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Therapeutic Drug Monitoring (TDM) protocol for pediatric

Vancomycin and Aminoglycosides

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1. Purpose:
   To establish a standardized pharmacokinetic approach for patient receiving drugs that are routinely monitored utilizing serum drug concentration at MOH hospitals.

2. Definition

   TDM: Therapeutic Drug Monitoring.

3. Functions Affected
   Clinical Pharmacist Specialist, Staff Pharmacists, Pharmacy Resident and Pharmacy Student.

4. Policy:

4.1. The Pharmacy Department has Therapeutic Drug Monitoring (TDM) service, using the latest and most updated MOH guidelines.

4.2. The Pharmacist in-charge of the service is a qualified pharmacist.

4.3. The TDM is the use of drug concentration measurements in body fluids as an aid to the management of drug therapy for the cure, alleviation, or prevention of disease.

4.4. The TDM service guidelines were developed to ensure safe and efficacious dosage regimens through the application of pharmacokinetic/pharmacodynamics principles and determination of drug serum concentrations.

4.5. The policy/procedure manual outlines standard guidelines which should be followed when providing clinical pharmacokinetic monitoring of the following drugs: aminoglycosides and vancomycin.

4.6. Educating pharmacists, physicians, nurses, and other clinical practitioners on pharmacokinetic principles and/or appropriate indications for clinical pharmacokinetic monitoring.

5. Procedures:

5.1 Therapeutic drug monitoring testing will be initiated by the ordering provider or Pharmacy Department.

5.2 Upon receiving order for pharmacy to dose a specific medication, a pharmacist will assess the patient and collect relevant information necessary to appropriately dose/monitor the specified drug so as to achieve therapeutic drug levels and minimize any potential risks of toxicity. Such items of information may include. But not are limited to:

a. Indication for therapy (i.e. type and site of infection for antibiotic dosing/monitoring consults).
b. Age.
c. Gender.
d. Height/Weight.
e. Renal/Hepatic function.
f. Estimated pharmacokinetic parameters.
g. Medication history.
h. Current/last known serum drug concentration.

5.3 The order should include the drug to be tested and, at minimum, the relative time when the sample should be drawn (peak, trough, random). Whenever possible, an exact time should be entered to correlate with drug administration time.

5.4 Once all patient information, laboratory and clinical data completed, the pharmacist in-charge start to follow sample guidelines and medication monitoring guidelines (Attached) to monitoring medication level, patient situation and follow-up the patient during therapy duration.

5.5 Laboratory and nursing staff will work together to determine the optimum time for specimen collection. For TDM to be meaningful, the patient should be in steady-state on the present dose of the drug. In general, samples should be taken after drug dosing has continued for at least four half-lives.

5.6 Unless otherwise specified, sampling times will utilize the following definitions:

a) Trough – Immediately before the next scheduled dose.
b) Peak – 1 Hour post dose (Time to peak may be used to determine alternative peak times).

5.7 In cases of suspected toxicity, waiting to attain steady-state is not necessary and a random drug level may be collected to aid in clinical decision making.

5.8 The laboratory department should deal with the drug level sample as urgent order and the result should be available in the system as soon as 1 – 2 hours maximum.

6. Responsibility:

6.1. TDM Pharmacist:

6.1.1. Responsible for receiving order from health care professionals or ordering and monitor the serum level during period of therapy and report it to the head of service and the physician responsible for the patient.

6.1.2. The working hours from 7:00 am-4:00 pm from Sunday to Thursday.

6.1.3. Responsible to monitor any new order & report it to the head of service and the physician responsible for the patient.

7. Equation:

7.1.1. Calculate creatinine clearance with the Cockcroft-Gault equation using an ideal body weight (IBW) or an adjusted body weight (ABW) if the patient is obese

7.1.2. CrCL (mL/min) = (140 – age) x IBW / SCr x 72 (x 0.85 for females)

8. Definitions:

8.1.1. Pediatrics age categories:

1-Premature newborns: < 37 weeks gestational age

2-Term newborns ≥ 37 weeks gestational age.

3-Neonate 0-30 days of age.

4-Infant 31 days up to 1 year.

