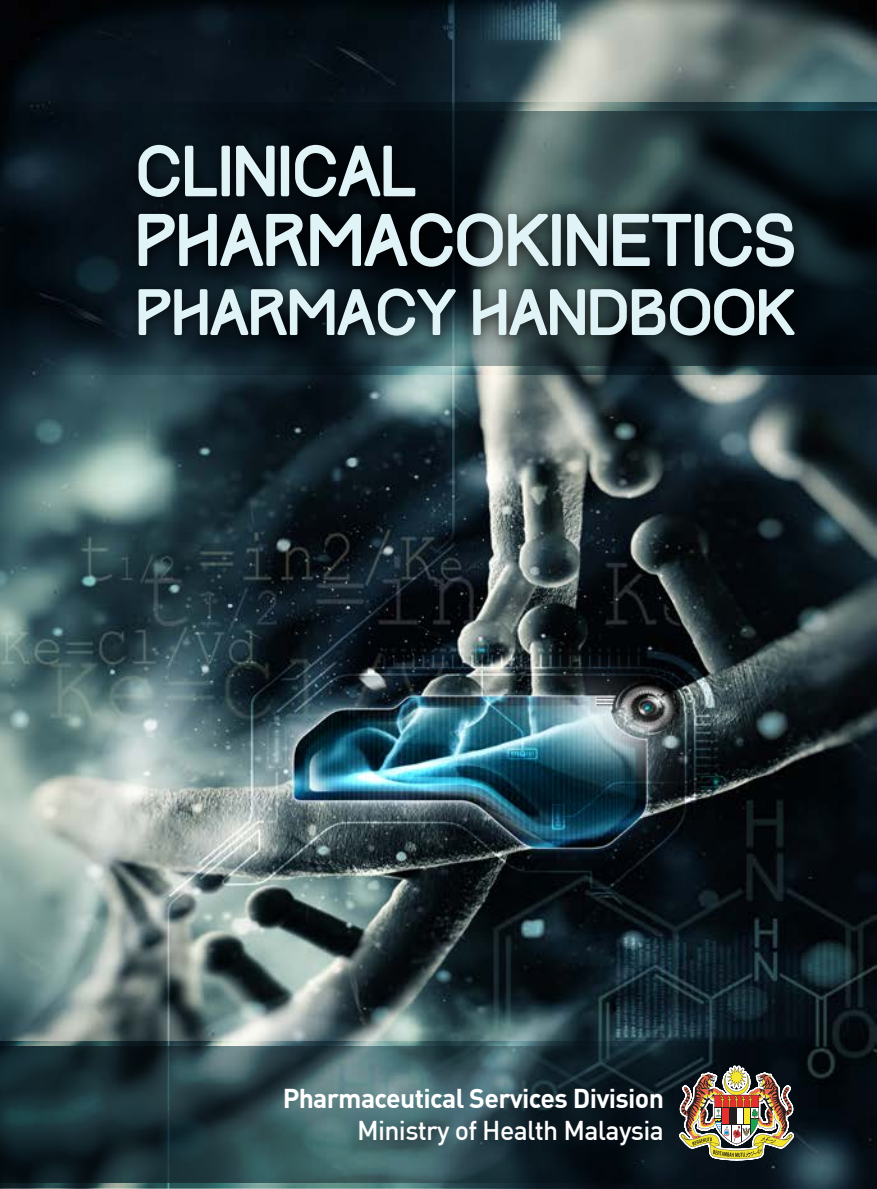
CLINICAL PHARMACOKINETICS PHARMACY HANDBOOK



Pharmaceutical Services Division
Ministry of Health Malaysia

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2015

PREPARED BY:

Clinical Pharmacy Working Committee
(Clinical Pharmacokinetics Subspecialty)
Pharmaceutical Services Division
Ministry of Health Malaysia

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FOREWORD

Clinical Pharmacy Service is an essential component of patient care which plays a role in managing medicines safely, effectively and efficiently central to the delivery of high quality care that is focused on the patient and gives value for money. In the 1980's, Therapeutic Drug Monitoring (TDM) service which is also known as Clinical Pharmacokinetics Service was introduced in Malaysia. Due to the rapidly expanding need for clinical pharmacokinetics service, it is timely and essential for the Pharmaceutical Services Division, Ministry of Health to develop and publish this handbook.

This Clinical Pharmacokinetics Pharmacy Handbook serves as a guide for the pharmacists involved in this service to ensure the standardisation of clinical pharmacokinetic services in all Ministry of Health (MOH) facilities.

The recommendations in this handbook have been made by taking into consideration the existing policies in the facilities pertaining to the practice of the clinical pharmacokinetics service. I believe the contents of this handbook will serve as a standard reference for pharmacists in managing the clinical pharmacokinetics service. I am confident that this handbook will also provide useful information in ensuring patients receive an optimal and safe treatment based on their individual needs and condition.

Last but not least, I would like to congratulate the Clinical Pharmacy Working Committee (Clinical Pharmacokinetics Subspecialty) for their efforts and contributions in the development of the '*Clinical Pharmacokinetics Pharmacy Handbook*'.

Thank you.

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
ALL	Acute lymphoblastic leukaemia
ALL BFM	Acute lymphoblastic leukaemia–Berlin-Frankfrut-Münster
AUC	Area under the curve
BCG	Bacillus Calmette-Guérin
CAPD	Continuous ambulatory peritoneal dialysis
CAVH	Continuous arteriovenous haemofiltration
CBC	Complete blood count
CL	Clearance
C max	Maximum concentration
C min	Minimum concentration
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
CSA	Cyclosporin
Css ave	Average plasma concentration at steady state
CVVH	Continuous venovenous haemoflitration
CVVHD	Continuous venovenous haemodialysis
CVVHDF	Continuous venovenous haemodiafiltration
D5W	Dextrose 5% solution in water
D10W	Dextrose 10% solution in water
F	Bioavailability
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
HD	Heamodialysis
HPLC	High performance liquid chromatography
HPLC/MS	High performance liquid chromatography – mass spectrometry
IBW	Ideal body weight
IM	Intramuscular
IMD	Initial maintenance dose
IP	Intraperitoneal dialysis
IV	Intravenous
JIA	Juvenile idiopathic arthritis
Ke	Elimination rate constant
Km	Michaelis-Menten constant
LCV	Leucovorin
LD	Loading dose
MD	Maintenance dose
MDD	Multiple daily dosing
MIC	Minimum inhibitory concentration
MMF	Mycophenolate mofetil
MR	Medium risk

MTX	Methotrexate
[MTX]	Methotrexate concentrations
N/A	Not applicable
NHL	Non-Hodgkin's lymphomas
NS	Normal saline
NSAID	Non-steroidal anti-inflammatory drug
PAE	Post antibiotic effect
Ph+ ALL	Philadelphia positive subtype of acute lymphoblastic leukaemia
PO	By mouth
RA	Rheumatoid arthritis
S	Salt form
SDD	Single daily dosing
SR	Standard risk
SWFI	Sterile water for injection
TAC	Tacrolimus
TDD	Total digitalising dose
TG	Total triglyceride
$t_{1/2}$	Half-life
Vd	Volume of distribution

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INTRODUCTION

Clinical Pharmacokinetics is a part of pharmacy service which plays a role in patient's care especially when it involves drugs with narrow therapeutic range.

Pharmacokinetics is defined as the study of time course of drug absorption, distribution, metabolism and excretion. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

The primary goal of clinical pharmacokinetics service includes enhancing efficacy and minimising toxicity of a patient's drug therapy. Pharmacokinetics is often studied in conjunction with pharmacodynamics. Pharmacodynamics is the study of the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse events.

Clinical Pharmacokinetics Pharmacy Handbook is the first Therapeutic Drug Monitoring guideline published by Pharmaceutical Services Division that will be used as a reference and as a training material for pharmacists in clinical pharmacokinetics area. It is produced from the efforts and initiative of experienced Clinical Pharmacokinetics Service Pharmacists, Clinical Pharmacy Working Committee (Pharmacokinetics Subspecialty) Pharmaceutical Services Division, Ministry of Health.

This handbook covers drugs frequently monitored such as Aminoglycosides, Vancomycin, Phenytoin, Carbamazepine, Valproic Acid, Phenobarbitone, Digoxin, Theophylline, Methotrexate, Tacrolimus, Sirolimus, Cyclosporine, Paracetamol and Salicylates. The contents included key pharmacokinetic parameters, drug dosages, drug interactions, standard sampling times, monitoring parameters, adverse drug reactions, proper dilution, administration and calculation formulas for each drugs mentioned.

Some basic pharmacokinetic definitions and principles as following:

Bioavailability (F)	Bioavailability is the percentage or fraction of the administered dose that reaches the systemic circulation of the patient. Factors that can alter bioavailability include the inherent dissolution and absorption characteristics of the administered chemical form (e.g., salt, ester), the dosage form (e.g., tablet, capsule), route of administration, the stability of the active ingredient in the gastrointestinal tract and the extent of drug metabolism before reaching the systemic circulation.[1]
Steady state	Point in time reached after a drug has been given for approximately five elimination half life. At steady state, the rate of drug administration equals to the rate of elimination, and drug concentration-time curves found after each dose on an even schedule (e.g every 8 hour) should be approximately superimposable.[1]

C_{max}, peak	The peak concentration is the highest or maximum concentration after any type of dosing method. It is concentration of drug that occurs immediately after Intravenous bolus dose, at the end of a dose infusion, or at particular time after dose administration for a drug requiring absorption. [1]
C_{min}, trough	The trough is the lowest or minimum concentration after a dose given intermittently. It is concentration that occurs immediately before the next dose for drugs given intermittently in a multiple-dose fashion. [1]
C_{ss} Average	Css Ave is the average steady state concentration or a concentration approximately halfway between Cmax and Cmin at steady state.[1]
Creatinine Clearance (CrCl)	Creatinine clearance rate is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. [1]
Elimination Rate Constant (K_e)	The fraction or percentage of the total amount of drug in the body eliminated per unit of time.[1]
Half-life ($t_{1/2}$)	The time required for the total amount of remaining drug in the body to decline by 50%.[1]
Km, constant	Michaelis-Menten constant (in units of mcg/ml). It is the concentration at which the metabolic system is 50% saturated. [1]
Volume of Distribution (Vd)	The volume of distribution is the theoretical size of the compartment necessary to account for the total drug amount in the body if it were present throughout the body in the same concentration found in the plasma. Factors that may affect the volume of distribution include: protein binding and drug solubility. [1]
V_{max}	Maximum velocity of drug elimination for a drug following Michaelis-Menten (saturable enzyme) kinetics. It is the amount of drug that can be bio-transformed per unit of time (in units of mg/kg/day). [1]

Initiating therapy:
A Standard dose and interval may be used to initiated therapy, or may be individualized the dose and interval using population means of volume of distribution and clearance or half life. These population pharmacokinetic parameters are useful for estimating drug concentrations based on planned dose and dosage schedule. To adjust therapy, these values then may be compared to actual drug concentration measurements and integrated with the patient's therapeutic outcome.

Using population mean values:
Not all patients fit closely to the population means as some of these means were developed on small samples that do not represent the general population or the patient being monitored. Population means with standard deviations can provide useful information on reasonable ranges of the values to expect. However, patient's actual pharmacokinetic value may need to be determined to adjust therapy for desired outcome.

Considering other factors in pharmacokinetic monitoring:
In addition to the problems with population pharmacokinetic means, unexpected drug concentration measurement can occur for various reasons such as: [1]

- Non adherent with drug therapy drug
- Administration errors (wrong dose or time)
- Wrong sampling time
- Drug or disease interactions
- Inaccurate assays

Determined the need for dosage adjustments:
Drug concentration measurement and dosing information should be obtained and must be accurate as possible. Dosage adjustments are assessed based on pharmacodynamic response and patient outcomes. The need for dosage adjustment or the continuation of therapy should be based on patient response relative to measured drug concentration rafter than on drug concentration alone. [1]

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CHAPTER 1: AMINOGLYCOSIDE

CHAPTER 1
AMINOGLYCOSIDE

KEY PARAMETERS:[1,2]

Therapeutic range	Refer to 'Indication and Therapeutic Range'
Bioavailability (F)	Oral: <10% Intramuscular & Intravenous: ~100%
Volume of Distribution (Vd)	Adult: 0.2 – 0.3 L/kg Pediatrics: 0.3 – 0.5 L/kg
Clearance (CL)	100% unchanged in the urine
Half-life ($t_{1/2}$)	1.5 – 3 hours

A. PHARMACOKINETICS

Bioavailability:[1]

Oral: <10%
Intramuscular & Intravenous: ~100%

Volume of Distribution (Vd):

Neonates	0.4 – 0.6 L/kg[3]
Paediatrics	0.3 – 0.5 L/kg[1,2]
Adult	0.2 – 0.3 L/kg[1,2]
Obesity (>30% over IBW)	0.26 [IBW + 0.4 (TBW – IBW)][1]
Cystic fibrosis	0.35 L/kg[1]

Clearance (Cl):[1]

Elimination: Totally unchanged in the urine
Clearance is directly related to renal function
Hemodialysis clearance: Gentamicin ~50%, Amikacin ~20%

Factors that may influence Vd or/and Clearance:[4]

Increase Vd	Ascites, burn patient, cirrhosis, cystic fibrosis, critically ill, pancreatitis, Patent Ductus Arteriosus, post-surgery
Reduce Vd	Dehydration
Increase Cl	Burn patient, cystic fibrosis, dialysis, critically ill
Reduce Cl	Cirrhosis, prematurity, Patent Ductus Arteriosus

Half-life ($t_{½}$):[3]

Neonates (<1 week)	3 – 11.5 hours
Infant (>1 week -6 months)	3 – 3.5 hours
Adult	1.5 – 3 hours
Adult – Renal failure	50 hours (36 – 72 hours)
Adult – Obese	2 – 3 hours
Burn	1.5 hours

Indication and Therapeutic Range:[3]

Indication:
Aminoglycoside is used to treat susceptible bacteria infection, normally gram negative organisms, such as *Pseudomonas sp.*, *Proteus sp*, *Serratia sp* and other gram negative bacilli.

Dosing	**Gentamicin (mcg/ml)**		**Amikacin (mcg/ml)**	
	TROUGH	**PEAK**	**TROUGH**	**PEAK**
Neonates[5]	0.5 – 1	5 – 12	2 - 5	20 – 30
MDD [1,2]	<2	5 – 10	<10	20 – 30
SDD[1,2]	<1	20 – 30*	<1	60*
Synergy[1]	<1	3 – 5	N/A	N/A
Dialysis[3]**	<2	Not necessary	<10	Not necessary

**The target reference ranges vary and may be individualized based on institutional MIC value to achieve peak to MIC ratio of 10:1.*
*** For continuous dialysis i.e CRRT/ CAPD; random sampling shall be taken.*

B. DOSAGE

DOSING STRATEGIES

A. SINGLE DAILY DOSING (SDD)[6]

Based on their concentration-dependent bactericidal action, Aminoglycoside demonstrates more rapid bacterial killing by achieving a high peak concentration approximately ten times the MIC necessary for bacterial growth inhibition.[1,2] Besides, administration of larger and less frequent doses produce trough concentration lower than assay sensitivity limit (drug free period) between dose intervals which provides:

- Possibly less nephrotoxicity event by decreasing renal cortical Aminoglycoside concentrations.[18]
- Continued suppression of bacterial growth between 2 – 8 hours despite concentration falling below MIC (Post antibiotic effect).[12]
- Less development of adaptive resistance by allowing a recovery period during the dosing interval defined as a recovery period before organisms can resume growth after drug removal.[3]

Due to pharmacokinetic alterations, please use clinical judgment when using SDD for the following populations:

- Pregnancy (Pregnancy Category D). Only use when benefit outweighs risk
- Ascites
- Burns
- Gram positive infections (when AMG is used as synergy)
- Creatinine clearance <30ml/min
- Dialysis
- Neutropenic patients
- Heamodynamically unstable
- Cyctic fibrosis

Approach 1: SDD Initial Dosing[7]

In general adult dose for SDD: 4 – 7mg/kg/day for patients with normal renal function. Initial SDD dosing guide based on renal function is as follows:

Creatinine Clearance (ml/min)	Dose in 24 hours*	
	Gentamicin	Amikacin
>80	5mg/kg	15mg/kg
60 – 79	4mg/kg	12mg/kg
40 – 59	3.5mg/kg	7.5mg/kg
30 – 39	2.5mg/kg	4mg/kg
<30	Conventional dosing	Conventional dosing

*Dose interval may be adjusted based on serum level

Approach 2: SDD Initial Dosing based on Hartford Nomogram[6]

Using SDD pharmacodynamics concepts, Hartford method suggests initial use fixed dose of 7mg/kg of gentamicin and 15mg/kg of amikacin. The following dosing interval is indicated by the nomogram zone.

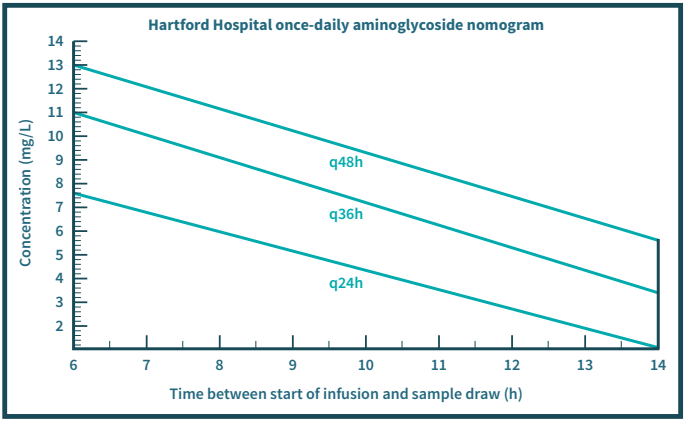

Figure 1.1 Nomogram for concentration monitoring and interval adjustment of gentamicin 7mg/kg & Amikacin 15mg/kg. Take one timed serum concentration taken 6 – 14 hours after dose and plot in the nomogram (divide level by two for amikacin) to determine the dosage interval. If level is above q48h, administer next dose when <1mg/L.

Alternatively, administer 7mg/kg of gentamicin or 15mg/kg of amikacin with the following dosage interval. Alter the subsequent dosage interval based on the serum concentration [1] (Refer instruction Figure 1.1)

Creatinine Clearance (ml/min)	Dose interval (hours)
≥60	24
40 – 59	36
20 – 39	48
<20	Monitor serial concentration, re-dose when <1mcg/ml

B. CONVENTIONAL DOSING

Conventional dosing is an approach of administering smaller and more frequent doses usually given every 8 – 12 hours or approximately two to three times the half life.[4] This dosing is commonly given in patients with significant pharmacokinetics alterations as stated in SDD exclusion criteria.[6]

Creatinine Clearance (ml/min)		Gentamicin	Amikacin
>60[8]		1.5 – 2mg/kg every 8 hourly	5 – 7.5mg/kg every 8 hourly
40 – 60[8]		1.5 – 2mg/kg every 12 hourly	5 – 7.5mg/kg every 12 hourly
20 – 40[8]		1.5 – 2mg/kg every 24 hourly	5 – 7.5mg/kg every 24 hourly
<20[8]		1.5 – 2mg/kg every 48 – 72 hourly*	5 – 7.5mg/kg every 48 – 72 hourly
RENAL REPLACEMENT DOSING	**HD**[3]	Loading dose: 2 – 3mg/kg followed by: 1 – 2mg/kg every 48 – 72 hourly*	5 – 7.5mg/kg followed by every 48 – 72 hourly*
	CRRT [3][9]	Loading dose: 3mg/kg followed by: 2mg/kg every 24 – 48 hourly*	Loading dose: 10mg/kg followed by: 7.5mg/kg every 24 – 48 hourly*
	CAPD[10]	**Intermittent:** IP 0.6mg/kg/per exchange/day **Continuous:** LD IP 8mg/L then MD 4mg/L in all exchanges	**Intermittent:** IP 2mg/kg/per exchange/day **Continuous:** LD IP 25mg/L then MD 12mg/L in all exchanges

* Redose when Gentamicin: <2mg/L (UTI), <3-5mg/L (G-ve infection) & Amikacin: <10mg/L

C. SYNERGISTIC DOSING[11,12]

Synergy dosing is a low dose of Aminoglycoside in combination with an antimicrobial agent (i.e. beta-lactams, glycopeptides) against Gram – positive bacterial infections (eg: endocarditis)

CrCl (ml/min)	Dose of Gentamicin
>60	1 mg/kg every 8 hourly
40 – 60	1 mg/kg every 12 hourly
20 – 40	1 mg/kg every 24 hourly
<20	1 mg/kg load*
HD	1 mg/kg every 48 – 72 hourly*
CRRT[9]	1 mg/kg every 24 – 36 hourly*

* Redose when Gentamicin: <1mg/L

AMINOGLYCOSIDE DOSING STRATEGIES–NEONATES[5]

a) Gentamicin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29	0 – 7 8 – 28 ≥29	5 4 4	48 36 24
30 - 34	0 – 7 ≥8	4.5 4	36 24
≥35	ALL	4	24

b) Amikacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29	0 – 7 8 – 28 ≥29	18 15 15	48 36 24
30 - 34	0 – 7 ≥8	18 15	36 24
≥35	ALL	15	24

C. INTERACTION[3]

Aminoglycoside use with the following drugs/conditions/disease may potentiate toxicity.

Nephrotoxicity	Ototoxicity
Concomitant Drugs	
• Amphotericin B • Cyclosporine • Diuretics (eg: Frusemide) • Other nephrotoxicy drugs • Vancomcyin	• N/A
Condition/disease	
• Advanced age • Dehydration • Pre-existing renal impairment	• Hearing loss • Tinnitus • Vertigo

D. SAMPLING

Dosing Type	SDD[2,4]	Hartford[6]	Conventional/ Synergistic[2]	Neonates[5]	Dialysis*[3]
Initial monitoring	After 1st dose	Single level drawn at 6 – 14 hours post initiation	On 3rd dose	24 hours	18 – 24 hours[13]
Sampling time[2]	Post 2 hours Post 6 hours (Or any two post sampling at least 2 t1/2 apart)		**Pre:** just before/within 30 minutes before the next dose **Post:** 30 minutes after completion of 30 minutes infusion		Pre HD

*** For continuous dialysis i.e CRRT/CAPD; random sampling shall be taken.

E. MONITORING PARAMETER

- Obtain serum levels if there are changes in renal function [11]
- Patient clinical characteristics such as
  - Renal function: creatinine and urea levels[1]
  - Input & output fluid balance[1,7]
  - Temperature[1]
  - White blood cell count[1]
- Culture & sensitivity[1]
- Sign and symptoms of auditory or vestibular toxicity[1]

F. ADVERSE DRUG REACTION

Increase risk of ototoxicity and nephrotoxicity[3]

1. Nephrotoxicity
2. Ototoxicity (auditory/vestibular)
3. Neurotoxicity (eg: vertigo and ataxia)

G. DILUTION AND ADMINSTRATION[3]

Dilution of drug:

Amikacin	• Diluent: Normal saline or Dextrose 5% • 500mg/vial – diluted into 100 – 200 ml of diluent • Concentration: 0.25 – 5 mg/ml
Gentamicin	• Diluent: Normal saline or Dextrose 5% • Diluted into 100 – 200ml of diluent

Drug administration:

Intravenous Infusion **Intramuscular** **Intraperitoneal**	30 – 60 minutes
Intravenous Bolus	Administer slowly over 2 – 3 minutes

H. CALCULATION

ESTIMATING INITIAL DOSE BASED ON POPULATION PHARMACOKINETICS[4]

1. Determine the dosing weight:
   - Determine patient's actual body weight (ABW) in kg
   - Determine patient's actual (IBW)
   - Compare ABW to IBW

Adjusted body weight = IBW + 0.4(ABW–IBW)

• If ABW/IBW is >0.9 to <1.2	=	Use ABW
• If ABW/IBW is >1.2	=	Use Adjusted body weight
• If ABW/IBW is >0.75 to <0.9	=	Use IBW
• If ABW/IBW is ≤0.75	=	Use ABW x 1.13

2. Determine the Volume distribution (Vd):
   (Refer to Vd chart for specific population Vd value)

$$Vd\ (L) = 0.26 \times BW\ (kg)$$

3. Estimate Creatinine Clearance (CrCl):

$$CrCL\ (ml/min) = \frac{(140\text{-age}) \times BW(kg) \times 1.04\ (F)\ \text{or}\ 1.23\ (M)}{Scr\ (\mu mol/ml)}$$

4. Estimate Aminogycoside Clearance (CL_{amg}):

$$CLamg\ (L/hr) = CrCl\ (ml/min) \times \frac{60\ min}{1{,}000\ ml}$$

5. Estimate Elimination Rate Constant (Ke):

$$Ke\ (hr^{-1}) = \frac{CLamg\ (L/hr)}{Vd\ (L)}$$

6. Estimate Half Life ($t_{1/2}$):

$$t_{½}\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

7. Estimate Dosing Interval (τ):
   (Round off the interval to logical administratin time)

$$\text{Dosing interval, } \tau\ (hr) = \frac{\ln \text{target Cmax} - \ln \text{Cmin target}}{Ke}$$

