# AMINOGLYCOSIDES – HIGH-DOSE EXTENDED INTERVAL DOSING

There are several studies suggesting that larger doses of aminoglycosides with extended intervals (e.g., q24hrs) are just as effective, and less toxic, than conventional dosing given three times a day. High-dose extended interval (HDEI) regimens take advantage of concentration-dependent killing through the optimization of peak concentration / MIC ratios. The HDEI policy has been used on the Trauma Surgery Service at the University of Kentucky HealthCare (UKHC) since 1993. This is also referred to as **"**Once-daily aminoglycoside dosing".

**Inclusion Criteria:** All adult patients ordered aminoglycosides for prophylaxis, empiric therapy, or documented infection. (Aminoglycosides are usually indicated as synergistic or adjunctive therapy with other antibiotics as double coverage for gram-negative infections).

## Exclusion Criteria:

1. Patients with ascites
2. Patients with burns on >20% of total body surface area
3. Pregnant patients
4. Patients on dialysis - please refer to specific guidelines for renal dysfunction
5. Patients with gram positive bacterial endocarditis
6. Pediatric patients (<18yo) – please refer to pediatric dosing guidelines
7. Patients with cystic fibrosis (CF) (with/without lung transplant) – please refer to specific guidelines for CF patients

## Special Populations:

- Orthopedic surgery services commonly will use gentamicin 5mg/kg for prophylaxis/pre-emptive therapy with open fracture
- Obstetrics will use gentamicin 5mg/kg based on post-partum dosing body weight - see below for OB guidelines
- Cystic fibrosis patients (without lung transplant) – guidelines below for pediatric and adult CF dosing
- Cystic fibrosis patients with lung transplant have been shown to have altered aminoglycoside pharmacokinetics (increased half-life) following transplant and dosing should be individualized based on concentrations

## Initial Dosing Guidelines for Adults:

1. Estimate Creatinine Clearance ($Cl_{cr}$) using actual body weight (ABW) for non-obese patients; in obese patients (*>125% IBW*) use dosing body weight (DBW)

   Males $Cl_{cr} = \frac{(140-Age)X\ ABW}{72\ x\ Scr}$ Females $Cl_{cr} = Cl_{cr} * 0.85$

2. Estimate Body Surface Area (BSA) using the Mosteller equation and standardize $Cl_{cr}$

   $BSA(m^2) = \frac{\sqrt{Ht(cm)X\ Wt\ (kg)}}{60}$ $Cl_{cr(std)} = Cl_{cr} * \frac{1.73m^2}{BSA}$

3. Determine weight to utilize for dosing
   a. Use ABW for non-obese patients [if ABW < ideal body weight (IBW), then use ABW]
   b. Use DBW for obese patients calculated using the following equations:

Calculate Ideal Body Weight (IBW) $IBW_{Males} = 50\ (kg) + [2.3\ (kg) x\ ea.\ inch\ over\ 5\ ft]$
$IBW_{Females} = 45\ (kg) + [2.3\ (kg) x\ ea.\ inch\ over\ 5\ ft]$

Calculate DBW: $DBW = IBW + 0.4\ (ABW - IBW)$

4. Calculate the patient's dose based on ABW (non-obese) or DBW (obese).

| | Tobramycin and Gentamicin | Amikacin |
|---|---|---|
| **$Cl_{cr(std)}$ ≥ 40 ml/min** | 7 mg/kg | 15-20 mg/kg |
| **$Cl_{cr(std)}$ < 40 ml/min** | 3 mg/kg | 7.5 mg/kg |

5. Infuse over 30 minutes.

6. Order two concentrations at 4 and 12 hours after the end of 1st dose.

## Monitoring:

**Initial Dose**: two concentrations (ordered as "random" concentrations) will be obtained:

1. ***1st* concentration** will be drawn ~***4 hours*** after completion of the ***1st dose***.

