

- **86 Hospitalized Patients**
  - **65 patients troughs < 2 ug/ml**
    - No rises in Serum Creatinine
  - **21 patient troughs > 2 ug/ml**
    - 8 had rise in Serum Creatinine
    - 13 did not have a rise in Serum Creatinine
Ototoxicity

- Incidence (2 - 43%)
- Mechanism
  - Active transport into inner ear
  - Cell death
  - Passive diffusion out of inner ear

Estimation of Pharmacokinetic Parameters based on Creatinine Clearance

**Method I**

\[ CL_{AG} = CL_{Cr} \]

**Method II (Dettli)**

\[ k_{AG} = 0.00293 \cdot CL_{Cr} \text{[ml/min]} + 0.014 \text{[h}^{-1}] \]

![Graph showing drug concentration over time](image)
Volume of Distribution

Use true peaks and troughs

\[ V_d = \frac{D}{k \cdot T} \cdot \frac{\left(1 - e^{-k \cdot T}\right)}{\left(C_{\text{max}} - C_{\text{min}} \cdot e^{-k \cdot T}\right)} \]

Once-a-day Aminoglycosides

• Rationale
  – Post Antibiotic Effect
  – Toxicity
  – Cost Effective
  – Adaptive Resistance

Once-a-day Aminoglycosides

• Dosing Method
  – Start with 7 mg/kg
  – Obtain a 10-12 hour random sample
  – Use nomogram to adjust interval
Once-daily tobramycin in cystic fibrosis better for clinical outcome than thrice-daily tobramycin but more resistance development?

Resistance Development

Clinical Efficacy

Vancomycin
Vancomycin Pharmacokinetics

Poor absorption from GI tract (oral only used for *C. difficile* colitis)

\[ \text{Vd} = 0.178 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 \text{ [L]} \] (or 0.7 L/kg)

Good tissue penetration (except bile, eye, noninflamed meninges)

80-90% eliminated by kidneys

\[ t_{1/2} \]

| Adults | 6-12 hours |
| Infants/Children | 2-4 hours |
| Newborn | 6-10 hours |

Vancomycin PK Parameters in Obese and Non-Obese Patients

Vd = 0.178 · age + 0.22 · TBW + 15 [L]

\[ Vd = 0.178 \cdot \text{age} + 0.22 \cdot \text{TBW} + 15 \text{ [L]} \]

Vancomycin TDM

- Initial dose based on actual body weight, even for obese patients
- Subsequent adjustments based on serum levels to reach target concentrations
- Continuous infusion regimens are unlikely to substantially improve patient outcome, compared with intermittent dosing
- Trough levels are most practical and accurate method for monitoring vancomycin effectiveness
- Obtain trough levels at steady state just before 4th dose

Vancomycin TDM

Target Levels

- Trough levels of 10-15 (15-20) µg/ml
- Loading dose of 25-30 mg/kg may be used to rapidly attain the target levels in critically ill patients
- Multiple high serum creatinine after several days of vancomycin therapy indicates vancomycin induced nephrotoxicity
- Monitoring peak levels is not necessary
- Maintaining trough levels at 10-15 (15-20) µg/ml is important to reduce incidence of nephrotoxicity

Typical Adult Vancomycin Dosing

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Interval</th>
<th>Adult dose is 15-20 mg/kg TBW over 60 min Q12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 mL/min (age &gt; 60)</td>
<td>Q12H</td>
<td>based on Cp</td>
</tr>
<tr>
<td>40-60 mL/min</td>
<td>Q24H</td>
<td></td>
</tr>
<tr>
<td>&lt; 40 mL/min</td>
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</tbody>
</table>

If TBW > 100 kg, consider using adjusted body weight
**Vancomycin Target Parameters**

- PK/PD index AUC/MIC ≥ 400
- Trough levels 10-15 mg/L
- Greater nephrotoxicity risk at troughs >15 mg/L
- In severe infections trough levels 15-20 mg/L

**PK-PD Parameter Best Describing Vancomycin Efficacy**

Based on study results, an

**AUC/MIC ratio of ≥400 µg*h/mL**

has been advocated as a target to achieve clinical effectiveness with vancomycin.