5-Children and adolescent more than 1 year up to 18 years.

8.1.2. Actual body weight: the use of actual body weight is recommended for Vancomycin dosing and adjusted body weight for obese patient.

8.1.3. Ideal body weight: the use of ideal body weight is recommended for Aminoglycoside dosing EXCEPT for neonate which actual body weight is recommended.

8.1.4. Ideal body weight:

a-1-18 years: IBW= height2 * 1.65 ÷1000 (IBW in kg, height in cm)

b-152 cm and taller:

IBW (Male) = 39+ 2.27 (for each 2.45 cm over 152.4 cm)

IBW (female) = 42.2+2.27 (for each 2.45 cm over 152.4 cm)

8.1.5. Renal function: Vancomycin and Aminoglycoside are exclusively eliminated through renal rout and their doses should be adjusted according renal function. The creatinine clearance in pediatrics should be calculated according to Schwartz equation. (bedside Schwartz equation is validated in ≥ 1-year baby (fixed K =0.413).

8.1.6. Schwartz equation: CrCl = K*ht (cm) *88.4/ SCr (micromole/L) where ht is patient height.

Age	K
Preterm ≤ 1yr	0.33
Full-term ≤ 1yr	0.45
2-12 yr	0.55

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Vancomycin dosing and monitoring in Neonates and Pediatrics

Vancomycin is a glycopeptide antibiotic that has activity against gram-positive organisms, including MRSA and Enterococcus. It has activity against MSSA, although it is inferior to the penicillinase-resistant penicillins (eg, oxacillin).

Dosing of vancomycin:

a. Neonatal Dose:

- ✓ The calculated dose should be rounded to the whole number for patients weighing less than 1 Kg, and to nearest 5 for the patients weighing more than or equal to 1 Kg.
- Adjust subsequent doses to achieve an AUC/MIC >400. In institution in which AUC calculation is not feasible, trough concentration 10 to 12 mg/ml is very highly likely (>90%) to achieve the goal of AUC (AUC/MIC >400) in neonate.
- **Loading dose:** All patients: IV: 20mg/kg once, followed by maintenance dose.

- **Maintenance dose:**

✓ **Renal function-based dosing:**

Gestational age	Serum creatinine	Dose
≤28 weeks	<0.5 mg/dl	15mg/kg/dose every 12 hours
	0.5 to 0.7mg/dl	20mg/kg/dose every 24 hours
	0.8 to 1mg/dl	15mg/kg/dose every 24 hours
	1.1 to1.4mg/dl	10mg/kg/dose every 24 hours
	>1.4mg/dl	15mg/kg/dose every 48 hours
Gestational age	Serum creatinine	Dose
>28 weeks	<0.7 mg/dl	15mg/kg/dose every 12 hours
	0.7 to 0.9mg/dl	20mg/kg/dose every 24 hours
	1 to 1.2mg/dl	15mg/kg/dose every 24 hours
	1.3 to1.6mg/dl	10mg/kg/dose every 24 hours
	>1.6mg/dl	15mg/kg/dose every 48 hours

Serum creatinine concentrations normally fluctuate and are partly influenced by transplacental maternal creatinine in the first week after birth. Cautious use of creatinine-based dosing strategy with frequent reassessment of renal function and vancomycin serum concentrations are recommended in neonates ≤7 days old.

✓ **Weight-directed dosing:**

Body weight	Postnatal age	Dose
<1.2kg	≤ 28 days	15mg/kg/dose every 18 to 24 hours
1.2 to 2 kg	< 7 days	10 to 15mg/kg/dose every 12 to 18 hours
	≥ 7 days	10 to 15mg /kg/dose every 8 to 12 hours
>2 kg	< 7 days	10 to 15 mg/kg/dose every 8 to 12 hours
	≥ 7 days	10 to 15mg/kg/dose every 6 to 8 hours

b. Infant, children and adolescent:

- **Loading dose:** 25mg/kg based on current actual body weight.

✓ Should be administered to all patients with normal renal function, initiating vancomycin therapy for complicated infection and suspected or documented MRSA infection.