   **NOTE:** The random concentration of gentamicin/tobramycin at **4 hours post-infusion** may **range from 4-13 mg/L** depending on renal function and volume status. Patients with normal renal function (>100 ml/min) usually average a **4-hour random ~5-8 mg/L.**

**The rationale for obtaining a "4-hour" sample versus a "peak" is to determine the serum concentration after the distribution phase. A prolonged distribution phase has been described in trauma patients (Jennings HR, et al. *Pharmacotherapy*. 2000;20(10):1265—SEE GRAPH BELOW) and healthy volunteers (McNamara DR, et al. *J Clin Pharmacol* 2001 Apr;41(4):374-7) who received 7 mg/kg. Post-distribution concentrations provide a more accurate calculation of elimination rate and the estimation of the 24-hour concentration.**

2. ***2nd* concentration** will be drawn ~***12 hours*** after completion of the ***1st* dose**.

   **NOTE:** The concentration at **12 hours post-infusion** will vary based on renal function. The **12-hour concentration of gentamicin/tobramycin** may be **<1 mg/L if normal renal function.**

**Patients with normal renal function should have a prolonged "drug-free" period. HDEI therapy should usually NOT be used as the single antibiotic agent and patients should not receive a dose of 7mg/kg of tobramycin/gentamicin more frequently than once every 24 hours until more studies are available. Some patients may warrant conventional dosing to maintain concentrations.**

**Subsequent Doses:** The goal of the initial concentrations after the 1st dose is to verify that the drug is eliminated appropriately before the 2nd dose and to establish the dosing interval. Subsequent doses will be the same as the initial dose, but the dosing intervals will be adjusted to achieve troughs **< 1 mg/L for gentamicin/tobramycin and < 4mg/L for amikacin (ideally undetectable though).**

- Appropriate dosing intervals include every 24, 36, or 48 hours
- Scr/BUN should be measured at baseline and 2X/week thereafter.

- **Patients with normal renal function will usually have a "drug-free" period with an undetectable trough concentration < 0.3 mg/L of gentamicin/tobramycin.**
- **For patients with trough concentration > 0.3 mg/L, renal function should be monitored closely and risks of nephrotoxicity and ototoxicity evaluated carefully.**
- **If the serum concentration after a 7mg/kg tobramycin/gentamicin dose requires > 48 hours to decline to <1mg/L, then 3mg/kg or conventional dosing may be warranted.**
- **Patients should not receive a single dose of 7mg/kg of gentamicin/tobramycin more frequently than every 24 hours until more studies are available.**

- A trough concentration should be obtained weekly to check for drug accumulation and assess risk of nephrotoxicity
- Consider targeting a peak of 8 to 10 times the MIC to achieve optimal bactericidal activity. Dosing should be based clinically by site/severity of infection, causative organism (especially MDR gram-negative infections), immunocompetence, etc.
- Scr/BUN should also be monitored at least 2X/week to assess any changes in renal function and risk of nephrotoxicity. Concomitant nephrotoxic drugs should be avoided.
- Ototoxicity should be monitored closely. Ototoxicity results from damage to the vestibular and cochlear portions of the eighth cranial nerve. **Auditory symptoms include tinnitus, roaring, ringing, or "buzzing" in the ears, and varying degrees of hearing impairment**. Loss of high-frequency perception is only detectable by audiometric testing and usually occurs before clinical hearing loss. **Vestibular symptoms include nausea, vomiting, dizziness, vertigo, nystagmus, oscillopsia, and ataxia. A feeling of fullness in the ears and tinnitus are early signs of ototoxicity. Symptoms are exacerbated in the dark.** Hearing loss may be irreversible, but patients usually retain normal conversational hearing. Other ototoxic drugs (e.g., furosemide) should be avoided if possible.

