RANCHO LOS AMIGOS
NATIONAL REHABILITATION CENTER

POLICY AND PROCEDURE MANUAL
PHARMACY SERVICES

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SECTION:	**CLINICAL PHARMACY SERVICES**		
		APPROVED:	Thinh Tran, Pharm. D
SUBJECT:	**AMINOGLYCOSIDE MONITORING PROTOCOL**	PAGES:	1 of 10

Purpose:

1. To provide a method of dosing aminoglycosides that will optimize patient therapy, minimize toxicities, contain costs, and allow consistent and reliable follow up on patients' aminoglycoside therapies.

2. To provide an educational tool for pharmacy and medical students and residents about aminoglycoside monitoring and pharmacokinetics.

Background:

The value of the aminoglycoside antibiotics in the treatment of gram-negative infections has been well documented. This class of antibiotics has demonstrated a concentration dependent bactericidal effect.

The higher the exposure level to a susceptible organism, the faster the killing rate and reduction in organisms are displayed by aminoglycoside's pharmacokinetics and pharmacodynamic properties. In addition, aminoglycosides exhibit a post-antibiotic effect (PAE) which is a period of continued suppression of bacterial growth after cessation of exposure of the bacteria to the aminoglycoside. The duration of PAE is affected by many factors including the type of organism, the class and concentration of antibiotic, and the duration of exposure of the organism to the antibiotic.

However, because there is a potential for concentration dependent oto- and nephrotoxicity associated with the aminoglycosides, serum concentration monitoring is necessary.

A patient's aminoglycoside therapy can be individualized and optimized with selected pharmacokinetic calculations and appropriately obtained serum levels.

Although dosing intervals of Q8H and Q12H are effective and conventional, in recent years the concept of single daily dosing (SDD), or once-a-day dosing, of aminoglycosides has been under review and is becoming popular. Investigators postulated that SDD would provide better efficacy by providing higher peak concentrations, decrease or prevent toxicity by reducing ear and kidney tissue exposure/ accumulation, and reduce the potential for adaptive post-exposure resistance by decreasing the contact time between organism and drug. To date, clinical trials have suggested that once-daily aminoglycoside administration may be as effective and safe as conventional regimens entailing shorter dosing intervals. In addition, SDD may provide substantial cost savings with less nursing time required, lower use of infusion devices, and possibly less need for drug concentration monitoring. However, as discussed below, SDD is not appropriate for all patient types.

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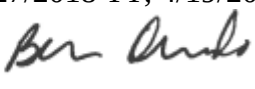
Approved By: 

Procedure:

1. The physician may request the pharmacist's involvement in adjusting aminoglycoside therapy for a given patient by placing an order "Consult to Pharmacy" through the EHR (electronic heath record) system and sending a consultation request to the Department of Medicine. The order must specify the specific aminoglycoside requested to be managed. Aminoglycoside therapy must be initiated by the requesting physician.

2. The clinical pharmacist will see the patient as soon as possible after the consultation request is received, review the patient's chart, and document the assessment and plan in the patient's EHR. The requesting physician is responsible for the aminoglycoside management until the patient has been seen by the clinical pharmacist.

3. If not available within the patient's EHR, the following will be ordered initially and as needed to evaluate the patient's therapy:
   (a.) Scr and BUN
   (b.) Aminoglycoside levels

4. The clinical pharmacist will evaluate the aminoglycoside levels and adjust the aminoglycoside dose accordingly. Dosage adjustment will follow pharmacokinetic calculations (see attachment) or the clinical pharmacist's clinical judgement.

5. The clinical pharmacist may sign-off on the consultation to the requesting physician once maintenance dose for aminoglycoside is established. The physician may re-consult clinical pharmacy when necessary.

6. Based on the site of infection, isolated organism(s), and patient's renal function, the pharmacist will determine the desired peak (maximum) and trough (minimum) of the aminoglycoside.

