

Therapeutic drug monitoring

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For full information on treatment side effects, cautions and contraindications, see electronic British National Formulary (www.bnf.org).

For information on preparing intravenous medicines for administration, see Medusa Injectable Medicines Guide for the NHS (see Medicines Formulary home page).

Introduction

Therapeutic Drug Monitoring aims to individualise drug therapy and avoid both sub-therapeutic and toxic plasma drug concentrations. Several factors influence drug concentrations and a single sample will only reflect the concentration at the sampling time.

When a new drug is introduced, 'steady state' will not be approached until four elimination half-lives have elapsed. Sampling prior to this time may not be beneficial unless a problem is anticipated (e.g. non-compliance or toxicity). Results must be judged in light of clinical observations and other relevant investigations.

Advice and assistance on blood volumes, tubes to use etc. can be obtained from the laboratories performing the tests. Advice on drug dose calculations and interpretation of measured plasma drug concentrations can be obtained from the ward or the on-call Pharmacist.

- Where initial dosing is based on body weight, the monographs will state whether the patient's actual, ideal or adjusted (for obese patients) body weight should be used. If weight is less than the calculated ideal body weight then always use actual bodyweight to calculate dose.
- **Calculation of Ideal Body Weight (IBW)**
 IBW Females = [45.5kg + (2.3 x every inch over 5ft)] kg
 IBW Males = [50kg + (2.3 x every inch over 5ft)] kg
- **Calculation of Adjusted Body Weight (for Aminoglycoside dosing in Patients whose ABW is > 20% more than their IBW)**
 Adjusted body weight = ideal body weight + 0.4 (actual body weight – ideal body weight)
- **Cockcroft and Gault equation for estimating creatinine clearance**
 Creatinine clearance (mL/min) = $\frac{Y \times (140 - \text{age}) \times \text{weight}}{\text{Serum creatinine micromol/L}}$
 Where Y = 1.23 for males and 1.04 for females

 Cockcroft and Gault does not apply to all patients. Exclusion criteria include: unstable serum creatinine, pregnancy, malnutrition, amputation and dialysis

Pharmacokinetic information in the following monographs relates to healthy adults unless otherwise specified. Information on neonates and children can be provided on request from the Pharmacy Department.

Estimated glomerular filtration rate (eGFR)

Renal function is often reported using estimated Glomerular Filtration Rate (eGFR), reported in mL/minute/1.73m². This is not the same as creatinine clearance estimates, which is calculated in mL/minute. Since eGFR estimates have not yet been validated for drug dosing, dose adjustment in renal impairment should be based on estimates of creatinine clearance (e.g. calculated from the Cockcroft and Gault equation or from a 24-hour urine collection).

1. Carbamazepine

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting levels/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Oral, rectal. The recommended rectal dose is 25% higher than the oral dose e.g. 100mg PO = 125mg PR. Suppositories licensed for a maximum of 7 days at a maximum daily dose of 1g.</p> <p>Loading dose: Not recommended</p> <p>Maintenance dose: For epilepsy; initially 100mg to 200mg BD increased by 100 to 200mg every 2 weeks according to response. Usual maintenance dose: 800mg to 1200mg daily in divided doses (maximum 2g daily).</p>	<p>Elimination half-life:</p> <ul style="list-style-type: none"> • 30 to 35 hours after single dose • 15 to 20 hours after multiple doses. <p>Time to steady state: Approximately 2-4 weeks after start of therapy (as carbamazepine induces its own metabolism). 5 days after a dose change.</p> <p>Metabolism: 98% hepatic metabolism with active metabolites.</p> <p>Elimination: 72% is excreted in the urine and 28% in the faeces.</p> <p>Volume of distribution: 0.8 to 1.9L/kg</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Lavender top.</p> <p>Lab performing assay: Referred out from Wirral Clinical Biochemistry.</p> <p>Emergency service: No. Samples taken out of hours should be taken to the laboratory.</p> <p>Sampling time: Trough level immediately before next dose.</p> <p>Resampling time: Do not resample within 1 week of dose change unless suspecting poor compliance or toxicity.</p> <p>Therapeutic range: 4 to 10 mg/L.</p>	<p>Drug interactions: Concurrent use with erythromycin, cimetidine, diltiazem, verapamil, isoniazid increases plasma concentration.</p> <p>Concurrent use with phenytoin or phenobarbital (phenobarbitone) decreases plasma concentration.</p> <p><i>Please refer to manufacturer's Summary of Product Characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Hepatic disease can decrease carbamazepine metabolism, thereby increasing plasma concentration.</p>	<p>Mild: Drowsiness, ataxia, slurred speech, nystagmus, dystonic reactions, hallucinations, nausea, vomiting, hyponatraemia, hypokalaemia, combativeness, hypothermia, mydriasis and decreased gut motility.</p> <p>Severe: Coma, seizures, respiratory depression, dysrhythmias, decreased myocardial contractility, pulmonary oedema and hypotension.</p> <p>Omit doses if level is high.</p>	<p>Carbamazepine induces its own metabolism. Avoid restarting high doses if drug therapy has been omitted for > 1 week or in non-compliant patients due to the increased risk of toxicity.</p> <p>Carbamazepine is an enzyme inducer and will affect the metabolism of many other drugs.</p> <p>Routine monitoring of carbamazepine levels is not necessary. Checking carbamazepine levels may be useful for assessing compliance or checking for toxicity.</p>

