

GUIDELINES FOR DRUG PRESCRIBING AND MONITORING

A. PHARMACOKINETIC MONITORING/GUIDELINES/PROTOCOLS

1. AMINOGLYCOSIDE PROTOCOL (PHARMACIST PROCEDURE)

PURPOSE

The purpose of this protocol is to ensure efficacy and safety for patients receiving aminoglycoside antibiotics. It provides for optimal dosing regimens and ensures proper collection of blood samples and accurate analysis of serum levels. The protocol also ensures consistent interpretation and application of clinical and pharmacokinetic data by all members of the aminoglycoside dosing service (i.e. RQHR pharmacists).

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PART I - GENERAL OVERVIEW

CERTIFICATION

RQHR pharmacists must be certified as per the Aminoglycoside Certification Program prior to independent utilization of this protocol. Pharmacists not certified must gain approval from a certified pharmacist prior to making any recommendations. This approval will be noted by a co-signature on the back of the antibiotic monitoring form and in the patient's chart. Deviations from this protocol must be well substantiated, documented in the patient chart and discussed with the patient's physician.

PROCEDURE

1. The physician may request the aminoglycoside monitoring service by writing "Pharmacy consult" on the patient's chart or by pre-authorizing consults for all their aminoglycoside orders (authorization records kept in Pharmacy). Initial dosing regimens must be ordered by the physician to ensure timely initiation of antibiotics. Once consulted, the pharmacist follows the patient's progress until the aminoglycoside is discontinued. Consulted patients automatically receive high dose extended interval therapy provided they do not have exclusion criteria (Part II). If exclusion criteria are present, traditional dosing is used (Part III).
2. The pharmacist is responsible for ordering aminoglycoside levels and other monitoring parameters as indicated in this protocol.
3. The pharmacist provides dosage recommendations based on dosing guidelines or estimated pharmacokinetic parameters, and/or interpretation of serum levels.
4. If preauthorized, the pharmacist may change the dosage regimen without contacting the physician. However, the physician will be contacted when required (e.g. situations outside the protocol, lack of patient response, increasing Scr, etc.).
5. Whether or not a change in the dosage regimen is made, the pharmacist must provide documentation in the patient progress section of the chart.
6. In order to calculate an initial dosing regimen and to monitor therapy optimally, the following information is desirable:

<ul style="list-style-type: none"> ◆ Age ◆ Sex ◆ Height & Weight* ◆ Creatinine/Blood urea nitrogen* ◆ CBC with differential* ◆ Temperature* 	<ul style="list-style-type: none"> ◆ Culture & sensitivity (C&S) reports ◆ Ins/Outs (if available) ◆ Concomitant antibiotics, ototoxins/ nephrotoxins (e.g. amphotericin B, acyclovir, cisplatin, carboplatin, IV ethacrynic acid, IV furosemide, IV vancomycin, vinblastine, NSAIDs, cyclosporin, mannitol, etc.)
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A pharmacist may order temperature, serum creatinine, BUN, body weight and CBC with differential for patients covered under this protocol.

7. Monitoring

Serum Creatinine/BUN - At least twice weekly in all patients (e.g. Mon & Thurs) to monitor for nephrotoxicity.

NOTE:

- If Scr $\uparrow \geq 50\%$, hold aminoglycoside and discuss options with the physician
- If Scr $\uparrow \geq 30\%$, repeat Scr daily until it plateaus or returns to baseline
- If Scr continues to rise on 2 consecutive days, contact physician to discuss alternate antibiotics. If therapy must be continued with an aminoglycoside, repeat levels.

Serum levels - Refer to Parts II & III

Whenever possible, levels will be ordered at times when the laboratory is well staffed (i.e. 0800-1600 hours, but especially prior to 2330h)

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PART I - GENERAL OVERVIEW, CONT'D . . .

Monitoring, cont'd . . .

Antimicrobial Monitoring Form

A pharmacist completes this for each patient. The pharmacist reviews the patient's chart daily and documents accordingly on the Antimicrobial Monitoring Form.

Additional monitoring parameters are:

Daily:

- ◆ Temperature (highest in last 24h). Note: Record lowest temperature for patients with signs of septic shock (e.g. hypotensive, tachycardic)
- ◆ Ins/Outs, if available
- ◆ Concomitant antibiotics and potential ototoxins or nephrotoxins (e.g. amphotericin B, acyclovir, cisplatin, carboplatin, IV furosemide, IV vancomycin, vinblastine, NSAIDs, cyclosporin, mannitol, etc.)

Periodically:

- ◆ CBC with differential
- ◆ Weights, if on long term therapy

8. Duration of therapy

Whenever possible, aminoglycoside therapy should NOT exceed 5 - 7 days to decrease the risk of oto- and nephrotoxicity. If therapy continues for > 10 days, the pharmacist will contact the physician to discuss total duration. If therapy must continue for >10 days (e.g. endocarditis), the pharmacist will discuss symptoms of ototoxicity with the patient and document this in the patient chart. (Refer to sample discussion and chart note regarding ototoxicity - Appendixes A & B). Patient information sheets on aminoglycosides are available on pharmacy intranet and should be given at this time.

Estimates of cochlear and vestibular toxicity are approximately <15% (2.5 - 13.9%) and <5% (1.4 - 3.7%), respectively, however may be much higher when sensitive measures are used, such as audiometry or electronystagmography. (J Antimicrob Chemother 1984; 13 (suppl A):9-22; DICP Ann Pharmacother. 1990;24:267-72.)

Symptoms of ototoxicity include vestibular (nausea, dizziness, vertigo, nystagmus) and auditory toxicities (e.g. ringing, fullness in the ears, decreased hearing) and are sometimes irreversible. These toxicities have not been correlated to toxic serum levels, but may increase in prevalence with longer durations of therapy or after multiple courses of aminoglycosides.

