Principles and Practice: 
Pk-Pd of Antimicrobial agents

Dr. Vikas Manchanda, MD, MBA
Associate Professor
Department of Microbiology
Maulana Azad Medical College
micromamc@gmail.com
Case

- A 4 year old boy presented with
  - Fever - 7 days
  - Difficulty in breathing - two days
- O/E –
  - Pulse rate - 100bpm, RR of 55/min. No cyanosis.
  - Crepts in LMZ and LLZ
  - Percussion dullness on left side
- Specimens collected
  - Blood - Culture, counts
  - Pleural tap was done - 100ml of thick pus like fluid withdrawn
- Child’s symptoms improved
- Patients was started with inj cloxacillin
- TLC 18000/mm$^3$ with 80% PMNs
- Direct gram’s stain - field full of pus cells & culture grew *S. aureus*
- After 12hrs blood culture bottle beeped and direct gram stain revealed gram-positive cocci in small pairs
  Culture grew MRSA
• What should be choice of antimicrobial agent?

• What is the frequency and duration of antimicrobial therapy?

• What antimicrobial can act as PO Switch?
**Organism** = Staphylococcus aureus ss. aureus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>MIC (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Resistant</td>
<td>4</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Susceptible</td>
<td>0.5</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Resistant</td>
<td>5</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Susceptible</td>
<td>2</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Susceptible</td>
<td>0.25</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>Resistant</td>
<td>4</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>Resistant</td>
<td>320</td>
</tr>
</tbody>
</table>

**Beta-lactamase** = Positive

**Comment** = MRSA isolated. Resistant to all Beta-lactams and BL/BLI combinations (hVISA)
• Should the antibiotic continues?

• What antimicrobial can act as PO Switch?

• What is the frequency and duration of antimicrobial therapy?
• TDM for Vancomycin helps optimizing therapy
• Trough, rather than peak, levels should be monitored
  – Checked just before the fourth dose
  – Frequent monitoring in patients with fluctuating renal function
  – Target >10 mg/L to prevent the development of resistance
  – Recommended trough levels of 15 to 20 mg/L are recommended for MIC of 1 mg/L or higher
    • endocarditis, osteomyelitis, meningitis, and HCA pneumonia
  – For prolonged courses, at least weekly vancomycin levels
Dose titration

Dose \rightarrow \text{Black box} \rightarrow \text{Response}

\text{PK/PD}

\text{PK} \rightarrow \text{Body} \rightarrow \text{PD} \rightarrow \text{pathogen} \rightarrow \text{Response}

Dose \text{ scaled by MIC} \rightarrow \text{Body} \rightarrow \text{pathogen} \rightarrow \text{Response}
Key Terms

- **MIC**: for antimicrobial agents is the concentration at which the drug inhibits growth of the organism *in vitro*.

- **PK**: Time course of drug absorption, distribution, metabolism, and excretion
  - “what the body does to the drug”

- **PD**: Relationship between drug concentration and effect/toxicity
  - “what the drug does to the body/microbe”
Drug Absorption Curve

- Peak serum concentration of a drug following administration of a dose ($C_{max}$)
- Minimum serum concentration of drugs ($C_{min}$)
- Peak serum concentration of a drug following administration of a dose ($C_{max}$)
- Time to peak serum concentration ($T_{max}$)
- Area under serum concentration–time curve (AUC)
- Half-life ($T_{1/2}$) – time required for serum concentration reduced by 50%
- MIC
- Amount of time serum concentration above the minimum inhibitory concentration ($T > MIC$)
- Minimum serum concentration of drugs ($C_{min}$)
- Time to peak serum concentration ($T_{max}$)
<table>
<thead>
<tr>
<th>Time Dependent (T&gt;MIC)</th>
<th>Concentration Dependent (Cmax:MIC)</th>
<th>Both (AUC/MIC ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Beta Lactams</td>
<td>- Aminoglycosides</td>
<td>- Fluoroquinolones</td>
</tr>
<tr>
<td>- Carbapenems</td>
<td>- Metronidazole</td>
<td>- Aminoglycosides</td>
</tr>
<tr>
<td>- Linezolid</td>
<td>- Fluoroquinolones</td>
<td>- Azithromycin</td>
</tr>
<tr>
<td>- Erythromycin</td>
<td>- Daptomycin</td>
<td>- Tetracyclines</td>
</tr>
<tr>
<td>- Clarithromycin</td>
<td></td>
<td>- Vancomycin</td>
</tr>
<tr>
<td>- Clindamycin</td>
<td></td>
<td>- Tigecycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Linezolid</td>
</tr>
</tbody>
</table>
Concentration dependent antimicrobials