Guidelines for peak and trough levels*:

	Gentamicin/Tobramycin		Amikacin	
	peak (mcg/ml)	trough (mcg/ml)	peak (mcg/ml)	trough (mcg/m1)
Uncomplicated UTI	4-6	< 2	12-20	5-8
Complicated UTI/ pyelonephritis	4-8	<2	17-23	5-8
Osteomyelitis	5-10	<2	20-30	5-10
Soft tissue infection	5-10	<2	20-30	5-10
Respiratory infection/ pneumonia/ bronchitis	8-10	<2	25-30	5-10
Sepsis	8-10	<2	26-36	5-10
Synergism with other Antibiotics	3-5	<1.5	7-21	5-8

* Peak and trough levels for conventional dosing intervals (Q6H, Q8H, Q12H) not SDD. Alternative levels may be used based on individual patient parameters and clinical judgement.

7. Drawing of Aminoglycoside Serum Levels:

Peak serum levels should be drawn 30 minutes after the end of a 30 minute IVPB infusion and trough levels should be drawn 30 minutes prior to the next scheduled dose. For hemodialysis patients, the aminoglycoside trough should be drawn 30 minutes prior to the scheduled hemodialysis treatment and the peak 2 hours after the end of the infusion.

In order for the pharmacist to make accurate calculations and adjustments, the exact time the levels are drawn must be noted.

Not all patients require initial sets of aminoglycoside levels. Patients who are predisposed to aminoglycoside toxicity, secondary to their renal function should have initial levels drawn.

Aminoglycoside serum levels are indicated in the following patients:

a. life threatening infections
b. patients who remain febrile, retain an elevated WBC, and/or show signs of continued or worsening infection
c. changing renal function
d. estimated CrCl < 40 mL/min
e. clinically stable patients who have been on therapy over seven to ten days
f. patients with one of the following conditions:
   - emaciation
   - amputation
   - extreme obesity
   - ascites
   - severe burn

8**. Loading Dose with Conventional Dosing:** Based on the patient's condition, if rapid attainment of therapeutic levels is needed, 2 mg/kg of gentamicin or tobramycin should give a peak of 6-8 mcg/ml; 6.0 to 7.5 mg/kg of amikacin should give a peak of 26-34 mcg/ml. Ideal body weight (IBW) or adjusted body weight (ABW), if the patient's actual weight is >120% of their IBW, should be used in calculating the loading dose.

9. **Once Daily Dosing of Aminoglycosides:**

Until further studies are available concerning efficacy and safety, the following patients should be restricted to conventional aminoglycoside dosing:

spinal cord injury patients
neutropenic patients
cystic fibrosis patients
severe burn patients
pediatric patients
pregnant patients
endocarditis patients
ascites patients

In addition, patients with renal dysfunction (estimated CrCl <30 ml/min) should not receive single daily dosing of aminoglycosides. SDD in renal dysfunction may result in drug accumulation which studies have shown to have a higher incidence of toxicity and may prevent the overcoming of adaptive resistance.