9. Documentation

The pharmacist documents all recommendations in the patient progress section of the chart. See Appendixes B to F for sample chart notes.

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PART II – HIGH-DOSE EXTENDED INTERVAL AMINOGLYCOSIDES – ADULTS**Rationale/Background**

Aminoglycosides administered in a high dose extended interval has several advantages.

- ◆ More rapid bactericidal activity (due to achieving peak serum levels approximately 10x the MIC of the offending organism)
- ◆ Post-antibiotic effect (Trough serum levels allowed to drop below the MIC with continued antibiotic effect. It also thought to result in less nephro- & ototoxicity.)
- ◆ Convenience
- ◆ Reduced ancillary costs (e.g. preparation, administration, drug level monitoring)

Patient Selection

ALL PATIENTS WILL RECEIVE HIGH DOSE EXTENDED INTERVAL DOSING OF AMINOGLYCOSIDES, UNLESS:

- ◆ < 12 years old
- ◆ Pregnant
- ◆ Ascites
- ◆ Burns >20% of Body Surface Area
- ◆ Cystic Fibrosis
- ◆ Clcr < 20mL/min
- ◆ Single dose prophylaxis prior to operative procedure
- ◆ Synergistic therapy for Gram positive infection (e.g. aminoglycoside + β -lactam or vancomycin for enterococcal, *S. aureus*, *Strep viridans* or *S. epidermidis* endocarditis)

Note:

- ◆ High dose extended interval dosing may be used in febrile neutropenic patients and in post-partum patients on day 2. Traditional dosing will be used in all other patients. Refer to Part III.
- ◆ High Dose aminoglycosides may exhibit a neuromuscular blocking effect and result in the need for less neuromuscular blocking agents during intubation. It may also inhibit the ability to wean a patient off a ventilator, so it is suggested this process be attempted approximately 12h after a high dose extended interval dose administration.

DOSE/ADMINISTRATION

The recommended dose of gentamicin or tobramycin is 7mg/kg based on desired dosing weight (DDW*), rounded to the *nearest* 20mg.

Calculate desired dosing weight. DDW will be used for all patients, *except* in those whose actual body weight (ABW) is less than DDW. In these situations use actual body weight.

Ideal Body Weight (IBW) **(Equation 1)**

IBW female (kg) = 45.5 + 2.3 (inches > than 60)

IBW male (kg) = 50 + 2.3 (inches > than 60)

DDW = IBW + 0.4 (ABW - IBW) **(Equation 2)**

If a patient has already received a dose of aminoglycoside, see Section IV to determine timing of the next dose.

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PART II - HIGH DOSE EXTENDED INTERVAL AMINOGLYCOSIDES - ADULT, CONT'D. . .

Dosing Interval

Estimate the patient's creatinine clearance (Cl_{cr})* and choose the corresponding dosing interval from Table 1.

$$\text{* Males: Estimated } Cl_{cr} \text{ (mL/min)} = \frac{(140 - \text{age}) \times 90}{\text{Scr } (\mu\text{mol/L})}$$

(Equation 3)

$$\text{* Females: Estimated } Cl_{cr} \text{ (mL/min)} = Cl_{cr} \text{ (male)} \times 0.85$$

Table 1 - Dosing Interval Based on Estimated Clcr for High Dose Extended Interval

CREATININE CLEARANCE (mL/min) *	DOSING INTERVAL
≥ 60	q24h
40 - 59	q36h
20 - 39	q48h
<20	Use Traditional Dosing

Monitoring

Serum Levels

Routine peak and trough serum levels will NOT be done.

A single serum level will be drawn 6-14 hours after the 1st or 2nd dose and weekly thereafter in the following patients only:

- ◆ >65 years of age
- ◆ In ICU
- ◆ Para/Quadriplegic or amputee
- ◆ Dosing interval >q24h
- ◆ Exposure to contrast media
- ◆ On concurrent nephrotoxins (e.g. amphotericin B, IV acyclovir, IV furosemide, IV vancomycin, NSAIDs, cyclosporin, cisplatin, carboplatin, mannitol, etc.)

Additionally, a pharmacist may order a level in patients with extremes of weight.

In all other patients, a single serum level will be drawn 6-14 hours after a dose if therapy continues for more than 5 days.

Plot the level on the following nomogram to determine the recommended dosing interval. If the level falls on a borderline, use the longer interval.

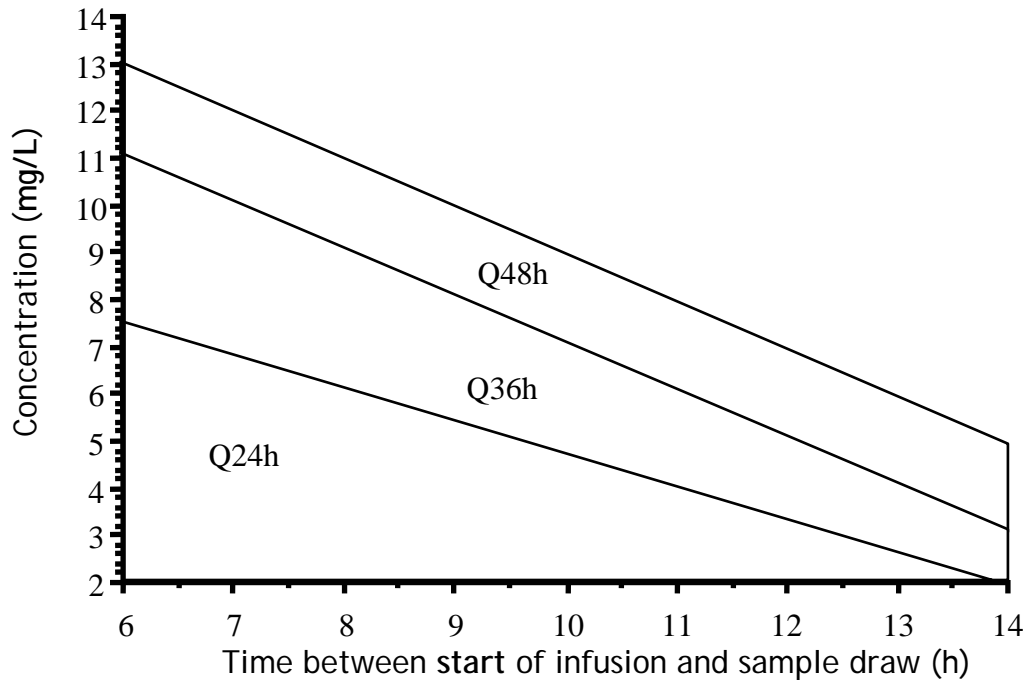
If the level falls above the q48h dosing interval, reevaluate the need for continued aminoglycoside therapy and discuss suitable alternatives with the physician.