• If the concentration is increased, the rate and extent of killing of bacteria is also increased

• Observed in aminoglycosides and fluoroquinolones

• Cmax/MIC ratio and AUC/MIC ratio
**The MIC** is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.

\[ \text{C}_{\text{MAX}} \] (maximum concentration) is the highest concentration of drug in the blood that is measured after a dose.

AUC is an overall amount of drug in the bloodstream after a dose.

The **MIC** is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.
Post Antibiotic Effect

- PAE – Agents continue to exhibit bactericidal effects even after clearance of the agent from the infected site
  - Observed with inhibitors of nucleic acid and protein synthesis
    - Aminoglycosides
    - Quinolones
    - With betalactams against *Staphylococcus aureus*
PAE

• Increasing drug concentrations with less frequently dosing – OD - has resulted in greater cidal activity as opposed to giving the same total daily dose given several doses

• These agents exhibit a prolonged PAE and have been seen in agents which inhibit protein synthesis or nucleic acid synthesis
Time-dependent

• Kills bacteria at the same rate and to the same extent after reaching a threshold concentration.

• Kills bacteria when concentration > MIC, but once the concentration > 4 times the MIC at site, the additional killing is only modest.

• The extent of bacterial killing is dependent on time of exposure because these agents have very short or no PAE especially for GNR.
Goal of therapy in time dependent kinetics

- Maintain serum concentrations above the MIC for as long as possible during the dosing intervals

- Included in this group are beta-lactams, clindamycin, linezolid and vancomycin
Time dependent kinetics

- There are several ways by which you can increase the T>MIC. These include:
  - Increasing the dose
  - Increasing the dosing frequency
  - Improving the pharmacokinetic profile (such as extended-release formulations)
  - Increasing the duration of infusion or by giving parenteral drugs by continuous infusion
  - Use another drug (e.g. probenecid) that interferes with elimination.

- Most drugs in this group with short half lives may be given every 4-6 hrs, or as continuous infusion depending on the stability of the drug
Classification of antibiotics based on pharmacokinetic/pharmacodynamic parameters of efficacy and bacterial eradication.

<table>
<thead>
<tr>
<th>Pattern of Activity</th>
<th>Antibiotics</th>
<th>Goal of Therapy</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Aminoglycosides</td>
<td>Maximize concentrations</td>
<td>24h-AUC/MIC ratio, Cmax/MIC ratio</td>
</tr>
<tr>
<td>Concentration-dependent killing and prolonged persistent effects</td>
<td>Daptomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II-A</td>
<td>Carbapenems</td>
<td>Maximize duration of exposure</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td>Time-dependent killing and Minimal persistent effects</td>
<td>Cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penicillins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II-B</td>
<td>Azithromycin</td>
<td>Maximize amount of drug</td>
<td>24h-AUC/MIC ratio</td>
</tr>
<tr>
<td>Time-dependent killing and Moderate to prolonged persistent effects</td>
<td>Clindamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxazolidinones</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoglycosides

- Have concentration-dependent bacterial killing
- Have a prolonged PAE
- Single daily dose of aminoglycosides achieve higher peak serum concentrations and decrease the risk for nephrotoxicity and ototoxicity
- Tobramycin the most active agent against *P. aeruginosa* and *A. baumannii*, with MICs that were 2- to 4-fold lower than those for gentamicin
  - Tobramycin preferred against non-fermenters
- Against Enterobacteriaceae, amikacin usually presents lower resistance rates than gentamicin and tobramycin
Once-daily vs. Conventional Three-times Daily Aminoglycoside Regimens

Concentration (mg/L)

Once-daily regimen
Conventional (three-times daily regimen)

Cmax:MIC model
For optimal response,
Peak concentration: MIC ratio should be between 8-12.1

