Pulse Dosing of Aminoglycosides

Recommendation:
Pharmacy dosing of aminoglycosides will be by the Pulse Dosing method, unless the patient has an exclusion criteria, or the physician orders for pulse dosing not to be used.

Description of Pulse Dosing of Aminoglycosides:
Gentamicin or tobramycin 5 mg/kg, or 15 mg/kg of amikacin is given Q24-48 hours depending on the patient's renal function. Peak serum levels achieved are 15-20 mcg/ml for gentamicin and tobramycin or 40-60 mcg/ml for amikacin (8-12 times the MIC of most bacteria). A dosage interval of Q24-48H is selected to allow the trough to drop to $\leq$ 0.3 mcg/ml for gentamicin and tobramycin and $\leq$ 0.9 mcg/ml for amikacin. This will prevent tissue accumulation and decrease the chance of toxicity.

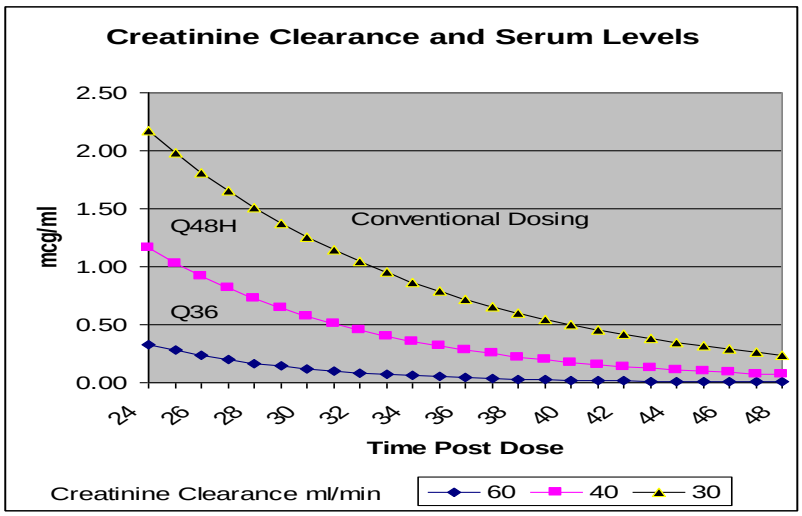
Advantages:
- Therapeutic levels are obtained with the first dose.
- Equal or more effective than conventional dosing regimens.
- Equal or less nephrotoxicity than conventional dosing regimens.
- Equal or less ototoxicity than conventional dosing regimens.
- Greater convenience for nursing and pharmacy personnel with reduced preparation and administration cost.
- Ease of dosage adjustments as only the interval is adjusted using a nomogram.
- Monitoring:
  Fewer serum levels, 14 hour post dose levels are routinely monitored twice weekly by the pharmacist. True peaks and true troughs are not used for monitoring or dosage adjustments.
  Renal function monitoring is the same as traditional dosing. Serum creatinine and BUN are ordered QOD while the patient is receiving aminoglycosides by the pharmacist.
- Decreased cost of therapy.

Rationale:
- Concentration dependent killing: The rate and extent of bacterial killing for gram-negative organisms is more rapid and extensive with higher aminoglycoside concentrations.
- Prolonged post antibiotic effect (PAE): Higher peak concentrations give a prolonged PAE, i.e. suppression of growth of gram-negative aerobic bacterial when no extracellular drug is present. A post antibiotic effect of 4-10 hours is expected in vivo.
- First-exposure effect or adaptive resistance: Aminoglycosides require active transport across lipid membranes of bacteria to get to their intracellular sites of action. Initial exposure down-regulates subsequent uptake of the drug. Bacteria develop temporary resistance in the presence of aminoglycosides that reverses after the bacteria are not exposed to the drug for a period of time.
- Reduced emergence of resistant organisms with high peak concentrations: Drug concentrations of 8-10 times the MIC have been shown in vitro to eliminate the emergence of drug resistant populations.
- Nephrotoxicity: Is related to the amount of drug accumulated in the renal cortex. The rate of cortical uptake is nonlinear and becomes saturated at relatively low serum levels. The uptake is more efficient with low sustained drug concentrations than with high intermittent concentrations.
- Ototoxicity: Is related to the amount of drug accumulated in the vestibular and cochlear tissues. The rate of uptake is saturable.