✓ May also be considered in cases where rapid attainment of target serum concentration is desired.

- **Maintenance dose (MD):**

✓ 15 to 20 mg/kg/dose every 6 hours to be given as IV infusion over 2 hours (based on type of infection).
✓ Adjust subsequent dose to achieve a target AUC/MIC >400. In institution in which AUC calculation is not feasible, trough concentration 10 t 15 mg/ml for mild infection and 15 to 20 mg/ml for severe infection.
✓ The calculated dose should be rounded to the nearest 10.

- **Dose adjustment in renal impairment:**

GFR	Infants	children	adolescent
30 to 50 ml/min/1.37 m^2	10 to 15 mg/kg/dose every 12 hours		
10 to 29 ml/min/1.37 m^2	10 to 15 mg/kg/dose every 18 to 24 hours		
<10 ml/min/1.37 m2 Intermittent hemodialysis Peritoneal dialysis (PD)	10 to 15 mg/kg/dose once, check vancomycin random level after 24-48 hr, re-dose with 10mg/kg/dose when the level is less than 10-15 mg/ml.		
Continuous renal replacement therapy (CRRT)	10 to 15 mg/kg/dose every 12 to 24 hours		

- **Target trough concentration:**

-Recent pediatric literatures suggested serum trough goal of 10 to 20 mg/L may not correlate well with AUC/MIC ratio > 400 in pediatric patients.
Desired serum concentrations; a 24-h AUC: MIC of 400 mg·h/L is recommended based on adult studies of invasive MRSA infections. In situations in which AUC calculation is not feasible, a trough concentration 10–12 mg/L is very highly likely (90%) to achieve the goal AUC target in neonates when the MIC is 1 mg/L and 10 to 15 mg/ml for mild infection or 15 to 20 mg/ml for severe infection in pediatric patients.

- Neonate:

Type of infection	Target trough concentration
Infection in neonate	Target trough concentration: 10 to 12 mg/ml

- Infant, children and adolescent:

Type of infection	Target trough concentration
Uncomplicated infection: soft and skin infection	10-15 mg/l

Complicated infection (endocarditis, osteomyelitis, bacteremia, pneumonia and meningitis)	15-20mg/l

- **Monitoring:**

✓ **Rational:**

Therapeutic drug monitoring (TDM) of vancomycin is very essential to ensure efficacy, prevent development of resistance and toxicity.
The AUC/MIC >400 is the most accurate and appropriate pharmacodynamic target to monitor vancomycin efficacy in pediatrics.
Trough is most practical method for monitor vancomycin efficacy.

Clinical situation	Obtain trough	When to obtain
Empiric short course (<3 days) therapy (≥51ml/min, stable renal function, hemodynamic stable)	No	-
Empiric therapy ≥ 3 days	Yes	30 mins before 4th dose
Empiric therapy (neonate, cystic fibrosis, hematology/oncology, CrCl 10-50ml/min unstable renal function, hemodynamic unstable.	Yes	30 mins before 4th dose
<10 ml/min AKI Intermittent hemodialysis Peritoneal dialysis (PD) CRRT	No-do random level	Within 24-48 hours of initial dose.

✓ **Renal function monitoring:**

Monitor renal function for nephrotoxicity three time per week and more frequently when vancomycin combined with another nephrotoxic drugs (piperacillin- tazobactam, aminoglycoside. furosemide, tacrolimus, cyclosporin, acyclovir, amphotericin B …etc.).

✓ **Infusion related reaction monitoring:**

Monitor for infusion related event, including hypotension and red man syndrome. Rapid IV administration (<60 minutes) may increase risk of red man syndrome and may result in hypotension, flushing, erythema, urticaria, pruritus and cardiac arrest.

✓ CBC monitoring:

Periodic monitoring for CBC should be done to screen for neutropenia and thrombocytopenia in patient with prolong vancomycin therapy or those whose receive concomitant drug that cause bone marrow suppression.