If the level is <2mg/L, assess the patient's clinical status and continue current regimen if the patient is clinically stable or improving. If patient is not clinically improving, re-evaluate clinical situation (e.g. repeat level, change to traditional dosing, change antibiotics, etc.).

Note: Trough levels with high dose extended interval aminoglycoside regimens should be negligible [$< 0.2\text{mg/L}$] and are not recommended for routine monitoring. Peak levels are not monitored, but are expected to be $\approx 20\text{mg/L}$ for gentamicin and tobramycin, and $\approx 40\text{mg/L}$ for amikacin.

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Hartford Hospital High Dose Extended Interval Aminoglycoside Nomogram



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PART III -TRADITIONAL DOSING AMINOGLYCOSIDES – ADULTS

Use this for patients who do not meet the criteria for high dose extended interval. Refer to Part VI for Renal Failure Patients.

1. If a first dose has not been received, calculate a loading dose (LD)

$$LD = \text{weight (kg)} \times Vd(\text{L/kg}) \times C_{p\text{desired}} \quad \text{(Equation 4)}$$

$C_{p\text{desired}}$ = desired peak concentration (mg/L)
Doses should be in multiples of 20mg

Use estimated Vd from Table 2 and desired peak concentration from Table 3 (see below)

Calculate desired dosing weight (DDW). DDW will be used for all patients, except those whose actual body weight (ABW) is less than DDW. In these situations, use actual body weight.

Ideal Body Weight (IBW) (Equation 1)

IBW female (kg) = 45.5 + 2.3 (inches > than 60)

IBW male (kg) = 50 + 2.3 (inches > than 60)

DDW = IBW + 0.4 (ABW - IBW) (Equation 2)

To estimate the volume of distribution (Vd), the hydrational status of the patient must be considered.

TABLE 2 - Estimated Vd ^(1,3,14)

Hydrational Status	Vd (L/kg)
Normal	0.25
Dehydrated ¹	0.2
Overhydrated ²	0.3

- 1) High fever, ++ vomiting and diarrhea, orthostatic hypotension, tachycardia, and/or over-diuresed
- 2) Intake > output: Indicates overhydration, evidence of pulmonary edema, ascites, uncontrolled congestive heart failure or peripheral edema. Other conditions associated with ↑ volume of distribution include hypoalbuminemia [albumin < 25 μmol/L] and neutropenia.

TABLE 3 - Desired Peak Concentrations for Traditional Dosing Regimens

Infectious Process	Desired Peak (mg/L)
Cystic Fibrosis	12 - 14
Pneumonia, Severe G-ve Sepsis, Neutropenia, Burns	8 - 10
Soft Tissue & Wound Infections, Diverticulitis, Cholangitis, Peritonitis, Complicated UTI (e.g. Pyelonephritis, Cystitis with Anatomical/Structural Abnormalities affecting urine flow)	6 - 7
Cystitis (Uncomplicated UTI); Synergy for G+ve Infections (e.g. endocarditis)	3 - 5

The desired peak concentration must take into account the source of the infection, the pathogenicity of the organism and the clinical status of the patient.

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The desired trough concentration is <2mg/L for gentamicin and tobramycin.⁽⁷⁾ For the purposes of calculating the regimen desired trough ($C_{p_{min}}$) = 1mg/L.

Undetectable levels are <0.2mg/L for gentamicin and tobramycin.

Part III - Traditional Dosing Aminoglycosides - Adults, cont'd. . .

2. **Estimate Dosing Interval (τ):** To estimate an appropriate interval^(4,10) prior to receiving any serum level determinations, use the calculations below:

$$\tau = \frac{-1}{kd} \ln \frac{C_{p_{min}}}{C_{p_{max}}} + t^1 \quad \text{(Equation 5)}$$

τ = dosing interval

t^1 = infusion duration (assume 1h)

$C_{p_{min}}$ = desired trough concentration

$C_{p_{max}}$ = desired peak concentration

kd estimate (gentamicin) = 0.015 + (0.00285 x Clcr)

kd estimate (tobramycin) = 0.010 + (0.0031 x Clcr)

τ rounded off to an acceptable interval (e.g. q8h, q12h, q16h, q18h, q24h, q36h, q48h, q72h, q96h)

3. **Estimate a Maintenance Dose (MD):** To estimate the dose prior to receiving any serum level determinations, use the estimated τ , kd, Vd & desired $C_{p_{max}}$ to calculate empiric maintenance dose.

$$MD = C_{p_{max}} Vd kd \frac{1 - e^{-kd\tau}}{(1 - e^{-kd t^1})} \quad \text{(Equation 6)}$$