2. Ciclosporin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Oral, intravenous infusion (over 2 to 6 hours). May be used as a continuous infusion in ulcerative colitis.</p> <p>The injection contains polyethoxylated castor oil that may lead to anaphylactic reactions if injected too rapidly. Generally, the recommended intravenous dose is one third of the oral dose.</p> <p>Due to differences in bioavailability, the prescriber should specify the brand of oral ciclosporin, e.g. Neoral®, Sandimmun®, Deximune®.</p> <p>Loading and maintenance doses: Different doses are used for different clinical indications. Please refer to the patient's transplant unit, manufacturer's Summary of Product Characteristics or Pharmacy Department for full details.</p>	<p>Elimination half-life: 6 to 21 hours (unchanged in ESRF)</p> <p>Time to steady state: Approximately 72 hours.</p> <p>Metabolism: Extensive metabolism in the liver.</p> <p>Elimination: Primarily biliary excretion.</p> <p>Volume of distribution: 3.9L/kg</p> <p>90% protein bound. Therefore increased risk of toxicity in hypoalbuminaemia.</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Lavender top.</p> <p>Lab performing assay: Referred out from Wirral Clinical Biochemistry.</p> <p>Emergency service: No. Samples taken out of hours should be taken to the laboratory.</p> <p>Sampling time: Trough level immediately before next dose; peak level not routinely monitored. Random level if on continuous infusion, see guidance.</p> <p>Therapeutic range: Depends on indication. Please refer to the patient's transplant unit or Pharmacy Department if for ulcerative colitis.</p>	<p>Drug interactions: Concurrent use with fluconazole, itraconazole, clarithromycin, erythromycin and verapamil increases plasma concentration.</p> <p>Concurrent use with hepatic enzyme inducers decreases plasma concentration.</p> <p>Numerous potential drug interactions. Always check when new drugs are initiated. <i>Please refer to manufacturer Summary of Product Characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Renal and hepatic disease can reduce the clearance of ciclosporin and predispose toxicity.</p> <p>High intake of grapefruit juice can reduce ciclosporin metabolism, thereby increasing the plasma concentration.</p>	<p>Oral: Headache, nausea, CNS depression, transient renal insufficiency, hypertension, dysesthesias, taste abnormalities, facial flushing, GI upset, tremor, fasciculations, peripheral oedema and abdominal swelling.</p> <p>Parenteral: Severe metabolic acidosis, seizures, renal failure, atrial fibrillation and cyanosis.</p> <p>Levels required when converting to intravenous therapy, suspected toxicity, interacting therapy, changing renal function.</p>	<p>Dermatology guidance:: Ciclosporin in dermatology - shared care guideline</p> <p>Rheumatology guidance: Ciclosporin in rheumatology - shared care guideline</p> <p>Ciclosporin or infliximab as salvage therapy for acute, severe ulcerative colitis</p> <p>For use in renal transplant patients: Please contact the renal pharmacist.</p> <p>Dosage and plasma concentrations are variable depending on the type of transplant and the date when the transplant took place.</p> <p>Routine monitoring of levels usually only needed in transplant patients.</p>