Animal studies and limited human data appear to demonstrate that vancomycin is not concentration dependent, but that the AUC/MIC is a predictive pharmacokinetic parameter for vancomycin.

AUC is the total AUC over 24h at steady state.

**Vancomycin – Lack of Concentration Dependency**

2, 4, 8, 16 and 64x MIC of vancomycin (S. aureus & S. epidermidis)
Vancomycin
Protein Binding

Panel A: Free and total vancomycin concentration (% of free vancomycin in individual samples) ranked by increasing value with mean (solid line) and median (dotted line).

Panel B: correlation between free and total vancomycin concentrations for each individual sample with 95% confidence interval (dotted lines)

Berthoin K et al, Int. J. Antimicrob. Ag. 2009; 34: 555-560

24-Hr AUC/MIC Values and Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Pneumonia N=59</th>
<th>Bacteremia, Endocarditis N=230</th>
<th>Bacteremia, Endocarditis N=20</th>
<th>Septic Shock N=65</th>
<th>Bacteremia N=182</th>
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<td>Single Center</td>
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<tr>
<td>≥350 Failure=37%</td>
<td>≥350 Failure=49%</td>
<td>≥231 Failure=19%</td>
<td>≥2451 Failure=33%</td>
<td>≥373 Failure=16%</td>
<td></td>
</tr>
<tr>
<td>&lt;350 Failure=68%</td>
<td>&lt;421 Failure=81%</td>
<td>&lt;211 Failure=63%</td>
<td>&lt;451 Failure=82%</td>
<td>≥373 Failure=28%</td>
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<tr>
<td>P-value 0.054</td>
<td>P-value 0.008</td>
<td>P-value 0.002</td>
<td>P-value 0.003</td>
<td>P-value 0.045</td>
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</tbody>
</table>

PK/PD Goal = 24-Hr AUC/MIC ≥ 400


AUC

Eradication

Persistence

Persistence

Eradication

AUC/MIC

Derendorf - Drug level monitoring and dosing recommendations - facts and myths

**AUC/MIC**

**Median Eradication**
- 10 days vs. >30 days
- Odds Ratio = 7.19

**AUC/MIC**

**Survival**
- no difference AUC/MIC < 400 and AUC/MIC ≥ 400

**CART**
- AUC/MIC > 373 reduced mortality

**Vancomycin Trough Concentrations**
- no difference survivors/nonsurvivors
- no AUC difference
What does an AUC/MIC of 400 mean?

The average plasma concentration over 24h is 16.6 fold the MIC.

24-HR AUC/MIC for Stasis and 1 Log Kill with Vancomycin at Inocula of 10^6 and 10^7 against Strains of MRSA and S. pneumoniae in Opposite Thighs of Neutropenic Mice

<table>
<thead>
<tr>
<th>Inocula</th>
<th>S. aureus</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ± SE (Free)</td>
<td>24-HR AUC/MIC</td>
</tr>
<tr>
<td>Stasis</td>
<td>1 Log Kill</td>
<td>Stasis</td>
</tr>
<tr>
<td>Low 10^6</td>
<td>33 ± 5 (24.5)</td>
<td>85 ± 14 (62.6)</td>
</tr>
<tr>
<td>High 10^7</td>
<td>212 ± 31 (157)</td>
<td>399 ± 60 (295)</td>
</tr>
</tbody>
</table>


Vancomycin Trough Levels

Nephrotoxicity when trough > 15 mg/L

Vancomycin and Nephrotoxicity

- Systemic review of 15 studies evaluating vancomycin troughs of 15-20 mg/L versus lower values
- Higher troughs associated with higher odds ratio (2.67; CI 1.95 to 3.65) for nephrotoxicity. Risk persisted after adjustment for other causes of nephrotoxicity
- Longer duration of therapy also increased rate of nephrotoxicity
- Most nephrotoxicity was reversible and few patients (3%) required dialysis