8. Estimate peak, (C_{max}) and trough (C_{min}) concentration:

$$Cmax\ (mcg/ml) = \frac{Dose\ (mg)}{Vd\ (L) \times (1 - e^{-Ke\tau})}$$

$$Cmin\ (mcg/ml) = Cmax \times e^{-Ke\tau}$$

Cmin	=	Trough or minimum concentration (mcg/ml)
Cmax	=	Peak or max conc. (mcg/ml)
τ	=	Dosing interval (h)

ESTIMATING NEW DOSE BASED ON PATIENT-SPECIFIC PHARMACOKINETICS[2]

Conventional Dosing: When pre & post levels are available

(Both levels must have detectable value. For single value/undetectable level please refer to population pharmacokinetic above)

1. Estimate elimination rate constant(K_e):

$$Ke\ (hr^{-1}) = \frac{\ln C2 - \ln C1}{T - (t2 - t1)}$$

2. Estimate half-life ($t^{1/2}$):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

3. Estimate peak, (C_{max}) and trough (C_{min}) concentration:

$$Cmax\ (mcg/ml) = \frac{Dose\ (mg)}{Vd\ (L) \times (1 - e^{-Ke\tau})}$$

$$Cmin\ (mcg/ml) = Cmax \times e^{-Ke\tau}$$

4. Determine the Volume distribution (Vd):

$$Vd\ (L) = \frac{Dose\ (mg)}{Cmax\ (1 - e^{-Ke\tau})}$$

5. Using the calculated Ke, estimate new dose:

$$New\ Dose\ (mg) = Cmax\ (mg/L) \times Vd\ (L) \times (1 - e^{-ke\tau})$$

$$Cmin\ (mg/L) = Cmax \times e^{-ke\tau}$$

Single Daily Dose (SDD): When two post sampling levels are availables[1]

(Recommended sampling: Post 2 hour (C_2) & post 6 hour (C_6))

1. Estimate elimination rate constant (K_e):

$$Ke\ (hr^{-1}) = \frac{\ln C6 - \ln C2}{t6 - t2}$$

2. Estimate half life($t_{1/2}$):

$$t_{½}\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

3. Estimate the expected C_{peak} concentration:
(Used when sample was taken at a time beyond the expected peak, assuming peak concentration occurs 1 hour after the start of administration)

$$Cmax = Cpost\ (C2) \times e^{Ke\,t'}$$

4. Estimate the expected C_{trough} concentration:

$$Cmin = Cmax \times e^{-Ke\tau}$$

5. Determine the Volume distribution (Vd):

$$Vd\ (L) = \frac{(Dose\ (mg)}{Cmax\ (1 - e^{-Ke\tau})}$$

6. Calculate the Drug Free Period (DFP):
(Ensure DFP within 2 – 8 hours. If exceeds 8 hours, consider adjust interval/dose)

   - First, calculate the time required for Cmax to fall to MIC (tMIC):

$$tMIC\ (hr) = \frac{\ln Cmax - \ln CMIC}{Ke}$$

   - $DFP\ (hr) = \tau - tmax - tMIC$
   Assume tmax = 1 (1 hour after the start of administration)

C2	=	Post 2 hours level (mcg/ml)
C6	=	Post 6 hours level (mcg/ml)
t'	=	Time difference between Cmax and Cpost (hours)
τ	=	Dose interval (hours)
tpeak	=	Time of Cmax or Cpeak (hours)
tMIC	=	Time to reach MIC concentration (hours)
Cmax	=	Peak concentration (mcg/ml)
CMIC	=	MIC value (mcg/ml), please use institutional MIC value

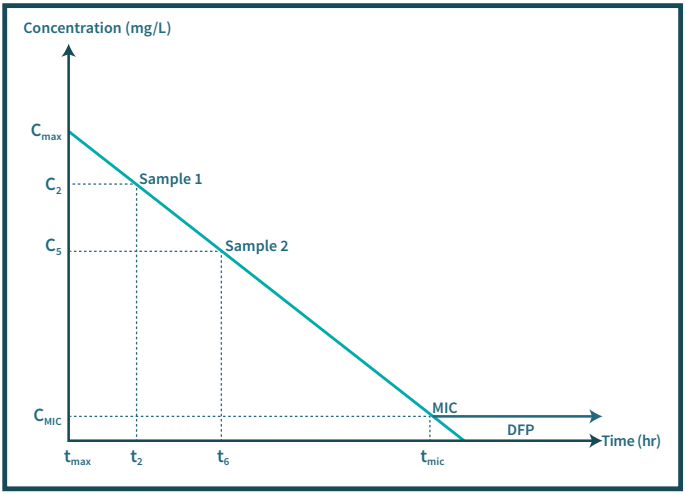

Figure 1.2: Example of two post samplings in SDD monitoring, post 2 hours (sample 1) and post 6 hours (sample 2)

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic	• Fluid overload • Wrong sampling time • Insufficient dose • Drug interaction • Burn • Ascites • Dialysis	Poor	If sampling time is satisfactory, correct the fluid imbalance (if fluid overload) give incremental loading dose STAT, then continue current dose or increase the dose appropriately & resample
		Good	Continue current dose
Within normal therapeutic range		Poor	If sampling time is satisfactory & hydration status is fair, increase the dose (not more than max recommended)
		Good	Continue current dose
Potential Toxic/ Toxic	• Dehydration • Renal failure • Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Nephrotoxicity • Ototoxicity	Withold treatment (if necessary), hydrate the patient (if dehydrated) then adjust dose accordingly

**The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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CHAPTER 2: CARBAMAZEPINE

CHAPTER 2
CARBAMAZEPINE

KEY PARAMETERS:

Therapeutic range	4 – 12mcg/ml[1,2,4]
Bioavailability (F)	80%[1]
Salt Factor (S)	1[1]
Volume of Distribution (Vd)	Neonates: 1.5 L/kg Paediatric: 1.9 L/kg Adults: 0.6 – 2L/kg (Based on actual body weight)[2]
Clearance (CL)	Monotherapy: 0.064 L/kg/hr[1] Polytherapy: 0.10 L/kg/hr[1] Paediatric (monotherapy): 0.11 L/kg/hr[1]
Half-life ($t_{1/2}$)	Paediatric: 4 – 12 hours[1] Adult monotherapy: 15 hours[1] Adult polytherapy: 10 hours[1]

A. PHARMACOKINETIC

Bioavailability (F):[1]

Oral (Immediate release tablets, chewable tablets and oral suspension): 80%

Volume Distribution (Vd):

Neonates	1.5 L/kg
Paediatric	1.9 L/kg
Adults:	0.6 – 2L/kg

(Based on actual body weight)[2]

Carbamazepine distributes into all tissues.[5]

The concentration of carbamazepine in breast milk is about 25 – 60% of concentration of mother's plasma.[2]

carbamazepine rapidly crosses the placenta and accumulates in fetal tissue.[2]

Protein Binding: 75 – 90%[2]

Carbamazepine binds to albumin and to alpha-1-acid glycoprotein (AAG).[2]
The concentration of AAG and the free fraction of carbamazepine may vary with the presence of inflammation, trauma, concurrent antiepileptic drug therapy and age.[2]

Clearance (CL):[1]

Carbamazepine is eliminated almost exclusively by the metabolic route, with less than 2% of an oral dose being excreted unchanged in the urine.

Adult Monotherapy	0.064 L/kg/hr
Adult Polytherapy	0.10 L/kg/hr
Paediatric (monotherapy)	0.11 L/kg/hr

The increase in clearance associated with chronic therapy is apparently due to auto-induction of its metabolic enzymes.

AUTOINDUCTION:[3]

- Carbamazepine induced its own metabolism via the hepatic microsomal enzyme CYP3A4 system.
- When dosing is initiated, serum concentrations increase according to the baseline clearance and half-life.
- After a few doses of carbamazepine, enough auto-induction has occurred that clearance increases, half-life decreases and drug accumulation slows down.
- With additional exposure of liver tissue to carbamazepine, clearance continues to increase and half-life continues to shorten.
- As a result, concentration decline and ultimately stabilise in accord with the new clearance and half-life values.

Half Life ($T_{½}$):

The half-life changes with continued dosing and is affected by other drugs.[2]

Paediatric	4 – 12 hours[1]
Adult monotherapy	15 hours[1]
Adult polytherapy	10 hours[1]

Indication and Therapeutic range:

Bipolar disorder	4 – 12 mcg/ml[1,2,4]
Epilepsy	
Trigeminal neuralgia	

B. DOSAGE

Paediatric[9]

Epilepsy:

Child 1 month – 12 years:
Initially 5mg/kg at night or 2.5mg/kg twice daily, increased as necessary by 2.5 – 5mg/kg every 3 – 7 days; usual maintenance dose 5mg/kg 2 – 3 times daily; doses up to 20mg/kg daily have been used

Child 12-18 years:
Initially 100 – 200mg 1 – 2times daily, increased slowly to usual maintenance dose 200mg – 400mg 2 – 3times daily; in some cases doses up to 1.8g daily may be needed

Adult[7]

Epilepsy:

Initial: 400mg/day in 2 divided doses or 4 divided doses (oral suspension)

Maintenance: Increase by up to 200mg/day at weekly intervals using a twice daily regimen of extended release tablets or capsules, or a 3 – 4 times daily regimen of other formulations until optimal response and therapeutic levels are achieved

Maximum: 2,400mg/day

Bipolar disorder:

Initial: 400mg/day in two divided doses

Maintenance: May adjust by 200mg/day increments

Maximum: 1,600mg/day

Trigeminal neuralgia:

Initial: 200mg/day in 2 divided doses or 4 divided doses (oral suspension) with food, gradually increasing in increments of 200mg/day as needed

Maintenance: 400 – 800mg daily in 2 divided doses or 4 divided doses (oral suspension)

Maximum: 1200mg/day

Renal Impairment:[7]

Infants, Paediatric and Adolescents:
GFR ≥10ml/minute/1.73m^2: No dosage adjustment required

GFR <10ml/minute/1.73m^2: Administer 75% of normal dose

Intermittent haemodialysis: Administer 75% of normal dose; on dialysis days give dose after haemodialysis

Peritoneal dialysis (PD): Administer 75% of normal dose

Continuous renal replacement therapy (CRRT): Administer 75% of normal dose; monitor serum concentrations

Note: Renally adjusted dose recommendations are based on doses of 10-20mg/kg/day divided every 8-12 hours.

Adults:
GFR ≥10ml/minute: No dosage adjustment required

GFR <10ml/minute: Administer 75% of dose

Intermittent haemodialysis: Administer 75% of normal dose; on dialysis days give dose after haemodialysis

Peritoneal dialysis (PD): Administer 75% of normal dose

Continuous renal replacement therapy (CRRT): No dosage adjustment recommended

Hepatic Impairment:[3]

Patient with liver cirrhosis or acute hepatitis have reduced carbamazepine clearance because of destruction of liver parenchyma. This loss of functional hepatic cells reduces the amount of CYP3A4 available to metabolise the drug and decreases clearance.[3]

Carbamazepine serum concentrations and the presence of adverse drug effects should be monitored frequently in patients with liver cirrhosis.

C. INTERACTION

Carbamazepine has many drug interactions resulting both from CYP3A4 inhibition and CYP3A4 induction which alter observed concentrations.[1]

CYP 3A4 **inhibitors** which inhibit carbamazepine metabolism and increase plasma carbamazepine include	CPY 3A4 **inducers** which induce the rate of carbamazepine metabolism and decrease plasma carbamazepine include
Increased Plasma Carbamazepine	**Decreased Plasma Carbamazepine**
Clarithromycin	Cisplatin
Diltiazem	Doxorubicin
Erythromycin	Phenobarbital
Fluoxetine	Phenytoin
Grapefruit juice	Primidone
Isoniazid	Rifampicin
Loratadine	Theophylline
Valproate	
Verapamil	
Azole antifungals: Fluconazole, Itraconazole, Ketoconazole	
Protease inhibitors: Indinavir, Nelfinavir, Ritonavir	

D. SAMPLING

Time to monitor serum concentration (at steady state)

The time to steady state depends on the completion of auto-induction.[2]

Initiation:

2 – 3 weeks (dose changes is not recommended during this period)[3]

After initiation (2 – 3weeks) and dose changes:

2 – 5 days[7]

Sampling Time

Pre-sample: just before next dose[1]

E. MONITORING PARAMETER[2]

- Carbamazepine blood concentrations; periodically to optimize efficacy and reduce toxicity
- Complete blood count, including platelets and differential; before initiating therapy and periodically thereafter
- Hepatic function tests, especially in patients with a history of liver disease; prior to initiation of therapy and periodically thereafter
- Complete urinalysis and BUN determinations; baseline and periodically during therapy
- Improvement in seizure control may be indicative of efficacy
- Reduction in pain of trigeminal neuralgia and other neurological syndromes may indicate efficacy
- Improvement in symptoms of bipolar disorder may indicate efficacy

F. ADVERSE DRUG REACTION

Common[4]

Cardiovascular	Hypotension
Dermatologic	Pruritus (8%), rash (7%)
Gastrointestinal	Constipation (10%), nausea (29%), vomiting (18%), xerostomia (8%)
Neurologic	Asthenia (8%), ataxia (15%), dizziness (44%), somnolence
Ophthalmic	Blurred vision (6%), nystagmus

Serious[4]

Cardiovascular	Atrioventricular block, cardiac dysrhythmia, congestive heart failure, eosinophilic myocarditis, hypersensitivity, syncope
Dermatologic	Stevens-Johnson syndrome, toxic epidermal necrolysis
Endocrine metabolic	Hypocalcemia, hyponatremia (4% to 21.7%), water intoxication syndrome
Gastrointestinal	Pancreatitis
Hematologic	Agranulocytosis, aplastic anaemia, bone marrow depression, eosinophilia, leukopenia, pancytopenia, thrombocytopenia
Hepatic	Hepatitis, hepatotoxicity, liver failure, vanishing bile duct syndrome
Immunologic	Drug hypersensitivity syndrome
Neurologic	Acute intermittent porphyria
Renal	Azotemia, renal failure
Respiratory	Pulmonary hypersensitivity
Other	Angioedema

Overdosage/Toxicology:[4]

Poisoning is common and there are several deaths each year from carbamazepine poisoning.

Peak serum levels less than 30 mcg/ml are generally associated with mild to moderate toxicity. Peak levels more than 40 mcg/ml may be associated with coma, seizures and hypotension.

Management of overdosage/toxicology:

- Supportive care is mainstay treatment
- Activated charcoal may be considered in asymptomatic patients who are likely to have medication remaining in their GI tract, or in symptomatic patients who have a secure airway. Whole bowel irrigation may be considered for patients with severe toxicity involving ingestion of a large amount of a sustained release formulation. Gastric lavage may be considered for very large overdoses presenting early.
- Antidote: none
- Haemoperfusion or high flux haemodialysis may be useful in severe, life-threatening overdose.
- Monitor Carbamazepine serum concentration every 4 hours until the concentration has peaked and is clearly declining.

G. DILUTION AND ADMINISTRATION[8]

Drug Administration

To be taken with food.

Controlled Release tablet: Swallow whole, do not chew/crush.

H. CALCULATION

A) Dose Initiation

Maintenance dose: Oral

1. Estimate Clearance (CL):
   (Refer to CL chart for specific population CL value)

$$\text{CL (L/hour)} = \text{CL (L/kg/hour)} \times \text{BW (kg)}$$

2. Determine C_{ss} target (4 – 12mcg/ml) & calculate the maintenance dose

$$\text{MD (mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{(\text{S} \times \text{F})}$$

B) Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (L/hour)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg)}}{\text{Interval (hour)} \times \text{Css (mcg/ml)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{(CL(L/hour)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{(\text{S} \times \text{F})}$$

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subtherapeutic < 4mcg/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction	Poor	If compliance & sampling time is satisfactory, increase the dose appropriately & resample
		Good	Continue current dose
Within normal therapeutic range 4 – 12 mcg/ml		Poor	If compliance & sampling time is satisfactory, increase the dose (not more than max. recommended)
		Good	Continue current dose
Potential toxic/ Toxic > 12mcg/ml	• Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Diplopia • Hyponatremia • Seizure • Arrythmia • Dizziness	Withold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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CHAPTER 3: CYCLOSPORINE

CHAPTER 3
CYCLOSPORINE

KEY PARAMETERS:

Therapeutic range	C_0 ~100 – 500mcg/L C_2 ~ 600 – 1700 mcg/L
Bioavailability (F)	0.3
Salt Factor (S)	1
Volume of Distribution (Vd)	3 – 5L/kg
Clearance (CL)	5 – 10ml/kg/min
Half-life ($t_{1/2}$)	8.4 hours (ranges 5 – 18 hours)

A. PHARMACOKINETIC

Bioavailability (F):

Oral Cyclosporine (modified) - bioavailability of capsule and oral solution are equivalent.
Paediatric (1 – 10 years): 43% (range 30 – 68%)[1,4]
Adult: Approximately 30%[1-3]

Volume of Distribution (Vd):

Cyclosporine is widely distributed in tissues and body fluids including the liver, pancreas and lungs; also crosses placenta and enters breast milk.[1]

The volume of distribution is 3 – 5 L/kg.[2,3,4]

This relatively large Vd is due to cyclosporine significantly bound to plasma and blood elements that is probably tissue outside the vascular phase.[2]

Protein Binding: 90 – 98% to lipoproteins.[1]

Clearance (CL):

Cyclosporine is primarily by hepatic metabolism via CYP3A4.[1]

Oral	0.42 – 0.48 L/kg/h (7 – 8ml/kg/min)[2,3]
Intravenous	0.30 – 0.42 L/kg/h (5 – 7ml/kg/min)[2,3]

*Paediatric may have higher clearance; 10 – 15ml/kg/min[3]
For patient with liver failure; 3ml/kg/min[1]

Half-life ($t_{½}$):

Generally, half life of Cyclosporine is around 8.4 hours (ranges 5 – 18).[1-3]
Half-life of cyclosporine may be prolonged in patients with liver failure (20 hours) and shorter in paediatric (6 hours) due to the higher metabolism rate.[1,5]

Indication and Therapeutic Range:

Cyclosporine inhibits production and release of interleukin II and inhibits interleukin II-induced activation of resting T-lymphocytes.[1]

Cyclosporine is indicated for:

- Patients in whom donor specific transplantation cannot be carried out and in young children to minimize side effects of steroids
- Bone marrow transplant
- Solid organ transplant
- Severe rheumatoid arthritis not responding to other second line drugs
- Idiopathic nephrotic syndrome who are steroid toxic or poor response to Cyclophosphamide
- Severe aplastic anemia, pure red cell aplasia
- Recalcitrant psoriasis and atopic eczema

Reference ranges vary based on settings, indications and duration of transplant. Kindly discuss with physicians based on clinical judgment.

Assay used: Monoclonal Fluorescence Polarization Immunoassay.

Recommended Pre-dose Cyclosporine Concentration (C_0):

<table>
<tr><th>Indications</th><th>C_0 level (mcg/L)</th></tr>
<tr><td>Bone marrow transplant</td><td>Paediatric : 100 – 250[6]
Adult : 250 – 500[3]</td></tr>
<tr><td>Kidney transplant</td><td>Paediatric[6]
<3 months: 300 – 400
>3 months: 100 – 300

Adult – based on rejection risk[7]
<table>
<tr><th>Months</th><th>Low Risk</th><th>Moderate Risk</th><th>High Risk</th></tr>
<tr><td>0 – 6</td><td>150 – 275</td><td>175 – 325</td><td>200 – 350</td></tr>
<tr><td>7 – 12</td><td>100 – 200</td><td>125 – 225</td><td>150 – 250</td></tr>
<tr><td>>12</td><td>50 – 150</td><td>75 – 175</td><td>100 – 200</td></tr>
</table>
</td></tr>
</table>

Indications	C_0 level (mcg/L)
Liver transplant	Paediatric[6] <3 months: 200 – 250 >3 months: 100 – 125 Adult: 200 – 500[3]
Others transplant (heart, lungs)	Paediatric: 100 – 400[6] Adult: 300 – 500[3]
Ulcerative colitis (Severe)	150 – 350[4]
Aplastic anemia	75 – 200[4]
Graft versus host disease	200 – 600[4]

Recommended 2-hour (±15minutes) Post-dose Cyclosporine Concentration (C_2):

Indications	C_2 level (mcg/L)
Kidney transplant[7]	

Duration	C_2 level (mcg/L)
1 month	1,700
2 months	1,500
3 months	1,300
4 – 6 months	900 – 1,000
7 – 12 months	700 – 900
>12 months	700 – 800

Indications	C_2 level (mcg/L)
Liver transplant[6]	

Duration	C_2 level (mcg/L)
0 – 3months	1,000
4 – 6months	800
> 6 months	600

B. DOSAGE:

Injection cyclosporine is in non-modified formulation (Sandimmune®). Oral cyclosporine is in modified formulation (Neoral®).

The IV dose is generally one-third the oral dose and should be adjusted based on clinical response, predefined blood concentrations, and tolerability. Because of the risk of anaphylaxis with the IV formulation, reserve IV administration for patients who are unable to tolerate oral cyclosporine formulations.[4]

Paediatric:

Category	Dosage
Cardiac/Liver/Renal transplant rejection, in combination of Corticosteroid; treatment or prophylaxis[4]	6 months or older – refer to adult dose.
Graft versus host disease; prophylaxis[4]	*IV:* 1.5mg/kg in 2 divided doses *PO:* 6.25mg in 2 divided doses
Nephrotic syndrome[8]	*PO:* 1 month – 18 years, 3mg/kg BD, for maintenance reduce to lowest effective dose according to whole blood-cyclosporine concentrations, proteinuria and renal function
Psoriasis[1]	*PO:* 2.5mg/kg/day in 2 divided doses may increase dose by 0.5mg/kg/day if insufficient response is seen after 4 weeks. Maximum: 4mg/kg/day
Rheumatoid arthritis[1]	*PO:* 2.5mg/kg/day in 2 divided doses may be increased by 0.5 to 0.75mg/kg/day if insufficient response is seen after 8 weeks of treatment. Maximum: 4mg/kg/day

Adult:

Category	Dosage
Cardiac/Liver/Renal transplant rejection, in combination of Corticosteroid; treatment or prophylaxis[4]	*IV:* 5 to 6mg/kg/day, with the first dose 4 to 12 hours before surgery and continue the initial daily dose postoperatively until the patient can tolerate oral administration. Alternatively, 1mg/kg/day preoperatively, increased by 1mg/kg/day every 24 hours until a maintenance dose of 4mg/kg/day is reached. *PO:* 15mg/kg to be given 4 to 12 hours before transplant or postoperatively, followed by 15mg/kg/day given in 2 divided doses for 1 to 2 weeks period, titrated based on clinical response, predefined trough blood concentrations and tolerability.
Lung transplant rejection; prophylaxis[4]	*IV:* 2.4mg/kg/day given as a continuous infusion over 24 hours. *PO:* 5mg/kg/day in 2 divided doses.
Graft versus host disease; prophylaxis[4]	*IV:* 3 to 5mg/kg/day, usually administered as a continuous infusion beginning 1 or 2 days prior to transplantation. *PO:* 4 to 10mg/kg/day.
Aplastic anemia[4]	*PO:* 5mg/kg/day in two divided doses.
Psoriasis[4]	PO 2.5mg/kg/day in 2 divided doses. After 4 weeks, the dose may be increased 0.5mg/kg/day at 2-week intervals, depending on clinical response and tolerability. Maximum: 4mg/kg/day.
Rheumatoid arthritis[4]	*PO:* 2.5mg/kg/day in 2 divided doses, may be increased by 0.5 to 0.75mg/kg/day after 8 weeks and again after 12 weeks, depending on clinical benefit and tolerability. Maximum: 4mg/kg/day.

Renal impairment:

Dosing alterations of cyclosporine during haemodialysis and peritoneal dialysis is not needed[4]

Category	Dosage
Cardiac/Liver/Renal Transplantation[4]	Reduce the dosage if nephrotoxicity develops.
Psoriasis[1,4]	Decrease the dose by 25% to 50% for an elevation of serum creatinine of 25% or more above pre-treatment level on 2 tests 2 weeks apart or for any elevation of 50% or more above pre-treatment level. Discontinue treatment if reversibility of serum creatinine to within 25% of baseline is not attained after 2 dose reductions.
Rheumatoid Arthritis[4]	Decrease the dose by 25% to 50% for an elevation in serum creatinine of 30% above pre-treatment level. Discontinue treatment if the dose reduction does not control the abnormality or if the abnormality is severe.