## Calculate Parameters:

1) Calculate k:

$$k = \frac{Ln\,(C1_{random}/C2_{random})}{T'}$$

$C1_{random}$ = 1st random ~4hrs after dose
$C2_{random}$ = 2nd random ~12hrs after dose
T' = time between $C1_{random}$ and $C2_{random}$

2) Calculate t½:

$$t_{1/2} = \frac{0.693}{k}$$

3) Calculate $C_{tr}$ at 24 hours:

$$C_{tr} = C2_{random} * e^{-kt'}$$

t' = time between $C2_{random}$ and $C_{tr}$
Goal for tobramycin/gentamicin <1 mg/L
Goal for amikacin <4 mg/L
(Ideally, $C_{tr}$ will be undetectable at 24 hours)

If 24hr $C_{tr} \leq$ goal, continue q24hr dosing
If 24hr $C_{tr}$ > goal, extend dosing interval to q36 or 48 hrs. If >48 hrs required, then switch to conventional dosing or use lower dose (3mg/kg tobramycin/gentamicin or 7.5mg/kg amikacin)

4) Calculate $C_{max}$ (back to end of infusion)

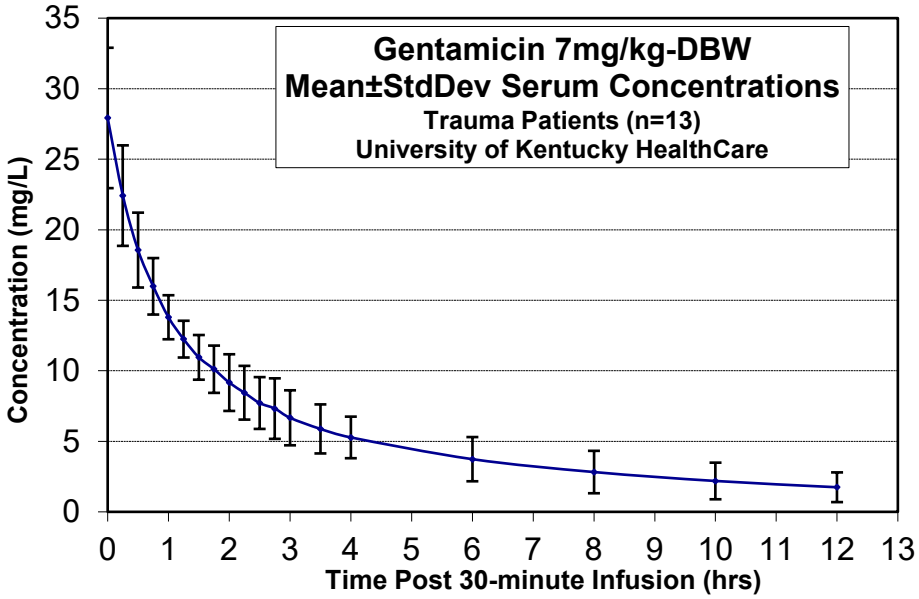
$$C_{max} = C1_{random}/e^{-kt'}$$

t' = time between $C1_{random}$ and $C_{max}$

5) Calculate Vd (include in documentation)

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})}$$

MD = maintenance dose
t = infusion time (usually 0.5 hrs)
Simplified equation that provides a reasonable estimate: $Vd = Dose/C_{max}$


Gentamicin 7mg/kg-DBW
Mean±StdDev Serum Concentrations
Trauma Patients (n=13)
University of Kentucky HealthCare
Concentration (mg/L)
Time Post 30-minute Infusion (hrs)
0
5
10
15
20
25
30
35
0 1 2 3 4 5 6 7 8 9 10 11 12 13