3. Digoxin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Tablets, oral solution, intravenous infusion. Dosage forms have different bioavailabilities; doses need adjusting accordingly:</p> <ul style="list-style-type: none"> • Intravenous bioavailability: 100% • Tablet bioavailability: 50-90% • Elixir bioavailability: 80% <p>Loading dose: Only needed in AF: 750micrograms to 1500micrograms in divided doses (6 hours apart; assess response before deciding whether 2nd part of dose is needed). Use the oral route when feasible. Intravenous loading only recommended if the patient is nil by mouth (NBM), as the response is no more rapid than following oral administration.</p> <p>Maintenance dose: 62.5 to 500 micrograms daily (higher doses may be divided) depending on indication and renal function.</p>	<p>Elimination half-life: 50 to 100 hours (normal renal function). Prolonged in renal failure.</p> <p>Time to steady state: 7 days with normal renal function.</p> <p>Metabolism: Hepatic metabolism to active metabolites.</p> <p>Elimination: Mainly excreted unchanged in the urine.</p> <p>Volume of distribution: 7 to 8L/kg.</p>	<p>Volume of blood: Fill to the line.</p> <p>Tube to use: Red top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry.</p> <p>Sampling time: Ideally trough sample taken immediately before next dose. Sample must be at least 6 hours after an oral dose and 4 to 6 hours after an intravenous dose.</p> <p>Resampling time: Sample within 24 hours of loading dose to confirm if target concentration achieved. Sample after 7 days to assess maintenance dose.</p> <p>Therapeutic range: 1 to 2 micrograms/L for AF. Consider re-loading if level very low.</p>	<p>Drug interactions: Concurrent use with amiodarone, verapamil, quinine, ciclosporin and possibly atorvastatin increase plasma concentration. Phosphate binders may reduce absorption by 25%. <i>Please refer to manufacturer Summary of Product Characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Renal impairment may predispose to toxicity. Electrolyte imbalances (hypokalaemia, hypomagnesaemia, hypercalcaemia), small body mass, female gender and heart disease can potentiate toxicity. Thyroid dysfunction may alter clinical response; hypothyroidism increases the patient's sensitivity to digoxin whereas hyperthyroidism confers resistance. Digoxin is not cleared by HD so avoid where possible in dialysis patients</p>	<p>It can be difficult to distinguish between some toxic effects and clinical deterioration. The plasma concentration alone doesn't indicate toxicity but the likelihood of toxicity increases progressively with concentrations > 1.5micrograms/L.</p> <p>Signs: Cardiac – almost any arrhythmia, heart block and heart failure. Neurological – headache, facial pain, fatigue, weakness, general malaise, dizziness, drowsiness, disorientation, mental confusion, bad dreams, delirium, psychoses and hallucinations. Gastrointestinal – anorexia, nausea, vomiting and abdominal pain. Visual – blurred and/or yellow vision.</p> <p>High levels – omit digoxin until level falls. Consider Digifab. Maintain adequate potassium levels.</p>	<p>Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected.</p> <p>Blood levels are required when:</p> <ul style="list-style-type: none"> • Poor compliance is suspected. • Response to treatment is poor. • There is deterioration in response to treatment. • Renal function is fluctuating. • Drugs that interact are co-prescribed. • Confirmation of clinical toxicity is needed. • It is unknown if cardiac glycosides have been taken in previous 2 weeks.