Hepatic impairment:

It may require lower doses of modified cyclosporine for micro emulsion to maintain blood concentrations within the recommended range.[4]

C. INTERACTION

Drugs that inhibit cytochrome P450 (CYP3A4) and P-glycoprotein (increase cyclosporine concentrations)[2]	Drugs that induce cytochrome P450 (CYP3A4) and P-glycoprotein (reduce cyclosporine concentrations)[2]
Calcium channel blockers Diltiazem Verapamil **Antibiotics** Clarithromycin Erythromycin Metronidazole **HIV protease inhibitors** Indinavir Ritonavir **Gastrointestinal prokinetic agents** Metoclopramide **Immunosuppresants** Sirolimus[1] Tacrolimus[1] **Antifungal agents** Flucanazole Itraconazole Ketoconazole Voriconazole **Others** Bromocriptine Cimetidine Ethinyl estradiol Methylprednisolone Grapefruit juice NSAIDs Other CYP3A4 inhibitors	**Antibiotics** Rifampicin Imipenem[1] **Antifungal** Caspofungin Terbinafine[4] Griseofulvin[4] **Anticonvulsants** Carbamazepine Phenobarbital Phenytoin **Others** Orlistat[3] St. John's Wart Other CYP3A4 inducers

D. SAMPLING

Time to monitor serum concentration (at steady state): ~ 3 – 5 days

Monitor every 4 to 7 days after conversion from non-modified to modified formulation. Monitored at least twice a week when converting patients to modified formulation at doses greater than 10mg/kg/day, and daily if the initial dose exceeds 10mg/kg/day, until the concentration is stabilised.[4]

Sampling time

Most commonly used method: Trough level[2]
Concentration at 2 hours is a more sensitive predictor for acute rejection (especially during first year after transplantation).[2,9-11] There is a 15-minute period before and after the 2-hour time point, during which the C_2 sample can be taken to remain within an acceptable margin of error[2]

*Please use EDTA tube as whole blood need to be processed.

E. MONITORING PARAMETER

Monitor blood pressure and serum creatinine after any cyclosporine dosage changes or addition, modification or deletion of other medications.[1]

Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.[1]

F. ADVERSE DRUG REACTION

Most of the adverse drug reactions resolved with dose reduction or discontinuation[3]

Adverse drug reaction (>10%):	
Cardiovascular	Hypertension, oedema
Central nervous system	Headache
Dermatologic	Hirsutism, hypertrichosis
Endocrine & metabolic	TG increased, female reproductive disorder
Gastrointestinal	Nausea, diarrhoea, gum hyperplasia, abdominal discomfort, dyspepsia
Neuromuscular & skeletal:	Tremor, paresthesia, leg cramps
Renal	Renal dysfunction, creatinine increased
Respiratory	Upper respiratory infection
Miscellaneous	Infection

Overdosage/Toxicology:

Cyclosporine ingestion is an uncommon cause of poisoning. Ingestions are usually unintentional, and rarely result in severe manifestations.

No antidote is available. Management of toxicity is mainly supportive. Activated charcoal may be given. Haemodialysis has no benefit.[4]

G.DILUTION AND ADMINSTRATION[1]

Oral[1]	May dilute oral solution with orange juice or apple juice. Avoid changing diluents frequently. Mix thoroughly and drink at once. Mix in a glass container and rinse container with more diluents to ensure total dose is taken. Do not administer liquid from plastic or Styrofoam cup.
Intravenous[1]	May administer by IV intermittent infusion or continuous infusion. For intermittent infusion, dilute 1ml (50mg) of concentrated injection solution in 20 – 100ml of D5W or NS, infuse over 2 – 6 hours.

H. CALCULATION

A) Dose Initiation

1. Estimate clearance

$$\text{CL (L/hour)} = \text{CL (ml/kg/min)} \times \text{BW(kg)} \times 0.06$$

2. Determine the Css target and calculate the maintenance dose

$$\text{MD (mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S x F}} \times \frac{1}{1000}$$

3. Estimation of steady state concentration

$$\text{Css (mcg/L)} = \frac{\text{S X F X Dose(mcg)}}{\text{CL (L/hour)} \times \text{Interval (hour)}}$$

4. For calculation of intravenous dose (continuous infusion rate)

$$\text{ko (mcg/hr)} = \text{CL (L/kg)} \times \text{Css target (mcg/L)}$$

B) Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (L/day)} = \frac{\text{S x F x Dose (mcg/day)}}{\text{Css (mcg/L)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg/day)} = \frac{\text{CL (L/day)} \times \text{Css target (mcg/L)}}{\text{S x F}} \times \frac{1}{1000}$$

Alternatively, assuming linear relationship between dose and concentration:

$$\text{Desired Dose (mg)} = \frac{\text{(Css Desired)}}{\text{(Css Current)}} \times \text{Current Dose (mg)}$$

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CHAPTER 4: DIGOXIN

CHAPTER 4
DIGOXIN

KEY PARAMETERS:

Therapeutic range	CHF: 0.5 – 0.9ng/ml[1-4] AF: 0.8 – 2ng/ml[4-7]
Bioavailability (F)	Tablets: 0.7[4] IV and soft gelatine capsule: 1[4] Elixir: 0.8[4]
Salt Factor (S)	1[4]
Volume of Distribution (Vd)	4 – 7 L/kg[8]
Clearance (CL)	0.57 – 0.86ml/kg/min[4]
Half-life ($t_{1/2}$)	2 days[4]

A. PHARMACOKINETIC

Bioavailability (F):[4]

The bioavailability of digoxin varies depending on dosage form. The bioavailability ranges from 0.5 to greater than 0.9. The soft gelatine capsules of digoxin appear to be completely absorbed (100% bioavailability). The intravenous route is assumed to have 100% bioavailability. The elixir appears to have bioavailability of approximately 0.8. On the other hand, the bioavailability for tablet ranges from 0.5 to greater than 0.9. For tablets, the average of 0.7 may be used in dosage calculation.

Volume of Distribution (Vd):

Digoxin distribution follows a two-compartment model: First distributes into a small initial Vd (plasma and other rapidly equilibrium organ), and then distributes into larger and more slowly equilibrium tissues (myocardium).[4]

The average volume of distribution is approximately ~7.3 L/kg and is influenced by disease and concomitant drugs used.[8]

Volume of distribution	
Normal renal function	6 - 7 L/kg[8]
Renal disease	4 - 6 L/kg[8]
Neonates, full-term	7.5 -10 L/kg[8]
Paediatric	16 L/kg[8]

Vd in obese patient appears to be more closely related to the non-obese or IBW. Digoxin Vd is also decreased in hypothyroid patients and vice versa.[4] Hyperkalaemia and hyponatremia will decrease digoxin distribution to myocardium. In other hand, hypokalaemia will increase digoxin distribution to myocardium.[8]

Common factors that alter digoxin Vd:

- Quinidine: 0.7[9]
- Thyroid:
  - Hypothyroid: 0.7[4]
  - Hyperthyroid: 1.3[4]

**Factor should be multiplied by calculated $Vd_{digoxin}$.*

Protein Binding: 30%, increased free fraction in uremic patients.[9]

Clearance (CL):

The metabolic clearance of digoxin ~0.57 to 0.86ml/kg/min and the renal clearance is approximately equal to CrCl. Same like Vd, digoxin clearance also influence by disease (CHF) and concomitant drugs used.[6]

Common factors that alter Digoxin clearance:

- CHF: (refer formula)[4]
- Amiodarone: 0.5[4]
- Quinidine: 0.5[9]
- Verapamil: 0.75[4]
- Thyroid function
- Hypothyroid: 0.7[4]
- Hyperthyroid: 1.3[4]

**Factor should be multiplied by calculated $CL_{digoxin}$ in L/hr or L/day.*

Half-life ($t_{½}$):

The half-life for Digoxin depends on age and renal function.[8]

Half-life	
Premature neonates	61 – 170 hours
Full-term neonates	35 – 45 hours
Infants	18 – 25 hours
Paediatric	35 hours
Adults	38 – 48 hours
Adults anephric	4 – 6 days

Indication and Therapeutic Range:

Due to its inotropic and chronotropic effects, digoxin is used for the treatment of congestive heart failure (CHF) and atrial fibrillation (AF). Positive inotropic effects of digoxin were seen with low Digoxin concentration hence the lower therapeutic range is used in CHF. This lower target range is based on the fact that most patients with CHF do not demonstrate additional therapeutic benefits from higher digoxin concentration.[1-2]

CHF: 0.5 – 0.9ng/ml[1-4]

Since the goal for digoxin in AF is rate control, hence higher therapeutic concentration is needed.[10]

AF: 0.8 – 2ng/ml[4-7]

Digoxin maximum target concentration of 2 ng/ml was determined based on toxicity rather than efficacy. Heart rate at all levels of exercise in most patients with chronic AF is not adequately controlled by any therapeutic concentration of digoxin for which combination with other rate control agents should be considered.[7,9]

B. DOSAGE

Paediatric:[8]

Age	Total digitalising dose (TDD[a] (mcg/kg[b])		Daily maintenance dose[c] (mcg/kg[b])	
	Oral	IV/IM	Oral	IV/IM
Preterm infant[b]	20 – 30	15 – 25	5 – 7.5	4 – 6
Full-term infant[b]	25 – 35	20 – 30	6 – 10	5 – 8
1 mo – 2 y/o[b]	35 – 60	30 – 50	10 – 15	7.5 – 12
2 – 5 y/o[b]	30 – 40	25 – 35	7.5 – 10	6 – 9
5 – 10 y/o[b]	20 – 35	15 – 30	5 – 10	4 – 8
>10 y/o[b]	10 – 15	8 – 12	2.5 – 5	2 – 3

[a] Loading dose: Initially give one-half of TDD, then give one-quarter of TDD in 2 subsequent doses at 8 to 12 hours interval. Obtained ECG 6 hours after each dose to assess potential toxicity. If control has been achieved, omit the remaining TDD.

[b] Based on lean body weight and normal renal function for age.

[c] Given in two divided doses for infants and paediatric less than 10 years old.

Adult:[8]

Total digitalising dose (TDD)[a] (mg)		Daily maintenance dose (mg)	
Oral	**IV/IM**	**Oral**	**IV/IM**
0.75 – 1.5	0.5 – 1	0.125 – 0.5	0.1 – 0.4

[a] Initially give one-half of TDD, then give one-quarter of TDD in 2 subsequent doses at 8 to 12 hours interval. Obtain ECG 6 hours after each dose to assess potential toxicity. If control has being archived, omit the remaining TDD.

Renal Impairment:[9]

Digoxin renal clearance should be reduced in patient with impaired renal function.

Renal dosage adjustment	
CrCl 10 – 50ml/minutes	Administered 25% to 75% of dose every 36 hours
CrCl < 10ml/minutes	Administered 10% to 25% of dose every 48 hours

TDD should be reduced 50% in end stage renal disease.

*Digoxin is not dialyzable (~ 5%).

C. INTERACTION

Increased drug concentration/effects:	Decreased drug concentration/effects:
Beta blocker – may have additive effects on heart rate[8]	Amiloride and Spironolactone – reduce the inotropic response to digoxin[8]
Amiodarone – reduced Digoxin clearance[8]	Cholestyramine and metoclopramide: reduce Digoxin absorption[11]
Quinidine – reduced Digoxin clearance[9]	Levothyroxine and other thyroid hormone - increased clearance[8]
Erythromycin/Clarithromycin	
Other CYP3A4 inhibitors– inhibits CYP3A4 which minimally metabolized digoxin[6,12]	

D. SAMPLING[4]

Time to monitor serum concentration (at steady state):

When to obtain serum digoxin level (after dose initiation or adjustment)	
With Loading dose	12 – 24 hours
Without Loading dose	Depends on half-life (≈5 half-life) (Normally 7 – 14 days after any change in maintenance dose)

Note: In patient with end stage renal disease, it may take 15 – 20 days to reach steady state.

Maintenance dose:

Oral	30 minutes prior OR just before next dose. If dose already taken wait at least 6 hours post dose.
IV	30 minutes prior OR just before next dose. If dose already taken wait at least 4 hours post dose.

**The sampling time for post dose (6 hours for oral and 4 hours for IV) is acceptable to avoid distribution phase.*

Suspected toxicity:

If toxicity is suspected, blood may be drawn at any-time (random).

E. MONITORING PARAMETER

Symptomatic improvement:[6]	
Congestive Heart Failure	An improvement in common signs and symptoms of heart failure suggests therapeutic success. Common signs and symptoms of heart failure proposed by New York Heart Association NYHA.[3] a. Left-sided failure: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, tachypnea, cough, haemoptysis, pulmonary oedema, S3 gallop, plueral effusion, Chyne-stokes respiration. b. Right sided failure: abdominal pain, anorexia, nausea, bloating, constipation, ascites, peripheral oedema, jugular venous distention, hepatojugular reflux, hepatomegaly. c. General symptoms: fatigue, weakness, nocturia, CNS symptoms, tachycardia, pallor, digital cyanosis, cardiomegaly.

Atrial Fibrillation	Heart/ventricular rate (usually <100 beats/min) and electrocardiogram.
Possible interactions/toxicity potentiation:	
Electrolyte imbalance	Monitor for potassium level (hypokalaemia) especially if patient is on concomitant ACE inhibitor/diuretics). Monitor for Hypomagnesaemia and hypercalcemia.
Renal function	a. Clinically unstable renal function: 2 – 3 times weekly monitoring. b. Stable renal function patient may only need monitoring of the serum creatinine when deem necessary.

F. ADVERSE DRUG REACTION

Researcher has found an increased incidence of adverse events when Digoxin serum concentration exceed >2mcg/L : Increased incidence of ADR.[6]

Adverse drug reaction:[6]	
Serum concentration >2.5mcg/L	~50% will exhibit some form of toxicity involving: a. Gastrointestinal: anorexia, nausea, vomiting, diarrhoea, abdominal pain & constipation. b. Central nervous system: headache, fatigue, insomnia, confusion, vertigo. Visual disturbances symptoms: blurred vision, change in colour vision, coloured halos around objects times involving the yellow-green spectrum. c. Cardiovascular: atrioventricular block/dissociation, bradycardia, premature ventricular contractions, ventricular tachycardia. New arrhythmia while receiving digoxin treatment shall be accounted for possible digoxin toxicity.
Other related ADR:[8]	
Dermatologic	Maculopapular rash; erythematous; scarlatiniform popular; vesicular or bullous rash; urticaria; pruritis; facial; angioneurotic or laryngeal oedema; shedding of fingernail or toenails; alopecia.
Neuromuscular & skeletal	Weakness.

Overdosage/Toxicology:[15]

Patients with acute poisoning may develop severe bradycardia, heart block, vomiting, and shock. Hyperkalemia is a marker of severe acute toxicity and serum potassium level is the best predictor of cardiac glycoside toxicity after acute overdose. Severe chronic toxicity causes ventricular dysrhythmias and varying degrees of heart block.

Treat hyperkalemia if potassium level >5.5mEq/L. Activated charcoal should be considered in all cases that present within 1 to 2 hours of ingestion as digoxin is well absorbed by charcoal. Haemodialysis does not increase the clearance of digoxin.

G. DILUTION AND ADMINSTRATION

Drug administration:

Drug administration	
IV Bolus	May be infused undiluted. Administration rate >5 minutes.[13]
Intermittent IV Infusion	To be infused 10 – 20 minutes with max concentration 32 mcg/ml.[13] *IM route associated with muscle necrosis hence not recommended. If needed, not more than 500mcg (adult) or 200mcg (paediatrics) should be injected into a single site.[13]

Dilution of drug:

Dilution of drug	It can be given undiluted for iv bolus or diluted for iv infusion. a. Dilute in normal saline or dextrose 5% or water for injection.[13-14] b. Undiluted for IV bolus.[8,13,14] c. Further diluted the initial volume with >4 fold of compatible diluents as above, used less diluent may cause precipitation. *Diluted solution stable for 48 hours (room/fridge)[14]

H. CALCULATION

1. Dose Initiation

Maintenance dose: Oral/Intravenous

1. Estimate Clearance (CL)

$$\text{CrCL (ml/min)} = \frac{(140 - \text{Age})\ (\text{BW in kg})}{\text{Scr } (\mu\text{mol/L})} \times 1.23\ (\text{male})\ \text{ or } 1.04\ (\text{female})$$

CL Dig (L/hr) =

Patient without CHF = [(0.8 × BW) + CrCL] × 0.06

Patient with CHF = [(0.33 × BW) + (0.9 × CrCL)] × 0.06

2. Determine Css target and calculate maintenance dose (MD)

$$\text{MD (mcg)} = \frac{\text{CL Dig (L/hr)} \times \text{Css target (ng/ml)} \times \text{Interval (hour)}}{S \times F}$$

Loading Dose

1. Estimate volume of distribution (Vd)

$$\text{Vd (L)} = (3.8 \times \text{BW}) + (3.1 \times \text{CrCL})$$

2. Determine Css target and calculate loading dose (LD)

$$\text{LD (mcg)} = \frac{\text{Vd(L)} \times \text{Css target (ng/ml)}}{S \times F}$$

2. Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (L/day)} = \frac{S \times F \times \text{Dose } (\mu\text{g/day})}{\text{Css (ng/ml)}}$$

2. Determine Css target and calculate new maintenance dose

$$\text{MD (mcg)} = \frac{\text{Cl (L/day)} \times \text{Css target (ng/ml)} \times \text{Interval (day)}}{S \times F}$$

I. RESULT EVALUATION

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic < 0.5 ng/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction • Hypoalbuminemia • Renal failure	Poor	If compliance & sampling time is satisfactory, give incremental loading dose STAT (for patient in ward), then continue with current dose & resample
		Good	Continue current dose
Within normal therapeutic range 0.5 – 2.0 ng/ml		Poor	Determine other factors that may contribute to poor response and treat accordingly
		Good	Continue current dose
Potential toxic/ Toxic >2.0ng/ml	• Overdosage • Underlying disease/ factors • Possible drug interaction • Renal failure • Hypokalemia • CHF	Toxic effect: • Vomiting • Hyperkalemia • Sinus bradycardia • Hyponatremia • Ventricular arrythmia • Weakness	Withhold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

J. REFERENCES

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CHAPTER 5: METHOTREXATE

CHAPTER 5
METHOTREXATE

KEY PARAMETERS:

Toxic range	Variable; Refer to specific protocols In general: Toxic if >0.1 µmol/L
Bioavailability (F)[10]	Parenteral: completely absorbed Oral: Low doses (<30mg/m^2) - rapidly absorbed; Higher doses incompletely absorbed
Volume of Distribution(Vd)[9]	Initial Vd: 0.18 – 0.2 L/kg Steady state Vd: 0.4 – 0.8 L/kg Protein binding: 50 – 60%
Metabolism[12,13]	Minimally metabolized
Clearance(CL)[9]	Parent drug and metabolites: Renal Urine (48 – 100%); Biliary (<10%) CL_{drug} ≈CrCl, Estimated to be 1 – 2 times (≈1.65) the CrCl
Half-life($t_{1/2}$)[14,15,16]	Biexponential: Initial phase, α: 1.5 – 3.5 hours (≈3 hours, when Methotrexate concentrations[MTX] >0.5 µmol/L) Terminal, ß: 8 – 15 hours (≈ 10 hours, become apparent when Methotrexate concentrations[MTX] ≤0.5 µmol/L) Paediatric: 0.7 – 5.8 hours

A. PHARMACOKINETIC

Bioavailability (F):[10]

Parenteral : completely absorbed
Oral : Low doses (<30mg/m^2) - rapidly absorbed;
Higher doses incompletely absorbed

Volume Distribution (Vd):[9]

Initial Vd : 0.18 – 0.2 L/kg
Steady state Vd : 0.4 – 0.8 L/kg
Protein binding : 50 – 60%

Clearance (CL):[9]

Parent drug and metabolites: Primarily renal
Urine (48 – 100%); Biliary (<y610%)

With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours.

CL_{drug} ≈ CrCl, CLdrug is estimated to be 1-2 times (≈1.65) the CrCl.

Half Life ($t_{½}$):[14,15,16]

Biexponential:

Initial phase, α:

1.5 – 3.5 hours (≈3 hours, when[MTX] >0.5µmol/L)

Terminal, ß:

8 – 15 hours (≈10 hours, become apparent when[MTX] ≤0.5µmol/L)

Paediatric: 0.7 – 5.8 hours

Indications:[4]

Oncology-related uses:

Treatment of trophoblastic neoplasms (gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole), acute lymphocytic leukemia (ALL), meningeal leukemia, breast cancer, head and neck cancer (epidermoid), cutaneous T-Cell lymphoma (advanced mycosis fungoides), lung cancer (squamous cell and small cell), advanced non-Hodgkin's lymphomas (NHL), Osteosarcoma

Non-oncology uses:

Treatment of psoriasis (severe, recalcitrant, disabling) and severe rheumatoid arthritis (RA), including polyarticular-course juvenile idiopathic arthritis (JIA)

B. DOSAGE

Refer specific protocols
(Pharmacist must identify the protocol used with prescriber before interpretation is done)

Summary of Protocols

Protocol	Dosage	Infusion Time	Leucovorin Rescue	MTX Level	Target (µmol/L)
ALL BFM SR/MR[22]	3g/m²	24 hours	Start 36 hours	48 hours	<0.25
ALL BFM Protocol M	3g/m²	24 hours	Start 36 hours	48 hours	<0.25
ALL BFM HR[22]	5g/m²	24 hours	Start 42 hours	48 hours	<0.1
Ph+ ALL[24]	5g/m²	24 hours	Start 42 hours	48 hours	<0.1
Relapsed ALL[19]	1g/m²	36 hours	Start 48 hours	60 hours	<0.1
Burkitt/NHL Group B[21]	3g/m²	3 hours	Start 24 hours (Complete 12 doses)	36 hours	<0.1
Burkitt/NHL Group C[21]	8g/m²	4 hours	Start 24 hours (Complete 12 doses)	36 hours	<0.1
Baby Brain Protocol[23]	3g/m²	24 hours	Start 36 hours	48 hours	<0.1
Osteosarcoma[18]	12g/m² (max 20g)	4 hours	Start 24 hours (Complete 7 doses)	24 hours	<0.1

Renal Impairment:[2,3,4]

CrCl 61-80ml/min : Decrease dose by 25%
CrCl 51-60ml/min : Decrease dose by 33%
CrCl 10-50ml/min : Decrease dose by 50% to 70%
CrCl<10ml/minute : Avoid use
Hemodialysis : Not dialyzable (0-5%); supplemental dose is not necessary
Peritoneal dialysis : Supplemental dose is not necessary
CAVH effects : Unknown

Hepatic Impairment:

The FDA-approved labelling does not contain dosage adjustment guidelines

Chemotherapy protocols/Methotrexate Dosage/Leucovorin rescue dose

Leucovorin (a.k.a Folinic acid) as the rescue drug for Methotrexate toxicity if started early and guided by Methotrexate level, seems to be safe as the mainstay therapy.[7]

Leucovorin Protocol

Serum MTX (µmol/L)	<0.05	0.05 – 0.5	0.5 – 5.0	>5.0
Post 24 hours of Methotrexate infusion. to be measured 24 hourly till[MTX] <0.05 µmol/L	No Leucovorin	10mg/m^2 6 hourly	100mg/m^2 6 hourly	1,000mg/m^2 6 hourly

Generally, methotrexate concentrations <0.1 µmol/L is considered to be non-toxic for most of the cases. However, for certain patients or in certain centres, a non-toxic margin of methotrexate concentrations <0.05 µmol/L may be preferred.

Available Methotrexate Protocols

1. UMMC MA SPORE ALL 2003
2. ALL BFM 95 – SR / MR
   a. ACTUAL PROTOCOL
   b. ALL BFM 95 – PROTOCOL M
   c. PROTOCOL M (ANZCHOG ALL STUDY 8 – PILOT, PHASE III)
   d. ALL HR PROTOCOL (COG-AALL0232)
3. RELAPSED ALL (ALL-REZ BFM 2002 – PROTOCOL FOR TREATMENT OF CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA)
4. OSTEOSARCOMA GUIDELINE (CHILDREN'S ONCOLOGY GROUP APPENDIX FOR AOST0331, PHASE III INTERROUP STUDY)
5. BABY BRAIN PROTOCOL (UKCCSH Infant Ependymoma Interim Guidelines)
6. BURKITT'S / NON-HODGKIN LYMPHOMA (UKCCSG, NHL GROUP; GUIDELINES FOR THE MANAGEMENT OF BURKITT/BURKITT LIKE AND B LARGE CELL NON-HODGKIN LYMPHOMA)

1. UMMC MA SPORE ALL 2003

MTX Dose	5g/m^2 over 24 hour
[MTX] monitoring	At 24 hours and then every 24 hours till methorexate SDC <0.4 µmol/L

Leucovorin Dose
15mg/m^2 every 6 hourly at 42 hours, 48 hours, 54 hours after start of IV methorexate (3 doses)

[MTX] after starting MTX Infusion (µmol/L) At 24 hours	>150			<150		
	15mg/m^2 every 6 hourly at 36 hours			15mg/m^2 every 6 hourly at 42 hours, 48 hours, 54 hours		
[MTX] after starting MTX Infusion (µmol/L) At 48 hours	>5	4.1 – 5	3.1 – 4	2.1 – 3	1.1 – 2	0.4 – 1
	>20mg/kg over 1 hour	75mg/m^2	60mg/m^2	45mg/m^2	30mg/m^2	15mg/m^2

2. ALL BFM 95 – SR / MR

a. ACTUAL PROTOCOL

[MTX] at 24, 36, 42, 48, 54 and 72 hours from start of infusion
If [MTX] at 24 hours is NORMAL (<150 µmol/L) - start Leucovorin at 42 hours
If [MTX] >150 µmol/L - recheck level of methatrexate at 36 hours:
If [MTX] <3 µmol/L - start Leucovorin at 42 hours
If [MTX] >3 µmol/L - start Leucovorin immediately

b. ALL BFM 95 – PROTOCOL M

MTX Dose	Protocol M: 3g/m^2 of MTX over 24 hours[4 courses]
[MTX] Monitoring	At 48 hours and every 24 hours until[MTX] <0.25 µmol/L (0.25 µmol/L)
Leucovorin Dose	30mg/m^2 stat at 36 hours after start of IV MTX then 15mg/m^2 every 6 hourly for 7 doses.

c. PROTOCOL M (ANZCHOG ALL STUDY 8 – PILOT, PHASE III)

MTX Dose	Protocol M: 5 g/m^2 of MTX over 24hours [4 courses]
[MTX] Monitoring	At 48 hours and every 24 hours until[MTX] <0.25 µmol/L (0.25 µmol/L)
Leucovorin Dose	30mg/m^2 stat at 36 hours after start of IV MTX then 15mg/m^2 every 6 hourly for 7 doses.