# AMINOGLYCOSIDES – CONVENTIONAL DOSING

- Utilized in adult patients with renal dysfunction who fail HDEI dosing or meet one of the HDEI exclusion criteria noted above
- Primarily used as double coverage or synergy with β-lactams for aerobic gram-negative infections (e.g. *Pseudomonas, Enterobacter, Proteus, E. coli, Serratia*)
- Can be used for synergy with some gram-positive infections (e.g. *Enterococcus, Staphylococcus*)
    - Typically utilize gentamicin 1mg/kg IV q8hrs
    - Exception: if utilized in combination with ceftriaxone or penicillin for streptococcal endocarditis, can use 3mg/kg IV daily. Pre-dose (trough) concentrations should be ≤1 mg/L and post-dose (peak, 30 min after injection) should be ~10-12 mg/L (*Eur Heart J* 2015;36:3036-7)

## Timing of Sampling and Frequency

- Relative to Dose
    - Trough (tr) within 30 min prior to dose
    - Peak (pk) at 30 min after end of 30 min infusion (IV); 1 hr after injection (IM)
    - At steady state (SS) (4 to 5 estimated half-lives; normal renal function: t½ = 2-3 hrs) usually around 3rd maintenance dose (or later) preferably during day

- Recommended Frequency of Sampling
    - Routine Use in "Uncomplicated" Patients
        - Initial pk and tr at SS
        - Scr and BUN at least 2x/week; monitor other signs of renal function
        - Repeat pk and tr q 1-2 wks, when duration of therapy > 2 wks
    - Routine Use in "Complicated" Patients (e.g., diminished or changing hydration status and/or renal function, concurrent ototoxic or nephrotoxic drugs)
        - Initial pk and tr at SS
        - Repeat pk and tr, at new SS, if initial values differ > 25% from predicted (i.e. suggestive of unusual kinetic parameters or deviation from sampling guidelines)
        - Scr and BUN daily
        - Repeat pk and tr weekly (or more frequently as dictated by clinical condition).

## Therapeutic Range (Conventional Dosing)

- Patients with normal renal function: Conventional dosing for gentamicin and tobramycin ~1-2 mg/kg /dose q8hrs and amikacin ~5mg/kg /dose q8hrs (DBW if obese, ABW if non-obese). NOTE: Elderly patients often require a q12hr or longer dosing interval.

| Concentration | Gentamicin/Tobramycin | Amikacin |
|---|---|---|
| Peak (mg/L) | 5 - 10 | 25 - 35 |
| Trough (mg/L) | 0.5 - 2<br>(prefer ≤ 1) | 4 - 10<br>(prefer ≤ 4) |

*Desired $C_{pk}$ and $C_{tr}$ concentrations for conventional aminoglycoside dosing should be d*etermined clinically by site/*severity of infection, causative organism, immunocompetence of patient, intent of therapy, etc. in addition to a pharmacokinetic assessment.*

| Types of Infections | Suggested Target Peak ($C_{max}$) Concentrations (mg/L) | |
|---|---|---|
| | **Gentamicin or Tobramycin** | **Amikacin** |
| Abdominal infections | 6-8 | 20-30 |
| Bacteremia | 6-8 | 20-30 |
| Endocarditis, Bacterial (prevention & treatment)<br>gram positive (*synergy: 1mg/kg/q8hrs)*<br>gram negative | <br>3-5<br>8-10 | <br>Not utilized<br>20-30 |
| Osteomyelitis | 8-10 | 20-30 |
| Eye infections | 6-8 | 25-30 |
| Meningitis | 8-10 | 25-35 |
| Neutropenic patients | 6-10 | 20-35 |
| Pneumonia | 8-10 | 25-35 |
| Skin and soft tissue infections | 6-8 | 20-30 |
| Urinary tract infections | 4-6 | 15-20 |

## Initial Dosing

1. Estimate K (elimination rate constant):

$$k = 0.00293 * Cl_{cr} + 0.014$$

2. Estimate Vd*:

$$Vd = 0.25\ L/kg, average$$
$$Vd = 0.20\ L/kg, if dehydrated$$
$$Vd = 0.30\ L/kg, with\ CHF, volume\ overload, ICU\ patients$$

