1. Introduction

The aim of Therapeutic Drug Monitoring (TDM) is to provide information that assists in optimising drug dosing. In general, routine measurements are not required but taken to resolve a specific clinical problem, e.g. inadequate response, signs of toxicity. Routine TDM is required for; lithium, some immunosuppressants, IV aminophylline, phenytoin and some antimicrobials.

Appropriate and documented specimen collection time is vital

When taking a level, the following must be considered to avoid misleading results:

1. For dosage adjustment guidance, sampling at 'steady-state' is essential (unless confirming toxicity) and thus four to five elimination half-lives must have elapsed since the last change of maintenance dose.
2. Samples must be taken at an appropriate time during a dose interval.

Interpretation of most results is made in relation to the therapeutic range but clinical decisions should not be based on drug concentrations alone. The range for individual drugs is only a guide derived from a normal population and some patients will respond or exhibit toxicity outside the expected ranges. Concentrations can be affected by factors such as age, drug interactions, protein binding and drug metabolism. Also, liver and/or renal impairment may reduce clearance and increase the risk of toxicity, especially after a dose increase.

In any instance of acute poisoning please seek further guidance on features and clinical management from www.toxbase.org. Individual advice on more serious or complex cases is available via the National Poisons Information Service (NPIS) 24-hour telephone service 0344 892 0111.

For advice 09:00-17:00 Mon to Fri (excluding bank holidays), please contact the Duty Biochemist (0116 258 6560). Out of hours there is an on-call Consultant Chemical Pathologist / Clinical Scientist available who can be contacted via switchboard. Find the latest Blood Sciences User Handbook here, this contains the most up to date information including expected turnaround times for results. Information about the LGH Transplant Laboratory for immunosuppressive drug monitoring can be found here.

2. Scope

This guideline applies to all adult patients receiving drug therapy with narrow-therapeutic windows.

It is intended for use by any member of the Multidisciplinary Team (MDT) treating these patients.

This guideline does not cover children. Nor does it include reference ranges for antimicrobials. Please see the Antimicrobial Website (or access via the Apps section on UHL Connect) for details on therapeutic drug monitoring for antimicrobials.

3. Recommendations, Standards and Procedural Statements

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Aminophylline Infusion	10 – 20mg/L (lower levels e.g. 5-15mg/L may be clinically effective)	1 – 2	Check plasma theophylline level within 4-6 hours of starting maintenance infusion. Re-check level after any dose adjustment, within 4-6 hours. Check plasma theophylline level every 24 hours, even if no adjustments are made.	Nausea, vomiting, anorexia, tachycardia, arrhythmias, agitation	5mL Serum Gel Tube
Interpretation and Management: Aminophylline is a salt of theophylline, **request plasma theophylline levels** when completing therapeutic drug monitoring. Please refer to the full UHL Adult Intravenous Aminophylline Prescribing Guideline **Levels below 9.9mg/L – I**NCREASE rate by 25% if still symptomatic. Note some patients may get benefit from sub-therapeutic levels **Levels between 10-14.9mg/L –** maintain rate of infusion **Levels between 15-19.9mg/L -** DECREASE rate by 10% to provide a greater margin of safety even if current dosage is tolerated. **Levels between 20-24.9mg/mL –** Stop infusion for 24 hours. If restarting ensure level <15mg/L and DECREASE rate by at least 25% **Levels above 25mg/L -** Stop infusion for 24 hours. Consider if overdose treatment required. If restarting check level <15mg/L and DECREASE rate by at least 50%					
Carbamazepine	4 – 12mg/L	2 – 5	Trough measurement before a dose	Nausea, vomiting, dizziness, visual disturbances, ataxia, headache	5mL Serum Gel Tube
Interpretation and Management: Measurement of anti-epileptic drug levels (apart from phenytoin) is not a useful index of efficacy and therefore routine monitoring is unhelpful. Optimum dosage mainly determined by seizure control. Levels may be useful when considering compliance, suspected toxicity and during pregnancy. Therapeutic ranges are not clearly defined and often vary between individuals.					
Ciclosporin (cyclosporin(e)) Not to be confused with cyclo**ser**ine.	Varies according to indication, confirm with prescribing specialty.	4	Oral: trough level. IV (twice daily dosing): trough level IV (continuous infusion): anytime	Nausea, vomiting, tremor, headache, altered taste, altered limb sensation, drowsiness, oedema, flushing, hypertension. Note: many drug interactions	5mL EDTA (purple)
Interpretation and Management: Seek advice from the prescribing specialty. Where possible, patient's should be maintained on the same brand formulation, switching between formulations may impact trough levels. NB: Analysed by external lab, for urgent, same day reporting, samples must be received by LGH Transplant Laboratory before 12:00pm. No weekend service.					