[MTX] After starting MTX infusion at 48 hours	<1 µmol/L	1 – 5 µmol/L	>5 µmol/L
	15mg/m^2 6 hourly	Increase dose according to treatment graph	May maximize dose to 100mg/m^2 3 hourly

d. ALL HR PROTOCOL (COG-AALL0232)

MTX Dose	3 g/m^2 of MTX over 24 hours[4 courses]
[MTX] Monitoring	At 48 hours. Targetted non-toxic[MTX] <0.1 µmol/L
Leucovorin Dose	Start Leucovorin rescue at 42 hours from start of MTX

e. ALL HR PROTOCOL (COG-AALL0232)

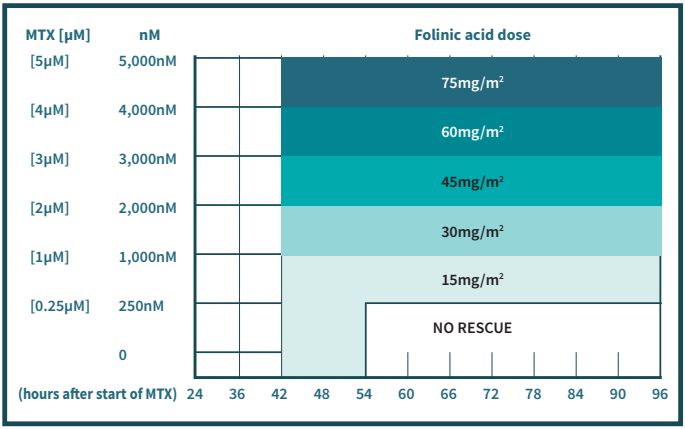

Figure 5.1 Diagram for calculating Folinic Acid Dose, based on MTX-Level (Calculated dose to be given at 6 hourly intervals)

3. RELAPSED ALL (ALL-REZ BFM 2002 – PROTOCOL FOR TREATMENT OF CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA)

MTX Dose	• 1g/m² over 36 hours[9 courses]
[MTX] Monitoring	• At 60 hours (before 3rd dose Leucovorin) • To adjust Leucovorin dose if high[MTX] • Targetted non-toxic[MTX] <0.1 µmol/L
Leucovorin Dose	• Start Leucovorin rescue at 48 hours from start of methotrexate

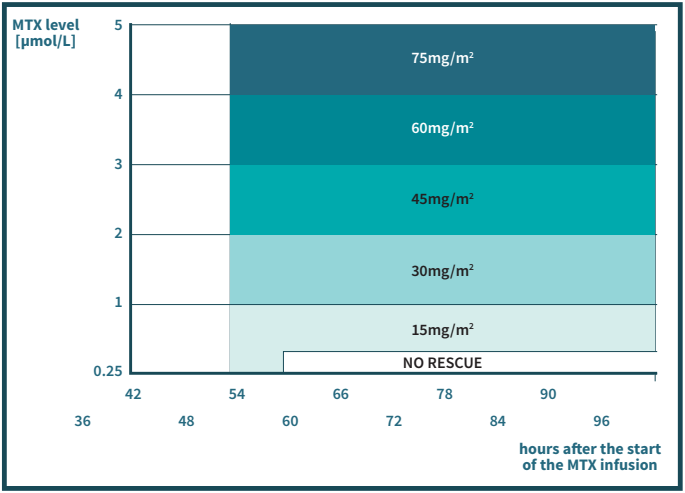

Figure 5.2 Leucovorin rescue for Methotrexate (1g/m²/36h)

Hours after start of the MTX infusion	Expected MTX level (µmol/L)	Deviations of MTX level (µmol/L)
Post 36 hours	≤10.0	>10.0
Post 48 hours	≤0.5 µmol/L	>0.5

- Determine a methotrexate level every 6 hours (may include a level at 42 hours)
- Rescue (IV LCV) every 6 hours until level ≤ 0.25 µmol/L
- LCV dosed according to the diagram above using the methotrexate level measured 6 hours earlier (if methotrexate at 42 hours >5.0 µmol/L, use the methotrexate level at 42 hours, however)
- To be started as soon as the methotrexate level at 48 hours (or 42 hours) is available

Hours after start of the MTX infusion	MTX level (µmol/L)	Management
Post 48 hours	>2.0 µmol/L	• Forced alkaline diuresis at 3 L/m^2
Post 48 hours	>5.0 µmol/L	• Carboxypeptidase • Forced alkaline diuresis at 4.5 L/m^2 • LCV dose (mg) = weight (kg) x MTX level at 42 hours (µmol/L) • Additional LCV doses are calculated based on the methotrexate level measured 6 hours earlier until this level falls below 5 µmol/L.

4. OSTEOSARCOMA GUIDELINE (CHILDREN'S ONCOLOGY GROUP APPENDIX FOR AOST0331, PHASE III INTERROUP STUDY)

MTX dose	• 12 g/m2 over 4 hours - Pre-op 4 courses - Post-op 8 courses
[MTX] monitoring	• At 24 hours - Targeted non-toxic[MTX] <0.1 µmol/L
Leucovorin Dose	• 10mg/m2 at 24 hours after start of IV MTX then 15mg/m^2 every 6 hourly for total of 7 doses • Continue dose till[MTX] <0.1 µmol/L, usually to complete all doses

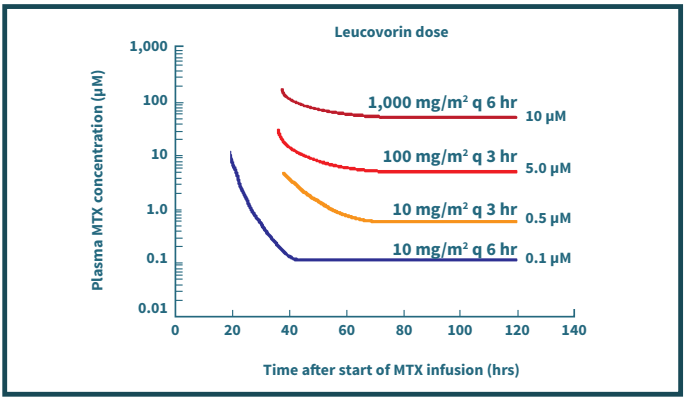

Figure 5.3 Leucovorin rescue for Methotrexate

5. BABY BRAIN PROTOCOL (UKCCSH Infant Ependymoma Interim Guidelines)

MTX dose	• 3g/m2 as intravenous infusion - 10% dose over 1 hour, 90% dose over 23 hours, concurrent and post hyperhydration with NaHCO3 • 100mg/kg in paediatric <10 kg
[MTX] monitoring	• At 24 hours - Non-toxic if concentration of methotrexate <0.1 µmol/L
Leucovorin dose	• 15mg/m2 at 36 hours after start of IV methotrexate - 15mg/m2 every 3 hourly for 5 doses then 6 hourly till concentration of methotrexate <0.1 µmol/L at 48 hours - Minimum 8 doses

Leucovorin rescue for Methotrexate (3g/m²/24h)

Time after starting MTX	Methotrexate plasma concentration (µmol/L)				
	<0.1	**0.1 – 2**	**2 – 20**	**20 – 100**	**>100**
48 h	None[a]	15mg/m² 6h	15mg/m² 6h	10mg/m² 3h	100mg/m² 3h
72 h	None	15mg/m² 6h	10mg/m² 3h	100mg/m² 3h	1g/m² 3h
96 h	None	15mg/m²6h	10mg/m² 3h	100mg/m² 3h	1g/m² 3h
120 h[b]	None	15mg/m² 6h	10mg/m² 3h	100mg/m² 3h	1g/m² 3h

a. No extra Leucovorin is required provided methotrexate levels are below 0.1 µmol/L at 48 hours.

b. At time points after 120 hours Leucovorin administration should be continued as recommended for 120 hours.

6. BURKITT'S / NON-HODGKIN LYMPHOMA (UKCCSG, NHL GROUP; GUIDELINES FOR THE MANAGEMENT OF BURKITT/BURKITT LIKE AND B LARGE CELL NON-HODGKIN LYMPHOMA)

MTX dose	• Group B – 4 courses of 3 g/m2 of MTX over 3 hours • Group C – 4 courses of 8g/m2 of MTX over 4 hours
[MTX] monitoring	• MTX level at 36 hours (Before 3rd dose Leucovorin) • To adjust Leucovorin dose if high MTX level • Targetted non-toxic MTX level <0.1 μM
Leucovorin dose	• Start Leucovorin rescue at 24 hours from start of MTX • Total of 12 doses – to complete all doses or more

Leucovorin rescue for Methotrexate

Time after starting MTX	Methotrexate plasma concentration (micromoles/L)				
	<0.1	**0.1 – 2**	**2 – 20**	**20 – 100**	**>100**
48 h	None[a]	15mg/m^2 6h	15mg/m^2 6h	10mg/m^2 3h	100mg/ m^2 3h
72 h	None	15mg/m^2 6h	10mg/m^2 3h	100mg/ m^2 3h	1g/m^2 3h
96 h	None	15mg/m^2 6h	10mg/m^2 3h	100mg/ m^2 3h	1g/m^2 3h
120 h[b]	None	15mg/m^2 6h	10mg/m^2 3h	100mg/ m^2 3h	1g/m^2 3h

a. No extra Leucovorin is required provided methotrexate levels are below 0.1 micromoles/L (107 M) at 48 hours

b. At time points after 120 hours Leucovorin administration should be continued as recommended for 120 hours.

C. INTERACTION[2,4]

Increase MTX level	Decrease MTX level
Ciprofloxacin Cyclosporine NSAIDs Penicillin Loop diuretics Proton pump inhibitors High dose salicylate	Bile acid sequestrants (decreased absorption of methotrexate)
Increased/enhances adverse/toxic effect of MTX	**Decrease MTX immunosuppressive effect**
Acitretin Trimethoprim Sulphonamide derivatives Doxycycline	N/A

D. SAMPLING[6,17]

Time to monitor serum concentration (at steady state)

- Usually measured at 24, 48, and 72 hours after starting the methotrexate infusion.
- Serum methotrexate level at 24, 42 & 48 hours must be determined immediately.
- Serum methotrexate level at 36 hours supposed to be optional.
- However, if serum MTX level at 24 hours is >150μM or/and suspicious of methotrexate overdose clinically (i.e significant increase in serum creatinine, decrease diuresis in spite of Frusemide), in such a case, the serum methotrexate level at 36 hours must be determined immediately and to begin promptly at an increased value with the Leucovorin rescue as shown in the graph.
- It is advisable to start methotrexate infusion at 1,400H in the respected institute so that the acceptance and measurement of the serum methotrexate level in the laboratory fall into the regular office hour.

E. MONITORING PARAMETER[4]

Patients with cancer[Baseline and frequently during treatment]:

- CBC with differential and platelets,
- Renal profile (Serum creatinine)
- Liver Function Tests,
- Chest x-ray (baseline)
- Methotrexate levels
- Urine pH
- Pulmonary function test (if methotrexate-induced lung disease suspected)

F. ADVERSE DRUG REACTION[4]

Adverse drug reactions (Concentration dependent toxicity)

- Delayed drug clearance is one of the major factors responsible for methotrexate toxicity.
- Toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to drug rather than peak level achieved.
- Renal dysfunction, third spacing (e.g. effusion) may delay methotrexate elimination causing methotrexate concentrations remain elevated for prolonged periods and this may increase toxicity

PLASMA CONCENTRATION	SYMPTOMS
≥0.1 µmol/L for 48 hours or more	Myelosuppression (leukopenia, pancytopenia, thrombocytopenia, oral and gastrointestinal mucositis and acute hepatic dysfunction. Other clinical manifestations of toxicity include nausea, vomiting, diarrhoea, mucositis, stomatitis, esophagitis, elevated hepatic enzymes, renal failure, rash, myelosuppression acute lung injury, tachycardia, hypotension and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma).

G. DILUTION AND ADMINISTRATION

Drug Dilution

Refer to specific protocols

Drug Administration[4]

In chemotherapy protocol, Methotrexate is usually administered as Intravenous infusion (4 – 24 hours depending on specific protocols) and intrathecal.

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CHAPTER 6: PARACETAMOL

CHAPTER 6
PARACETAMOL

KEY PARAMETERS:

Bioavailability (F)	Oral: 85% to 98%[1]; rapidly absorbed in GI[1]
Volume of Distribution (Vd)	• Paediatrics, 0.7 – 1.2 L/kg[1] • Adults, 0.7 – 1 L/kg[1] • Protein Binding : 10% - 25%[1,2] 8% - 43% at toxic dose[2] • Crosses blood brain barrier[1] • May cross placenta[1]
Clearance (CL)	Total Body Clearance[1] • Paediatrics, 0.12 – 0.34 L/hr/kg • Adults, 0.27 L/hr/kg
Half-life ($t_{1/2}$)[1,2]	Neonate: 4 – 11 hours Paediatrics: 1.5 – 4.2 hours Adult : 2 – 3 hours (immediate release formulation), ~3hours (extended-release formulation)

A. PHARMACOKINETIC

Metabolism:[1]

Paracetamol is metabolised mostly in the liver by conjugation with glucuronide, conjugation with sulphate and oxidation via the CYP isoenzyme system, mainly via CYP2E1.

The toxic reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is formed via the oxidative metabolism pathway and is conjugated with glutathione to form cysteine and mercapturic acid.

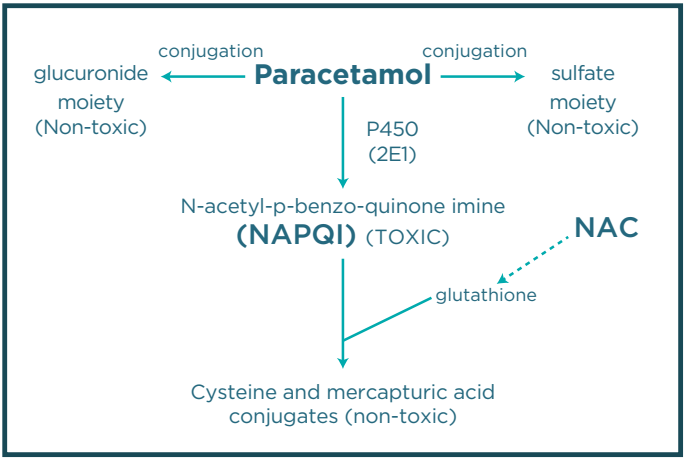


Figure 6.1 Paracetamol metabolism
(Adapted from Acetaminophen Toxicity, Medscape)

Metabolism of paracetamol may be slower but is similar in patients with liver impairment and in healthy subjects. Intra-patient environmental factors such as nutrition, alcohol use, smoking, etc, do not appear to significantly affect paracetamol metabolism.[1]

Indication and Toxic ranges:[3]

Paracetamol is commonly used for treatment of mild-to-moderate pain and fever (analgesic/antipyretic).

Minimum toxic doses of paracetamol for a single ingestion, posing significant risk of severe hepatotoxicity, are as follows:

- Paediatric : 150mg/kg; 200mg/kg in healthy paediatric aged 1 – 6 years[3]
- Adults : 7.5 – 10g[3]

B. DOSAGE

Paediatric:

Oral : 10 – 15mg/kg/dose every 4 – 6 hours.[1,2] Maximum: 75mg/kg/day (infants and children)[1] up to 4g/day (children)[1]

Rectal : Infant and children ≤12 years, less than 60kg : 10 – 20mg/kg/dose every 4 – 6 hours. Maximum: 5 doses (2.6g) per day[1,2].
Children ≥ 12 years and adolescent) : 325 – 650mg every 4 – 6 hours or 1,000mg 3 – 4 times daily. Maximum: 4g/day.[1,2]

Adult:[1,2]

Oral : 650mg – 1,000mg every 4 – 6 hours. Maximum: 4g/day

Rectal : 325 – 650mg every 4 – 6 hours or 1,000mg 3 – 4 times daily. Maximum: 4g/day

Renal Impairment:[1]

A longer dosing interval and a reduced total daily dose of paracetamol may be warranted in cases of severe renal impairment (CrCl 30ml/min or less).

It has been recommended to increase the dosing interval to every 8 hours in paediatric patients with severe renal failure (GFR less than 10ml/min). No dose adjustments are required for paediatric patients with GFR 10ml/min or greater.

Hepatic Impairment:[1]

Reduction of the total daily dose of paracetamol may be warranted when hepatic function is impaired. However, acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease.

C. INTERACTION[2]

Paracetamol may increase levels/effects of:	Levels/effects of Paracetamol may be increased by:	Levels/effects of Paracetamol may be decreased by:
Aripiprazole Imatinib Vitamin K antagonist	Isoniazid Probenecid	Phenytoin Barbiturates Carbamazepine Cholestyramine resin Peginterferon Alfa-2b

Paracetamol increases the risk of liver damage in chronic alcoholics.

D. SAMPLING[4,5]

Sampling Time:

Acute overdosing:
1 – 8 hours after ingestion: Sample at least 4 hours after ingestion
8 – 24 hours after ingestion: Sample immediately on admission
>24 hours after ingestion: Sample immediately on admission
* For unknown time of ingestion: sample immediately on admission

Repeated supratherapeutic ingestion (chronic ingestion):
Sampling: immediately on admission

E. MONITORING PARAMETER[3]

Most patients who have taken an overdose of paracetamol will initially be asymptomatic, as clinical evidence of end organ toxicity often does not manifest until 24 – 48 hours after an acute ingestion.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels begin to rise within 24 hours after an acute ingestion and peak at about 72 hours. In severe overdose, transaminase elevation can be detected as early as 12 – 16 hours post-ingestion.

Toxicity is defined as serum AST or ALT levels greater than 1,000 IU/L. A rapid progression of transaminase values to 3,000 IU/L or higher reflects worsening hepatotoxicity.

Recommended serum studies are follows:[3,4,6]

- Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin [total and fractionated], alkaline phosphatase)
- Prothrombin time (PT) with international normalized ratio (INR)
- Glucose
- Renal function studies (electrolytes, BUN, creatinine)
- ECG
- Lipase and amylase (in patients with abdominal pain)
- Salicylate level (in patients with concern of coingestants)
- Arterial blood gas and ammonia (in clinically compromised patients)

Chronic ingestion or repeated supra-therapeutic dosing is generally defined as occurring over more than 4 – 8 hours.

In such cases, paracetamol concentration should be obtained along with liver function and coagulation profiles if the paracetamol concentration above 10mcg/ml.

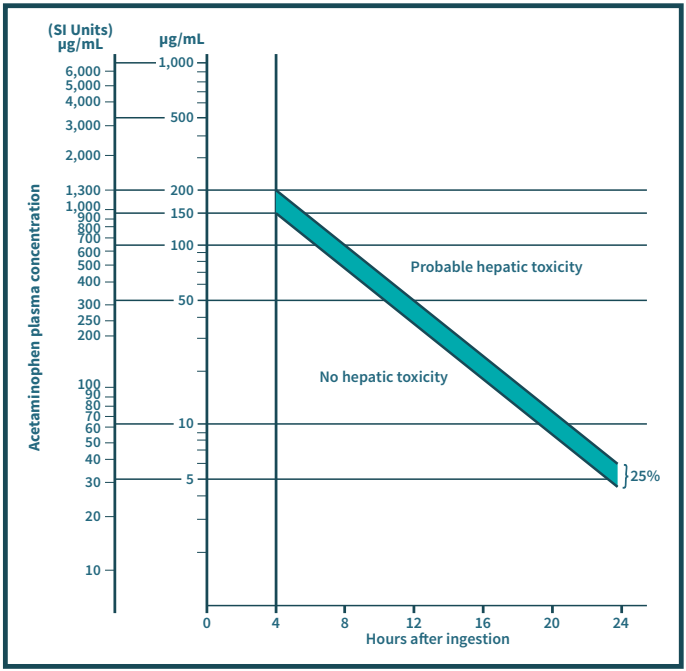


Figure 6.2 Rumack-Matthew Nomogram (Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55(6): 871–876, 1975)

The Rumack-Matthew Nomogram predicts the risk of hepatotoxicity at a single level in time.[3] Nomogram tracking begins 4 hours after ingestion and ends 24 hours after ingestion.[3,6,9] Paracetamol plasma levels drawn earlier than 4 hours may not be reliable. Levels obtained 4 – 18 hours post-ingestion are most reliable.[3]

The nomogram cannot be used if the patient presents more than 24 hours after ingestion or has a history of multiple paracetamol ingestions. Its reliability decreases for ingestions of extended-release paracetamol formulations.[3, 6]

If the paracetamol plasma level marked at the 'probable hepatic toxicity' line, it would be potentially hepatotoxic and requires antidote treatment. However, to provide safety buffer for patients who may have risk factors and a small margin of error against the estimation time of paracetamol ingestion, the 'treatment line' is plotted lower by 25% from the probable hepatic toxicity line .[7]

F. ADVERSE DRUG REACTION

The clinical course of paracetamol toxicity generally is divided into four phases. Physical findings vary, depending primarily on the level of hepatotoxicity.[3]

Phases of acute paracetamol poisoning.[3,6]

Phase	Duration	Description
Phase 1	0.5 – 24 hours after ingestion	• Patients may be asymptomatic or report anorexia, nausea or vomiting and malaise • Physical examination may reveal pallor, diaphoresis, malaise and fatigue
Phase 2	18 – 72 hours after ingestion	• Patients generally develop right upper quadrant abdominal pain, anorexia, nausea, and vomiting • Right upper quadrant tenderness may be present • Tachycardia and hypotension indicate ongoing volume losses • Some patients may report decreased urinary output (oliguria)
Phase 3: Hepatic phase	72 – 96 hours after ingestion	• Patients may have continued nausea and vomiting, abdominal pain, and a tender hepatic edge • Hepatic necrosis and dysfunction are associated with jaundice, coagulopathy, hypoglycaemia, and hepatic encephalopathy • Acute renal failure develops in some critically ill patients • Death from multi-organs failure may occur
Phase 4: Recovery phase	4 days to 3 weeks after ingestion	• Patients who survive critical illness in phase 3 have complete resolution of symptoms and complete resolution of organ failure

G.MANAGEMENT OF TOXICITY

For algorithm of paracetamol toxicity management, please refer appendix.

Activated Charcoal:

Activated charcoal may be given if paracetamol is likely to still remain in the GI tract. [6] Oral activated charcoal avidly adsorbs paracetamol and may be administered if the patient presents within 1 hour after ingesting a potentially toxic dose.[3,4]

N-Acetylcysteine (NAC):[3,6,7]

N-Acetylcysteine (NAC) is an antidote for paracetamol poisoning. This drug is a glutathione precursor that decreases paracetamol toxicity by increasing hepatic glutathione stores and possibly via other mechanisms. It helps prevent hepatic toxicity by inactivating the toxic paracetamol metabolite NAPQI before it can injure liver cells. However, it does not reverse damage to liver cells that have already occurred. Toxicity may still be reduced if it is started up to 24 hours after ingestion.

Delay in treatment with NAC can be associated with worse outcomes. Therefore treatment should be started immediately in children who present >8 hours after a significant ingestion or who are symptomatic of toxicity.

NAC Dose, Dilution and Administration

Intravenous NAC[1-6]

Three stage 20 hour infusion for patient <20kg
1. 150mg/kg NAC: diluted in 3ml/kg 5% dextrose, infused over 60 minutes
2. 50mg/kg NAC: diluted in 7ml/kg 5% dextrose, infused over next 4 hours
3. 100mg/kg NAC: diluted in 14ml/kg 5% dextrose, infused over the next 16 hours

Three stage 20 hour infusion for patient 20kg to 50 kg
1. 150mg/kg NAC: diluted in 100ml 5% dextrose, infused over 60 minutes
2. 50mg/kg NAC: diluted in 250ml 5% dextrose, infused over next 4 hours
3. 100mg/kg NAC: diluted in 500ml 5% dextrose, infused over the next 16 hours

Three stage 20 hour infusions for patient >50kg
1. 150mg/kg NAC: diluted in 200ml 5% dextrose, infused over 60 minutes
2. 50mg/kg NAC: diluted in 500ml 5% dextrose, infused over next 4 hours
3. 100mg/kg NAC: diluted in 1,000ml 5% dextrose, infused over the next 16 hours

Management for Acute Ingestion of Paracetamol[7]

Management of acute ingestion depends on time of paracetamol ingestion. For patient who are identified has been taken paracetamol within 1 hour; gastrointestinal decontamination with activated charcoal is recommended. However, study shows that efficacy of activated charcoal decreased beyond 60 min after toxic ingestion.