***Use ABW unless patient is obese (>125% IBW or TBW/IBW > 1.25)**
**If obese use dosing body weight: DBW = IBW + 0.4 (TBW-IBW)**

3. Calculate dosing interval (τ) :

$$\tau = \frac{\ln(C_{max\ desired}/C_{tr\ desired})}{k} + t + T$$

t = infusion time (usually 0.5 hrs)
T= time between end of infusion & $C_{max\ desired}$ (e.g, 0.5hr)

4. Calculate dose:

$$Maintenance\ dose = Vd\ x\ (C_{max\ desired} - C_{tr\ desired})$$

5. Calculate loading dose (LD) if needed (i.e., critically ill)

$$LD = Vd * C_{max\ desired}$$

## Calculating Parameters for Dosage Adjustment:

*Using Sawchuk-Zaske Method*

**Assumptions:** Concentrations represent steady-state conditions; 1-compartment model; principle of superposition; linear elimination.

1. Verify administration and sampling times.

2. Calculate k:

$$k = \frac{Ln\ (C1/C2)}{T'}$$

**T' is determined by subtracting the time difference between C1 and C2 from the Tau. For example, if the time difference between C1 and C2 was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs.**

3. Calculate t½:

$$t_{1/2} = \frac{0.693}{k}$$

4. IF peak concentration is drawn late, calculate back to end of the infusion ($C_{max}$):

$$C_{max} = \frac{C1}{e^{-kt'}}$$

$C_{max}$= concentration at end of infusion
$C1$ = peak concentration drawn late
t'= time between late $C1$ and $C_{max}$

5. IF trough concentration is drawn early (e.g., >30min prior to dose), calculate if drawn at correct time:

$$C_{tr} = C2 * e^{-kt'}$$

$C_{tr}$ = trough concentration drawn at appropriate time
$C2$ = trough concentration drawn early
t'= time between early $C2$ and $C_{tr}$

6. Calculate Vd. If doses have reached **steady state** (e.g., previous doses on time, concentrations drawn appropriately), use

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})(1-e^{-k\tau})}$$

MD = maintenance dose (mg)
t = infusion time (e.g., 0.5hr)
τ = dosing interval

7. IF measured $C_{tr}$ is high, calculate time required to achieve desired $C_{tr}$. This will determine when the next dose should be administered:

$$t' = \frac{ln\ (C_{tr\ high}/C_{tr\ desired})}{k}$$

t' = time required from $C_{tr\ high}$ to $C_{tr\ desired}$

8. Calculate new dosing interval (τ) using your desired $C_{max}$ and $C_{tr}$:

$$\tau = \frac{\ln(C_{max\ desired}/C_{tr\ desired})}{k} + t + T$$

t = infusion time (usually 0.5 hrs)
T= time between end of infusion & $C_{max\ desired}$ (e.g, 0.5hr)
(τ typically equals ~ 3 x $t_{1/2}$)

9. Calculate new maintenance dose (MD):

$$MD = \frac{C_{max\ desired} V_d\ k\ (1-e^{-k\tau})t}{(1-e^{-kt})}$$

τ = dosing interval
t = infusion time (usually 0.5 hrs)
T= time between end of infusion & $C_{max\ desired}$ (e.g, 0.5hr)

10. Round dose to nearest 10mg or available stock bag dose (80,100,120mg) then recalculate the actual $C_{max}$ if you would like to double check the concentrations that are likely after rounding:

$$C_{max\ desired}\ X\ \frac{actual\ (rounded)\ dose}{calculated\ dose} = C_{max\ actual}$$

11. Estimate trough to be obtained with above MD and $\tau$:

$$C_{tr} = C_{max\ actual} e^{-kT'}$$

**T' is determined by subtracting the time difference between Cmax and Ctr from the Tau. For example, if the time difference between Cmax and Ctr was 1.5hrs and the Tau = q8hrs, then T' = (8 - 1.5) = 6.5hrs.**

# GUIDELINES FOR DOSING IN RENAL IMPAIRMENT

## Conventional Intermittent Hemodialysis (IHD)

Monitor based on duration of therapy

- Serum concentrations not necessary in patients on therapy <5 days
- Serum concentrations recommended in patients with culture positive infection or expected duration of therapy > 5 days.