Vancomycin Trough Levels

- VISA (MIC≥4 mg/L) strains have appeared
- Inducible hVISA (strains within susceptible range of 0.5-2 mg/L)
  - associated with persistent MRSA bacteremia
- Direct correlation between low trough levels and emergence of hVISA and VISA
- Trough <10 mg/L may predict therapeutic failure and emergence of hVISA and VISA
  - 10-15 mg/L: severe infections 15-20 mg/L
Percent Target Attainment

The corridor is getting narrow

Probability of Achieving AUC/MIC Ratio ≥ 400
Voriconazole

Voriconazole-PKPD Index

Fungicidal or fungistatic activity of voriconazole against *Aspergillus fumigatus* shown by time kill studies.

Voriconazole Pharmacokinetics

- Oral bioavailability (%): >90
- Protein (plasma binding (%)): 18
- Volume of distribution at t=0 (L/kg): 4.6
- Clearance (L/h): 0.2–0.5
- Peak plasma concentration (μg/mL): 6 mg/kg q12h on day 1, maintenance dose 2 mg/kg q12h
- Cmax: 1–5 μg/mL on day 1; maintenance dose 1–2 μg/mL
- AUC: 0–24h / 0–5h (μg·h/mL): 6–13
- Elimination half-life (h): 6
- Time to reach peak plasma concentration (h): <2
- Major route of excretion: hepatic and renal degradation
Voriconazole-Therapeutic Drug Monitoring (TDM)

- Nonlinear and saturable PK
- Numerous drug drug interactions
- Liver disease, Age, Genetic polymorphism of CYP2C19

Voriconazole
Population Average Parameters

Vmax 1.82 mg/h/kg^{0.75}
Km 1.54 mg/L
Vc 1.2 L/kg
F 0.85
k12 0.4 h^{-1}
k21 0.15 h^{-1}

Voriconazole Expected Plasma Concentrations

- 8mg/kg IV q12h
- 4mg/kg IV q12h
Vmax
1.82 mg/h/kg^{0.75}

Vmax/70 kg
44 mg/h
= 528 mg/12h
= 7.5 mg/kg q12h

8 mg/kg exceeds Vmax
A Prospective, Observational Study of Voriconazole Therapeutic Drug Monitoring Among Lung Transplant Recipients

Incidence of treatment failure and visual or auditory hallucinations in patients below and above voriconazole concentration limits identified from ROC analysis

Boxplot of relationship between voriconazole daily dose and voriconazole trough concentration


The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections

Initial or final voriconazole trough level. A, The solid circle or square denotes a severe adverse event, the gray circle or square denotes a non-severe adverse event, and x indicates drug discontinuation due to an adverse event. A dotted line represents the mean value. B, A solid circle or square denotes a complete response, an empty circle or square denotes a partial or mixed response, and x indicates treatment failure. A dotted line represents the mean value


The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections

Time to voriconazole-related adverse events (AEs) and time to drug discontinuation due to AEs

**Dried Blood Spot (DBS) Analysis**

Viable approach for quantitative drug measurements

Diagramatic representation of DBS analysis

No. of publications/year for DBS analysis

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**DBS Analysis-Advantages**

- Sampling by patient himself
- Reductions in:
  - Sample volumes required
  - No. of animals/patients in PK studies
  - Cost of shipping/storage of samples
- In essence, it is the whole blood sample
- Total conc. is proportional to unbound fraction when hematocrit and blood cell partitioning are constant.

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**Dried Blood Spot Analysis Suitable for Therapeutic Drug Monitoring of Voriconazole, Fluconazole, and Posaconazole**

Clinical validation of DBS analysis between drug concentrations in DBSs and plasma

Concentrations of Voriconazole in patient plasma and DBS