Exclusion Criteria:
Renal dysfunction (estimated Clcr < 30 ml/min)
Severe liver disease
Ascites
Anasarca
Extensive burns (>20% of body surface area)
Pregnancy or breast-feeding
Enterococcal endocarditis
Monotherapy outside of urinary tract
History or signs of hearing loss or vestibular dysfunction
Exclusion Criteria (continued)
Cystic fibrosis
Osteomyelitis
Age < 18 years old
Neuromuscular Disorders

Dosing Considerations:

- The same total daily dose of gentamicin or tobramycin, 5 mg/kg, or 15 mg/kg of amikacin is given Q24-48 hours depending on the patient's renal function. The dose of gentamicin or tobramycin is rounded to the nearest milligram amount evenly divisible by 40, as they are supplied in 40 mg/ml concentrations.
- Patients with estimated creatinine clearance < 30 ml/min or with dosage intervals greater than 48 hours are not candidates for Pulse Dosing. These patients are dosed using traditional pharmacokinetic dosing aiming for peaks of 4-10 mcg/ml and troughs of 0.5-1.5 mcg/ml for gentamicin and tobramycin. Amikacin levels for traditional dosing are peaks of 20-30 mcg/ml and troughs of < 5 mcg/ml.
- If the MIC of the bacteria being treated is > 2 mcg/ml for gentamicin or tobramycin, or > 4 mcg/ml for amikacin, an aminoglycoside with a lower MIC should be selected or traditional pharmacokinetic dosing should be used. The goal of Pulse Dosing is a peak of 8-12 times the MIC of the bacterial being treated.
- Timed levels are monitored twice weekly and <u>should be drawn 14 hours after the completion of the infusion</u> for uniformity and ability to differentiate the correct dosage interval for the patient. If the concentration falls in the area designated Q24H, Q36H, or Q48H on the nomogram, the interval selected is every 24, 36, and 48 hours, respectively. However, if the point is on the line, the longer interval is chosen. If the concentration is above the Q48H interval, Pulse Dosing should be stopped and serial concentrations followed to determine the appropriate time of the next dose (< 1 mcg/ml) and traditional pharmacokinetic dosing should be instituted. The nomogram is designed to allow the true trough to fall to <u>≤</u> 0.3 mcg/ml for gentamicin/tobramycin or <u>≤</u> 0.9 mcg/ml for amikacin.
  The 14 hour post dose sampling time has been selected to ensure that the measured levels will be within assay range and will allow the four dosing groups (q24, q36, q48, and conventional) to be differentiated from one another for dosage adjustment. <u>Traditional troughs 0.5 hours before the dose will NOT be drawn.</u>
  Rationale for levels 14 hours post dose:
  - Drugs assays have maximal accuracy in the middle of the assay range. As levels approach either end of the assay range accuracy decreases and standard deviation increases.
  - Over time the levels for all dosing intervals approach the same value of zero and the lines merge.
  - If levels are drawn at 48 hours post dose all patients with creatinine clearance down to 30 ml/min with have levels below assay and the levels can not be use to tell what interval the patient should be on.
  - If levels are drawn at 36 hours post dose only patients with a creatinine clearance of approximately 35 ml/min or less will be in assay range and you can not tell if patients with levels below assay should be on a 24, 36 or 48 hour interval.
  - If levels are drawn at 24 hours post dose only patients with creatinine clearance of approximately 50 ml/min or less can be differentiated from one another. Patients that should be on q24 hour dosing intervals and some patients requiring q36h dosing are below assay range and can not be differentiated from one another.



<u>Acceptable Timing</u> of serum level (hours after completion of infusion)

	Gentamycin /Tobramycin / Amikacin	
Clcr	Dosage Interval	Time Post Dose
> 60	Q24H	8-14 hours
41-60	Q36H	10-20 hours
30-40	Q48H	14-24 hours

- Desired troughs at time of next dose are:
  - Gentamicin / Tobramycin < 0.3 mcg/ml
  - Amikacin <0.9 mcg/ml
- Expected Peaks:
  - Gentamicin / Tobramycin 15-20 mcg/ml
  - Amikacin 40-60 mcg/ml
- Dosing Weight used in calculations, nomograms, and dosing charts:
  - LBW(kg)
    - Males = 50 + 2.3 (height in inches over 60 inches)
    - Females = 45.5 + 2.3 (height in Inches over 60 inches)
  - Dosing Weight
    - Actual weight if actual weight <= LBW
    - Adjusted weight if actual weight > LBW
      - Adjusted weight = LBW(kg) + 0.4 (Actual Weight(kg) - LBW(kg))

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