4. **$C_{p_{min}}$ & $C_{p_{max}}$:** In order to check the calculation and estimate what the $C_{p_{min}}$ and $C_{p_{max}}$ will be with the rounded off figures, or to estimate $C_{p_{min}}$ and $C_{p_{max}}$ of a current regimen.

$$C_{p_{max}} = \frac{ko}{Kd Vd} \frac{(1 - e^{-kd t^1})}{(1 - e^{-kd\tau})} \quad \text{(Equation 7)}$$

$$C_{p_{min}} = C_{p_{max}} (e^{-kd(\tau-t^1)}) \quad \text{(Equation 8)}$$

5. **Pre and Post Serum Levels** will be obtained *at steady state* (4 - 5 half lives), except if receiving aminoglycosides at synergistic dosing for Gram positive organisms with an expected duration of ≤ 5 days, in which case levels are not required.

Repeat serum levels weekly on long-term therapy (e.g. endocarditis, osteomyelitis) or more frequently if changing renal function or volume of distribution.

Acceptable times for obtaining serum levels in relationship to a dose are:

Pre level: 0 - 60 minutes before administration of the aminoglycoside

Post level: 30 - 60 minutes after the end of the infusion

Although not recommended, if using intramuscular (IM) route, blood samples should be collected ½ hour before the dose and 1 hour after an IM injection. The “infusion time” for calculation purposes is 1 hour and the measured peak level equals the extrapolated peak level.

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Serial blood samples (2 - 3 post levels after 1st dose) should be drawn after the first dose for patients whose dosing interval is >24h, or if time to steady state is expected to be > 3 days and/or if the patient is critically ill. See guidelines Part VI, D. Acute Renal Failure and Table 4 below for suggested sampling times. Calculate the patient's actual kinetic parameters as outlined in point 6 below (Equations 9 & 10, then 5 & 6).

PART III - TRADITIONAL DOSING AMINOGLYCOSIDES - ADULTS, CONT'D. . .

TABLE 4 - Suggested Sampling Times for Serial levels

Creatinine Clearance (mL/min)	Sampling Times*
51 - 125	1, 4, 6h
21 - 50	1, 8, 12h
10 - 20	1, 12, 20h
< 10	1, 24, 36h

* # hours after the end of a 1h infusion. Sampling times are based on being drawn over at LEAST one half-life

- 6. Interpreting Serum Levels:** The patient's *actual* kinetic parameters are calculated to obtain a maintenance dose and dosing interval.

Plot the data obtained and determine the $t_{1/2}$ (read off graph).

Calculate the elimination rate constant (kd).

$$kd = \frac{0.693}{t_{1/2}} \quad \text{(Equation 9)}$$

Calculate the volume of distribution (Vd).

$$Vd = \frac{k_0}{kd} \frac{(1 - e^{-k_d t^1})}{(C_{p_{max}} - C_{p_{min}} e^{-k_d t^1})} \quad \text{(Equation 10)}$$

t^1 = Infusion time (h)

k_0 = Dose (mg/h)

Using the desired peak and trough and the patient's own kd, calculate an appropriate dosing interval using Equation 5.

Calculate the maintenance dose using Equation 6.

Check your calculations and estimate $C_{p_{min}}$ and $C_{p_{max}}$. Round calculations to most appropriate dose and dosing interval. (Equations 7 & 8)

Note: Monitoring and follow-up will be done as indicated elsewhere (See sample note Appendix F)

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PART IV – DOSING AFTER THERAPY HAS BEEN INITIATED

If adjustments are required to achieve the desired peak and trough, calculate a new maintenance regimen using Equations 5 & 6. To determine when to give the next dose, the concentration at a particular time $[C_p(t)]$ can be estimated using the formula below*:

$$C_{p(t)} = C_{p_0}e^{-kd(t)} \quad \text{(Equation 11)}$$

C_{p_0} = observed level, or estimated $C_{p_{max}}$ calculated from the dose given & an estimated V_d
 $C_{p_{max}}$ estimate = dose (mg)/wt (kg) x V_d (L/kg)
 t = time (h) from C_{p_0} to $C_{p(t)}$

* This is useful to determine when the level will $<2\text{mg/L}$ and the patient requires another dose. [e.g. switching from high dose extended interval aminoglycosides to traditional dosing, or when changing the interval (e.g. from q8h to q12h)]

PART V – PREGNANT PATIENTS

ANTEPARTUM (DURING PREGNANCY):

Traditional dosing as only limited data on high dose extended interval in this patient population.⁶

- Dosing Weight:** Use weight prior to becoming pregnant (pre-pregnancy DDW*) and add the weight gained during the pregnancy.
 - Pre-pregnancy DDW* + weight gained (kg) = Dosing weight
 * Pre-pregnancy DDW = IBW + 0.4 [estimated pre-pregnancy weight (kg) - IBW]
- Volume of distribution (V_d): estimated 0.25L/kg - 0.3L/kg. Select a larger V_d in third trimester (e.g. after 27 weeks gestation).
- Estimated creatinine clearance (Cl_{cr}) is generally well over 100mL/min, however the dosing interval should never be more frequent than q8h.

INTRAPARTUM (DURING LABOUR):

Traditional dosing as only limited data on high dose extended interval in this patient population.^{5,6}

- Most common indications for antibiotics are fever during labour and suspected chorioamnionitis
- Administration of 1st dose prior to delivery has consistently shown to reduce rates of neonatal infection^{1,2,3}

Labour & Birth Unit (L&B): 1.5-1.75mg/kg/dose^{4,9} based on Actual Body Weight (ABW) in kilograms (kg). See below for suggested dosing regimens.