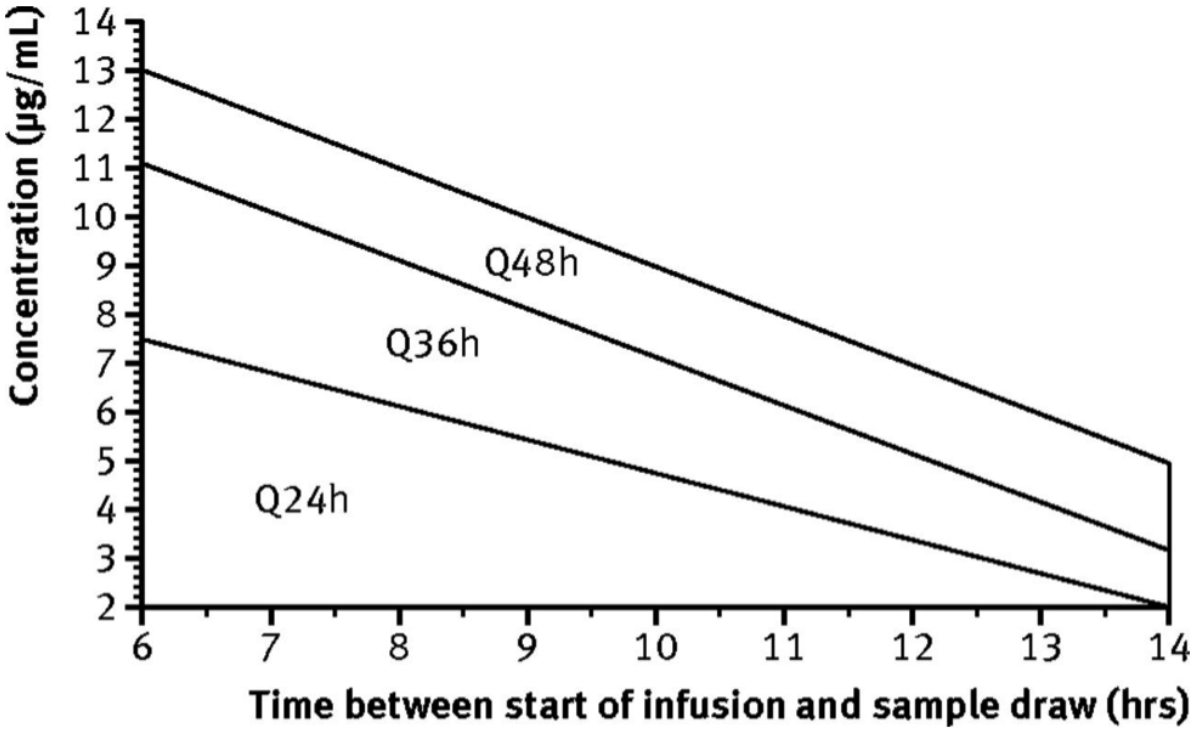
Therapeutic monitoring and dose adjustment in Once Daily Dosing
Levels should be obtained in the following situations:

a. Random serum levels 6-14 hours after start of the infusion of the first dose
b. Confirm an appropriate serum concentration after dosage adjustment, or to confirm unusual serum concentration (i.e., potential line draws, inappropriate time, etc.)
c. Suspected toxicity or changes in renal function
d. Weekly monitoring for prolonged therapy
e. When necessary, based on clinical pharmacist judgment

Dose adjustments made according to the Hartford Nomogram
(****Only applicable to 7 mg/kg dosage**. **See Figure 1)**

If a lower dose than 7 mg/kg is used, the resultant level should be multiplied by a factor equal to 7 mg divided by the dose used. Example: If a patient is receiving 5 mg/kg and the level was 2 mcg/ml, you would multiply the level by 1.4 (7 mg/5 mg) to result in a level of 2.8 mcg/ml, which would be plotted on the Hartford Nomogram. Plot serum level and use nomogram to confirm or modify dosage interval. If using amikacin, plot ½ of the serum concentration on the nomogram. If the level falls off the nomogram, traditional dosing should be used.