4. Lithium

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Oral solution and tablets.</p> <p>5ml Lithium citrate 250mg/5mL syrup (Priadel liquid) is equivalent to 204mg lithium carbonate (Priadel tablets).</p> <p>Loading dose: Not necessary.</p> <p>Maintenance dose: 400 to 1200mg/day</p>	<p>Elimination half-life: 18 to 36 hours.</p> <p>Time to steady state: 4 to 7 days.</p> <p>Elimination: Freely filtered at glomerulus with 80% reabsorbed</p> <p>Volume of distribution: 0.8L/kg</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Red top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry.</p> <p>Sampling time: 12 hours after previous dose. The time since the last dose should be stated.</p> <p>Resampling time: When commencing therapy, or after a dose change, concentrations should be checked after 4 to 5 days (never longer than 1 week), and thereafter every week until dosage has remained constant for 4 weeks. Check every 3 or 6 months thereafter.</p> <p>Therapeutic range: 0.4-1.0 mmol/L Aim for 0.8-1.0 mmol/L if treating acute mania. Aim for 0.4-0.8 mmol/L for maintenance. Note target may vary between patients, check individual lithium card.</p>	<p>Drug interactions: Common interactions include; NSAIDs, ACE inhibitors, diuretics all increase risk of toxicity (NB: loop diuretics are safer than thiazides).</p> <p>Antidepressants increase risk of serotonin syndrome. <i>Please refer to manufacturer Summary of Product characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Reduced renal function, presence of hypertension, diabetes, congestive heart failure, chronic renal failure, hyponatraemia, concurrent infection and older age can potentiate toxicity.</p>	<p>Toxic effects are often seen at levels > 1.5 mmol/L. Levels > 2mmol/L can be potentially life threatening and should be treated as a medical emergency.</p> <p>Management: Levels > 2mmol/L may require treatment with haemodialysis. Otherwise, treatment is supportive with attention to electrolyte balance, renal function and control of convulsions. See <i>BNF (emergency treatment of poisoning) for full details.</i></p> <p>Signs: Nausea & vomiting, diarrhoea, weight gain (these can occur within therapeutic range). Myoclonus (muscle jerks), confusion, convulsions, hand tremor, slurred speech, irritability, stupor, increased reflexes and renal failure.</p>	<p>Regular monitoring of plasma lithium concentrations is indicated (see resampling time). Especially if deterioration in renal function. Lithium dose may need to be omitted or reduced.</p> <p>Plasma concentrations should be checked if changing brand of lithium preparation. Close monitoring of perioperative fluid balance is important in patients taking lithium.</p> <p>Requirements of lithium monitoring are described the pharmacy SOP: Clinically checking an inpatient prescription for lithium</p>

5. Phenytoin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance								
<p>Dosage forms: Oral, slow intravenous injection (rate not exceeding 50mg/min). Give undiluted via syringe driver if possible, alternatively dilute with Sodium Chloride 0.9% but must use in-line filter due to precipitation risk. Intravenous and oral doses are equal bioavailability. 100mg phenytoin sodium (tablets/injection) is equivalent to 90mg phenytoin base (syrup).</p> <p>Loading dose: 20mg/kg according to actual body weight. Maximum dose of 1.8g.</p> <p>Maintenance dose: IV in status epilepticus: 100mg, by slow IV injection or infusion, every 6 to 8 hours.</p> <p>PO: 200-500mg daily at night adjusted according to clinical response and therapeutic drug monitoring. Start at 200mg daily in the elderly.</p>	<p>Elimination half-life: 7 to 42 hours (increases with concentration as elimination is concentration dependent).</p> <p>Time to steady state: 5 to 10 days.</p> <p>Metabolism & Elimination: Phenytoin is extensively metabolised in the liver.</p> <p>Volume of distribution: 0.6-0.7 L/kg</p> <p>Protein binding: 88 to 93% bound to plasma albumin. <i>To correct phenytoin levels for low albumin:</i></p> <p>1) CrCl > 20 mL/min: $\text{Corrected Concentration} = \frac{\text{Observed concentration}}{[(0.02 \times \text{albumin}) + 0.1]}$</p> <p>2) CrCl < 20 mL/min: $\text{Corrected Concentration} = \frac{\text{Observed concentration}}{[(0.01 \times \text{albumin}) + 0.1]}$</p> <p>In end-stage renal failure, protein binding can be affected by low albumin and uraemia. In patients with CrCl 10 to 25mL/minute, binding is unpredictably altered and plasma concentration can be difficult to interpret accurately. Contact pharmacy for further advice.</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Red top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry.</p> <p>Emergency service: Requests for analysis of samples taken outside normal hours must be arranged with the on-call Biochemist.</p> <p>Sampling time: IV in status epilepticus: 12 to 24 hours post-loading dose if concerns regarding efficacy/toxicity and then 3 to 5 days post-loading as a guide to whether the maintenance dose is suitable.</p> <p>Oral: Trough sample immediately before next dose. Time since the last dose should be stated.</p> <p>Resampling time: Do not resample within 2 weeks of change in dose unless question of compliance or toxicity.</p> <p>Therapeutic range: 8 to 15mg/L (Note: Some patients have a target of 10-20mg/L).</p>	<p>Drug interactions: Concurrent use with hepatic enzyme inducers decreases plasma concentration.</p> <p>Concurrent use with hepatic enzyme inhibitors increases plasma concentration.</p> <p><i>Please refer to manufacturer Summary of Product characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Chronic hepatic failure or renal impairment can potentiate toxicity. Acute hepatitis can decrease plasma phenytoin levels.</p> <p>Phenytoin undergoes dose-dependent elimination so increasing doses can cause disproportionately large increases in plasma concentrations. Increase maintenance dose carefully; use increments of 25mg to 50mg.</p> <p>Low levels may require a full or partial loading dose in patients at risk of seizures.</p>	<p>Mild toxicity - worsening co-ordination; horizontal nystagmus and unsteady gait.</p> <p>More serious intoxication - slurred speech, along with a gradually worsening mental status typified by lethargy, confusion, or coma, cardiac dysrhythmias and seizures may occur. Hyper-reflexia is occasionally seen.</p> <p>If levels are high and patient is symptomatic omit further doses until level falls. Refer to Toxbase if significantly elevated levels. Severe symptoms usually not seen unless levels over 30mg/L.</p>	<p>Regular monitoring of plasma-phenytoin concentration during maintenance treatment is not necessary unless problems are suspected.</p> <p>Blood levels are required:</p> <ul style="list-style-type: none"> To confirm adequate loading dose. During IV therapy in status epilepticus. Unexpected deterioration in seizure control. As an adjunct to the diagnosis of toxicity. When interacting drugs are added or withdrawn. In pregnancy. Poor compliance is suspected. <p>Dose adjustment:</p> <table border="1" data-bbox="1937 1157 2206 1340"> <thead> <tr> <th>Steady state concentration</th> <th>Maximum dose increase (per day)</th> </tr> </thead> <tbody> <tr> <td><6mg/L</td> <td>100mg</td> </tr> <tr> <td>6-10mg/L</td> <td>50mg</td> </tr> <tr> <td>10-14mg/L</td> <td>25mg</td> </tr> </tbody> </table>	Steady state concentration	Maximum dose increase (per day)	<6mg/L	100mg	6-10mg/L	50mg	10-14mg/L	25mg
Steady state concentration	Maximum dose increase (per day)												
<6mg/L	100mg												
6-10mg/L	50mg												
10-14mg/L	25mg												