Time (hours)
Aminoglycosides—Relationship Between $C_{\text{max}}$ : MIC Ratio and Clinical Response

Pharmacodynamics goals for aminoglycosides

- Dose of aminoglycosides to achieve a $C_{\text{max}}$/MIC ratio >10
Beta-Lactams: Optimising Exposure

• The optimum level of exposure varies within the beta-lactam class

• Required %T>MIC for efficacy:
  – ~ 50%–70% for cephalosporins
  – ~ 50% for penicillins
  – ~ 40% for carbapenems

Pharmacodynamics goals for Beta-lactam agents

- $T > MIC$ as a percent of interval with beta-lactams

<table>
<thead>
<tr>
<th>Class</th>
<th>Organism</th>
<th>Stasis (T&gt;MIC)</th>
<th>Maximum killing (T&gt;MIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>Gram neg bacilli, pneumococcus</td>
<td>40-50</td>
<td>70-80</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Gram neg bacilli, pneumococcus</td>
<td>30-40</td>
<td>60-70</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Gram neg bacilli, Staphylococcus</td>
<td>20-30</td>
<td>40-50</td>
</tr>
<tr>
<td></td>
<td>pneumococcus</td>
<td>10-20</td>
<td>25-40</td>
</tr>
</tbody>
</table>
# Beta-Lactam Agents

**Time required above MIC**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Penicillin</th>
<th>Carbapenem</th>
<th>Cephalosporin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram +</td>
<td>30 to 40%</td>
<td>20 to 30%</td>
<td>40 to 50%</td>
</tr>
<tr>
<td>Gram -</td>
<td>50 to 60%</td>
<td>40 to 50%</td>
<td>60 to 70%</td>
</tr>
</tbody>
</table>

**PAE**

<table>
<thead>
<tr>
<th>B-lactam Class</th>
<th>Staphylococci</th>
<th>Streptococci</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Carbapenems

- Used in CR GNB esp KPC producing Enterobacteriaceae

- CR Enterobacteriaceae (KPC) isolates present carbapenem MICs near to or even at the current susceptibility breakpoints, that is, 1–4 mg/L; this occurs especially for meropenem and doripenem

- Higher doses and optimal modes of administration, either by extended or continuous infusion of the drugs
  - An acceptable probability of attaining the PK/PD target for pathogens with carbapenem MICs between 1 and 8 mg/l, even in critically ill patients
Carbapenems
Pk/Pd

• Carbapenem MICs in CR non-fermentative organisms often high (>32mg/l)
  – More potent carbapenemases involved or other resistance mechanisms are additionally present

• Optimized Dosing
  – Bactericidal activity T>MIC exceeds 40%–50%
  – Bacteriostatic at T>MIC of 20%–30%

• Increase T>MIC by use of “prolonged” infusions

• Limitation: reconstituted carbapenems have limited stability at room temperature

T>MIC = percentage of dosing interval that drug conc
Extended infusion strategies for beta-lactam agents

• **Time dependent killing activity**
  – positive correlation between their efficacy and amount of time drug conc exceeds MIC value during dosing interval

  – Lengthening of carbapenem infusion from 30 min to 3hrs useful in *P. aeruginosa* & *Acinetobacter* species with intermediate resistance

  • *Not beneficial in Enterobacteriaceae where unusually high MICs in resistant strains*
Polymyxins (Colistin)

- Most common class of Abx used against CR GNB

- While polymyxin B is administered as its active form (polymyxin B sulfate), colistin is administered as an inactive pro-drug, colistimethate, which leads to different PK behaviours

- Resistance to colistin emerging

- Outbreak of colistin resistant strains reported

- Monotherapy is associated with poor outcomes

- Inhalational therapy – Intermittent aerosolization esp. in *P. aeruginosa* pneumonia useful

Polymyxins (Colistin) TDM

• Baseline assessment of renal function and regular monitoring throughout therapy

• Serum colistin concentration monitoring is required in all patients with renal impairment and in patients with severe infection to establish if a therapeutic level has been achieved
Polymyxins (Colistin)

TDM

• Patients with **normal renal function** should have
  – Pre-dose “trough”
  – 1 hour post infusion “peak” concentrations checked around the **fourth dose**
  – Repeat **weekly** for the duration of therapy

• Patients with **impaired renal function** should have
  – Peak and trough levels checked around the **second dose**
  – Twice **weekly** for the duration of treatment

• **Pre-dose “trough” level** (taken immediately before dose is given) : 2-6mg/L

• **“Peak” level** (taken 1 hour after completion of IV infusion) : 10-15mg/L
Where do bugs Hide?