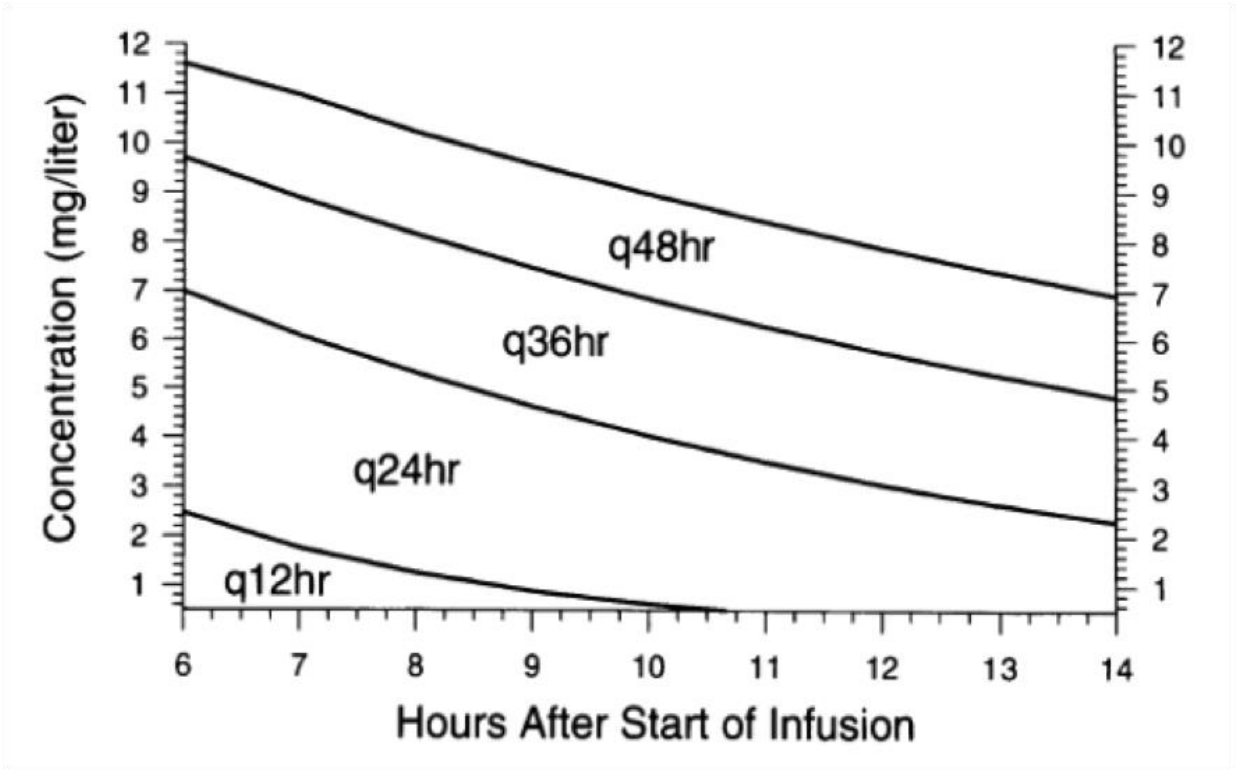
Figure 1: Hartford Nomogram



Dose adjustments made according to the Urban and Craig Nomogram
(Only applicable for 5 mg/kg dosage. See Figure 2)**

Random serum levels are obtained 6-14 hrs after start of the infusion of the first dose. Plot serum level and use nomogram to confirm or modify dosage interval.

Figure 2: Urban and Craig Nomogram.



- Calculation of Initial **Pharmacokinetic Parameters:**

1. Estimation of **Ideal Body Weight (IBW)**

Males 50 kg + 2.3 [Ht (in) > 60] Females 45.5 kg + 2.3 [Ht(in)>60]

2. Estimation **of Creatinine Clearance** (CrCl)

- CrCl (ml/min) = (140 - Age) (Wt in kg) (x 0.85 if female) 72 x Scr

For obese patients, Wt (kg) > 120% of IBW:

CrCl (ml/min) = (140 - Age) (ABW in kg) (x 0.85 if female) 72 x Scr

Where Adjusted Body Weight (ABW) = IBW + 0.4 [Wt (kg) -IBW]

Unstable Scr:

CrCl (ml/min) = 0.85 if female (28 - 0.2 Age) Wt _ 10 (Scr2 - Scrl) 0.5 (Wt) 24 t