6. Theophylline (aminophylline)

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Theophylline: oral Aminophylline: oral or intravenous. NB: prescribers should specify the brand for oral theophylline (non-equivalent bioavailability) e.g. Uniphyllin® or Slophyllin®.</p> <p>Loading dose: Intravenous aminophylline 5mg/kg (using the smaller of IBW or ABW) over 20 minutes. This loading only applies to patients who have not received theophylline or aminophylline in the last 24 hours (unless sub-therapeutic).</p> <p>Maintenance dose: Modified release theophylline 200mg to 500mg every 12 hours. Intravenous aminophylline 500 micrograms/kg/hr (using the smaller of IBW or ABW)</p>	<p>Elimination half-life: 8 to 24 hours.</p> <p>Time to steady state: 2-3 days.</p> <p>Metabolism & Elimination: 90% is metabolised in the liver to form inactive metabolites. 10% is excreted unchanged via the kidneys.</p> <p>Volume of distribution: 0.5L/kg.</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Red top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry.</p> <p>Emergency service: Yes.</p> <p>Sampling time: Oral modified release preparations: Trough sample should be taken immediately before the next dose. Time since the last dose should be stated. Intravenous: Check concentration 12 to 24 hours following start of maintenance infusion and then daily during maintenance treatment (this must be performed for ALL patients).</p> <p>Resampling time: New steady state concentrations will be reached approx. 48 hours after a change in dose.</p> <p>Therapeutic range: 10 to 20mg/L</p>	<p>Drug interactions: Metabolism of theophylline is affected by any process which alters activity of the liver's cytochrome oxidases CYP1A2, CYP2E1, and CYP3A4. Therefore, concurrent use with hepatic enzyme inducers decreases plasma concentrations and concurrent use with hepatic enzyme inhibitors increases plasma concentrations.</p> <p><i>Please refer to manufacturer Summary of Product Characteristics or Pharmacy Department for full details.</i></p> <p>Patient factors: Smoking can decrease plasma concentration. Congestive heart failure, pulmonary oedema, viral illness and liver disease can increase plasma concentration.</p>	<p>The frequency and severity of adverse effects increases at concentrations exceeding 15mg/L and toxicity is most commonly observed at concentrations greater than 20mg/L.</p> <p>Minor symptoms: Metabolic abnormalities (hypokalaemia, hyperglycaemia, metabolic acidosis, hypophosphatemia) coarse muscle tremor, vomiting, and abdominal pain.</p> <p>Severe/life-threatening: Tachycardia, seizures, hypotension, and arrhythmias. Death typically results from intractable ventricular arrhythmias.</p> <p>If levels high omit doses or stop infusion until levels fall.</p>	<p>For further guidance and dose adjustments according to levels see aminophylline guideline.</p>