Cytosol

L. monocytogenes
Shigella flexneri
Rickettsia spp

ER

Legionella pneumophilia
Mycobacterium spp

Endosomes

Phagosomes

Brucella spp
Salmonella spp
Francisella tularensis

Inclusions

Chlamydia spp

Early Endosomes

Lysosomes

Legionella pneumophilia
Coxiella bruneti
Staphylococcus aureus

Early Endosomes

Mycobacterium spp

Cytosol

L. monocytogenes
Shigella flexneri
Rickettsia spp

Nucleus
Use of Pharmacokinetics in Treatment

**Aminoglycosides**

**Good**
- Circulating organisms

**Poor**
- Soft tissue
- Bone and joints
- Abscesses
- Lungs
- CSF

**Beta lactams**

**Good-variable (Dependant on individual antibiotic)**
- Soft tissue
- Bone and joints
- Lungs
- CSF

**Poor**
- Abscesses

**Examples of good Tissue Penetrators**
- Tetracyclines
- Macrolides
- Quinolones
- Clindamycin
# Renal Function

Estimated Creatinine clearance (Cockcroft-Gault formula)

\[
140 - \text{Age} \times \text{Mass (Kg)} \times \text{Constant}
\]

Serum Creatinine in $\mu$mol/L

Constant 1.04 for Women, 1.23 for Men

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR(ml/min/1.73m$^2$)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>90+</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>60-89</td>
<td>Mild reduction</td>
</tr>
<tr>
<td>IIIa</td>
<td>45-59</td>
<td>Moderate reduction</td>
</tr>
<tr>
<td>IIIb</td>
<td>30-44</td>
<td>Moderate reduction</td>
</tr>
<tr>
<td>IV</td>
<td>15-29</td>
<td>Severe reduction</td>
</tr>
<tr>
<td>V</td>
<td>&lt;15</td>
<td>Very severe (End-stage)</td>
</tr>
</tbody>
</table>
Effect of Creatinine Clearance on the Half Life of an Antibiotic with a Normal Half Life of 1 Hour
Antibiotic Renal Handling

Major Renal Excretion i.e. ≥ 50%

- Dose adjustment required
  - Aminoglycosides
  - Polymyxin B, Colistin
  - Vancomycin
  - Amphotericin

- Dose adjustment usually not required
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Tetracyclines

Excretion Less than 15% in urine

- Generally no dosage adjustment required
  - Macrolides (erythromycin)
  - Clindamycin

- Dose adjustment required only at moderate to severe renal impairment

- Exception
  - Chloramphenicol
Major Renal Excretion i.e. ≥ 50%
Dose adjustment required

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Creatinine Clearance (CrCl)</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (Gentamicin 5mg/Kg trough levels after 1\textsuperscript{st} dose)</td>
<td>Reduced</td>
<td>↑ dose interval</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>↑ dose interval and ↓ dose</td>
</tr>
<tr>
<td></td>
<td>&lt;20</td>
<td>Avoid</td>
</tr>
<tr>
<td>In all cases monitor levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (1g BD, trough levels before 4\textsuperscript{th} Dose)</td>
<td>Reduced</td>
<td>Monitor Trough levels</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Give only after trough levels known</td>
</tr>
<tr>
<td>In all cases monitor levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin</td>
<td>Reduced</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Gentamicin monitoring

Hartford Nomogram

7 mg/Kg OD

• Precise Times of collection required
• Collection 6-12 hrs after dose
Gentamicin monitoring

• Gentamicin 5-7mg/Kg OD
  – Collect around 24hrs post dose
  – Aiming for <1mg/L
    • Checking if patient is clearing gentamicin

• High levels
  • Blood collected too early
  • Patient not clearing Gentamicin
  • Blood collected from lumen used to infuse Gentamicin earlier on
Gentamicin monitoring