ABW:	Suggested Dosing Regimen:
< 80 kg	120 mg IV q8h
81 – 95 kg	140 mg IV q8h
> 95 kg	160 mg IV q8h

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POSTPARTUM (POST DELIVERY):

If the patient was initiated on traditional dosing in the Labor and Birth unit, this regimen can be continued, or alternatively switched to high dose extended interval dosing as the Vd will return to normal 2-5 days post partum.⁷

If, however, aminoglycosides are to be *initiated post-delivery*, use high dose extended interval dosing as follows:

1. Calculate pre-pregnancy DDW as outlined above
2. Add weight (kg) patient has gained during pregnancy
3. Subtract 10kg (for volume shifts, baby weight, placenta)
4. Dose at 7mg/kg/dose, with interval selection as per Part II of this protocol

PART V – PREGNANT PATIENTS, CONT'D...

SERUM LEVELS* (as per recommendations in Parts II and III):

*In patients whom duration of therapy is expected to be short, levels are generally not required. If on traditional dosing and therapy is anticipated to extend past a week, consider levels on Day 3 of therapy.

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PART VI - RENAL FAILURE PATIENTS

A. CHRONIC RENAL FAILURE ON HEMODIALYSIS (HD)

Hemodialysis removes aminoglycosides at a faster rate than occurs when the patient is not on dialysis. Therefore, it is necessary to calculate doses on an individual basis.

NOTE:

- ◆ High-flux dialyzers currently used reduce the aminoglycoside serum level by approximately 50%
- ◆ Cockroff-Gault equation CANNOT be used as it overestimates clearance
- ◆ Estimated Cl_{cr} for patients on chronic dialysis is <10 mL/min

1. Loading Dose

Renal failure patients' volumes of distribution are quite variable. The volume may be normal following dialysis and gradually increases until the next dialysis (estimated V_d = 0.3-0.35L/kg). Generally a pre-dialysis weight is used, however, as for patient's dosed traditionally, a desired dosing weight (DDW) is generally calculated.

$$LD = DDW \text{ (kg)} \times Vd \text{ (L/kg)} \times C_{p\text{desired}} \quad \text{(Equation 4)}$$

C_{pdesired} = desired peak concentration (mg/L)
Doses should be in multiples of 20mg

Calculate desired dosing weight (DDW). DDW will be used for all patients, except those whose actual body weight (ABW) is less than DDW. In these situations, use actual body weight (i.e., pre-dialysis weight).

$$\text{Ideal Body Weight (IBW)} \quad \text{(Equation 1)}$$

$$\text{IBW female (kg)} = 45.5 + 2.3 \text{ (inches } > \text{ than } 60)$$

$$\text{IBW male (kg)} = 50 + 2.3 \text{ (inches } > \text{ than } 60)$$

$$DDW = IBW + 0.4 \text{ (ABW - IBW)} \quad \text{(Equation 2)}$$

2. Determine Half Life (t_{1/2}) & kd, vd

To determine subsequent doses, one needs to know the on and off dialysis kd (i.e. elimination rate constant) and half life.

Off-dialysis kd: Calculate using 2 - 3 serial levels as indicated below.

Level #1 is following the loading dose. This is drawn 2-4 hours post start of infusion to allow for tissue distribution.

Two further serum levels are ordered over at least one estimated half-life (e.g. gentamicin average t_{1/2} in renal failure = 34h).

Level #2 is usually drawn around noon the day after dialysis (approximately 18-24hr post infusion)

Level #3 is taken just before the next dialysis

Two serial levels are acceptable if drawn over at least one estimated half-life (i.e. Level #1 & #3).

Plot the serial levels to calculate t_{1/2}, V_d and off-dialysis kd.

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On-dialysis kd: On-dialysis kd can be calculated by plotting the pre-dialysis and post dialysis levels, however instead of this, estimate the post dialysis level by taking 50% of the actual pre-dialysis level to account for the removal by the high-flux dialyzer.

3. Determine Next Dose

Use the following formula:

$$\Delta C_p = C_{p(\text{desired})} - C_{p(\text{observed or estimated})} \quad \text{(Equation 12)}$$

ΔC_p - desired change in level

$$\text{Dose} = \Delta C_p(\text{mg/L}) \times V_d (\text{L}) \quad \text{(Equation 13)}$$

4. **If a series is not drawn after the first dose**, use estimated kinetic parameters to determine when the serum level will be approximately 2-2.5mg/L or the predialysis level is 2.5-5mg/L.

This will provide the estimated level at a particular time (i.e. pre-dialysis), to identify when subsequent doses are required.

$$C_{p(t)} = C_{p0}e^{-kd(t)} \quad \text{(Equation 11)}$$

C_{p0} = observed level or estimated $C_{p\text{max}}$ ** post dose

$K_{\text{dest}}=0.0201\text{h}$ (estimate based on arbitrary figure of Clcr of 2ml/min)

t = time (h) from C_{p0} to $C_{p(t)}$

Formula for estimating $C_{p\text{max}}$ after a given dose:

$$C_p = \frac{\text{Dose (mg)}}{V_d (\text{L/kg}) \times W_t (\text{kg})} \quad \text{(Equation 14)}$$

B. CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT)

(Pharmacist Note: Please use the [CRRT Antibiotic Monitoring form](#))

INITIATION OF THERAPY

1. Calculate a loading dose

	Gram +ve synergy dosage	Infection with Gram Negative Bacteria	
		Loading Dose	Maintenance dosage**
Gentamicin	1mg/kg q24-36h	3mg/Kg	2mg/Kg q24-48h
Tobramycin	Not Applicable	3mg/Kg	2mg/Kg q24-48h
Amikacin	Not Applicable	10mg/Kg	7.5mg/Kg q24-48h

**Note: Use a dosing interval of q24h if CVVHDF; q48H if CVVH

CVVHDF Continuous venovenous hemodiafiltration (most frequently used)

CVVH Continuous venovenous hemofiltration

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2. Do a series after the first dose
 - Level #1 - 2 - 4h after the start of the infusion
 - Level #2 - 24h after the start of the infusion

Part VI - Renal Failure Patients - CRRT, cont'd. . .