Scr2

Criteria: Scr2 ≤ 2 Scrl if increasing Scrl = serum creatinine drawn at time 1

Scr2 ≥ 1/2 Scrl if decreasing Scr2 = serum creatinine drawn at time 2 t = time interval (in hrs.) between Scr drawings

Aminoglycoside Clearance =

Creatinine Clearance (CrCl): Cl

(L/hr) = Clcr (mUmin) (0.06)

3. Estimation of Volume of Distribution (Vd)

Vd = 0.25 L/kg [Wt (kg)]

For obese patients, Wt (kg) > 120% of IBW:

Vd = 0.25 L/kg (IBW) + 0.1 [Wt (kg) - IBW]

For patients with 3rd spaced fluid:

Vd = 0.25 L/kg [Wt (kg)] + 1.0 L/kg (kg of fluid gain)

4. **Estimation of Elimination Rate Constant (Kel) and Half-life (T 1/2)**

$$\text{Kel (1/hr)} = \frac{Cl}{Vd} \qquad T\ 1/2 = \frac{0.693}{Kel} \quad \textbf{or} \quad \frac{0.693\ (Vd)}{Cl.}$$

5 Choose a dosing model: Bolus vs. Short Infusion (time of infusion for aminoglycosides is typically 30 minutes or 0.5 hrs.)

If 6 x time of infusion in hrs. <T 1/2 then use the BOLUS MODEL
If 6 x time of infusion in hrs. > T 1/2 then use the SHORT INFUSION MODEL

6 **Select appropriate τ [dosing interval] (usually between 2-3 T 1/2s)**

(Q8H, Q12H, Q24H) If T 1/2 > 12 hrs. most clinicians will keep τ = 24 hrs. to maintain adequate Cpmax and let Cpmin rise.

7 Calculation of dose by fixing a value for Cpeak or Ctrough and plugging previously determined parameters into the bolus or short infusion formula (depending on which has been determined as appropriate). Round dose to appropriate/realistic amount.

BOLUS MODEL FORMULA

$$\text{Dose} = \frac{(Cpss)\ (Vd)\ (1 - e^{-k\tau})}{e^{-kt}}$$

SHORT INFUSION MODEL FORMULA

$$\text{Dose} = \frac{(Cpss)\ (Cl)\ (tin)\ (1 - e^{-k\tau})}{(1 - e^{-ktin})\ (e^{-kt})}$$

Cpss = steady-state plasma concentration,
tin = duration of infusion in hrs. (0.5 hrs. in most cases)
t (BOLUS) = time from start of infusion to time of sampling (e.g. t = 1 hr. when level is drawn 30 min after end of 30 min infusion and Cpeak value is fixed)
t (SHORT) = time from end of infusion to time of sampling (e.g. t = 0.5 hrs. when level is drawn

30 minutes after end of 30 minutes infusion and Cpeak value is fixed)

8. **Predict expected peak and trough levels based on population parameters. ("peak" sampled 30 min. after 30 min. infusion; "trough" 30 min before next dose):**

BOLUS MODEL

$$Cpssmax = \frac{(SxFxD)}{Vd} \cdot \frac{e^{-ktI}}{(1 - e^{-k\tau})} \qquad Cpssmin = \frac{(SxFxD)}{Vd} \cdot \frac{e^{-kt2}}{(1 - e^{-k\tau})}$$

Cpssmax = maximum steady-state plasma concentration (measured peak not actual peak level) Cpssmin = minimum steady-state plasma concentration (measured trough not actual trough level) D = dose, S = salt fraction (= 1); F = fraction absorbed (=1); tin = duration of infusion in hrs. ti & t2 = time from beginning of infusion to time of level

SHORT INFUSION MODEL

$$Cpssmax = \frac{(SxFxD)/tin\ (1 - e^{-ktin})}{Cl} \cdot \frac{e^{-ktI}}{(1 - e^{-k\tau})} \sim Cpssmin = \frac{(SxFxD)/tin\ (1 - e^{-ktin})}{Cl} \cdot \frac{e^{-kt2}}{(1 - e^{-k\tau})}$$