Aminoglycosides dosing and monitoring in Neonates and Pediatrics

- Aminoglycosides are widely used for systemic treatment of gram-negative infections or for synergy in the treatment of certain gram-positive infections.
- Aminoglycosides demonstrate concentration-dependent killing of pathogens.
- Aminoglycosides have two way for administration, traditional approach for parenteral aminoglycoside dosing involve administration of a weight-based dose divided in two to three times daily and extended- interval aminoglycoside (also known as once-daily aminoglycoside) utilize a higher weight-based dose administered at an extended interval every 24 hour or longer for those with renal dysfunction.

1-connventional / traditional dosing:

A- Initial dose:

Initial dose for neonate and infant < 2 months of age is based on gestational age and postnatal age:

Empiric Dosage (mg/kg/dose) by Gestational and Postnatal Age

		<30 weeks		30-34 weeks		≥ 35 weeks	
Medication	**Route**	**0-14 day**	**>14 day**	**0-10 days**	**>10 days**	**0-7 days**	**>7 days**
Amikacin	IV, IM	15 q48h	15 q24h	15 q24h	15 q24h	25 q24h	17.5 q24h
Gentamicin	IV, IM	5q 48h	5q 36h	5 q36h	5 q36h	4 q24h	5 q24h

Initial dose in infant >2 months, children and adolescents:

- Gentamicin

Infection	Gentamicin dose
Septicemia, meningitis, other CNS infection, biliary tract infection, endocarditis, pneumonia	2 to 2.5mg/kg/dose every 8 hours
infection in cystic fibrosis	3.3mg/kg/dose every 8 hours

- Amikacin

Infection	Amikacin dose
General dosing, severe, susceptible infection	15 to 22.5 mg/kg/day divided every 8 hours
CNS infection	20 to 30 mg/kg/dose divided every 8 hours
infection in cystic fibrosis	10mg/kg/dose every 8 hours

Aminoglycoside starting dose and prolonged interval in patient with renal impairment or on dialysis:

Creatinine clearance ml/min	Gentamicin	Amikacin
30 to 50	2.5mg/kg/dose/every 12 to 18 hours	5 to 7.5 mg/kg/dose every 12 to 18 hours
10 to 29	2.5mg/kg/dose/every 18 to 24 hours	5 to 7.5 mg/kg/dose every 18 to 24 hours
<10	2.5mg/kg/dose/every 48 to 72 hours	5 to 7.5 mg/kg/dose every 48 to 72 hours
Intermittent hemodialysis (IHD)	2mg/kg/dose, re-dose as indicated by serum concertation	5mg/kg/dose, re-dose as indicated by serum concertation
Peritoneal dialysis	2 mg/kg/dose, re-dose as indicated by serum concertation	5mg/kg/dose, re-dose as indicated by serum concertation
CRRT	2 to 2.5 mg/kg/dose every 12 to 24 hours	7.5mg/kg/dose every 12 hours

- **Therapeutic drug monitoring:**
  - Timing:

✓ A trough level should be obtained immediately before administration of 3rd dose.
✓ A peak level should be obtained 30 minutes after the end of 3rd dose infusion.

- Target trough and peak of gentamicin:

Type of infection	Target trough	Target peak
Serious infection	< 2mg/L	6 to 8mg/L
Life threatening infection	< 2 mg/L	8 to 10 mg/L
Urinary tract infection	< 2 mg/L	4 to 6mg/ml
Synergy against gram- positive organism	< 2 mg/L	3to 5 mg/ml

- Target trough and peak of Amikacin:

Type of infection	Target trough	Target peak
Serious infection	<10mg/ml	20 to 25 mg/ml
Life threatening infection	<10mg/ml	25 to 40 mg/ml
Urinary tract infection	<10mg/ml	15 o 20 mg/ml

- Interpretation and action in response to the result of:

✓ **Gentamicin**

Trough	Peak	Meaning	Action
<2 mg/L	3 to 10mg/L	Within target	Continue same regimen and check again after 3-4 days
>2mg/L	Any result	High trough	Withhold next dose -recheck the level in 24 hours and if the result <2 mg/L resume the regimen with less frequent interval (e.g. Q8 to Q12). Re-check the trough and peak around 3rd dose.
<2 mg/L	>10mg/L	High peak	Reduce the dose by 25% and continue same interval. Re-check trough and peak around 3rd dose