3. Calculate patients actual $t_{1/2}$, V_d and k_d to determine subsequent dosing

V_d - is larger due to the critical nature of this population. CRRT can contribute to the larger V_d , but does offer some stability. If CRRT is kept constant, aminoglycoside elimination is likely to be kept constant.

$t_{1/2}$ - CRRT dialysis filters are capable of removing aminoglycosides at a rate equivalent to Cl_{cr} of 10-40mL/min which approximates a $t_{1/2}$ of 6-20h. This will usually result in a dosing interval in the range of 24-48 hours.

Desired peak levels will depend on the type of infection being treated. See Table 3.
4. If unable to do levels after the first dose use empiric dosing guidelines above and obtain a level at 24 hours to assess appropriateness of current dosing interval.
5. Due to the dynamic nature of CRRT and acute renal failure, obtain subsequent trough serum levels at least 3 times weekly to ensure trough levels <2mg/l to decrease potential for toxicity. Reference: Trotman RL et al. CID, 2005 (Oct);41:1159-66.
6. Chart Documentation: A progress note will be written by the pharmacist initially for patients starting on CRRT, thereafter, a daily aminoglycoside order and chart note will be written prior to 1600h whether or not a dose is required. (e.g. "No gentamicin today" or "Give gentamicin 120mg IV x1 today" as per AMG protocol/signature)

C. CHRONIC RENAL INSUFFICIENCY (CRI) (Not on Dialysis)

Refer to Part III and draw serum levels as per Table 4. It is acceptable to draw only Level #1 & #3.

D. ACUTE RENAL FAILURE (ARF)

This section refers to ARF patients that are oliguric (scanty urine output) or anuric (absence of urine production) on intermittent dialysis, or not on dialysis.

It is not possible to determine a maintenance dose or interval due to fluctuating renal function.

1. If possible, draw a single serum level 2-4 hours after the start of the loading dose. This level will provide the ability to calculate the actual V_d (Equation 4) and will provide a $C_{p(t)}$ (Equation 10) to estimate when future doses will be required or what the level will be at a certain point in time ($C_{p(t)}$)

$$C_{p(t)} = C_{p_0}e^{-k_d(t)} \quad \text{(Equation 11)}$$

C_{p_0} = observed level or estimated C_{pmax} post dose
 k_d estimate (gentamicin) = $0.015 + (0.00285 \times Cl_{cr})$
 k_d estimate (tobramycin) = $0.010 + (0.0031 \times Cl_{cr})$
 t = time (h) from C_{p_0} to $C_{p(t)}$.

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2. A follow up level can be drawn close to the time when you expect the level to be close to 2mg/L. Knowing this level you can confirm when it is time for another dose, and the amount of drug to bring the level back up to the desired peak level..

Using equations #13&14 to calculate the next dose

$$\Delta C_p = C_{p(\text{desired})} - C_{p(\text{observed or estimated})} \quad \text{(Equation 12)}$$

ΔC_p = desired change in level

$$\text{Dose} = \Delta C_p \times V_d \text{ (L)}$$

(Equation 13)

Part VI - Renal Failure Patients - CRRT, cont'd. . .

3. If a peak level was not drawn, do a spot level and estimate $C_{p_{\text{max}}}$, k_d , $t_{1/2}$ using Equation 5 to estimate when a dose is required. **Caution:** Because of fluctuating Scr , subsequent doses are based on daily spot levels taking into consideration when a patient is being dialyzed. If patients are dialyzed, a pre-dialysis level should be obtained

NOTE: Serial levels can not be used to calculate steady state kinetic parameters for patients with fluctuating renal function (i.e. ARF).

E. Peritoneal Dialysis

Antibiotics are given intraperitoneal (IP) by adding to the patient's dialysate solution. Doses are as preprinted orders (See RQHR Peritonitis Protocol preprinted orders PP-108).

Levels:

Serum levels are drawn on day 4 if therapy is anticipated to be >1 week. A trough level is drawn prior to the last dialysis bag (ie. prior to the last dose on day 4). Goal is a trough level of <2.5mg/L.

- If trough $\geq 2.5\text{mg/L}$, ↓ IP dose by 50%
- If trough $< 0.5\text{mg/L}$, assess patient clinically & if not improving ↑ IP dose by 20mg/L dialysate to a maximum of 40mg/L dialysate. Recheck level in 4 days.

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PART VII - PEDIATRIC GUIDELINES

There is no official RQHR Pediatric protocol. This section applies to term infants > 1 week of age to children <12 years of age. For preterm neonates and term neonates <1 week of age, refer to Part VIII Neonates.

- ◆ All pediatric patients are audited by a pharmacist, unless pharmacy is specifically consulted by the physician
- ◆ When consulted, the pharmacist must still discuss therapy changes and monitoring with the physician

DOSING

Aminoglycoside dosing is based on the recommendations in the Pediatric Drug Dosage Handbook; 8th edition; Winnipeg Health Sciences Centre, June 1998.

