Therapeutic Drug Monitoring (TDM)

The majority of systemic antibiotics do not need to have their levels monitored. However, for others it is essential:

- Aminoglycosides - Gentamicin, Tobramycin, Amikacin
- Glycopeptides – Vancomycin, Teicoplanin (doses in excess of 400mg)
- Chloramphenicol (children under 4 years old, the elderly and those with hepatic impairment)

Antibiotic assays should be taken at the correct times, usually:

- Peak - 1 hour after administration
- Trough - immediately before administration of the next dose

Serum samples should be sent at the time of the 3rd or 4th dose, approximately 2-4mls of blood = 1-2mls of serum, in red or yellow topped vacutainers. Subsequent levels should be checked twice weekly if renal function is stable or more frequently if renal function changes.

Hints and Tips

Best practice is to give the dose, take the peak as appropriate, **THEN** take the trough immediately before the next dose is given. For convenience the trough and peak levels are often taken around the same dose i.e. the trough is taken, the dose given, then the peak taken. Although adequate when the patient is on an established dose of antibiotic and their renal function is stable, this is not best practice.

It should be remembered that a trough level is related to the previous dose, (which may have been given many hours or days before) and shows how effectively the drug has been cleared by the patient's metabolism. If a patient's renal function has deteriorated since the last dose, clearance will be worse leading to an accumulation of the drug. Likewise an improving renal function would result in faster than expected clearance leading to under treatment.

Timing of Samples and Target Levels

Antibiotic	Timing of Sample	Target Level
Gentamicin BD or TDS	Peak (1hr after administration) Trough (immediately pre-dose)	Peak 5-10mg/L Trough <2mg/L
Gentamicin in Infective Endocarditis	Peak (1hr after administration) Trough (immediately pre-dose)	Peak 3-5mg/L Trough <1mg/L
Gentamicin OD	Trough (immediately pre-dose) **OR** 8 hours post-dose **OR** Follow locally agreed nomogram	Trough <1mg/L 8 hours 1.5-6mg/L **Note:** no peak level necessary
Tobramycin BD or TDS	Peak (1hr after administration) Trough (immediately pre-dose)	Peak 5-10mg/L Trough <2mg/L
Tobramycin OD	Trough (immediately pre-dose)	Trough <1mg/L
Amikacin BD or TDS	Peak (1hr after administration) Trough (immediately pre-dose)	Peak 20-30mg/L Trough <10mg/L
Amikacin OD	Trough (immediately pre-dose)	Trough <5mg/L

Timing of Samples and Target Levels Cont.

Antibiotic	Timing of Sample	Target Level
Vancomycin	Trough (immediately pre-dose)	Trough 10-20mg/L
Teicoplanin	Trough (immediately pre-dose) - Skin & soft tissue infection **OR** pneumonia - Osteomyelitis **OR** septic arthritis - Infective endocarditis	 Trough 15-60mg/L Trough 20-60mg/L Trough 30-60mg/L
Chloramphenicol QDS	Peak (2hr after administration) Trough (immediately pre-dose)	Peak 10-25mg/L Trough <15mg/L

Interpretation of TDM

Gentamicin, Tobramycin and Amikacin

- Peak level (post-dose) generally assesses whether a therapeutic level has been achieved, therefore levels not required for once daily dosing
  - If peak too low: dose inadequate therefore increase dose by approximately 10% (Graph A, Diagrammatic Interpretation of TDM)
  - If peak too high: dose too high therefore reduce dose by approximately 10% (Graph B, Diagrammatic Interpretation of TDM)
- Trough level (pre-dose) generally assesses whether toxic levels are accumulating
  - If trough too high: patient is unable to eliminate the antibiotic quickly enough therefore increase the time between doses, usually in 12 or 24 hour blocks of time (Graph C, Diagrammatic Interpretation of TDM)
  - In severe renal failure check levels daily and redose when target level achieved

Vancomycin

In order to interpret Vancomycin TDM, the dosing regimen must be followed accurately otherwise the result cannot be interpreted.