D = dose: S = salt fraction (=1); F = fraction absorbed (=1); tin = duration of infusion in hrs.; tl & t2 = time from end of infusion to time of level

- Revisions of Aminoglycoside Parameters after Steady State Levels are Drawn:

1. Revise Kel and T 1/2:

$$Kel = \frac{\ln (Cpss\ pk / Cpss\ tr)}{t} \qquad T1/2 = \frac{0.693}{Kel}$$

- Cpss pk = measured peak concentration at steady state
- Cpss tr = measured trough concentration at steady state

t = difference in time between Cpss pk and Cpss tr (in hrs.)

2. Determine Model to be used:

6 x tin < T 1/2, **BOLUS MODEL** is acceptable

6 x tin > T 1/2, **INFUSION MODEL** is required

3. **Revise Vd and Cl: (Select either Cpss pk or Cpss tr to revise Vd)**

BOLUS MODEL:

$$Vd = \frac{S(xFxD)}{Cpss\ e^{-kt}\ (1 - e^{-kt})} \qquad C1 = (Kel)(Vd)$$

D = dose; S = salt fraction (=1);
F = fraction absorbed Cpss =
steady-state plasma
concentration
t = time from beginning of infusion to time of peak level

SHORT INFUSION MODEL:

$$C1 = \frac{(SxFxD)/tin\,(1 - e^{-ktin})}{(1 - e^{-k\tau})}\,\frac{Coss}{}\,e^{-kt} \qquad Vd = \frac{Cl}{Kel}$$

D = dose: S = salt fraction (=1): F = fraction absorbed (=1) tin = duration of infusion in hrs.
Cpss = steady-state plasma concentration
t = time from end of infusion _o time of peak level

4. Select t (usually between 2-3 T 1/2s) (Q8H, Q12H, Q24H)

5. Select "Cpss peak" (depending on peak and trough guidelines for conventional dosing or desired intensity with **SDD)**

6. Calculate a new dose (round to appropriate amount) BOLUS

MODEL

$$Dose = \frac{(Cpss)\,(Vd)\,(I - e^{-k\tau})}{e^{-k\tau}}$$

t = time from beginning of infusion to time of peak level
Cpss = steady-state plasma concentration

SHORT INFUSION MODEL

$$Dose = \frac{(Cpss)\,(Cl)\,(tin)\,(1 - e^{-k\tau})}{(1 - e^{-ktin})\,(e^{-kt})}$$

t = time from end of infusion to time of peak level
Cpss = steady-state plasma concentration tin= duration of infusion in hrs.

7. Check peak and trough with rounded dose:

BOLUSMODEL

$$\text{"Cpsspk"} = \frac{S \times F \times (\text{Dose in mg})}{\frac{Vd \text{ (in L)}}{(1 - e^{-k\tau})}} e^{-kt}$$

Cpsspk = steady-state peak plasma concentration
t = time from beginning of infusion to time of peak level
S = salt fraction (=1); F = fraction absorbed (=1)

$$\text{"Cpsstr"} = \frac{S \times F \times (\text{Dose in mg})}{\frac{Vd \text{ (in L)}}{(1 - e^{-k\tau})}} e^{-kt}$$

Cpsstr = steady-state trough plasma concentration
t = time from beginning of infusion to time of trough level
S = salt fraction (=1); F = fraction absorbed (=1)

SHORT INFUSION MODEL

$$\text{"Cpsspk"} = \frac{S \times F \times (\text{Dose in mg})/tin\,(1 - e^{-ktin})}{Cl\,(1 - e^{-k\tau})} e^{-k\tau}$$

Cpsspk = steady-state peak plasma concentration
t = time from end of infusion to time of peak level
S = salt fraction (=1); F = fraction absorbed (=1) tin = duration of infusion in hrs.

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