Age/Indication	Dosing regimen
≥ 7 days - 5 years	7.5mg/kg/day divided q8h
6 - 10 years	6mg/kg/day divided q8h
> 10 years - < 12 years	4.5mg/kg/day divided q8h
≥ 12 years	Consider high dose extended interval dosing (7mg/kg/dose q24h), <i>if approved by pediatrician</i>
Cystic Fibrosis (CF) patients (all ages)	10mg/kg/day divided q8h, unless previous kinetics available to guide dosing (Aminoglycoside monitoring forms filed in patient's individual file in 4 th floor satellite, RGH) DO NOT use high dose extended interval dosing in the cystic fibrosis (CF) population as there is insufficient evidence to support use at this time.
Febrile Neutropenia (<12 years)	8-9 mg/kg/day divided q8h

SERUM LEVELS

Recommended if:

- ◆ Child ≤3 months of age (depends on anticipated duration of therapy)
- ◆ Critically ill patients in MPICU where varied kinetics are anticipated
- ◆ All cystic fibrosis (CF) patients once at steady state. Wait until day 3 or 4 to obtain levels in "repeat" patients.
- ◆ Duration of therapy likely to continue past 7 days
- ◆ Questioning therapeutic efficacy, or increased potential for toxicity (e.g. renal insufficiency)

Reference: Logsdon, B, SJ Phelps; "Routine Monitoring of Gentamicin Serum Concentrations in Pediatric Patients with Normal Renal Function is Unnecessary"; Ann Pharmacotherapy 1997; 31: 1514-8.

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PART VII - PEDIATRIC GUIDELINES, CONT'D. . .

TIMING OF LEVELS

- ◆ Trough level 0-60 minutes prior to the dose
- ◆ Peak level 30-60 minutes after *completion of drug infusion*
- ◆ Gentamicin & tobramycin are infused over **60** minutes
- ◆ Coordinate blood work whenever possible to minimize number of times the child has blood drawn

Target Serum levels

- ◆ Gentamicin in CF patients: Target peaks: 10-12mg/L
- ◆ Tobramycin in CF patients: Target peaks: 10-12mg/L
- ◆ Target troughs for all patients: <1mg/L

ASSESSMENT OF LEVELS

- ◆ **MUST** extrapolate levels to assess the true peak and trough values. This is particularly important in the cystic fibrosis patients where the extrapolated peak can be substantially higher than the reported value due to rapid clearance.

SERUM CREATININE

- ◆ Once weekly on all patients
- ◆ Order Scr to be drawn with drug levels ordered. Co-ordinate blood work whenever possible to minimize number of times the child has blood drawn.

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PART VIII – NEONATAL GUIDELINES

- ◆ Actual weight should be used for dose calculation unless the baby has hydrocephalus or hydrops fetalis where a smaller weight needs to be estimated.
- ◆ No differentiation is made for gentamicin/tobramycin for postnatal age (PNA) >7 days. The guideline below should be utilized for empiric dosing, but serum level assessment is recommended to facilitate individualization of dosing.

GENTAMICIN/TOBRAMYCIN EMPIRIC DOSING GUIDELINE (e.g. Neonates in NICU & Unit 2D, RGH)

PCA	Dose	Interval
≤ 29 weeks	3mg/kg/dose	q24h
30-34 weeks	3.5 mg/kg/dose	q24h
≥ 35 weeks	4mg/kg/dose	q24h

PCA = post-conceptual age

The physician should order the number of doses of antibiotic required instead of a duration of hours (eg: x 48 hours). If no duration is specified, the automatic stop date policy of RQHR will be utilized. (Neonatal Working Group Meeting, June, 2005)

MONITORING

Serum Levels

- ◆ Gentamicin/tobramycin peak and trough levels should be obtained around the 3rd dose if therapy will extend past 48 hours. *If duration of therapy is yet to be determined due to pending culture and sensitivity results, the levels may be delayed until around the 4th dose.*
- ◆ Trough level should be obtained 0-60 minutes before the start of the infusion
- ◆ Peak level should be obtained 30-60 minutes after the infusion and flush are complete
- ◆ The exact time infusion is initiated should be recorded on the Medication Administration Record to facilitate accurate extrapolation of the reported levels
- ◆ Doses should be administered following the Neonatal Medication Dilution Guidelines: i.e. infuse over 30 minutes followed by a NS flush over 5 minutes

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Part VIII Neonates, cont'd. . .

Therapeutic Target Concentrations

PEAK: 5 - 12mg/L

TROUGH: <2mg/L

Additional Monitoring

- ◆ CBC, renal panel, blood culture prior to initiation of therapy
- ◆ Serum calcium if therapy lasting longer than 3 days (Jackson, 2003)
- ◆ Daily urine output

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PART IX – AMIKACIN

Restricted to use for organisms with documented resistance to gentamicin *and* tobramycin.
For additional information refer to monograph in Micromedex® and RQHR Parenteral Manual

NOTE: Final concentration not to exceed 5mg/mL

High Dose Extended Interval

ADULT DOSE: 15mg/kg (rounded to nearest 50mg); max 1.5g/day

Dosing interval as indicated by estimated Cl_{cr} below:

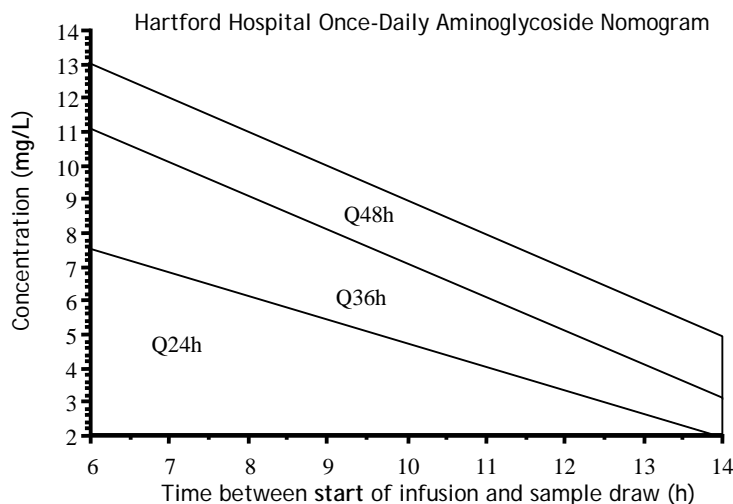
* Males: Estimated Cl_{cr} (mL/min) = $\frac{(140 - \text{age}) \times 90}{\text{Scr } (\mu\text{mol/L})}$ **(Equation 3)**
 * Females: Estimated Cl_{cr} (mL/min) = Cl_{cr} (male) x 0.85