Dosing Regimen Step 1: Give a Loading Dose

This is based on Actual Body Weight

Actual Body Weight (kg)	Dose (mg)	Volume of 0.9% sodium chloride (ml)*	Duration of infusion
<40	750	250	90minutes
40-59	1000	250	2 hours
60-90	1500	500	3 hours
>90	2000	500	4 hours

*5% Glucose may be used in patients with sodium restriction

Dosing Regimen Step 2: Give the Maintenance Dose

The dose and frequency is based on the Cockcroft Gault equation (see below) for Calculated Creatinine Clearance (CrCl). Dose Intervals are either 12, 24 or 48 hours after the Loading Dose.

$$\text{CrCl (ml/min)} = \frac{\mathbf{F} \times (140 - \text{age}) \times \text{weight in kg}}{\text{Creatinine in micromol/L}}$$

F =
1.23 (Male)
1.04 (Female)

The CrCl **MUST** be used not the Creatinine value as the Creatinine value does not give an accurate reflection of renal function on its own.

CrCl (ml/min)	Dose (mg)	Volume of 0.9% sodium chloride (ml)*	Duration of infusion (hours)	Dose Interval (hours)
<20	500	250	1	48
20-29	500	250	1	24
30-39	750	250	1.5	24
40-54	500	250	1	12
55-74	750	250	1.5	12
75-89	1000	250	2	12
90-110	1250	250	2.5	12
>110	1500	500	3	12

*5% Glucose may be used in patients with sodium restriction

Dosing Regimen Step 3: Measure the Trough Level
A Trough level should be taken within 48 hours of starting treatment (e.g. just before the 4th Maintenance Dose if on 12 hourly Dose Interval or just before the 1st Maintenance Dose if on 48 hourly Dose Interval), **THEN** at least every 3 days if stable renal function, to reach the target 10-20mg/L (15-20mg/L in severe or deep-seated infections).

Note: In changing renal function take Trough levels more frequently (i.e. just before every dose).

Trough concentration (mg/L)		Action: Suggested dose change
Too Low	<10	• Reduce Dose Interval by 12 hours (i.e. 48 hourly to 36 hourly **OR** 24 hourly to 12 hourly) • If Dose Interval **ALREADY 12 HOURLY** then increase dose by 50%
Target 10-20mg/L	10-15	• If patient responding to treatment then continue • If seriously ill, reduce Dose Interval **OR** increase dose (as per <10mg/L above) to achieve Trough Level of 15-20mg/L
	15-20	• Maintain dosing regime
Too High	>20	• **STOP** Vancomycin until trough <20mg/L • **THEN** restart at increased Dose Intervals • **Note:** How long did the patient's levels take to reduce below 20mg/L? e.g. if patient took 72 hours to reduce to 20mg/L then give dose every 72 hours and recheck Trough Level • Seek specialist advice, Microbiologist or Infectious Diseases Physician

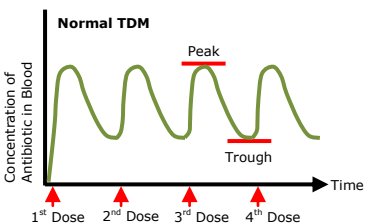
Teicoplanin

- Levels are not normally required unless patient is on high doses (>400mg)
  - If trough too low: patient is eliminating antibiotic too quickly therefore reduce time between doses in 12 or 24 hour blocks of time (Graph D and/or E, Diagrammatic Interpretation of TDM)
  - If trough too high: patient is unable to eliminate antibiotic quickly enough therefore increase the time between doses usually in 12 or 24 hour blocks of time (Graph C and/or F, Diagrammatic Interpretation of TDM)
  - In severe renal failure check levels daily and redose when target level achieved
- Occasionally it is necessary to reduce the dose in order to avoid too frequent dosing but this should be discussed with a Microbiologist beforehand

Chloramphenicol

- Peak level (post-dose) generally assesses whether a therapeutic level has been achieved
  - If peak too low: dose inadequate therefore increase dose by approximately 10% (Graph A, Diagrammatic Interpretation of TDM)
  - If peak too high: dose too high therefore reduce dose by approximately 10% (Graph B, Diagrammatic Interpretation of TDM)
- Trough level (pre-dose) generally assesses whether toxic levels are accumulating
  - If trough too high: patient is unable to eliminate antibiotic quickly enough therefore increase the time between doses usually to TDS then BD (Graph C, Diagrammatic Interpretation of TDM)

Diagrammatic Interpretation of TDM



Incorrect TDM Dosing:
A = Dose too low
B = Dose too high
C = Elimination too slow
D = Elimination too fast
E = Too infrequent dosing
F = Too frequent dosing