For patients who present within 1 to 8 hours from time of toxic ingestion, risk assessment is based on the serum paracetamol level plotted on the nomogram. Additional investigations such as liver function tests or a coagulation profile do not refine the risk assessment, and do not provide useful baseline data or change management in this group of patients. If serum paracetamol level shows "probable hepatic toxicity" on the nomogram, NAC should be administered within 8 hours from time of paracetamol ingestion.

In patients who present 8 hours or more after ingestion, evaluation of serum paracetamol and ALT levels should be obtained as soon as possible. NAC should be initiated immediately if the reported dose exceeds the threshold for possible toxicity or the patient shows clinical signs suggestive of paracetamol toxicity; without waiting for the levels of serum paracetamol and ALT results. If the serum paracetamol level is subsequently found to be below the nomogram line, N-acetylcysteine may be stopped; if above the line, NAC treatment should be continued.

If the time of ingestion is unknown, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the >8 hours scenario. If there is a detectable serum paracetamol level (>20mcg/ml) and the timing of ingestion cannot be accurately determined, NAC treatment should be initiated and serum ALT level measured.

Management for multiple or "staggered" Ingestion of Paracetamol[7]

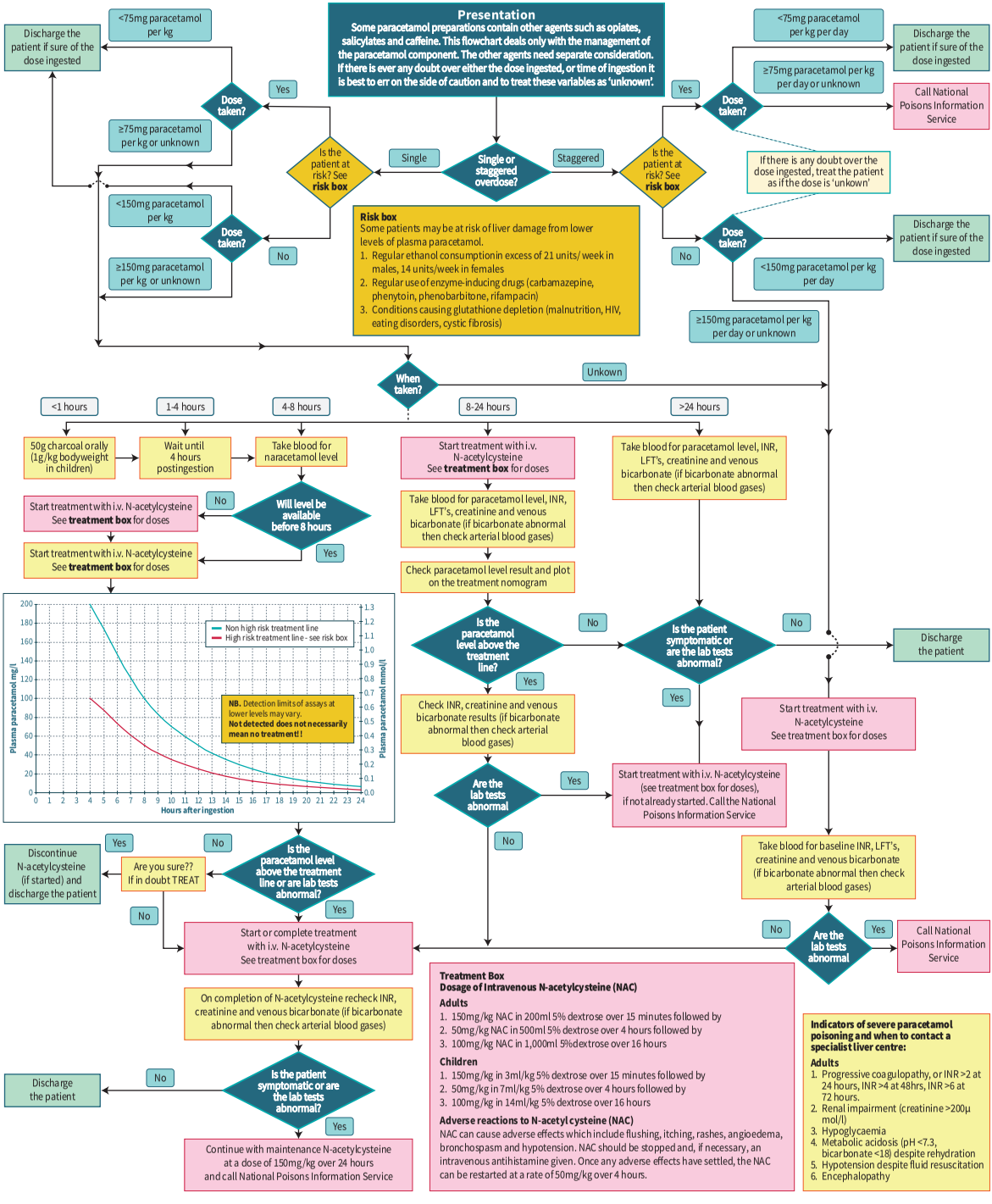
If the patient has been ingested paracetamol less than 8 hours since the first dose; patient can be treated according to the 1–8 hours scenario. This is due to the paracetamol rapid absorption. Therefore, any subsequent doses will only lead to overestimation of the risk. Nevertheless, patient has been ingested paracetamol *more* than 8 hours since the first dose; treat the patient accordingly following the more than 8 hours scenario.

Management for Overdose Ingestion of Sustained-Release Paracetamol[7]

If patient has ingested more than 200mg/kg or 10g (whichever is less), *NAC* treatment should be started immediately. However, if the amount ingested is less than 200mg/kg or 10g, the need for NAC can be determined by serum paracetamol levels.

In all cases, the levels of serum paracetamol levels should be taken at 4 hours or more post-ingestion and repeated 4 hours later. If the levels are above the nomogram line, *NAC* should be started or continued. However, if both levels fall under the nomogram line, NAC may be discontinued.

Appendix: Algorithm for management of Paracetamol toxicity [3]



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CHAPTER 7: PHENOBARBITONE

CHAPTER 7
PHENOBARBITONE

KEY PARAMETERS:

Therapeutic range	15 – 40mcg/ml[1]
Bioavailability (F)	Oral (capsules, tablets, elixir): 90 – 100%[1,2] Intravenous: 100%[1,2] Intramuscular: 100%[1,2] Rectal: 90%[1,2]
Salt Factor (S)	0.91[1]
Volume of Distribution (Vd)	Neonate: 0.9 L/kg (0.7 – 1.0 L/kg)[1] Paediatric and adults: 0.7 L/kg (0.6 – 0.7 L/kg)[1]
Clearance (CL)	Paediatric: 0.008 L/kg/hr[1] Adults & neonates: 0.004 L/kg/hr[1] Elderly (>65 years old): 0.003 L/kg/hr[1]
Half-life ($t_{1/2}$)	Neonates (<2 weeks): 77 to 145 hr[2] Infants (2 weeks to <1 year): 58 to 68 hr[2] Paediatric (1 to 19 years): 66 to 72 hr[2] Adults and geriatrics (>19 years): 83 to 109 hr[2]

A. PHARMACOKINETIC

Bioavailability (F):[1,2]

Oral (capsules, tablets, elixir)	90 – 100%
Intravenous	100%
Intramuscular	100%
Rectal	90%

Volume Distribution (Vd):[1]

Neonate	0.9 L/kg (0.7 – 1.0)
Paediatric and adults	0.7 L/kg (0.6 – 0.7)

Protein Binding:

General	All population	20 – 60%[4]
Specific	Neonate (2 weeks)	20 – 54%[2]
	Infants and paediatric (2 weeks – 19 years)	51%[2]
	Adult and geriatrics (>19 years)	51%[2]

Clearance (CL):[1]

Paediatric	0.008 L/kg/hr
Adults & neonates	0.004 L/kg/hr
Elderly (>65 years old)	0.003 L/kg/hr

Primarily metabolised by the liver.[1]
Renal excretion: 20%[1]

Half Life (T½):[2]

Neonates (<2 weeks)	77 to 145 hr
Infants (2 weeks to <1 year)	58 to 68 hr
Paediatric (1 to 19 years)	66 to 72 hr
Adults and geriatrics (>19 years)	83 to 109 hr

Conditions that might affect half-life of phenobarbitone:[2]

Cirrhosis	Increase
Pregnancy	Decrease
Prolonged starvation	Decrease
Renal failure (severe)	Increase
Hepato-renal	Increase

Indication and Therapeutic range

General: 15 – 40mcg/ml[1]

Clinical Condition[2]	Recommended Therapeutic Range[2]
Febrile convulsions	16 – 30mcg/ml
Hypoxic ischemic seizures in neonates (perinatal asphyxia)	20 – 30mcg/ml
Antenatal therapy to prevent intracranial haemorrhage in preterm infants	10 – 15mcg/ml
Generalized tonic-clonic seizures	10 – 25mcg/ml
Refractory status epilepticus	≥70mcg/ml (up to 100mcg/ml[10])
Cerebral salvage from hypoxic or traumatic brain damage	>75mcg/ml

B. DOSAGE

Paediatric[9]

Loading dose in emergency: Give 20 – 30mg/kg IM or IV over 30 min STAT
Ventilated: may repeat doses of 10 – 15mg/kg, up to 100mg/kg per day
Usual maintenance: 5mg/kg (adult 300mg) daily IV, IM or oral
Infant colic: 1mg/kg 4 – 8 hours oral

Adult[7]

Sedation:
Oral, IM: 30 – 120mg/day in 2 – 3 divided doses

Preoperative sedation:
IM: 100 – 200mg 1 – 1.5 hours before procedure

Anticonvulsant/Status Epilepticus:
Loading dose (IV): 10 – 20mg/kg (maximum rate ≤60mg/minute in patient ≥60 kg); may repeat dose in 20 minute intervals as needed (maximum total dose: 30mg/kg)

Maintenance dose: Oral, IV: 1 – 3mg/kg/day in divided doses or 50 – 100mg 2 – 3 times/day

Renal Impairment

CrCl<30 ml/min	Should be closely monitored[2]
CrCl <10ml/min	Administer every 12 – 16 hours[7]
Haemodialysis (moderately dialysable: 20% to 50%)	Administer dose before dialysis and 50% of dose after dialysis[7]
Peritoneal dialysis	Administer 50% of normal dose[7]
CRRT	Administer normal dose and monitor levels[7]

Hepatic Impairment

Dosing adjustment based on Child-Pugh Score[2]
If score >8, decrease 25-50% of initial daily dose.[2]

C. INTERACTION[7]

The level/effects of Phenobarbital may be increased by[7]	The level/effects of Phenobarbital may be decreased by[7]
Carbonic Anhydrase inhibitor	Amphetamine
Chlorampenicol	Cholestyramine Resin
Clarithromycin	Folic Acid
Hydroxyzine	Ketorolac
Magnesium Sulfate	Leucovorin Calcium
Methylphenidate	Mefloquine
Phenytoin	Multivitamins/ Minerals
Primidone	Orlistat
Quinine	Pyridoxine
Valproic Acid and Derivative	Rifamycin derivative
	Tipranavir

D. SAMPLING

Time to monitor serum concentration (at steady state):

Without loading dose: 2 – 3 weeks (after the initiation or a change in the regimen)[1]

Age[2]	Time to steady state (Days)
Neonates (<2weeks)	16 – 30
Infant (2 weeks to 1 year)	12 – 14
Paediatric (1 to 19 years)	14 – 15
Adults and geriatrics (>19 years)	17 – 23

Sampling Time:

Loading dose

2 – 3 hours after administration[2]

Maintenance dose

Oral& IV: Just before next dose[1]

Sampling should be repeated when known enzyme inhibitors or inducers are added, adjusted or discontinued.[2]

More frequent monitoring may be required during pregnancy and for 8 weeks following delivery.[2]

E. MONITORING PARAMETER

- Phenobarbitone serum level[2]
- Concentration related side effect[2] (refer to note section F)
- Seizure activity (Fit Chart)[2]
- Liver function test[7]

F. ADVERSE DRUG REACTION[5]

Common	
• Ataxia • Dizziness • Drowsiness • Dysarthria • Fatigue • Headache • Irritability • Nystagmus	• Parethesia restlessness • Vertigo • Geriatric patient: Excitement, confusion, depression • Paediatric patient: Paradoxical excitement/ hyperactivity
Less common	
• Mental dullness • Constipation • Diarrhoea • Nausea	• Vomiting • Megaloblastic (folate-deficiency) anaemia
Uncommon	
• Rash • Hypocalcaemia	• Hepatotoxicity
Rare	
• Steven-Johnson syndrome • Rickets	• Osteomalacia

Concentration related side effect:[2]

Adverse Effect	Phenobarbital concentration
Sedation	≥5 mcg/ml
Impaired cognition (with or without sedation)	19mcg/ml
Decreased neonatal feeding, respiration and muscle tone	>30mcg/ml
Sedation, slowness, and ataxia	35 – 80 mcg/ml
Potential coma	≥65mcg/ml
Coma without reflexes	≥80 mcg/ml

Overdosage/Toxicology:[4]

Poisoning is uncommon but toxicity may be severe and may occur via oral or parenteral routes.

Mild To Moderate Toxicity: Somnolence, slurred speech, nystagmus, confusion, and ataxia may occur.

Severe Toxicity: Coma, hypotension, decreased myocardial contractility, hypothermia and respiratory failure. Concentrations of 60-80mcg/ml are associated with coma and concentrations of 150-200 mcg/ml are associated with hypotension.

Management of Overdosage/Toxicology:

- Antidote: none
- Activated charcoal 0.25 to 0.5g/kg may be given every 2 to 4 hours.
- Urinary alkalinisation can enhance the elimination of phenobarbital. Administer 1 to 2 mEq/kg (2 to 3 ampules of sodium bicarbonate mixed in 1L of D5W given at 1.5 to 2 times maintenance fluid rates.
- Haemodialysis or haemoperfusion should be performed in patients who have haemodynamic instability not responding to supportive care or in patients who cannot tolerate a fluid load such as renal failure or congestive heart failure.

G. DILUTION AND ADMINISTRATION

Drug Dilution:[7]

Amount of Drug	Infusion volume	Infusion time
<100mg	50ml	30 minutes
>100mg	100ml	30 minutes

Dilute in Normal Saline or Dextrose 5% (D5W) or Dextrose 10% (D10W)

Drug Administration:

Intravenous

Avoid rapid IV administration >60mg/minute in adults and >30mg/minute in paediatric (may cause hypotension).[7]

Intramuscular

Inject deep into muscle. Do not exceed 5ml per injection site due to potential for tissue irritation.[7]

Commercial injection is highly alkaline and can cause local tissue necrosis.[5]

pH: 9.2 – 10.2[7]

H. CALCULATION

A) Dose Initiation

Maintenance dose: Oral/Intravenous

1. Estimate Clearance
   - Paediatric: 0.008 L/kg/hr or 0.2 L/kg/day
   - Adult and neonates: 0.004 L/kg/hr or 0.1 L/kg/day

2. Determine C_{ss} target and calculate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL(L/hour)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{(\text{S} \times \text{F})}$$

Loading Dose: Intravenous

1. Estimate Volume distribution (Vd):
   - Neonates: 0.9 L/kg
   - Paediatric and Adult: 0.7 L/kg

2. Determine C_{ss} targetand calculate loading dose (LD):

$$\text{LD (mg)} = \frac{\text{Vd(L) x Css target (mcg/ml)}}{(\text{S x F})}$$

B) Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (L/day)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg/day)}}{\text{Css (mcg/ml)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic <15mcg/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction	Poor	If compliance & sampling time is satisfactory, increase the dose appropriately & resample
		Good	Continue current dose
Within normal therapeutic range 15 – 40mcg/ml		Poor	If compliance & sampling time is satisfactory, increase the dose (not more than max recommended)
		Good	Continue current dose
Potential toxic/ Toxic >40mcg/ml	• Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Hypotension • Excessive sedation • Respiratory depression	Withold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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CHAPTER 08: PHENYTOIN

CHAPTER 8
PHENYTOIN

KEY PARAMETERS:

Therapeutic range	10 – 20mcg/ml	
Bioavailability (F)	1	
Salt Factor (S)	1	
Volume of Distribution (Vd)	0.6 – 0.7 L/kg	
Clearance (CL)	**Vm**	**Km**
	8.45mg/kg/day[6]	6.72mg/L[6]
	7mg/kg/day[1]	4mg/L [1]
Half-life ($t_{1/2}$)	Concentration dependant	

A. PHARMACOKINETIC

Bioavailability (F):[1]

		IV	Capsule	Susp/Chew Tab
Bioavailability, F	**F**	1	1	1
Salt Factor, S	**S**	0.92	0.92	1

Time to steady state:

No Loading Dose	7 - 14 days[2]
With Loading Dose	24 hours[1]

Volume of Distribution(Vd):[1,2]

Neonates	1 – 1.2 L/kg (premature)
	0.8 – 0.9 L/kg (term)
Infants	0.7 – 0.8 L/kg
Paediatric	0.7 L/kg
Adult	0.65 – 0.7 L/kg

Half life ($t_{½}$):[1,2]

Oral: 22 hours (range 7 – 42 hours)

Protein binding:[1,2]

Neonates	[3] 80% (£ 20% free)
Infants	[3] 85% (£ 15% free)
Adult	90 – 95 %

Metabolism:[3]

Hepatic
Dose dependent capacity (Michaelis-Menten pharmacokinetics)

Elimination:[3]

Urine

Clearance:

	Vm	Km
Adult	8.45mg/kg/day[6]	6.72mg/L[6]
	7mg/kg/day[1]	4mg/L[1]
Infant	10 –14mg/kg/day[1]	6mg/L[1]

[6] Data by local population

Indication and Therapeutic range:[4]

Clinical Condition	Recommended Therapeutic Range
Status Epilepticus / Anticonvulsant	10 – 20mcg/ml

B. DOSAGE

Paediatric:[4]

Status Epilepticus	LD	IV: 15 – 20mg/kg over 1 hour
	MD	5mg/kg/day in 2 divided doses
Anticonvulsant	LD	Oral: 15 – 20mg/kg in 3 divided doses every 2 – 4 hours
	IMD	5mg/kg/day in 2-3 divided doses
	MD	4 – 8mg/kg/day (maximum daily doses: 300mg)

Adult:[4]

Status Epilepticus	LD	IV: 10 – 20mg/kg over 1 hour
	MD	IV or oral: 100mg every 6 – 8 hrs
Anticonvulsant	LD	Oral: 15 – 20mg/kg in 3 divided dose every 2 – 4 hours
	IMD*	300mg in 3 divided doses
	MD	300 – 600mg daily

**Initial maintenance dose*

Renal Impairment:[4]

Phenytoin level in serum may be difficult to interpret in renal failure. Monitoring of free (unbound) concentrations or adjustment to allow interpretation is recommended.

Hepatic Impairment:[4]

Safe in usual doses in mild liver disease; clearance may be substantially reduced in cirrhosis and plasma level monitoring with dose adjustment advisable. Free phenytoin levels should be monitored closely.

C. INTERACTION

The level/effects of phenytoin may be increased by[4]	The level/effects of phenytoin may be decreased by[4]
Allopurinol	Carbamazepine
Amiodarone	Ciprofloxacin
Antifungal Agents (Azole derivatives)	Folic Acid
Calcium Channel Blocker	Methotrexate
Carbamazepine	Pyridoxine
Cefazolin	Rifampin
Chloramphenicol	Ritonavir
Fluoxetine	Theophylline
Fluvoxamine	Valproic Acid
Hydroxyzine	
Isoniazid	

D. SAMPLING

Time to monitor serum concentration (at steady state):[1]

After LD : 12 hours after completion of IV LD
24 hours after administration of an oral loading dose

Without LD : 8 – 10 days (after the initiation or a change in the regimen)

Sampling Time:

Loading dose
12 - 24 hours after administration[2]

Maintenance dose
IV/Oral: Just before next dose[1]

E. MONITORING PARAMETER[4]

- Complete Blood Count
- Liver Function
- Suicidality

F. ADVERSE DRUG REACTION

Dose related side effects:[4]
- Far lateral nystagmus (>20mcg/ml)
- Ataxia (>30mcg/ml)
- Diminished mental capacity (>40mcg/ml).

Gingival hyperplasia, hirsutism, coarsening of facial features, and peripheral neuropathy are not dose related side effects and is not an indication for TDM in patients receiving phenytoin.

Overdosage/Toxicology:[7]

There are thousands of exposures reported to poison centres every year, as phenytoin is a widely used anticonvulsant. However, deaths are extremely rare and severe manifestations occur in only a minority of cases.

Management of Overdosage/Toxicology:

- Treatment is supportive.
- Activated charcoal could be considered if the patient is awake, alert, and cooperative, and the ingestion is relatively recent (within the last hour). Gastric lavage should be avoided in most phenytoin overdoses as it is not life-threatening.
- No indication for haemodialysis, haemoperfusion, or urinary alkalinisation.
- Monitor phenytoin concentrations every 4 hours until the levels are clearly declining.

G.DILUTION AND ADMINISTRATION[7]

Dilution

- Adding phenytoin to dextrose or dextrose-containing IV infusions is NOT RECOMMENDED due to a lack of solubility and the chance of precipitation.
- Phenytoin sodium should be diluted in normal saline, to a final concentration no less than 5mg/ml. Do not refrigerate phenytoin Sodium once diluted.

Administration

- Injected slowly, not exceeding 50mg/min in adult or 1-3mg/kg/min in neonates and children.

Miscellaneous

- If giving phenytoin via a nasogastric tube or gastrostomy, tube feeds need to be held for 1 hour before and 1 hour after administration of Phenytoin.
- If giving phenytoin to a patient on intermittent hemodialysis, the dose should be given immediately after dialysis, not before as much of the phenytoin will be dialyzed off.

H. CALCULATION

1. Loading dose (LD):

$$\text{Loading Dose} = \frac{\text{Cp desired} \times \text{Vd} \times \text{BW}}{\text{S} \times \text{F}}$$

2. Incremental LD:

$$\text{Incremental LD} = \frac{(\text{Cp desired} - \text{Cp measured}) \times \text{Vd} \times \text{BW}}{\text{S} \times \text{F}}$$

3. Maintenance dose (MD):

$$\text{Dose (mg/day)} = \frac{\text{Vmax} \times \text{BW} \times \text{Cp desired (mcg/mL)}}{\text{(S)(F)(Km + Cp desired (mcg/mL)}}$$

4. To predict level from current dose:

$$\text{Cpss (mcg/mL)} = \frac{\text{Km} \times \text{S} \times \text{F} \times \text{Dose (mg/day)}}{\text{(Vmax} \times \text{BW)} - \text{(S)(F)(Dose (mg/day))}}$$

5. Clearance (CL):

$$\text{CL} = \frac{\text{Vm}}{\text{Km + Cp measured}}$$

6. If albumin is low (<2.5g/dL), use following equation:

$$\text{Cp Normal binding (mcg/mL)} = \frac{\text{(Phenytoin Concentration (mcg/mL)}}{\left[0.9 \times \frac{\text{Patient's Albumin (g/dL)}}{4.4}\right] + 0.1}$$

7. If albumin is low and CrCl is less than 10ml/minute, use the following equation:

$$\text{Cp Normal binding} \left(\frac{\text{mcg}}{\text{mL}}\right) = \frac{\text{Phenytoin Concentration (mcg/mL)}}{(0.48)(0.9) \times \frac{\text{Patient's Albumin (g/dL)}}{4.4} + 0.1}$$

8. Time to withhold therapy when level is toxic:

$$\text{T} = \left[\text{Km (mg/L)} \left(\ln \frac{\text{Cp measured}}{\text{Cp desired}}\right) + \text{(Cp measured - Cp desired)}\right] \text{x} \ \frac{\text{Vd (L)}}{\text{Vm (mg/day)}}$$

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic <10mcg/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction	Poor	If compliance & sampling time is satisfactory, increase the dose appropriately & resample
		Good	Continue current dose
Within normal therapeutic range 10 -20mcg/ml		Poor	If compliance & sampling time is satisfactory, increase the dose (not more than max recommended)
		Good	Continue current dose
Potential toxic/ Toxic > 20mcg/ml	• Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Hypotension • Excessive sedation • Respiratory depression	Withold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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CHAPTER 9: SALICYLATE

CHAPTER 9
SALICYLATE

KEY PARAMETERS:

Therapeutic range	Refer text
Bioavailability (F)	Aspirin; 50 – 75% (oral)[1]
Salt Factor (S)	Not indicated
Volume of Distribution (Vd)	10 L/kg
Clearance (CL)	Aspirin: via urine (75% as salicyluric acid, 10% as salicylic acid)
Half-life ($t_{1/2}$)	Aspirin: 15 – 20minutes Salicylate:3hours (300 – 600mg) 5 – 6 hours(>1g) 10 hours (higher doses)

A. PHARMACOKINETIC

Bioavailability (F):[1]

Acetyl salicylate (aspirin): 50 – 75% (oral)

Volume of Distribution (Vd):[1]

10 L/kg

Metabolism:[1]

Acetyl salicylate (Aspirin): hydrolysed to salicylate (active) by esterase in GI mucosa, blood synovial fluid.
Salicylate: metabolised primarily by hepatic conjugation (saturable pathway)

Clearance (Cl):[1]

Aspirin: via urine (75% as salicyluric acid, 10% as salicylic acid)

Half-life (t½)[1]

Aspirin (Parent drug) : 15 – 20 minutes
Salicylate (Dose dependent) : (300 – 600mg) 3hours
: (>1g) 5 – 6 hours
: 10 hours with higher doses

Indication and Therapeutic Range:[1]

- Mild to moderate pain, inflammation, and fever
- Prevention of acute coronary syndromes, acute ischaemic stroke and transient ischaemic episode.
- Management of rheumatoid arthritis rheumatic fever, osteoarthritis
- Salicylate serum concentration range:

Serum Salicylate concentration (mcg/ml)	Effects
~100	Antiplatelets, antipyresis, analgesia
150 – 300	Anti-inflammatory
250 – 400	Treatment of rheumatic fever
>400 – 500	Toxicity

Renal impairment:[1]

- CrCl <10ml/min: avoid use
- Dialysable: 50 – 100%

B. INTERACTION[1]

Salicylate may affect other drugs by:

Salicylate may increase drug concentration/effects:	Salicylate may decrease drug concentration/effects:
Alendronate	ACE Inhibitors
Anticoagulants	Hyaluronidase
Carbonic Anhydrase Inhibitors	Loop Diuretics
Corticosteroids (systemic)	Multivitamins/Fluoride (with A,D,E)
Dabigatran Etexilate	Multivitamins/Minerals (with A,D,E,K,
Heparin	Folate, Iron)
Hypoglycemic Agents	Multivitamins/Minerals (with A, E, No Iron)
Methotrexate	NSAID (Nonselective)
NSAID (COX-2 Inhibitor)	Probenecid
Rivaroxaban	Ticagrelor
Thrombolytic Agents	
Ticagrelor	
Tositumomab and Iodine (I-131)	
Valproic Acid and Derivatives	
Varicella Virus-Containing Vaccines;	
Vitamin K Antagonists	

Salicylate may be affected by other drugs by:

Salicylate may be increased by:	Salicylate may be reduced by:
Agents with Antiplatelet Properties Ammonium Chloride Antidepressants (Tricyclic, Tertiary Amine) Calcium Channel Blockers (Non-dihydropyridine) Ginkgo Biloba Glucosamine Herbs (Anticoagulant/Antiplatelet Properties) Influenza Virus Vaccine (Live/Attenuated) Ketorolac (Nasal & Systemic) Loop Diuretics Multivitamins/Minerals NSAID (Nonselective) Omega-3 Fatty Acids Pentoxifylline Potassium Acid Phosphate Selective Serotonin Reuptake Inhibitors Serotonin/Norepinephrine Reuptake Inhibitors Vitamin E	Corticosteroids(systemic) Ketorolac(Nasal/Systemic) NSAID (Non-selective) Floctafenine

Avoid using Salicylate concomitantly with Influenza virus vaccine (live/attenuated) and Ketorolac (Nasal/Systemic).