Table 1 – Dosing Interval Based on Estimated Clcr For High Dose Extended Interval

CREATININE CLEARANCE* (mL/min)	DOSING INTERVAL
≥ 60	q24h
40 – 59	q36h
20 – 39	q48h
< 20	Use Traditional Dosing

*Estimated Clcr as above (Equation 3)

Serum Levels: Divide by 2 the reported amikacin serum concentration (mg/L) before plotting on the *gentamicin/tobramycin nomogram* below. If the level falls on a borderline, use the longer interval. If the level falls above the q48h dosing interval, reevaluate the need for continued aminoglycoside therapy and discuss suitable alternatives with the physician. If the level falls below the nomogram, assess the patient’s clinical status and continue current regimen if the patient is clinically stable or improving. If patient is not clinically improving, re-evaluate clinical situation (e.g. repeat level, change to traditional dosing, change antibiotics, etc.).



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Part IX - Amikacin, cont'd . . .

Traditional Dosing Regimen, Adults: 7.5mg/kg per dose; max 1.5g/day

[PEDIATRIC DOSE: 15 - 22.5mg/kg/day in 2 - 3 doses]

Table 5 - Dosing Interval Based on Estimated Clcr for Traditional Dosing

CREATININE CLEARANCE* (mL/min)	DOSING INTERVAL
>75	q8h
50 - 75	q12h
40 - 49	q16-18h
< 40	Load, then as per levels

*Estimated Clcr as above (Equation 3).

Use computer program for gentamicin/tobramycin kinetics with actual reported amikacin levels in mg/L. Aim for target serum levels as indicated in table below.

Desired Serum Levels with Traditional Dosing Regimen:

Infectious Process	Desired Peak (mg/L)	Desired Trough (mg/L)
Life-threatening infections	25 - 30	4 - 8
Moderate to severe infections	20 - 25	1 - 4
UTI	15 - 20	1 - 4

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APPENDICES

Ototoxicity

APPENDIX A - Sample Discussion with Patient

Mr. Smith you are currently receiving gentamicin, an antibiotic to treat your infection. This is an important antibiotic to make you better, but I want to tell you about the side effects that may occur in patients who receive longer courses of therapy. This antibiotic can affect hearing and balance in 1 of 10 patients on long-term therapy. If you experience any of the following inform your doctor, and please have the nurse contact the pharmacist:.

- ◆ *Dizziness*
- ◆ *Problems with your balance*
- ◆ *Double vision*
- ◆ *Difficult hearing*
- ◆ *Ringing in your ears*
- ◆ *Pain or pressure in your ears*
- ◆ *Fullness in your head*

APPENDIX B - Sample Chart Note

April 15, 2005 (1520h) Pharmacist Note re: Gentamicin ototoxicity

Mr. Smith is at increased risk of otovestibular damage due to receiving >10 days of gentamicin. He has been counseled that if he experiences any dizziness, balance problems, double vision, difficult in hearing, ringing in the ears, pressure/pain in the ears and fullness in the head, he is to contact the nurse and pharmacist, and to discuss this with the doctor.

as per AMG protocol/Certified pharmacist's signature & printed name/credentials, pager #

High Dose Extended Interval Dosing

APPENDIX C - Sample Chart Note for Empiric Dosing

April 12/05 (1450h) Pharmacist Note re: Gentamicin dose

This patient meets the criteria for high dose extended interval gentamicin. Based on a CrCl = x (Scr = X mg/L) and weight = X kg, a dose of Gentamicin X mg (7mg/kg) qXh has been ordered. Levels will not be required unless therapy exceeds 5 days. We will continue to follow with you. Thank you for the consult.

as per AMG protocol/Certified pharmacist's signature & printed name/credentials, pager #

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APPENDIX D - Sample Chart Note for Interpretation Serum Levels

April 15/05 (1500h) Pharmacist Note re: Gentamicin levels

Mr. X is currently receiving gentamicin 520mg (7mg/kg) IV q24h . A gentamicin level drawn today 8 hours after the dose was X mg/L. This indicates the patient is clearing the drug as expected and no change in dose is required. We will continue to follow with you.

as per AMG protocol/Certified pharmacist's signature & printed name/credentials, pager #

Traditional Dosing

APPENDIX E - Sample Chart Note for Empiric Dosing

April 12/05 (1450h) Pharmacist Note re: Gentamicin Dose

Based on a Scr = X μ mol/L and weight = X kg, a dose of Gentamicin X mg qXh should provide a desired peak of X mg/L and trough <2mg/L. Levels will be ordered tomorrow when the patient is at steady state to ensure desired serum levels are obtained. We will continue to follow with you. Thank you for the consult.

as per AMG protocol/Certified pharmacist's signature & printed name/credentials, pager #

APPENDIX F - Sample Chart Note for Interpretation of Serum Levels

Pharmacist Note: Gentamicin levels

Pre and post serum levels obtained on Gentamicin X mg qXh resulted in an extrapolated peak of X μ mol/L and trough of X mg/L. Suggest continue same regimen *(or, based on this, we will change Gentamicin to Y mg qXh to achieve desired peak of x and trough of y.)* Repeat levels will be done in 1 week *(or are not required)*. We will continue to follow with you.

as per AMG protocol/Certified pharmacist's signature & printed name/credentials, pager #