7. Teicoplanin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Intravenous bolus, intravenous infusion (30 minutes if 800mg or under, 60 minutes if more than 800mg) or intramuscular injection.</p> <p>Loading dose and maintenance dose:</p> <p><u>Skin and soft tissue infections, pneumonia, complicated UTIs.</u> 6mg/kg every 12 hours for 3 doses then 24 hourly thereafter.</p> <p><u>Bone and joint infections and infective endocarditis.</u> 12mg/kg every 12 hours for 3 doses then 24 hourly thereafter.</p> <p>In all cases</p> <p>Maximum dose of 1.2g. Round up to nearest 200mg vial.</p>	<p>Elimination half-life: 150 hours (normal renal function); up to 230 hours in end stage renal failure.</p> <p>Metabolism & Elimination:</p> <p>> 97% excreted unchanged in urine.</p> <p>Volume of distribution: 0.94–1.4L/kg.</p>	<p>Volume of blood: Fill to line</p> <p>Tube to use: Ochre top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry.</p> <p>Emergency service: No.</p> <p>Sampling time: Initial trough level should be taken immediately before the 5th or 6th dose.</p> <p>Therapeutic range: Pre-dose trough should always be <60mg/L and then as below dependent on indication:</p> <ul style="list-style-type: none"> • Skin and soft tissue infections, pneumonia, complicated UTIs: >15mg/L • Bone and joint infections >20mg/L • Infective endocarditis >30mg/L <p>Resampling time: Check once a week if pre-dose levels within range and renal function stable.</p>	<p>Drug interactions: Teicoplanin should be used with care in conjunction with other drugs known to be nephrotoxic or ototoxic.</p> <p>Patient factors:</p> <p>Renal function Loading doses should not be adjusted for renal impairment but thereafter</p> <p>CrCl 30-80ml/min: administer the full dose every 2 days</p> <p>CrCl <30ml/min: administer the full dose every 3 days.</p> <p>Intravenous drug users may exhibit rapid clearance of teicoplanin. Doses may be amended based on trough levels to reflect this.</p>	<p>Renal failure, loss of hearing, vestibular disorders, tinnitus.</p> <p>There is some evidence to suggest that idiosyncratic thrombocytopenia is more likely at serum concentrations above 60mg/L.</p> <p>If levels are high, omit further doses until the level falls.</p>	<p>Plasma-teicoplanin concentrations can be used to optimise parenteral treatment in patients with, severe sepsis or burns, deep-seated staphylococcus infections (including bone and joint infection), proven or suspected MRSA bacteraemia, endocarditis, renal impairment, in elderly and in intravenous drug abusers.</p> <p>All patients discharged home on teicoplanin will have levels checked weekly.</p> <p>Pharmacy must be informed of all patients discharged home on iv teicoplanin.</p>