C. SAMPLING TIME FOR TOXICITY

Sampling:[1,2,4,5]

- Sampling should be taken at least 4 hours after ingestion and repeat the salicylic concentration test every 2 hours until the concentration falls.
- Nomogram can only be used for acute ingestion of non-enteric coated of aspirin.

D. MONITORING OF TOXICITY

Serum salicylate level[2,4]

- Toxicity due to chronic ingestion of Aspirin is common in elderly patients taking aspirin for analgesia.
- May occur in treatment of acute rheumatic fever (80 – 100mg/kg/day in 4 divided doses for 2 – 4 weeks).
- To do salicylic concentration on admission if signs and symptoms of toxicity are presence. Refer Appendix for Salicylate Toxicity Algorithm.

Table below shows serum salicylate concentrations and common adverse effects:-

Phase	Salicylate level	Clinical features
Mild Poisoning	Adult: 300 – 600mcg/ml Paediatric/elderly: 200–450 mcg/ml	Lethargy, nausea, vomiting, tinnitus, dizziness
Moderate Poisoning	Adults: 600 – 800mcg/ml Paediatric/elderly: 450 – 700mcg/ml	Mild features & tachypnoea, hyperpyrexia, sweating, dehydration, loss of coordination, restlessness
Severe Poisoning	Adults: > 800mcg/ml Paediatric/elderly: >700 mcg/ml	Hypotension, significant metabolic acidosis after rehydration, renal failure (oliguria), CNS features e.g. hallucinations, stupor, fits, coma

- Acid-Base Status, Volume Status and Electrolytes[4]
  - Salicylate poisoning causes respiratory alkalosis and by an independent mechanism, metabolic acidosis.
  - Reduction in serum bicarbonate is caused both by concomitant metabolic acidosis and by an initial respiratory alkalosis-induced bicarbonaturia.
  - Clinical severity is predicted by the acid-base status; adult patients exhibiting only respiratory alkalosis expected to have mild toxicity, while those with a normal or near normal serum pH (7.40 ± 0.05) with underlying respiratory alkalosis and metabolic acidosis are expected to have moderate poisoning. Acidaemia (pH < 7.35) is seen in severe poisoning.
  - Euvolaemia should be achieved. Hypovolaemia can worsen salicylate toxicity as well as impairing alkalinisation of the urine.

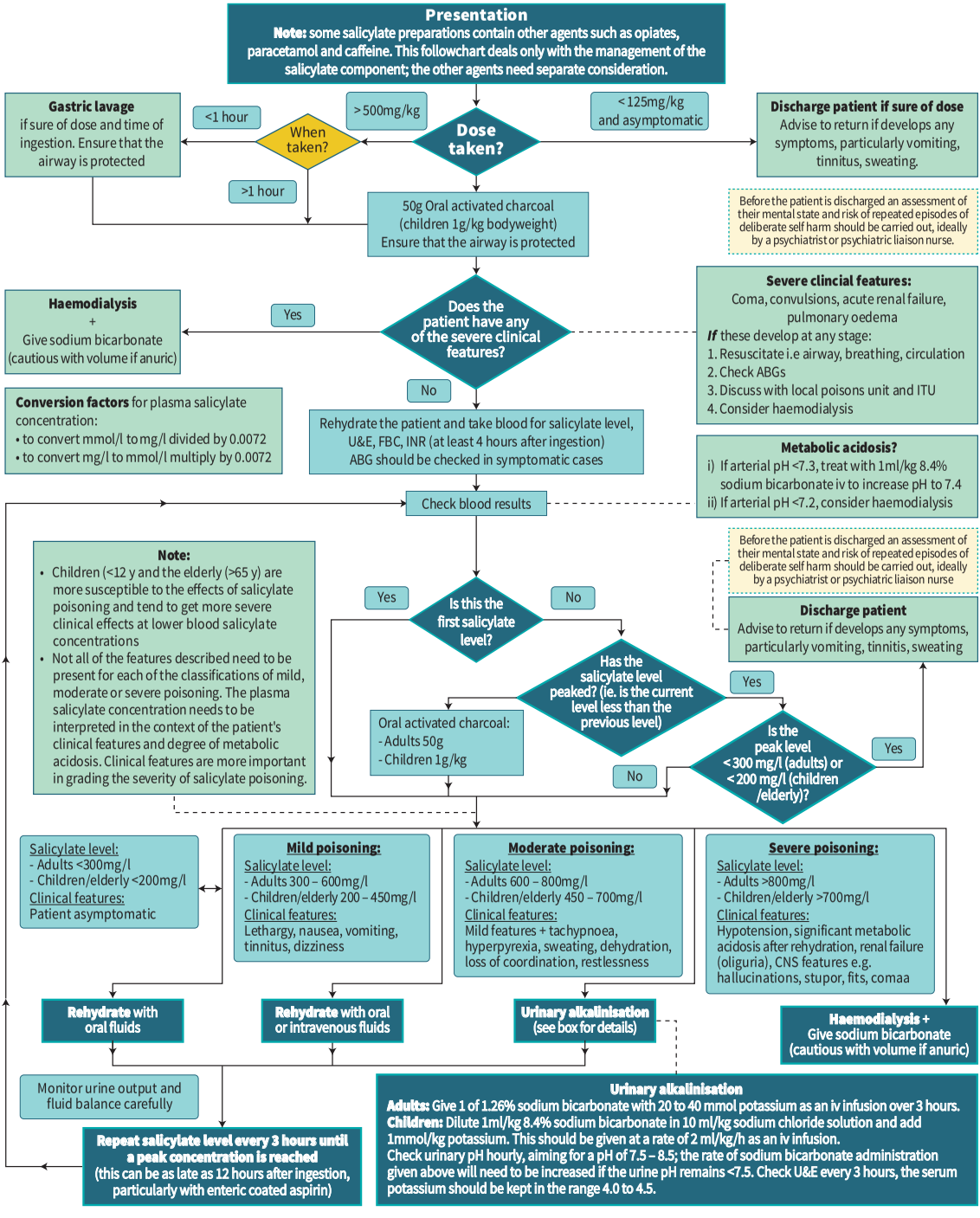
E. MANAGEMENT OF TOXICITY[1]

- **Airway Protection and Respiratory Status**
  - Assess airway, breathing and circulation (ABC). Intubation only if clinically required.

- **Gastrointestinal Decontamination**
  - Administration of activated charcoal administration or whole bowel irrigation may be considered.

- **Urine Alkalization**
  - Extracellular volume depletion should be corrected and diuresis should be induced with large volumes of isotonic sodium bicarbonate-containing IV fluids, as renal excretion of salicylates is more dependent on urine pH than on urine flow. Urine alkalinisation to a pH of 7.5 – 8.0 increases urinary excretion of salicylates more than 10-fold and should be considered for significant salicylate toxicity in patients with intact renal function, alone or in combination with haemodialysis.
  - Haemodialysis is very effective in the treatment of patients with salicylate toxicity since an increased fraction of free salicylate occurs in the serum following saturation of protein binding.

Appendix: Algorithm for management of salicylate toxicity [3]



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CHAPTER 10: SIROLIMUS (RAPAMYCIN)

CHAPTER 10
SIROLIMUS (RAPAMYCIN)

KEY PARAMETERS:

Therapeutic range	Therapeutic concentration (general): *4 – 24ng/ml[1,2]
Bioavailability (F)	Oral solution: 0.14[3] Tablets: 0.18
Salt Factor (S)	1
Volume of Distribution (Vd)	Adults: 12 ± 8 L/kg
Clearance (CL)	139 - 221ml/kg/hr
Half-life ($t_{1/2}$)	62 ± 16 hours

* Depending on time after graft and concomitant immunosuppressants.

A. PHARMACOKINETIC

Bioavailability (F):

Sirolimus is a lipophilic drug with systemic bioavailability of 14% for oral solution and 18% for tablets. Both formulations are not bioequivalent but clinically equivalent at the 2mg dose. Sirolimus levels should be monitored if changes in dosage forms are made. When administered with a high-fat meal, bioavailability of the oral solution is decreased but bioavailability is increased with the tablet form.[4] Fraction of unbound sirolimus in plasma was found to be 0.02-0.08.

Volume of Distribution (Vd):

The average volume of distribution in adults is 12 ± 8 L/kg. Sirolimus is highly protein-bound (92% bound mainly to albumin). It is also extensively partitioned into formed blood elements; with blood to plasma ratio found to be 36.[5]

Clearance (Cl):

The clearance of sirolimus in adult is approximately 139 to 221ml/kg/hr.[1] Paediatric (CL=485ml/kg/ml) and adolescents (CL=379ml/kg/hr) showed higher clearance compared to adults.[6]The immunosuppressive activity of sirolimus metabolites is less than 30% of the parent compound.[5]

Similar to other immunosuppressants, sirolimus is a substrate for CYP 3A4 and P-glycoprotein. Hence, impairment of hepatic function is expected to affect the metabolism of sirolimus. In mild and moderate hepatically impaired patients (Child-Pugh classification of A or B), sirolimus AUC and $t_{1/2}$ were increased 61% and 43% respectively, CL/F was decreased 33%.[5]

Half-life ($t_{½}$):

Sirolimus is excreted mainly in faeces and 2.2% eliminated in the urine

Adults	62 ± 16 hours[1]
Paediatric	11.8 ± 5.5 hours[1]
Liver impairment (Child-Pugh class A or B)	113 hours[2]

Indication and Therapeutic Range:

<table>
<tr><th colspan="2">General therapeutic range[1,2]</th></tr>
<tr><td colspan="2">4 – 24ng/ml</td></tr>
<tr><td>Kidney transplant*</td><td>
<table>
<tr><th>With CSA</th><th>Low to moderate immunologic risk (after CSA withdrawal)</th><th>High immunologic risk (with CSA)</th></tr>
<tr><td>4 – 12ng/ml</td><td><1 yr: 16 – 24ng/ml</td><td>>1 yr: 12 – 20 ng/ml10 – 15 ng/ml</td></tr>
</table>
</td></tr>
<tr><td>Combined with TAC + MMF without steroids</td><td>6 – 8ng/ml</td></tr>
<tr><td>Substitution for TAC, combined with MMF + steroids (4-8 wk post transplant)</td><td>8 – 12ng/ml</td></tr>
<tr><td>Following conversion from TAC to sirolimus (>6 mths post transplant - chronic allograft nephropathy)</td><td>4 – 6ng/ml</td></tr>
<tr><td>GVHD prophylaxis in allogeneic stem cell transplant</td><td>3– 12ng/ml</td></tr>
</table>

* based on HPLC methods

The target concentrations depend on the type of organ transplanted and immunosuppression protocols used in specific centres. Assay results vary according to the method of assay. Results generated from HPLC UV and HPLC/MS will generally be approximately 20 % lower than immunoassay techniques for whole blood concentrations.[7]

B. DOSAGE

Patient	Loading Dose (mg)	Daily maintenance dose (mg)
Paediatric[8]	3mg/m^2 STAT (Maximum: 6mg)	1mg/m^2 OD (Maximum MD: 2mg/day)
Adult[2]	Low to moderate immunologic risk <40kg: 3mg/m^2 >40kg: 6mg STAT High immunologic risk Up to 15mg STAT	 1mg/m^{2}OD 2mg OD 5mg OD (Maximum daily dose: 40mg)

Renal impairment:

No dosage adjustment is necessary in renal impairment.

Hepatic impairment:

Liver disease significantly increases bioavailability, reduces clearance and prolongs elimination half-life of sirolimus.

In patients with mild to moderate hepatic impairment, the maintenance dose should be reduced by approximately 33% and further reduced by half in patients with severe hepatic impairment. Loading dose is unchanged.[2]

C. INTERACTION

Increased SIROLIMUS concentration/effects[3]	Decreased SIROLIMUS concentration/effects[3]
Calcium channel blockers Diltiazem, Verapamil **Antibiotics** Clarithromycin, Erythromycin **HIV protease inhibitors** Indinavir, Ritonavir **Antifungal agents** Fluconazole, Itraconazole, Ketoconazole, Voriconazole	**Antibiotics** Caspofungin, Rifampicin **Anticonvulsants** Carbamazepine, Phenobarbitone, Phenytoin

Increased SIROLIMUS concentration/effects[3]	Decreased SIROLIMUS concentration/effects[3]
Gastrointestinal prokinetic agents Metocloperamide **Others** Bromocriptine, Danazole, Ethinyl estradiol, Methylprednisolone, Cyclosporine	
Herb-drug interaction: St. John's Wort may increase the rate of CYP3A4 activity and reduce sirolimus concentrations.[2]	
Food-drug interaction: Grapefruit juice reduces CYP3A4 activity; co-administration with sirolimus should be avoided.	
Vaccination: Immunosuppressants may affect response to vaccination. During treatment with sirolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.	

D. SAMPLING

Time to obtain serum sirolimus level (after dose initiation or adjustment):[2]

Adults : 5 – 7 Days
Paediatric : 3 – 5 Days[4]

Maintenance dose:
Oral: 30 minutes OR just before next dose

Suspected toxicity:
If toxicity is suspected, blood sample may be drawn at anytime (random sampling)

E. MONITORING PARAMETERS

Patient Selection for Monitoring

a. Paediatric patients
b. >13 years of age weighing <40kg.
c. Hepatic impairment[4]
d. On concurrent potent inducers of CYP3A4
e. On concurrent potent inhibitors of CYP3A4
f. If cyclosporine dose is markedly reduced/ discontinued
g. Patient receiving sirolimus plus low dose tacrolimus
h. Patients at high risk for acute rejection

Clinical monitoring parameters

a. Serum cholesterol & triglycerides (monitored once after 2-3 months, then annually)
b. Blood pressure (measured at each clinical visit)
c. Serum creatinine (monitored daily in the first week, 2-3 times/wk (in the 1st month after initiation), weekly (2-3 months post initiation), every 2 weeks (4-6th month), monthly (7-12th month) then every 2-3 months (after 1 yr)
d. Urinary protein (monitored once at the 1st month, then every 3 months in the 1st year, then annually after that)
e. Side effects/ADR of sirolimus
f. Lymphocele, known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in sirolimus-treated patients

F. ADVERSE DRUG REACTION[2]

Cardiovascular	Peripheral oedema, hypertension, oedema
Central nervous system	Headache, pain, insomnia
Dermatologic	Acne and rash
Endocrine & metabolic	Hypertriglyceridemia*, hypercholesterolaemia*, hypokalaemia
Gastrointestinal	Constipation, abdominal pain, diarrhoea, nausea
Genitourinary	Urinary tract infections
Hematologic	Anaemia and thrombocytopenia*
Neuromuscular & skeletal	Arthralgia
Renal	Serum creatinine increased
* The elevations of triglycerides and cholesterol and decreases in platelets and haemoglobin occurred in a dose-related manner	

Overdosage/Toxicology:

There is minimal experience with overdose. Only one case was reported of a patient receiving 150mg sirolimus and the patient experienced an episode of transient atrial fibrillation. General supportive measures have been suggested in case of overdose.[2]

G. DILUTION AND ADMINSTRATION

Drug administration:[2]

Available tablet strength: 1mg and 2mg (tablet should not be crushed, chewed or split)

Oral Solution 1mg/ml (stored refrigerated):
Amber oral dose syringe should be used to withdraw solution from the bottle. Syringe should then be emptied, or if a pouch is used, the entire contents should be squeezed out into a glass or plastic cup. The solution in the cup should be mixed with at least 60 to 120ml of water or orange juice. No other liquids should be used for dilution. Patient should drink diluted solution immediately. The cup should then be refilled with an additional 120ml of water or orange juice, stirred vigorously, and the patient should drink the contents at once. Sirolimus should be taken 4 hours after cyclosporine administration with or without food consistently to minimise variability of absorption.

Dosage Adjustment Based On Serum Concentrations

Serum concentration should not be used as the sole basis for dosage adjustment, especially during the withdrawal of cyclosporine. Dosage adjustments should be based on clinical signs and symptoms, tissue biopsy and laboratory parameters.

H. CALCULATION

Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (ml/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mcg)} \times 1000}{\text{Css (ng/ml)} \times \text{Interval (hour)}}$$

2. Determine Css target and calculate the new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (ml/hr)} \times \text{Css (ng/ml)} \times \text{Interval (hour)}}{(\text{S} \times \text{F})} \times \frac{1}{1000}$$

Alternatively, assuming linear relationship between dose and concentration:

$$\text{New Dose (mg)} = \frac{\text{Desired Css}}{\text{Measured Css}} \times \text{Current dose (mg)}$$

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CHAPTER 11: TACROLIMUS

CHAPTER 11
TACROLIMUS

KEY PARAMETERS:

Therapeutic range	Therapeutic concentration (general): 5 – 20 ng/ml[1,2]
Bioavailability (F)	0.25 (oral)[1,2] 1.0 (injection)[1,2]
Volume of Distribution (Vd)	Paediatric: 1.4 – 1.9 L/kg[3] Adult: 2.6 L/kg[3]
Clearance (CL)	Paediatric: 0.14 L/h/kg [3,4] Adult: 0.04 – 0.08 L/h/kg [3,4]
Half-life ($t_{1/2}$)	General: 8 – 12 hours (half-life is prolonged in patient with impaired hepatic function)[2,4]

A. PHARMACOKINETIC

Bioavailability (F):

Oral: Adults 7% to 28%, paediatric: 10% to 52% [1]

Volume of Distribution (Vd):

The plasma protein binding to tacrolimus is approximately 99%.[1, 5] Tacrolimus is bound mainly to albumin and alpha$_1$-acid glycoprotein, and high association with erythrocytes.[5]

The distribution of tacrolimus between whole blood and plasma depends on several factors, such as haematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration.[5]

Clearance (CL):

The elimination of tacrolimus is not affected by renal or mild hepatic dysfunction.[3] Patient with severe renal dysfunction/ hepatitis C, the clearance rate is prolonged.[3]

Children have higher clearance and require higher doses of tacrolimus to achieve similar target concentration.[2]

Half-life ($t_{½}$):

In liver transplant patient [5]	
Paediatric	12.4 hours
Adult	11.7 hours
In kidney transplant patient [5]	
Adult	15.6 hours

Indication and Therapeutic Range:

Indications: [5]

- Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants.
- Use concomitantly with adrenal corticosteroids.
- Use in conjunction with azathioprine or mycophenolate mofetil for kidney and heart transplant.

Limitations of uses: [5]

- Do not use concurrently with cyclosporine.
- Intravenous use only reserved for patient who cannot tolerate orally.
- For liver and heart transplant, use with sirolimus is not recommended.
- For kidney transplant, use with sirolimus has not been established.

<table>
<tr><th colspan="2">General therapeutic range[1,2]</th></tr>
<tr><td colspan="2">5 – 20ng/ml</td></tr>
<tr><td>Liver transplant[1]</td><td>Months 1 – 2: 5 – 20ng/ml</td></tr>
<tr><td>Kidney transplant[6]</td><td>
<table>
<tr><th>Time (months post-transplant)</th><th>Low rejection risk (ng/ml)</th><th>Moderate rejection risk (ng/ml)</th><th>High rejection risk (ng/ml)</th></tr>
<tr><td>0 – 6</td><td>6 – 12</td><td>8 – 12</td><td>8 – 15</td></tr>
<tr><td>7 – 12</td><td>5 – 8</td><td>5 – 10</td><td>6 – 12</td></tr>
<tr><td>>12</td><td>4 – 8</td><td>5 – 10</td><td>6 – 12</td></tr>
</table>
</td></tr>
<tr><td>Heart transplant[1]</td><td>Months 1 – 3: 10 – 20ng/ml
Months ≥4: 5 – 15ng/ml</td></tr>
</table>

B. DOSAGE

Paediatric: [7]

Age	Liver transplantation (Starting within 12 hours of transplantation)		Kidney transplantation (Starting within 24 hours of transplantation)		Heart transplantation (without antibody induction, starting 12 hours of transplantation)		Heart transplantation (following antibody induction, starting within 5 days of transplantation)
	Oral	IV infusion	Oral	IV infusion	Oral	IV infusion	Oral
Neonate	Initial 0.15 mg/kg BD	0.05mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD	0.075 – 0.1 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD (8-12 hours after discontinuation of IV infusion)	0.03 – 0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.05 – 0.15mg/kg BD
1 month – 18 years old	Initial 0.15 mg/kg BD	0.05mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD *a*	0.075 – 0.1 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.15 mg/kg BD (8-12 hours after discontinuation of IV infusion)	0.03 – 0.05 mg/kg over 24 hours for up to 7 days then transfer to oral therapy	Initial 0.05 – 0.15mg/kg BD

*a*A lower initial dose of 0.1mg/kg twice daily has been used in adolescents to prevent very high 'trough' concentration.

Adult: [1]

Liver transplantation		Kidney transplantation		Heart transplantation	
Oral	**IV infusion**	**Oral**	**IV infusion**	**Oral**	**IV infusion**
0.10 – 0.20mg/kg/day in two divided doses (start approximately 6 hrs after the completion of liver transplant)	0.01 – 0.05 mg/kg/day	0.15 – 0.30 mg/kg/day in two divided doses (start approximately within 24 hrs of kidney transplant)	0.05 – 0.10mg/kg/day	0.075 mg/kg/day in two divided doses	Initial 0.01mg/kg/day

Renal impairment: [1,8]

Patients should receive the lowest effective dose of the recommended intravenous and oral dosing ranges.

Haemodialysis	No dosing adjustment is needed. Not removed by haemodialysis, no supplemental dose is needed.
Peritoneal dialysis	No dosing adjustment is needed. Significant drug removal is unlikely based on psychochemical characteristics.
Continuous renal replacement therapy (CRRT)	No dosing adjustment is needed.

Hepatic impairment: [4,5]

Dose reduction is not necessary. Close monitoring is needed as the half-life of the drug is prolonged and the clearance reduced after intravenous administration. The bioavailability of tacrolimus is increased after oral administration.

C. INTERACTION: [2,5,9]

Tacrolimus is metabolised by CYP3A4 and is a substrate for P-glycoprotein.