• Corrective measures
  – Re-check levels
  – Stop, look for alternative antibiotic
  – Omit dose and repeat levels after 12hrs

• Frequency
  – 2-3x/week after steady state
    • More frequently if renal function changing or concurrent nephrotoxic drugs
Vancomycin Monitoring

• Glycopeptide
  – ONLY active against Gram-positive bacteria including MRSA
  – IV only except for *Clostridium difficile* associated diarrhea when oral route is used (NOT absorbed from GI and not enough levels get into GI by IV route)
  – 1g BD IV standard dose

• Vancomycin trough levels
  – Collect serum specimen **30 minutes or less before next dose**
  – Frequency of collection:
    • First level at steady state (3rd - 5th dose)
    • Subsequent levels once or twice/week
    • More frequently if renal function changing or concurrent nephrotoxic drugs
# Hepatic Failure

## Antibiotic Handling Comments

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Handling</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines</td>
<td>Concentrated in the liver and excreted via bile and reabsorbed in the intestine. Eliminated in urine</td>
<td>Avoid or use with caution</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Significant metabolism by liver</td>
<td>Avoid</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Liver metabolism</td>
<td>May worsen liver dysfunction, avoid</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>85-95% conjugated in the liver</td>
<td>Avoid, increased probability of bone marrow toxicity</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Kidneys</td>
<td>Safe</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Kidneys</td>
<td>Safe</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Kidneys</td>
<td>Generally safe in liver failure, check individual drug for possible cholestatic jaundice</td>
</tr>
</tbody>
</table>

- Hepatic Failure
Determination of a dose for a quinolone

\[
Dose = \frac{Clearance \text{ (per hours)} \times \left( \frac{AUC}{MIC} \right)_{BP} \times MIC}{fu \times F\%}
\]

Breakpoint value e.g. 80

Bioavailability

Free fraction

PD
Key Concepts

• Pharmacokinetics (PK): the effect of the body on the drug

• Pharmacodynamics (PD): the effect of the drug on the body

• Understanding the PK and PD of antibiotics helps achieve maximum benefit with less side effects

• Drug concentrations change over time after administration
Key Concepts

• Each antibiotic has its own pharmacokinetic profile

• Each class of antimicrobials has a different pharmacodynamic profile based on different kill/inhibitory characteristics on bacteria

• Individualized dosing regimens using known PK/PD characteristics are important to optimize patient outcomes and minimize antimicrobial resistance

• PK profiles change over time in critically ill patients – warranting periodic reconsideration of dosing regimens
### Key Concepts

**Pharmacodynamic properties by antibiotic class**

<table>
<thead>
<tr>
<th></th>
<th>Concentration-dependent killing</th>
<th>Time-dependent killing</th>
<th>PAE Gram+</th>
<th>PAE Gram-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td>Beta-lactams</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
<td></td>
<td>Glycopeptides</td>
<td>Quinolones</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
<td>Macrolides</td>
<td>Carbapenems</td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
<td></td>
<td>Streptogramins</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chloramphenicol</td>
<td>Tetracycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rifampin</td>
<td>Glycylcyclines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oxazolidinones</td>
<td>Oxazolidinones</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketolides</td>
<td>Ketolides</td>
</tr>
</tbody>
</table>
Key Messages

• Beta lactams - frequent dosing - successful therapeutic outcome
  – Missing doses will lead to treatment failure

• Aminoglycosides - given as a large single dose (except in infective endocarditis) for a successful therapeutic outcome
  – Multiple small doses will lead to treatment failure and likely to lead to renal toxicity
Key Messages

• When selecting an antibiotic consider the following;
  – Where is the infection?
  – Which antibiotics will reach the site of infection
• Match the two and select your antibiotic
Key Messages

• Aminoglycosides are toxic drugs and require monitoring
  – Avoid use in renal failure but safe in liver failure
  – Avoid concomitant use with other renal toxic drugs
  – Check renal clearance, frequency according to renal function

• Vancomycin dosing should be 12hrly dose and adjusted according to levels at steady state
  – Frequency of monitoring depends on renal function

• Beta lactams are the safest antibiotics in renal and hepatic failure
  – Adjustments to dose may still be required in severe failure