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Clozapine	350 – 600 micrograms/L	5	Trough measurement before a dose or 12 hours post dose.	Drowsiness, delirium, tachycardia, hypersalivation, respiratory depression, orthostatic hypotension, nocturnal enuresis, seizures, constipation.	1mL EDTA
Indication for levels: Blood clozapine level monitoring is advised in certain clinical situations such as when a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity. **Requesting:** Please liaise with the Clozapine team at LPT (0116 295 8989, option 2, option 4) to arrange an assay kit which includes details of where to send to. Once analysed, Magna Laboratories emails the assay results to the LPT team plus the patient's consultant. **Interpretation and Management:** Interpretation of clozapine levels is complex as many factors can affect clozapine levels such as gender, age, body weight, ethnicity, co-prescribed enzyme inducing/inhibiting drugs. The ratio of clozapine levels to norclozapine levels is needed to interpret results. Seek advice from a specialist mental health pharmacist to help interpret levels and decide a course of action. Seek advice from the prescribing specialty if doses need to be adjusted.					
Digoxin	0.5 – 2.0 micrograms/L (Heart failure:0.5-1.0 micrograms/L)	7 – 14	Oral and IV: at least 6 hours after dose, trough measurement before a dose is preferred.	Anorexia, headache, nausea, vomiting, diarrhoea, visual disturbances, confusion, arrhythmias. Risk of toxicity increased by electrolyte disturbances, e.g. hypercalcaemia, hypokalaemia, hypomagnesaemia	5mL Serum Gel Tube
Indication for Levels: Routine digoxin management and measurement is not recommended in clinically and biochemically stable patients, but may be warranted if there are changes in the patient's clinical state; adverse effects suggestive of toxicity, concomitant use of interacting medicines, deteriorating renal function, thyroid disease, advancing age or suspected poor adherence. **Interpretation and Management:** A specific plasma concentration may be therapeutic or toxic in an individual patient depending on factors other than dosage (e.g., serum electrolytes, acid-base balance, concurrently administered drugs, thyroid status, underlying disease states). Digoxin has a long half-life 30-40 hours, and up to 100 hours in anuric patients. Serum concentrations of digoxin should be interpreted in the overall clinical context; thus, an isolated serum concentration measurement should not be used alone as the basis for adjusting dosage.					

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Lamotrigine	2 – 15 mg/L	3 – 7 (in absence of interacting drugs)	Trough measurement before a dose	Nystagmus, ataxia, nausea, vomiting, drowsiness, dizziness, tachycardia	5mL Serum Gel Tube
Interpretation and Management: Measurement of anti-epileptic drug levels (apart from phenytoin) is not a useful index of efficacy and therefore routine monitoring is unhelpful. Optimum dosage mainly determined by seizure control. Levels may be useful when considering compliance, suspected toxicity and during pregnancy. Therapeutic ranges are not clearly defined and often vary between individuals.					
Levetiracetam	12 – 46mg/L (upper limit not established)	2	Trough measurement before a dose	Vomiting, sedation, agitation, drowsiness, respiratory depression, ataxia, headache	5mL Serum Gel Tube
Interpretation and Management: Measurement of anti-epileptic drug levels (apart from phenytoin) is not a useful index of efficacy and therefore routine monitoring is unhelpful. Optimum dosage mainly determined by seizure control. Levels may be useful when considering compliance, suspected toxicity and during pregnancy. Therapeutic ranges are not clearly defined and often vary between individuals.					
Lithium	0.4 - 1.0 mmol/L Target level determined by specialist. >1.5 mmol/L indicates toxicity	5	12 hours post dose. Trough measurement just before time of dose.	Fine tremor increasing to coarse tremor, muscle twitching, nausea, vomiting, severe diarrhoea, muscle weakness, lethargy, drowsiness, blurred vision, dehydration, confusion, ataxia, dysarthria, nystagmus, vertigo, tinnitus, restlessness	5mL Serum Gel Tube
Interpretation and Management: Changes in hydration, sodium balance and renal function can affect plasma lithium levels. Seek advice from the prescribing specialty before adjusting therapy. **Important**: Use **brown serum gel tubes**, levels have been reported high, incorrectly, when samples have been collected in orange lithium heparin bottles.					