Drug that inhibit CYP3A4 and P-glycoprotein	Drug that induce CYP3A4 and P-glycoprotein
Calcium channel blockers Diltiazem Verapamil Amlodipine **Antibiotics** Clarithromycin Erythromycin **Antifungal agents** Fluconazole Itraconazole Ketoconazole **Protease inhibitors** Indinavir Ritonavir **Prokinetic agents** Metoclopramide **Others** Bbromocriptine Danazol Ethinyl estradiol Grapefruit juice, Methylprednisolone	**Antibiotics** Caspofungin Nafcillin Rifampicin **Anticonvulsants** Carbamazepine Phenobarbital Pheytoin Primidone **Others** St. John's wort

D. SAMPLING[2,4]

Time to monitor serum concentration (at steady state):

When to obtain serum tacrolimus level (after dose initiation or adjustment):	
Trough sample only	Trough concentration should be assessed 3 – 5 days after initiation of therapy, after a dosage adjustment, or after discontinuation or initiation of known CYP3A4 inhibitors or inducers. Sample should be stored into ethylene-diamine-tetra-acetic acid [EDTA] tube.

Suspected toxicity:

If toxicity is suspected, blood sample may be drawn at any-time (random sampling).

E. MONITORING PARAMETER[1,5]

Constant monitoring of renal function, liver function, serum electrolytes, glucose and blood pressure (3 times/week) during first few weeks of treatment.

For IV tacrolimus, signs and symptoms of anaphylaxis should be monitored during the first 30 minutes of infusion, and frequently thereafter.

The frequency of monitoring of the following parameters can gradually decrease as patient stabilises.

- Blood pressure (hypertension is a common side effect; proper antihypertensive agents selection is required)
- ECG periodically during treatment, especially in patients at risk for QT prolongation (concomitant use of other QT prolongation drugs or CYP3A inhibitors)
- Blood glucose level; frequently
- Serum potassium levels (especially in patients receiving other medications associated with hyperkalaemia, e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers)
- Renal function; frequently (particularly when use in high dose, dose reduction is needed. Consideration change to other immunosuppressant should be made if patient unresponsive to dosage adjustment of tacrolimus.)
- Liver function; frequently
- Neurotoxicity (particularly when use in high dose).
- Posterior reversible encephalopathy syndrome [PRES] (most severe neurotoxicity). Symptoms of PRES: headache, altered mental status, seizures, visual disturbances, and hypertension. Diagnosis may be confirmed by radiological procedure. Immediate dose reduction is advised.

F. ADVERSE DRUG REACTION[1,5]

Adverse drug reaction (occurrence ≥ 15 %)	
Cardiovascular	hypertension, oedema, chest pain, pericardial effusion
Central nervous system	headache, insomnia, pain, fever, dizziness
Dermatological	pruritus, rash
Endocrine & metabolic	hypophosphataemia, hypomagnesemia, hyperglycaemia, hyperkalaemia, hyperlipidaemia, hypokalaemia, diabetes mellitus
Gastrointestinal	diarrhoea, abdominal pain, nausea, constipation, anorexia, vomiting, dyspepsia
Genitourinary	urinary tract infection
Haematological	anaemia, leukopenia, leukocytosis, thrombocytopenia
Renal	abnormal kidney function, creatinine increased, BUN increased, oliguria
Hepatic	liver function test abnormal, ascites

Overdosage/Toxicology: [5]

Limited data on cases with tacrolimus overdoses.

A chronic overdose is known to cause nephrotoxicity (elevation of serum creatinine and decrease in urine output). Acute overdoses of up to 30 times the therapeutic dose have occurred with tacrolimus and almost all cases have been asymptomatic and recovery uneventful.

In severe cases, it may manifest as seizure, delirium or coma.

Management of overdosage/toxicology:[10]

- Treatment is supportive and symptomatic.
- Consider activated charcoal following oral ingestion. Emesis is not indicated.
- Hypertensive disorder: Mild/ moderate asymptomatic hypertension usually does not require treatment. Nitroprusside or nitroglycerin may be considered with severe episodes.
- Seizure: IV benzodiazepines, barbiturates.
- Haemodialysis: Based on high protein binding, large molecular weight, and extensive partitioning of tacrolimus into red blood cells, haemodialysis is not anticipated to be effective following overdose.
- Monitoring of patient: Monitor vital signs and neurological status.
- Obtain serial CBC with differential and electrolytes following a significant exposure.
- Monitor renal and hepatic function after significant overdose.

G. DILUTION AND ADMINSTRATION

Dilution of drug: [1]

Dilution of drug	Dilute with 5% dextrose of injection or 0.9% sodium chloride injection to a final concentration between 0.004mg/ml and 0.02 mg/ml. Diluted solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. Diluted solutions should not keep in PVC container due to decreased stability and potential for extraction of phthalates.

Drug administration: [1,3]

Drug administration	
Oral	Administer on empty stomach; be consistent with timing and composition of meals. The presence of food, particularly high-fat meal, decreases the rate and extent of tacrolimus absorption.
Intravenous infusion	To be administered as continuous infusion. Conversion from IV to oral tacrolimus is recommended once patient can tolerate orally. This normally occurs within 2 – 3 days. The first of oral therapy should be given 8 – 12 hours after discontinuing the Iv infusion.

H. CALCULATION[4]

A) Dose Initiation

1. Estimate clearance

$$\text{CL (L/hour)} = \text{CL (L/kg/hour)} \times \text{BW (kg)}$$

Mean Tacrolimus clearance (Adult) = 0.06 L/h/kg
Tacrolimus clearance (Paediatric) = 0.14 L/h/kg

2. Determine Css target and calculate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}} \times \frac{1}{1000}$$

S = 1.0
F = 0.25 (oral); 1.0 (injection)

B) Dose Adjustment

1. Estimate CL from the obtained level

$$\text{CL (L/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mcg)}}{\text{Css (mcg/L)} \times \text{Interval (hour)}}$$

2. Determine Css target and calculate a new maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mcg/L)} \times \text{Interval (hour)}}{\text{S} \times \text{F}} \times \frac{1}{1000}$$

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CHAPTER 12: THEOPHYLLINE

CHAPTER 12
THEOPHYLLINE

KEY PARAMETERS:

Therapeutic range	5 – 20mcg/ml*
Bioavailability (F)	1
Salt Factor (S)	1, Aminophylline : 0.8
Volume of Distribution (Vd)	Neonates : 0.8 L/kg[1] Infants : 0.5 – 0.7 L/kg[1] Paediatric & Adults : 0.5 L/kg[1]
Clearance (CL)	0.04 L/kg/hr
Half-life ($t_{1/2}$)	Adults: Average 8 hours

*Subject to specific indication

A. PHARMACOKINETIC

Bioavailability:

Intravenous: 100%[2]
GIT: Well absorbed (90 – 100% bioavailability), dosage form dependent[2,3]
Rectal: Slowly & erratically, vehicle dependent[1]

Volume of Distribution (Vd):

Distributes poorly into body fat, dose should be based on ideal body weight.[1,4,5]

Protein Binding: 40%.[1,2]

Unbound fraction of theophylline is freely distributed into body fluid, cerebrospinal fluids, placenta and breast milk.

The binding is affected by pH and by non-esterified fatty acid concentration, and these factors may be of greater importance in disease states.[6]

Clearance (CL):

Premature Neonate	Paediatric	Adults
3 – 15 days: 0.017 L/kg/hr[1]	1 – 4 years: 0.102 L/kg/hr[1]	16 years old – 60 years old: 0.04 L/kg/hr (based on lean or IBW)[7]
25 – 57 days: 0.038 L/kg/hr[1]	4 – 12 years old: 0.096 L/kg/hr[1]	Elderly (>60 years old): 0.025 L/kg/hr[1]
Term infants (day 1 – 30 weeks): No report	13 – 15 years old: 0.054 L/kg/hr[1]	

Half-life ($t_{½}$):

The half-life for theophylline depends on age and renal function.[9]

Condition	Half-life
Premature neonates (postnatal age 3 to 15 days)	Mean 30 hours (17 to 43 hours)
Premature neonates (postnatal age 25 to 57 days)	Mean 20 hours (9.4 to 30.6 hours)
Term infants (postnatal age 1 to 2 days)	Mean 25.7 hours (25 to 26.5 hours)
Term infants (postnatal age 3 to 30 weeks)	Mean 11 hours (6 to 29 hours)
Paediatric (1 to 4 years)	Mean 3.4 hours (1.2 to 26.5 hours)
Paediatric (6 to 17 years)	Mean 3.7 hours (1.5 to 5.9 hours)
Adults (16 to 60 years, non-smoking asthmatics)	Mean 8.7 h (range 6.1 h to 12.8 h)
Elderly (greater than 60 years)	Mean 9.8 h (range 1.6 h to 18 h)
Acute pulmonary oedema	Median 19 hours (3.1 to 8.2 hours)
COPD (elderly over 60 years age)	Mean 11 hours (9.4 to 12.6 hours)
Cystic fibrosis (age 14 to 28 years)	Mean 6 hours (1.8 to 10.2 hours)
Fever (acute viral respiratory illness children 9 to 15 years)	7 hours (1 to 13 hours)
Acute hepatitis:	Mean 19.2 hours (16.6 to 21.8 hours)
Cirrhosis	Median 32 hours (10 to 56 hours)
Cholestasis	Mean 14.4 hours (5.7 to 31.8 hours)
Pregnancy	• First trimester: mean 8.5 hours (3.1 to 13.9 hours) • Second trimester: mean 8.8 hours (3.8 to 13.8 hours) • Third trimester: 13 hours (8.4 to 17.6 hours)
Sepsis	Mean 18.8 hours (6.3 to 21.4 hours)
Hypothyroid	Mean 11.6 hours (8.2 to 25 hours)
Hyperthyroid	Mean 4.5 hours (3.7 to 5.6 hours)
Adults (16 to 60 years, non-smoking asthmatics)	Mean 8.7 h (range 6.1 h to 12.8 h)

Note: Highly variable and dependent upon age, liver function, cardiac function, lung disease and smoking history.[2]

Indication and Therapeutic Range:

Asthma/COAD: 10 – 20mcg/ml[1]

5 – 15mcg/ml enhances safety and gives up, if any, therapeutic benefit.[1]
Improvement in respiratory function can be observed with concentrations as low as 5mcg/ml.[7]

Apnea/Bradycardia in Neonates: 5 – 10mcg/ml[1]

- However, many neonates respond at low concentrations.[1]
- Therapy should be started at low concentrations and can be increased in increments of 3mcg/ml as necessary.[1]
- Ventilator Weaning in Neonates: 5 – 20mcg/ml[1]
- Aminophylline has shown diuretic effect and could be used as adjunct therapy with frusemide.[1,10,15]

**Conversion factor:mcg/ml x 5.55 = µmol/L

B. DOSAGE

Paediatric:

Loading Dose for Paediatric:
5mg[11] – 10mg[12]/ kg IV infusion over 20 – 60 minutes

a) Acute Asthma

With previous theophylline therapy
1 month – 18 years old: 5mg/kg over at least 20 minutes[11]

Without previous theophylline therapy
1 month – 12 years old: 1mg/kg/hr adjusted according to plasma theophylline concentration[11]
12 – 18 years old: 500 – 700mcg/kg/hr adjusted according to theophylline concentration[11]

b) Apnoea

Neonates: initially 6mg/kg, then 2.5mg/kg every 12 hours via intravenous injection over 20 minutes (increase if necessary to 3.5mg/kg every 12 hours).[11]

Maintenance Dose:

Group	Oral Theophylline (mg/kg/day)	IV Aminophylline
Neonates 1st week of life[12]	-	2.5mg/kg/12 hourly
Neonates 2nd weeks of life[12]	-	3mg/kg/12 hourly
Premature & term neonates, <6 weeks[2]	4	5mg/kg/day
6 weeks – 6 months[2]	10	12mg/kg/day
6 months – 1 year old[2]	12 – 18	15mg/kg/day
1 – 9 years old[2]	20 – 24	1mg/kg/h
9 – 12 years old[2]	16	0.9mg/kg/h
12 – 16 years old[2]	13	0.7mg/kg/h

Dosage varies from different reference. Please refer to other paediatric references for more information.

Adult:

Loading Dose:

With previous theophylline therapy
Check for serum theophylline concentration
LD = (Concentration desired – Concentration measured) x Vd

Without previous theophylline therapy
LD: 4.6mg/kg of theophylline or 5.7mg/kg of aminophylline (over 30 minutes)[2]

Maintenance Dose:

Group	Oral Theophylline (mg/kg/day)	IV Aminophylline (mg/kg/h)
Smoking adults[2]	16	0.9
Non-smoking adults[2]	10 (not exceed 900mg/d)	0.5
Older patients and patients with Cor-pulmonale, congestive heart failure or liver failure.[13]	6 (not exceed 400mg/d)	0.25

Dosage may be increased by approximately 25% at intervals of 2 – 3 days as long as drug is tolerated.[2]

If dose is >600mg/day, titrate dose according to serum theophylline levels[9]

Note: Dose based on Ideal Body Weight

Renal Impairment

- Neonates: ~50% of the theophylline dose is excreted unchanged in the urine. Requires dose reduction and frequent monitoring.[2]
- Adults and paediatric >3 months of age: 10% excreted by the kidney unchanged, no dosage adjustment for renal insufficiency.[2]
- Theophylline is dialyzable. Patients may require dosage adjustments to account for increased elimination during dialysis.[9]
- Haemodialysis significantly shortens the half-life of theophylline in patients taking oral theophylline tablets on a regular every 6 hours schedule. It has been recommended to administer 150% of the patient's usual dose of theophylline once, prior to each haemodialysis. In the period between each dialysis, therapy can resume on a regular dosage schedule.[9]
- In patients receiving sustained-release theophylline (every 12 hours), 125% of the normal dose should be administered prior to dialysis.[9]

C. INTERACTION

Factors affecting theophylline clearance.[7]

Increase theophylline clearance	CL Factor	Decrease theophylline clearance	CL Factor
Smoking	1.6	Severe COPD	0.8
Phenytoin	1.6	Erythromycin	0.75
Phenobarbitone	1.3	Ciprofloxacin	0.7
Rifampicin	1.3	Cimetidine	0.6
Cystic fibrosis	1.5	Propanolol	0.6
		Influenza vaccines	0.5
		Acute Pulmonary Oedema	0.5
		Acute Viral Illness	0.5
		Hepatic Cirrhosis	0.5
		CHF	0.4

Factors present must be multiplied by the average clearance value.[13]

D. DRUG INTERACTION

The level of Theophylline may be increased by[2]	The level Theophylline may be decreased by[2]
Alcohol Allopurinol (>600mg/day) Beta-blockers Calcium channel blockers Cimetidine Clarithromycin Corticosteroids Erythromycin Esmolol Isoniazide* Loop diuretics* Methotrexate Propranolol Thyroid hormones Verapamil	Carbamazepine* Isoniazide* Ketoconazole Loop diuretics* Nevirapine Phenobarbitone Phenytoin Rifampicin Ritonavir Sympathomimetics

*Loop diuretic, Isoniazid, and Carbamazepine may increase or reduce theophylline clearance.[13]

E. SAMPLING

When to obtain serum theophylline level (after dose initiation or adjustment):[1]

Premature Neonates	150 Hours ~6 Days
Newborn	5 Days
Infant	1 – 5 Days
Paediatric	1 – 2 Days
Adults	2 Days

Oral Maintenance dose:

- Oral: 30 minutes OR just before next dose.[13]

If dose already taken wait at least

- 1 – 2 hours: Rapid release tablet.[11]
- 4 – 6 hours: Sustained released tablet.[11]

Intravenous:

- Loading dose: 30 minutes after LD given (end of infusion)[9,13] to determine the maintenance dose.
- Continuous infusion: 12 – 24 hours after administration (initiation of infusion) or change in dose of continuous infusion.[2,11]

- If toxicity is suspected, blood may be drawn at any time (random sampling).[13]
- In patients receiving any dosage form of theophylline other than (continuous) infusions, routine monitoring of theophylline concentration is probably most reliable when troughs are obtained.[7]

F. MONITORING PARAMETER

- Symptomatic improvement: Reduction in asthmatic symptoms.[13]
- Pulmonary function test.[13]
- Vital Signs; Respiratory rate, heart rate, arterial or capillary blood gases (if applicable).[2]
- Liver profile.[13]
- Renal profile.[13]
- Drug & disease interactions.[13]

Note:

Asthma or COAD[13]

- Decrease in severity of wheezing and rales.
- Respiration rate normalization.
- Improvement of FEV_1.
- Decrease in the ventilator support required.

Apnoea or bradycardia in neonates[13]

- Decrease in number and depth of apnoeic and bradycardia episodes.
- Heart rate normalization.
- Decrease in the ventilator support required.

G.ADVERSE DRUG REACTION

Concentration related adverse reactions of Theophylline (adults)[1,13]
If >20mcg/ml: nausea, vomiting, diarrhoea, headache, irritability, insomnia, tremor.

If >35mcg/ml: hyperglycaemia, hyperkalaemia, hypotension, cardiac arrythmias, hyperthermia, seizure, brain damage.

Sign and symptoms of toxicity (neonates)[1,13]

- Tachycardia (beats >180bpm)
- Irritability
- Seizures
- Vomiting (“coffee ground” like appearance)

Overdosage/Toxicology:

Classification of toxicity	Symptoms	Management
Mild to moderate toxicity[9]	**Nausea and/or vomiting**	• IV Metoclopramide; Adults: 10mg, repeat every 8 hours if needed • Paediatric: Up to 1 year; 1mg BD, 1 – 3 years; 1mg BD/TDS, 3 – 5 years; 2mg BD/TDS, 5-9 years; 2mg TDS, 9 – 14 years; 5mg TDS[11] • Electrolyte imbalance may occur as a result of severe vomiting. Administer IV fluids to maintain hydration and electrolyte balance.
Severe toxicity[9]	**Agitation/ restlessness**	• The primary treatment is sedation with benzodiazepines (such as lorazepam 1 to 2mg IV every 5 min titrated to effect); high doses may be required.
	Tachycardia	• IV Esmolol; Give loading dose of 500mcg/kg over 1 minute, follow with a 50mcg/kg/min infusion for 4 minutes. • Inadequate response, repeat LD (500mcg/kg) over 1 minute, increase maintenance infusion to 100mcg/kg/min. This regimen can be repeated until therapeutic effect is achieved with maximum maintenance dose of 200mcg/kg/ min. • To be diluted to a final concentration of not more than 10mg/ml in IV drips (e.g. 2.5g in 250ml NS or 5g in 500ml NS)
	Hypokalaemia	• Hypokalaemia is corrected by IV infusion of potassium chloride • IV doses should be incorporated into the patient's maintenance IV fluids. • Dose: Adults; 10-20 mmol/dose to infuse over 2-3 hours (max dose: 40mmol over 1 hour). Paediatric; 0.5-1 mmol/kg/dose to infuse at 0.3-0.5 mmol/kg/hour (max dose: 1mmol/kg/hour)[2] • ECG monitoring whenever necessary
	Seizures/ convulsions	• Seizures (severe, recurrent) may be controlled by IV administration of diazepam, 5-10mg slow bolus injection, every 10-15 minutes as necessary up to a max dose of 30mg, may repeat in 2 to 4 hours if needed[9]

Note:

- Haemodialysis should be performed in patients with severe toxicity, and patients with high serum theophylline concentrations (80 to 100mcg/ml after acute overdose, 40 to 60mcg/ml with chronic toxicity).
- For over dosage of oral formulation, the stomach should be emptied if the patient presents within 2 hours. Elimination of theophylline is enhanced by repeated doses of activated charcoal by mouth.
- Antidote: There is no specific antidote

H. DILUTION AND ADMINSTRATION

Dilute in Normal Saline or Dextrose 5% (D5W) or Dextrose 10% (D10W)[2,13,14]
Diluents for neonate – NS, D5W[13]
Diluents for adult – NS, D5W, D10W[2,14]

Loading & Maintenance Dose[4]

Dose	Infusion time	Dilution
0 – 250mg	20 – 30 minutes	50ml
251 – 500mg	20 – 30 minutes	100ml

Continuous Infusion[4]

Dose	Infusion time	Dilution
500mg	Titrate	500ml

Fluid Restriction[4]

Dose	Infusion time	Dilution
500mg	Titrate	250ml

- Dilute with IV fluid to a concentration of 1mg/ml and infuse over 20 – 30 minutes.[14]
- Stable for 48 hours at Room Temperature[15]

Drug administration

Maximum Infusion Rate: 0.5mg/kg/hr (0.36mg/kg/min) or 20 – 25mg/min[2]

Maximum Infusion Rate for patient with:

- Cardiac Failure (CF): 0.25mg/kg/hr[9]
- Liver Disease (LD): 0.25mg/kg/hr[9]
- CF, cor-pulmonale, LD, sepsis with multi-organ failure, or shock: 0.2mg/kg/hr (Not to exceed 400mg/day, unless serum levels indicate the need for a larger dose).[4]
- Rapid IV injection (should not exceed 20 – 25mg/min) has produced dizziness, faintness, palpitations, syncope, precordial pain, flushing, severe hypotension and cardiac arrest. Sudden deaths have been reported.[1,2,13]
- Administration through IM is not recommended as it will cause intense local pain and sloughing of tissue.[2]

Note: Calculation is based on Ideal Body Weight

I. CALCULATION

A) Dose Initiation

Maintenance dose: Oral/Intravenous

1. Estimate Clearance (CL):

$$\text{CL (L/hour)} = \text{CL (L/kg/hour)} \times \text{BW (kg)}$$

$$\text{CL total (L/hour)} = \text{CL (L/hour)} \times \text{CL factor*}$$

*refer to table in Interaction

2. Determine Css target and calculate Maintenance Dose (MD):

$$\text{MD (mg)} = \frac{\text{CL (L/hour)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

Loading dose: Intravenous

1. Estimate Volume distribution (Vd):

$$\text{Vd (L)} = (0.5\ \text{L/kg}) \times \text{BW (kg)}$$

2. Determine the Css target and calculate Loading Dose (LD):

$$\text{LD (mg)} = \frac{\text{Vd (L)} \times \text{Css target (mcg/ml)}}{\text{S} \times \text{F}}$$

B) Dose Adjustment

1. Estimate Clearance (CL) from the obtained level:

$$\text{CL (L/day)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg/day)}}{\text{Css (mcg/ml)}}$$

2. Determine Css target and calculate the new Maintenance Dose (MD):

$$\text{MD (mg)} = \frac{\text{CL (L/day)} \times \text{Css target (mcg/ml)} \times \text{Interval (day)}}{\text{S} \times \text{F}}$$

J. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic < 10mcg/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction	Poor	If compliance & sampling time is satisfactory, give incremental loading dose STAT (for patient in ward), then increase the dose if required or continue with current dose & resample
		Good	Continue current dose
Within normal therapeutic range 10 – 20mcg/ml		Poor	Determine other factors that may contribute to poor response and treat accordingly
		Good	Continue current dose
Potential toxic/ Toxic >20mcg/ml	• Overdosage • Underlying disease/factors • Possible drug interaction • Renal failure • Hypokalemia • CHF	Toxic effect: • Vomiting • Hyperkalemia • Sinus bradycardia • Hyponatremia • Ventricular arrythmia • Weakness	Withold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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CHAPTER 13: VALPROIC ACID

CHAPTER 13
VALPROIC ACID

KEY PARAMETERS:

Therapeutic range	Seizures: 50 – 100mcg/ml[1,3,4] Psychiatric Disorder: 50 – 125mcg/ml[1,2,4]
Bioavailability (F)	Intravenous: 100%[1] Oral: 100%[1] Sustained Release Tablet: 90%[1] Extended Release Tablet: 80 – 90%[1]
Salt Factor (S)	1.0[1,2]
Volume of Distribution (Vd)	Paediatric: 0. 22 (+ 0.05) L/kg[2] Adults: 0.15 (+ 0.10) L/kg[2]
Clearance (CL)	**Paediatric** Monotherapy: 10 – 20ml/kg/hr[3] Polytherapy: 20 – 30ml/kg/hr[3] **Adult** Monotherapy: 7 – 12ml/kg/hr[3] Polytherapy: 15 – 18ml/kg/hr[3]
Half-life ($t_{1/2}$)	**Paediatric** Monotherapy: 6 – 8 hours[3] Polytherapy: 4 – 6 hours[3] **Adult** Monotherapy: 12 – 18 hours[3] Polytherapy: 4 – 12 hours[3]

A. PHARMACOKINETIC

Bioavailability (F)

Valproic acid is completely absorbed with bioavailability (F) and salt forms (S) are 1.0 for the intravenous, oral solution and capsules. The bioavailability of enteric-coated tablets is similar to capsule as the tablet is not sustained in their release but it only delay the absorption of drug after ingestion.[1,3]

The bioavailability of extended release tablet is between 80% - 90%. It has more sustained plasma profile like continuous infusion model. The bioavailability of sustained release tablet is 90%.[1]

Volume of Distribution (Vd)

Valproic acid is highly bound to serum albumin with typical values of 90 – 95%.[1,2,3] Binding of valproic Acid to serum albumin will become saturated within the therapeutic range (or when valproic Acid concentration exceed 50mcg/ml).[1,3] This concentration dependent protein binding of valproic acid causes the drug to follow nonlinear pharmacokinetics (less protein binding and higher unbound fraction of drug at higher concentrations).[3]

Table below shows disease states and conditions that alter valproic acid plasma protein binding.