✓ **Amikacin**

Trough	Peak	Meaning	Action
<10mg/L	20 to 40mg/l	Within target	Continue the same regimen.
≥10mg/L	Any result	High trough	Withhold next dose -recheck the level in 24 hours and if the

			result <10 mg/L resume the regimen with less frequent interval (e.g. Q8 to Q12). Re-check the trough and peak around 3rd dose.
<10mg/L	>40mg/L	High Peak	Reduce the dose by 25% and continue same interval. Re-check trough and peak around 3rd dose

- Others monitoring parameters:

✓ Serum creatinine should be measured at least every other day while patient on aminoglycosides therapy.
✓ Check CBC twice weekly.

2- Once-Daily Dosing of Aminoglycosides:

- Aminoglycosides demonstrate concentration-dependent killing of pathogens, suggesting a potential benefit to higher serum concentrations achieved with once-daily dosing.
- Regimens giving the daily dosage as a single infusion, rather than as traditionally split doses every 8 hours, are effective and safe for normal hosts and immune-compromised hosts with fever and neutropenia and may be less toxic.
- Experience with once-daily dosing in children is increasing, with similar encouraging results as noted for adults.
- A recent Cochrane review for children (and adults) with cystic fibrosis comparing once-daily with 3-times–daily administration found equal efficacy with decreased toxicity in children.
- Once-daily dosing should be considered as effective as multiple, smaller doses per day and is likely to be safer for children; therefore, it should be the preferred regimen for treatment.

✓ Rational:

extended interval dosing has become preferred method of administration of aminoglycoside for following reasons:

- Aminoglycoside is concentration depended killer.
- Increase drug -free period.
- Takes advantage of post-antibiotic effect of aminoglycoside.
- Less nephrotoxic.
- Less frequent.

- Less monitoring.

✓ Exclusion criteria:

- Neonatal patient (Gestational age < 44 weeks)
- Pediatric patient with significant renal dysfunction (<20ml/min).
- Patient on hemodialysis and peritoneal dialysis.
- Patient with alteration in volume of distribution:
  1- burn patient (>20% body surface area).
  2- Patient with ascites
- When aminoglycoside used as synergistic to treat gram-positive infection.
- Patient known with auditory/ vestibular disease.
- Patient with osteomyelitis. (lack of evidence)

✓ Dosing:

-Gentamicin

Infection	Gentamicin
usual dose	4.5 to 7.5 mg/kg/dose every 24 hours
infection in cystic fibrosis	10 to 12 mg/kg/dose every 24 hours

-Amikacin

Infection	Amikacin
usual infection	15 to 22.5mg/kg/dose every 24 hours
infection in cystic fibrosis	30 to 35mg/kg/dose every 24 hours

✓ Therapeutic drug monitoring:

- Timing:
- Trough level should be checked before second dose.
- Dose of aminoglycoside should not be given to patient who are at increased risk of nephrotoxicity unless trough level result within target.
- Trough level should be checked every 3-4 days thereafter, unless trough level not within target.

- Target trough:

Drug	Target trough
Gentamicin	<1mg/L
Amikacin	<5mg/L

- Interpretation and action in response to result of:

- Gentamicin

Trough	Mean	Action
<1mg/ml	Within target	Continue same regimen and recheck every 3-4 days
1-2mg/ml	Slightly high	Provided renal function is unchanged increase the dose interval to 36 to 48 hours.
>2mg/ml	high	Check when the level was taken. Omit next dose, re-assay in 24 hours. Re-dose if clinically indicated when level fall≤ 1mg/l but extend the dosing interval accordingly for subsequent doses.

- Amikacin

Trough	Mean	Action
<5mg/ml	Within target	Continue same regimen and recheck every 3-4 days
≥5mg/ml	high	Check when the level was taken. Omit next dose, re-assay in 24 hours. Re-dose if clinically indicated when level fall≤ 1mg/l but extend the dosing interval accordingly for subsequent doses.

- Monitoring:

✓ Serum creatinine should be measured at least every other day while patient on aminoglycosides therapy.
✓ Check CBC twice weekly.

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