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Phenytoin	10 – 20mg/L	7	Oral: trough level IV: at least 2 hours after end of infusion IV for status epilepticus: 12-24 hours after the loading dose. Be aware, this is not a steady state level and may fluctuate, further levels will be needed.	Ataxia, slurred speech, nystagmus, diplopia, lethargy. **Note, patients much more likely to become toxic, despite seemingly therapeutic levels, in conditions that are associated with hypoalbuminemia e.g. CKD. See notes below about interpretation & management**	5mL Serum Gel Tube

Interpretation and Management:
Phenytoin is highly protein bound (>90%), primarily to albumin. When protein binding is reduced, as in patients with low albumin levels, the total phenytoin plasma level at steady state will decrease, and the free fraction will be higher. However, the free phenytoin level, which is the pharmacologically active component, remains unchanged. In these cases, caution should be exercised when interpreting total phenytoin plasma levels. For example, a patient with low albumin (<35g/L) may have a low total phenytoin level but a therapeutic level of free phenytoin. An online calculator is available that provides an albumin-corrected total phenytoin level, which can be compared with the target concentration range (10-20mg/L). However, this correction only provides a rough estimate, and the patient's clinical condition and status should always take precedence over concentration measurements when considering dose adjustments.

Phenytoin maintenance dose adjustment:
If seizures are not controlled, adjust the dose as below:
< 5 mg/L – if patient is definitely/ likely compliant, increase dose by up to a maximum of 100mg/day (also contact neurology on call via switchboard to determine whether a reload is needed). If non-compliant encourage patient to maintain adherence. If seizures are uncontrolled or other clinical concerns (e.g, option of reloading) discuss with neurology (via switchboard).
5 – 10 mg/L – Increase dose by 50mg/day and recheck levels in 2 weeks
10 – 15 mg/L - Increase dose by 25mg/day and recheck levels in 2 weeks
16 – 20 mg/L – consider increasing dose by 25mg/day using clinical judgement and recheck levels in 2 weeks

If seizures are **controlled**, no immediate action needed. Only contact neurology if there are clinical concerns.
If symptoms of toxicity (diplopia, ataxia, nausea etc) **and levels are >20mg/L** – withhold further doses and check levels every 24 hours until target concentration achieved (10 – 20mg/L). Then take advice from neurology on call via switchboard regarding a new maintenance dose.
If no clinical toxicity **and levels are >20mg/L**, contact neurology on call via switchboard for timely advice before withholding a dose.
Due to the non-linear pharmacokinetics of phenytoin, small dose changes can lead to large changes in phenytoin concentrations. Repeat phenytoin serum levels should be not be obtained for at least 7-10 days after any dose changes.

If patient is known to UHL neurology team please contact the relevant consultant neurologist via email if phenytoin dose is adjusted.

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Sodium Valproate	<100 mg/L	2 – 4	Trough measurement before a dose	Nausea and vomiting, agitation, dizziness, drowsiness, hypotension, hypothermia and tachycardia. In acute massive overdose; CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis and hypotension.	5mL Serum Gel Tube
Interpretation and Management: Measurement of anti-epileptic drug levels (apart from phenytoin) is not a useful index of efficacy and therefore routine monitoring is unhelpful. Optimum dosage mainly determined by seizure control. Levels may be useful when considering compliance, suspected toxicity and during pregnancy. Therapeutic ranges are not clearly defined and often vary between individuals.					
Sirolimus	4 – 15 ng/mL (depends on indication & concomitant immunosuppressant use. Seek specialist advice)	5 – 7	Trough measurement before a dose	Consistent with known adverse effects of therapy, more pronounced in cases of high levels; infection, anaemia, pyrexia etc. Note: many drug interactions	5mL EDTA (purple)
Interpretation and Management: Seek advice from the prescribing specialty about patient specific targets. The 500 microgram tablet is not bioequivalent to the 1 mg and 2 mg tablets. Multiples of 500 microgram tablets should not be used as a substitute for other tablet strengths. If switching from oral solution to tablet, take a trough level 1-2 weeks after switching. NB: Analysed by external lab, for urgent, same day reporting, samples must be received by LGH Transplant Laboratory before 12:00pm. No weekend service.					