8. Gentamicin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage form: Slow intravenous bolus injection (over at least 3 minutes); doses over 4mg/kg or 400mg must be given by intravenous infusion; intramuscular injection.</p> <p>Starting dose: Normal renal function: 4mg/kg using the smaller of ABW or IBW; use adjusted body weight in obese patients (for advice on calculating IBW see above). Severe renal impairment or dialysis: 3mg/kg IBW. 1 to 2mg/kg in endocarditis.</p> <p>Maintenance dose: Contact the Pharmacy Department for individualised dosing regimes.</p>	<p>Time to steady state: 12 hours to 4 days (depending on renal function).</p> <p>Elimination half-life: 2 to 3 hours (normal renal function); up to 20 hours in end stage renal failure.</p> <p>Major route of elimination: 90% excreted unchanged in urine.</p> <p>Volume of distribution: 0.3L/kg.</p> <p>For dialysis patients confirm 1 hour post dose peak and then check trough level on HD and re-dose only if level less than 2mg/L.</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Ochre or green top.</p> <p>Lab performing assay: Wirral Clinical Biochemistry</p> <p>Emergency service: Yes, but analysis of samples taken outside normal hours must be arranged with the on-call Biochemist through the on-call Pharmacist.</p> <p>Sampling times: Two timed samples: 1 hour post dose and contact pharmacy for guidance about timing of second level. Liaise with pharmacy following results to calculate maintenance dose.</p> <p>Resampling time: Dependent on clinical status of the patient. As a guide pre- and post-dose levels are usually checked twice weekly.</p> <p>Therapeutic range: One-hour post-dose 'peak' 8 to 12mg/L, pre-dose 'trough' <2mg/L (ideally < 1mg/L).</p> <p>When used in combination with other antibacterials for endocarditis due to gram positive bacteria, one-hour post-dose 'peak' 3 to 5mg/L, pre-dose 'trough' <1mg/L. Trough levels are associated with toxicity, if the level is high, omit further dose until falls below 1mg/L.</p>	<p>Patient factors: Plasma concentration increased in renal impairment and decreased in ascites, cystic fibrosis and sepsis.</p> <p>Drug interactions: Gentamicin should be used with care in conjunction with other drugs known to be nephrotoxic or to have ototoxic potential.</p>	<p>Renal toxicity: monitor serum creatinine 18–24 hours after the first dose. If the patient is haemodynamically stable with stable renal function measure creatinine a minimum of three times a week. Deteriorating renal function whilst on gentamicin therapy may indicate gentamicin induced nephrotoxicity or nephrotoxicity from other causes such as hypovolaemia or sepsis. It may not be appropriate to continue with gentamicin therapy.</p> <p>Cochlear toxicity: fullness in ears, tinnitus or new hearing loss. Consider audiometric testing.</p> <p>Vestibular toxicity: dizziness, nausea and vomiting, oscillipsia (visual blurring with head movement), true vertigo and/or nystagmus.</p>	<p>Dosage is related to the severity of the infection, the age of the patient and the patient's renal function. Lower peak concentrations (5mg/L) may be acceptable in patients with urinary tract infections. All patients should be counselled re toxicity and given a gentamicin leaflet. Consent should be obtained (where possible) before treatment is commenced.</p>

9. Tacrolimus

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Oral, intravenous infusion (over 24 hours).MHRA alert advises prescribers to specify brand with oral preparations due to differences in bioavailability e.g. Prograf®, Adoport® (immediate release) or Advagraf® (MR).</p> <p>Loading and maintenance doses: Vary depending on clinical indication. Refer to SPC</p> <p>Frequency of monitoring: Twice weekly in early post-transplant period, after dose adjustments, or if potential interactions are occurring. Periodically thereafter. If giving IV, wait 24–48hours before checking level.</p> <p>Therapeutic range: Contact patient’s transplant centre. Target (whole blood) level depends on indication: -Renal transplant: 10 to 20microgram/L -Auto-immune disease: 5 to 15microgram/L -Liver and heart transplant: 10 to 20microgram/L (induction), 5 to 15microgram/L (maintenance) If IV treatment is required, target blood levels should be based on clinical judgment. As a guide, concentrations >25microgram/L warrant dose reduction to achieve a blood level of 15 to 25microgram/L.</p>	<p>Elimination half-life: 43 hours in healthy patients.11-15 hours in patients with hepatic/renal transplants (low protein and haematocrit levels, which cause higher levels of unbound drug, are thought to result in higher clearance rates in transplant patients)</p> <p>Oral bioavailability: 20–25%</p> <p>Major route of excretion: Liver</p> <p>Time to steady state: 72 hours.</p> <p>Protein binding: 98.8% bound to plasma proteins. Tacrolimus concentration results refer to whole blood concentrations (i.e. free drug and plasma protein bound drug).</p> <p>Volume of distribution: 1,300L</p>	<p>Volume of blood: Fill to line.</p> <p>Tube to use: Purple top.</p> <p>Lab performing assay: Royal Liverpool (or the transplant hospital) Results can take 72 hours to be reported.</p> <p>Emergency service: The requesting clinician should liaise with WUTH labs if urgent levels are required. If appropriate, samples can be sent by taxi to Clinical Biochemistry Department, 4th Floor Duncan Building, Royal Liverpool University Hospital, Liverpool, L7 8XP.</p> <p>Sampling time: Trough level (12 hours after previous dose)</p>	<p>Factors affecting plasma concentration: Increased by CYP 3A4 inhibitors — e.g., azole antifungals, macrolide antibiotics (e.g. clarithromycin), protease inhibitors. See SPC</p> <p>Decreased by CYP 3A4 inducers — e.g., rifampicin, phenytoin, St John’s Wort, phenobarbital, high-dose corticosteroids. See SPC</p>	<p>Toxic effects: Levels above 20µg/L may be associated with toxicity. This manifests as tremor, headache, nausea and vomiting, urticaria, lethargy, increase blood nitrogen, elevated creatinine and alanine aminotransferase.</p>	<p>The injection contains polyethoxylated castor oil that may lead to anaphylactic reactions when injected too rapidly.</p> <p>IV adsorbs to PVC. In practice do not have to use PVC free giving set. Use giving set for 72 hours, levels may fall briefly on changing set.</p> <p>Available as syrup/sachets for NG administration.</p> <p>When converting from oral to IV, the oral dose should be approximately divided by 5 (e.g. 10mg, orally, daily is equivalent to 2mg IV over 24 hours). Subsequent doses should be informed by blood levels.</p>