Hypoalbuminaemia[3] (Albumin level below 3g/dL are associated with high Valproic acid unbound fractions in the plasma)[3]	• Liver disease • Nephrotic syndrome • Pregnancy • Cystic fibrosis • Burns • Trauma • Malnourishment • Elderly
Displacement by endogenous substances [3]	• Hyperbilirubinaemia (>2mg/ml) • Jaundice • ESRF (CrCl<10 – 15ml/min) with uremia (BUN >80 – 100mg/dL)
Displacement by exogenous substances [3]	• Drugs that are highly bound to albumin (warfarin, Phenytoin, Aspirin >2g/d and some highly bound NSAID)

* Vd of valproic acid in these clinical conditions may be larger because of reduced plasma protein binding.[3]

Metabolism

Valproic Acid metabolism is enhanced by other drugs that can induce hepatic enzymes activity[1]. One of the metabolite (4-en-valproic acid) may be associated with the drug's propensity to cause hepatotoxicity.[3]

Clearance (CL)

Valproic Acid is almost entirely eliminated through hepatic metabolism (>95%) and less than 5% eliminated by the renal route.[1]

	Monotherapy[3]	**Polytherapy[3]**
Paediatric	10 – 20ml/kg/hr	20 -30ml/kg/hr
Adult	7 – 12ml/kg/hr	15 -18ml/kg/hr

* Clearance of Valproic acid may correlate better with ideal body weight rather than total body weight in obese patient[2,3]

* Liver Dysfunction (Liver Cirrhosis, Acute Hepatitis) have reduced valproic acid clearance (Cl: 3 – 4ml/kg/hr) due to reduces amount of enzymes as destruction of liver parenchyma.[3,4]

Half-life ($t_{½}$)

	Monotherapy	Polytherapy
Paediatric	6 – 8 hr[3]	4 – 6 hr[3]
Adult	12 – 18 hr[3]	4 -12 hr[3]

* Average half life for valproic acid in patients with liver disease is 25 hours.

Time to Peak[1]

Oral: 1 to 3 hours (before meal)
Oral: 6 to 8 hours (after meal)
Intravenous: at the end of 1 hour infusion

Indication and Therapeutic Range

Indication	Therapeutic Range at steady state
Generalized, partial and absence seizures (petit mal)[3]	50 – 100mcg/ml[1,3,4]
Mania with bipolar disorder[3], anxiety, depression, psychosis, substance-abuse withdrawal and other behavioral disturbances[1]	50 – 125mcg/ml[1,2,4]

* Valproic Acid concentrations exceeding 100mcg/ml are often required in patients with partial seizure[1]
* IV Valproate is not recommended for post-traumatic seizure prophylaxis in patients with acute head trauma due to increased mortality compared to IV Phenytoin[4]
* Valproate Acid should be withdrawn gradually to minimize the potential of increased seizure frequency (Unless safety concern requires a more rapid withdrawal)[4]

B. DOSAGE

Paediatric

For generalize or partial seizure

Initially: 5mg/kg for 8 to 12 Hourly[5]

Monotherapy	Polytherapy
10mg/kg/day[3]	20mg/kg/day[3]

Increase dose if required to max 20mg/kg for 8 to12 Hourly[5]

Adult

For generalize or partial seizure

Loading Dose: 20 – 25mg/kg[2]
Maintenance: 15mg/kg/day up to 60mg/kg/day [1]

Monotherapy	Polytherapy
7.5mg/kg/day[3]	15mg/kg/day[3]

Dose adjustment 5 – 10mg/kg/day at weekly intervals[4]

	For psychiatric disorders 25mg/kg/day up to 60mg/kg/day [1]
	For migraines 500mg OD for 7 days followed by 1,000mg daily thereafter [1]

Note: Dose based on Ideal Body Weight for obese patient[3]

Renal Impairment

No dosage adjustment necessary but renal function needs to be monitored closely. High urea level can displace valproic acid from binding site (decreased protein binding) and unbound valproic acid will be higher in this clinical condition.[3,4]

Valproic Acid is not removed efficiently by haemodialysis[2,3]

Hepatic Impairment

Valproic acid has been associated with hepatic damage and patients with existing liver disease should be classified according to liver dysfunction index (child-pugh score) before initiation of the drug.[3]

Test/Symptom	Score 1 point	Score 2 points	Score 3 points
Total Bilirubin (mg/dL)	<2.0	2.0 – 3.0	>3.0
Serum Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
Prothrombin time, prolongation (secs)	<4	4 – 6	>6
Ascites	Absent	Mild	Moderate
Hepatic Encephalopathy	None	Moderate	Severe

*Child-pugh score for patients with liver disease.

A Child–Pugh score greater than 8 is grounds for a decrease of 25 – 50% in the initial daily drug dose for valproic acid.[3]

Severe impairment: contraindicated.[4]

C. INTERACTION

Valproic Acid is an enzyme inhibitor and is subject to enzyme induction[2]

Valproic Acid may increase level/effects of the following drugs	The level/effects of Valproic Acid may be increased by	The level/effects of Valproic Acid may be decreased by
Amitriptyline[3] Carbamazepine Epoxide (by inhibition of epoxide prolase)[2,3] Clonazepam[3] Ethosuximide[2,3] Lamotrigine[2,3] Lorazepam[2] Nortriptyline[3] Phenobarbital[1,2] Phenytoin[1,2,3] Primidone[3,4] Risperidone[4] Zidovudine[3]	Cimetidine[3] Chlorpromazine[3] Felbamate[3] Topiramate[4]	Carbamazepine[1,2,3] Carbapenem[4] Lamotrigine[3] Phenytoin[1, 2, 3] Phenobarbitone[1, 2] Primidone[2] Rifampicin[2]

D. SAMPLING

Steady State: 2 to 4 days[1]

Sampling time:
Oral/Intravenous maintenance dose: 30 minutes OR just before next dose.[1]

Monitoring is recommended in the following condition:
- Initiation of therapy
- Change in a dosing regimen
- Addition of other antiepileptic drugs to the patient's regimen
- Change in patient's clinical course (decrease in seizure control or laboratory/physical finding consistent with valproic acid toxicity)
- Any claims/complains of valproic acid side effects

E. MONITORING PARAMETER

- Liver enzymes (at baseline and frequently during therapy especially during the first 6 months)[4]
- Full blood count with platelets (baseline and periodic intervals)[4]
- Serum ammonia (with symptoms of lethargy, mental status change)[4]
- Bodyweight
- Blood Pressure
- Heart rate

F. ADVERSE DRUG REACTION

Side effects[1,3]	• Alopecia • Abdominal cramps • Diarrhoea • Nausea • Pancreatitis • Hyperammonemic encephalopathy • Hepatotoxicity • Weight gain • Vomiting
Patients at higher risk of hepatotoxicity[1]	• Young patient (hepatic failure resulting in fatalities has occurred in patient <2 years of age)[4] • Patient with developmental delayed • Metabolic disorders • Patient receiving anticonvulsant combination therapy

Some concentration related side effects:

Concentration	Side effects
When serum concentration (>75mcg/ml)[3]	Tiredness, lethargy, sedation and ataxia
When serum concentration (>100mcg/ml)[3]	Tremor
When serum concentration(>110mcg/ml for female, >135mcg/ml for male)[4]	Probability of thrombocytopenia
When serum concentration (>175mcg/ml)[2,3]	CNS toxicity, coma and stupor

* Sedation and drowsiness can be due to interaction between valproic acid and other concomitant anticonvulsant therapy.[1]
* Pharmacodynamic interaction between valproic acid and lamotrigine may lead to an increased incidence of tremor and rash.[2]
* It was reported that a four fold increase in congenital malformations happen during the first trimester of pregnancy.[4]

Overdosage/Toxicology:

Mild to moderate toxicity of valproic acid generally presented with CNS depression such as lethargy, sedation, vomiting and tachycardia. In severe toxicity, patients typically develop more severe CNS depression such as coma, myotic pupils, tachycardia, hypotension, QT prolongation, and respiratory depression.[9]

Management of Overdosage/Toxicology:

1) Mild to moderate toxicity:[9]
   - **Activated charcoal** may be considered if the ingestion is recent. Repeat valproic acid levels every 4-6 hours and consider multiple dose activated charcoal if the level is increasing.
2) Severe toxicity:[9]
   - Antidote: **L-cartinine**
     Indication: Valproic acid-induced coma, hyperammonemia, hepatotoxicity, concentration of valproic acid >450mcg/ml.
     Dose: IV L-cartinine 100mg/kg over 30 minutes (maximum 6 g) followed by 15mg/kg every 4 hours until clinical improvement.
   - **Naloxone** may be considered in patients with CNS depression, Valproic acid-induced coma and/ or significant respiratory depression.
   - **Haemodialysis/haemoperfusion** are reserved for patients who are not responding to supportive care, especially with concomitant severe metabolic disturbance and/ or a serum valproic acid level >1,000mcg/ml.

*Monitor valproic acid concentrations every 4 – 6 hours until the concentrations are clearly declining and symptoms have resolved.[9]

G.DILUTION AND ADMINSTRATION

Dilution of drug	Reconstitute with 3.8ml WFI (provided) to give 100mg/ml(If 4ml WFI solvent is used, the resulted concentration will become 95mg/ml)[6] Can be diluted further in 50 – 100ml of NS/D5W for infusion[6]

- Stable for 24 hours at room temperature[1]
- Each vial is for single dose injection only. Any unused portion should be discarded[6]

Drug administration	Infusion Rate
Rapid infusion[3]	5 – 10 min (<45mg/kg)
IV intermediate infusion[3]	60 min (<20mg/min)

H. CALCULATION[1]

A) Dose Initiation

1. Calculate Clearance (CL):

$$\text{CL (L/hr)} = \frac{\text{CL (ml/kg/hr)} \times \text{BW (kg)}}{\text{1000ml}}$$

2. Calculate volume of distribution (Vd):

$$\text{Vd (L)} = \text{Vd (L/kg)} \times \text{BW (kg)}$$

3. Calculate elimination rate constant (K_e):

$$\text{Ke (hr}^{-1}\text{)} = \frac{\text{CL (L/hr)}}{\text{Vd (L)}}$$

4. Calculate half life ($t_{½}$):

$$t_{½}\text{ (hr)} = \frac{0.693}{\text{Ke (hr}^{-1}\text{)}}$$

To initiate loading dose

*Recommended loading dose is 20 – 25mg/kg[2]

$$\text{LD (mg)} = \frac{\text{Css desired (mcg/ml)} \times \text{Vd (L)}}{\text{S} \times \text{F}}$$

To initiate maintenance dose

$$\text{MD (mg)} = \frac{\text{CL (L/hr)} \times \text{Css desired (mcg/ml)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

B) Dose Adjustment

1. Estimate Clearance (CL) from the obtained level:

$$\text{Cl (L/hr)} = \frac{\text{S} \times \text{F} \times \text{Dose (mg)}}{\text{Css measured (mcg/ml)} \times \text{Interval (hour)}}$$

2. Determine Css target and calculate new maintenance dose

$$\text{MD (mg)} = \frac{\text{Cl (L/hr)} \times \text{Css target (mcg/ml)} \times \text{Interval (hour)}}{\text{S} \times \text{F}}$$

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic <50mcg/ml	• Compliance • Wrong sampling time • Insufficient dose • Drug Interaction • Hypoalbuminemia • Renal failure	Poor	If compliance & sampling time is satisfactory, increase the dose appropriately & resample. For patient in ward, oral dose can be converted to IV dosing
		Good	Continue current dose
Within Normal Therapeutic Range 50 – 100mcg/ml		Poor	If compliance & sampling time is satisfactory, increase the dose (not more than max recommended)
		Good	Continue current dose
Potential toxic/ Toxic >120mcg/ml	• Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Deep sleep • Coma • Confusion • Hyponat-remia • Ataxia • Arrhythmia • Leukopenia	Withold treatment, monitor level and treat signs & symptoms of toxicity (if required), then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

J. REFERENCES

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CHAPTER 14: VANCOMYCIN

CHAPTER 14
VANCOMYCIN

KEY PARAMETERS:

Therapeutic range	Trough: Non-complicated: 10 – 15mcg/ml[5] Complicated: 15 – 20mcg/ml[5] Peak: 25 – 40mcg/ml[4]
Bioavailability (F)	Oral:<5%[1] IV: 100 %[1]
Elimination Rate (Ke)	Ke (hr^{-1}) = 0.0044 + (CrCl x 0.00083)[3]
Volume of Distribution (Vd)	Vd (L)= 0.7 L/kg
Clearance (CL)	CL (L/hr) = 0.06 x CrCl (ml/min)[1]
Half-life ($t_{1/2}$)	Adult: 5 – 11 hours[4] Paediatric: 2– 3 hours[4]

A. PHARMACOKINETIC

Bioavailability (F):[1]
Oral: <5%
Intravenous: 100%

Volume of Distribution (Vd):
The average Vd for vancomycin in non-obese adults with normal renal function is 0.7 L/kg. However, it can be calculated using these equations:

Vd (L)= 0.17 (age) + 0.22 (TBW) + 15 [2]

or

Vd (L)= (0.5 – 1) L/kg X BW (kg)[2]

Clearance (CL):
In healthy subject 30% of the systemic vancomycin clearance is by non-renal mechanism and the non-renal clearance is concentration dependent. Assuming protein binding to be between 10% and 20%, renal vancomycin excretion is predominantly by glomerular filtration.[13]

CL = 0.695 (CrCl,ml/min) + 0.05[7]

Clearance also can be calculated using: Vd/Ke (L/hr)

Half-life ($t_{½}$):

Neonates	6 – 10 hr[4]
Paediatric	2 – 3 hr[4]
Adult	5 – 11 hr[4]
Adult, renal failure	120 – 140 hr[7]
Adult, obese	3 – 4 hr[7]
Burn patient	4 hr[1]

Indication and Therapeutic Range:

Vancomycin is used to treat severe gram positive infections. It exhibits time-dependent antibiotic. Thus, trough serum concentration is the most accurate and practical method for monitoring vancomycin effectiveness.

Trough:

Non-complicated: 10 – 15mcg /ml[5]
Complicated*: 15 – 20mcg/ml[5]

*Complicated infection (bacteremia, endocarditis, osteomyelitis, meningitis, pneumonia) caused by microorganism such as MRSA, *Enterococcus Faecium* and *Staphlococcus Aureus* coagulase negative.

For continuous infusion: 15 – 25mcg/ml[16,17]

Peak:

25 – 40mcg/ml[4]

Conversion Factor:mcg/ml (~mcg/ml) x 0.69= µmol/L

B. DOSAGE

Paediatric:

Age	Dose
Neonate less than 29 weeks postmenstrual age	15mg/kg OD[14]
29 – 35 weeks postmenstrual age	15mg/kg BD[14]
Over 35 weeks postmenstrual age	15mg/kg TDS[14]
Infant >1 month & Paediatric	10 – 15mg/kg every 6 h[4]

Dose and interval will be adjusted according to vancomycin serum concentration.

Adult:

Normal renal function[4]: 2 – 3g/day (20 – 45mg/kg/day) in divided doses every 6 – 12 h; maximum 4g/day[5]
Obese: Dosed based on TBW

Continuous Infusion:[9]

LOADING DOSE	
<40kg	500mg IV in 100ml 0.9% sodium chloride or 5% glucose over 1 hour
<70 kg	1g IV in 250ml 0.9% sodium chloride or 5% glucose over 2 hours
≥ 70 kg	1.5g IV in 250ml 0.9% sodium chloride or 5% glucose over 2.5 hours

Central administration: the final concentration should not exceed 10mg/ml
Peripheral administration: the final concentration should not exceed 5mg/ml

Start the maintenance IV infusion immediately after the loading dose. The dose depends on the patient's renal function. Infusions should be administered in 250ml 0.9% sodium chloride or 5% glucose over 12 hours. The total daily dose should be split into two and the infusion rate set at 20.8ml/hr.

MAINTENANCE DOSE		
Creatinine Clearance* (ml/min)	**Daily maintenance dose**	**Dose in each 250ml infusion bag for administration over 12 hours**
<20	500mg	250mg
20-34	750mg	375mg
35-59	1000mg	500mg
60-79	1500mg	750mg
80-99	2000mg	1000mg
>100	2500mg	1250mg

For dosage adjustments

Vancomycin Concentration	Suggested dosage change
<15mcg/ml	Increase the daily dose by 500mg
15 – 25mcg/ml	No change
>25mcg/ml	Decrease the dose by 500mg**
>30mcg/ml	Stop the infusion and recheck serum level next morning. Restart at a lower dose

**If the patient is only receiving 500mg/day, reduce the dose to 250mg/day.

Renal Impairment:[4]

CrCl (ml/min)	Dosage Adjustment
>50ml/min	15 – 20mg/kg/dose every 12 hours (usual: 750 – 1,500mg)
20 – 49ml/min	15 – 20mg/kg/dose every 24 hours (usual: 750 – 1,500mg)
<20ml/min	Need longer intervals, determine by serum concentration monitoring

For more options: see appendix

Dialysis (D)

Conventional: poorly dialysable (0 – 5%)[4]
High-flux membranes & CRRT: increase vancomycin clearance & requires replacement dosing[4]

Type of Dialysis	Dosage
Haemodialysis (HD)[4]	Following loading dose of 15 – 20mg/kg, given 500mg to 1,000mg after each dialysis session. Pre dosing based on pre-HD level:* <10mcg/ml : Administer 1,000mg after HD 10 – 25mcg/ml : Administer 500-750mg after HD >25mcg/ml : Hold vancomycin *based on clinical judgement
CAPD[9]	*Intermittent dose (once/day):* 15 – 30mg/kg every 5 – 7 days (Interval can be adjusted based on vancomycin level) *Continuous dose (per/L exchange):* Loading: 1,000mg/L Maintenance: 25mg/L
CVVH[4]	Following loading dose of 15 – 20mg/kg, give 1g every 48 hours (Interval can be adjusted based on vancomycin level)
CVVHD / CVVHDF	Following loading dose of 15 – 20mg/kg, give 1g every 24 hours (Interval can be adjusted based on vancomycin level)

C. INTERACTION

Drug-drug interaction:

Increase effect/toxicity	Vancomycin may increase the level/effects of: aminoglycosides, colistmethate, gallium nitrate and neuromuscular-blocking agent[4]
Decreased drug concentration/effects	Vancomycin may decrease the level/effects of typhoid vaccine and BCG vaccine[4]

Drug- disease interaction:

Burn	Increase vancomycin CL, require more frequent dose[1]
Hepatic insufficiency	Reduce degree of vancomycin protein binding (20%), require higher than normal dose (>30mg/kg/day in adult)[1]
Renal failure	Vancomycin total clearance decrease proportionally to decrease in CrCl[7]
Obesity	Increase vancomycin clearance, Vd does not changes significantly with obesity and is best dosed with IBW for patient who are >30% overweight[7]

D. SAMPLING

Time to monitor serum concentration (at steady state):

When to obtain serum vancomycin level (after dose initiation or adjustment):
Normal renal function: After 3rd dose[3,5,8]
Impaired renal function: After 24 hours (after 1st dose)

Intermittent dose:
Trough : just before next dose[4]*
Peak : 1 hour after end of infusion[4]
**Based on current practice only trough level is required because vancomycin is a time dependent antibiotic.*

Stat dose (unstable renal function):
Random depending on the serum concentration[4] or trough monitoring 24 hours after 1st dose.[8]

Continuous Infusion:
Take a sample after 12 – 24 hours of starting the continuous infusion then every 1 – 2 days or daily if the patient has unstable renal function.[16]

E. MONITORING PARAMETER

- Culture & sensitivity[7,8]
- White blood cell count[4,7]
- Renal function[4,7]
- Symptomatic improvement, temperature[7,8]
- Audiogram[4]

F. ADVERSE DRUG REACTION

Parenteral:[4]

>10 %	1 – 10 %	<1%
CVS: hypotension accompanied by flushing	CNS: Chills, drug fever	Ototoxicity, nephrotoxicity, thrombocytopenia, vasculitis
Dermatologic: Red man syndrome (Can be reduced by prolonged the duration of infusion)	Hematologic: Eosinophilia, reversible neutropenia	-

G. DILUTION AND ADMINSTRATION

Dilution of drug:

Dilution of drug	Reconstitute vials with 20ml of SWFI for each 1 g of vancomycin (500mg/10ml). The reconstituted solution must be further diluted with at least 100ml of compatible diluents per 500mg of vancomycin prior to parenteral administration.[4] Diluent: Normal saline or D5W.[4] Maximum concentration: not to exceed 5mg/ml(4) For fluid restriction patient, maximum concentration: 10mg/ml[8] Stability: Reconstituted – room temperature or under refrigeration for 14 days[4] Diluted – under refrigeration for 14 days or at room temperature for 7 days[4]

Drug administration:

Infusion over at least 60 minutes[4,8] or a maximum infusion rates of 10mg/min, whichever is longer[8]

H. CALCULATION

A) Dose initiation

1. Determine the Volume distribution (Vd):
   - Refer to Vd chart for specific population Vd value

   $$Vd\ (L) = 0.7 \times BW\ (kg)$$

2. Estimate creatinine clearance (CrCl):

   $$CrCL\ (ml/min) = \frac{(140\text{-}age) \times BW\ (kg) \times 1.04\ (F)\ or\ 1.23\ (M)}{Scr\ (\mu mol/ml)}$$

3. Estimate Vancomycin clearance (CL):

   $$CL\ (L/hr) = 0.06 \times CrCl\ (ml/min)$$

4. Estimate elimination rate constant (K_e):

   $$Ke = \frac{(CL\ (L/hr)}{Vd\ (L)}$$

5. Estimate half life ($t_{1/2}$):

   $$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

6. Estimate peak, (C_{max}) and trough (C_{min}) concentration:

   $$Cmax\ (mcg/ml) = \frac{Dose\ (mg)}{Vd\ (L) \times (1 - e^{-ke\tau})}$$

   $$Cmin\ (mcg/ml) = Cmax \times e^{-ke\tau}$$

B) Trough & Peak level available[2]

1. Calculate elimination rate constant(K_e):

$$Ke\ (hr^{-1}) = \frac{\ln Cpost - \ln Cpre}{T - (tpost - tpre)}$$

2. Calculate half life ($t_{1/2}$):

$$t½\ (hr) = \frac{0.693}{Ke\ (hr^{-1})}$$

3. Calculate peak concentration (C_{max}):

$$Cmax = Cpost \times e^{ket}$$

4. Calculate trough concentration (C_{min}):

$$Cmin = Cmax \times e^{-KeT}$$

5. Calculate Volume distribution (Vd):

$$Vd = \frac{Dose\ (mg)}{Cmax\ (1 - e^{-KeT})}$$

6. To decide new dosing regimen, calculate;

$$New\ dose = \frac{C\ min\ target \times V\ (L) \times (1 - e^{-KeT})}{(\ S \times F \times e^{-KeT}\ )}$$

$$Expected\ Cmax = \frac{New\ Dose\ (mg)}{Vd \times (1 - e^{-KeT})}$$

$$Expected\ Cmin = Expected\ Cmax \times e^{-KeT}$$

T	=	Dosing interval (h)
t	=	Different time between complete of injection and post sampling (h)

C) If only trough level available[2]

1. $C_{max} = \frac{C_{min} + S \times F \times Dose\ (mg)}{V\ (L)}$

2. $K_e = \frac{\ln C_{max} - \ln C_{min}}{T}$

3. $t_{1/2} = \frac{0.693}{K_e}$

4. $\text{New dose} = \frac{C_{peak\ target} \times V\ (L) \times (1 - e^{-K_eT})}{S \times F \times e^{-K_eT}}$

5. $\text{Expected } C_{max} = \frac{\text{New dose (mg)}}{(V(L) \times (1 - e^{-K_eT})}$

6. $\text{Expected } C_{min} = \text{Expected } C_{max} \times e^{-K_eT}$

D) Area Under the Curve 24hr

2 methods:

1. $\text{AUC 24 (mg.h/L)} = (24 \times C_{min}) + \left[(0.5 \times T)(C_{max} - C_{min})\left(\frac{24}{T}\right)\right](0.33)$

2. $\frac{\text{AUC 24}}{\text{MIC}} = \frac{\text{Vancomycin total daily dose}}{Cl\ (L/hr) \times \text{MIC (mg/L)}}$

For a pathogen with an MIC of 1mg/L, the minimum trough concentration should be at least 15mg/L, in order to generate the target AUC_{24}/MIC of 400. [5]

I. RESULT EVALUATION*

LEVEL	CONTRIBUTING FACTOR	RESPONSE	RECOMMENDATION
Subthera-peutic	• Fluid overload • Wrong sampling time • Insufficient dose • Drug interaction • Burn • Ascites • Dialysis	Poor	If sampling time is satisfactory, correct the fluid imbalance (if fluid overload) give incremental loading dose STAT, then continue current dose or increase the dose appropriately & resample
		Good	Continue current dose
Within Normal Therapeutic Range		Poor	If sampling time is satisfactory & hydration status is fair, increase the dose (not more than max recommended)
		Good	Continue current dose
Potential Toxic/ Toxic	• Dehydration • Renal failure • Overdosage • Underlying disease/ factors • Possible drug interaction	Toxic effect: • Nephrotoxicity • Ototoxicity • Red man syndrome • neutropenia	Withhold treatment (if necessary), hydrate the patient (if dehydrated) then adjust dose accordingly

** The evaluation of result is a general approach in managing clinical pharmacokinetic cases. Do not evaluate the case based on the result only. Patient specific pharmacokinetic – pharmacodynamic parameter and clinical condition should be considered before making any recommendations.*

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