Drug	Therapeutic range	Number of days before steady state	Optimum sampling time and sampling information	Common signs and symptoms of toxicity	Type of sample required
Tacrolimus	5 – 15 micrograms/L (depends on indication, seek specialist advice / refer to local guideline)	3	Trough level taken immediately before the next dose is due. Note, there are standard release and modified release oral preparations. Levels should only be routinely monitored in patients receiving oral treatment.	Nausea, vomiting, tremor, infections, urticaria, nephrotoxicity Note: many drug interactions	5mL EDTA (purple)
Interpretation and Management: Seek advice from the prescribing specialty about patient specific targets. Where possible, patient's should be maintained on the same brand formulation, switching between formulations may impact trough levels. NB: Analysed by external lab, for urgent, same day reporting, samples must be received by LGH Transplant Laboratory before 12:00pm. No weekend service.					
Theophylline	10 – 20mg/L (lower levels e.g. 5-15mg/L may be clinically effective)	2	4 to 6 hours after taking dose Measure levels 5 days after starting oral treatment and at least 3 days after any dose adjustment or 2 days after switching from IV therapy	Nausea, vomiting, tachycardia, arrhythmias, agitation. Anorexia and oesophagitis may be present in chronic poisoning.	5mL Serum Gel Tube
Interpretation and Management: *Uniphyllin Continus is currently the only available prolonged theophylline preparation available in the UK. Oral aminophylline has been discontinued by the manufacturer and is no longer available in the UK.* **Levels below 5mg/L –** increase dose by 25% **Levels between 5-10mg/L –** consider increasing dose. Note some patients may get benefit from sub-therapeutic levels **Levels above 20mg/mL –** consider omitting doses and decrease dose, seek guidance from specialist team. Recheck the plasma level three days after any dosage adjustment and every 6-12 months thereafter.					

4. Education and Training

None.

5. Monitoring and Audit Criteria

The following table lists the monitoring arrangements for this policy:

Key Performance Indicator	Method of Assessment	Frequency	Lead
Datix medication incidents involving therapeutic drug monitoring for drugs with narrow therapeutic windows	Datix incident reporting tool, reporting to Medicines Optimisation Committee.	Monthly	Medicines safety officer

6. Legal Liability Guideline Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional, it is fully appropriate and justifiable – such a decision to be fully recorded in the patient's notes.

7. Supporting Documents and Key References

- Summary of Product Characteristics accessed via Electronic Medicines Compendium (www.medicines.org.uk/)
- Specialist Pharmacy Services website. Accessed via https://www.sps.nhs.uk/
- Toxbase. Accessed via http://spib.axl.co.uk
- American Hospital Formulary Service Drug Information. Wisconsin : American Society of Health-System Pharmacists. Accessed via www.medicinescomplete.com
- Micromedex®. Thomson Micromedex, Greenwood Village, Colorado accessed via http://www.micromedexsolutions.com/
- UHL Blood Sciences User Handbook. Version 19, February 2024
- LGH Transplant Laboratory Service User Manual, Paul Dunn, November 2022
- Convulsive Status Epilepticus in Adult UHL Emergency Department, Dr Martin Wiese, October 2023.
- Epilepsy and pregnancy, Obstetricians Working Party, May 2022
- BK Polyomavirus Interstitial Nephritis in Renal Transplant UHL Renal Transplant Guideline, Dr Gang Xu, November 2023
- Immunosuppression and Malignancy in Renal Transplant UHL Renal Transplant Guideline, Dr Sue Carr, January 2020
- Immunosuppression Therapy Following Kidney Transplant UHL Renal Transplant Guideline, Mr Atul Bagul, July 2023

8. Key Words

TDM, therapeutic drug monitoring, drug levels, therapeutic range, steady state, aminophylline, carbamazepine, ciclosporin, cyclosporin, clozapine, digoxin, lamotrigine, levetiracetam, lithium, phenytoin, sodium valproate, tacrolimus, theophylline, sirolimus

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Appendix 1

Specimen collection bottles

If taking multiple samples, they should be taken in the order below.

Order of draw	Name and cap colour	Example cap
1	Blood Culture collection kit	
2	Brown top Serum gel bottle	
3	Green Sodium Citrate bottle	
4	Orange Lithium Heparin bottle	
5	Purple EDTA bottle	
6	Pink/Red EDTA bottle	
7	Yellow Fluoride EDTA bottle