10. Vancomycin

Drug and prescribing information	Pharmacokinetics	Sampling information and target levels	Factors affecting plasma concentration/ toxicity	Signs of toxicity	Further information & guidance
<p>Dosage forms: Oral, intravenous infusion.</p> <p>Oral (levels not required) 125mg 6 hourly in mild <i>Clostridium difficile</i> infection for 10 to 14 days,</p> <p>250 to 500mg 6 hourly in severe <i>Clostridium difficile</i> infection for 10 to 14 days.</p> <p>Intravenous Loading dose: See product monograph in main Trust antibiotic formulary. Maintenance dose: See product monograph in main Trust antibiotic formulary. Therapeutic range: Pre-dose 'trough' 10 to 15mg/L; trough concentrations up to 20mg/L may be required in deep-seated or resistant infections. In MRSA bacteraemias concentrations up to 20mg/L may be required, in deep-seated or resistant infections In MRSA bacteraemia aim for trough ~15mg/L</p>	<p>Elimination half-life: 6 to 10 hours (normal renal function); up to 216 hours in end stage renal failure. Major route of elimination: 80 to 90% excreted unchanged in urine. Vd: 0.7L/kg (0.9L/kg in ESRF)</p> <p>Oral bioavailability: Poorly absorbed</p> <p>Time to steady state: dependent on renal function.</p>	<p>Sampling Volume of blood: Fill to line Tube to use: Ochre or green top. Lab performing assay: Wirral Clinical Biochemistry. Emergency service: Yes, but should not be necessary. Sampling times: The Pharmacy Department will advise on levels to be taken. Trough levels should be taken immediately before a dose is given. Peak levels are not usually required. Resample time: Dependent on clinical status of patient. In patients who require monitoring; as a guide, a trough level is usually taken on day 2 or 3 of therapy and repeated weekly. Check more frequently if unstable renal function. Reporting procedure: Available via Cerner.</p>	<p>Factors affecting plasma concentration: Increased in renal impairment Decreased in severe burns.</p> <p>Increased risk of nephrotoxicity if vancomycin is administered with other nephrotoxic drugs such as: aminoglycosides, NSAIDs, ciclosporin and tacrolimus.</p> <p>Vancomycin may lead to a raised INR in patients taking warfarin.</p> <p>Vancomycin may reduce clearance of digoxin.</p>	<p>Toxic effects: Hypotension and anaphylactic reactions occur if given too quickly. Ototoxicity and nephrotoxicity are rare, although risk is increased if co-administered with aminoglycosides. Groups at special risk include patients with impaired renal function and the elderly. Increased incidence of ototoxicity and nephrotoxicity at high trough concentrations.</p>	<p>Vancomycin is administered by the intravenous route in the treatment of infections caused by Gram-positive cocci including multi-resistant staphylococci such as MRSA.</p> <p>Oral vancomycin is not absorbed but can be used for the treatment of pseudomembranous colitis due to <i>Clostridium difficile</i>. It must not be used by this route for any other indication. TDM is not required.</p> <p>Intraperitoneal administration of vancomycin may be used in the treatment of peritoneal dialysis associated peritonitis. See Renal Unit guidelines for initial dose and contact the renal pharmacists for advice on monitoring.</p>