Initial dosing

- Assume Vd – 0.3-0.35 L/kg
- Use ABW in non-obese and DBW in obese patients
- Synergy dosing with gentamicin
    - Loading dose 1.5-2 mg/kg
    - Maintenance dose 1mg/kg after each IHD
- Moderate to severe infections (aggressive management)
    - Loading dose 2-3 mg/kg (7.5-10 mg/kg for amikacin)
    - Maintenance dose 1-2 mg/kg (5-7.5 mg/kg for amikacin) after each IHD

Effect of hemodialysis

- Removes approximately 30-50% with typical HD session (e.g., 3-4 hours)
- Levels taken 1 hour post dialysis are true troughs; levels taken prior to dialysis can be used during the 30-50% removal assumption.

Concentrations

- Single drug level approach (synergy dosing)
    - Pre-dialysis (random) concentration
    - Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal during a 4 hour dialysis session
    - Target of trough < 1 mg/L (< 4 mg/L for amikacin) to conserve remaining kidney function and minimize risk for ototoxicity.
- Multiple drug level approach (aggressive management)
    - Peak concentration drawn 2 hours after dose
    - Pre-dialysis (random) concentration

Maintenance dosing (multiple drug levels)

- Calculate $K_e$off IHD
    - $K_e$off IHD = (Ln Cp1/Cp2)/t
        - Cp1 = Peak concentration; Cp2 = Pre-dialysis (random)
        - t = time between Cp1 and Cp2
- Calculate half-life off IHD
    - $t_{1/2} = 0.693/k_e$off IHD
    - Extrapolate actual peak concentration
    - Extrapolate post-dialysis concentration (trough) by assuming 50% drug removal during dialysis
- Determine Vd (use either first dose or steady-state Vd equations as appropriate)
- Calculate maintenance dose using desired peak concentration ($C_{max}$)
    - Dose = $(C_{max(des)} – C_{tr})$ x Vd
    - Typical dosing above

## Continuous Renal Replacement Therapy (CRRT)

Dosing Recommendations for Critically Ill Adults Receiving CRRT

| | *Loading Dose* | *CVVH[a] [b] low flow 1-2L/hr* | *CRRT[a] [b] high flow rates >2L/hr* | *CVVHD[a] [b]* | *CVVHDF[a] [b]* |
|---|---|---|---|---|---|
| ***Amikacin*** | *25mg/kg* | *10 -15 mg/kg q24–48h* | *10-20 mg/kg q24-48h* | *10 -15 mg/kg q24–48h* | *10 -15 mg/kg q24–48h* |
| ***Tobramycin*** | *5-7 mg/kg* | *GNR infection: 2-3 mg/kg q24–48h*<br>*higher starting doses may be warranted for high-flow rates >2L/hr* | | | |
| ***Gentamicin***<br>***Gram-Positive*** | *2-3mg/kg* | *1mg/kg q24h-36h* | | | |
| ***Gram-Negative*** | *5-7mg/kg* | *2-3 mg/kg q24-48h*<br>*higher starting doses may be warranted for high-flow rates >2L/hr* | | | |

[a] CVVH: continuous venovenous hemofiltration, CRRT: continuous renal replacement therapy, CVVHD: continuous venovenous hemodialysis, CVVHDF: continuous venovenous hemodiafiltration

[b] Dialysis information is found under "orders→dialysis→ Right click on the dialysis order to "View→ all orders in this set" CRRT setting, and UF, replacement or dialysate rates will be listed

Guidelines for Monitoring

- Typical dosing interval during CRRT is q24-48h
- Target concentrations
  - Conventional synergy dosing yields target peaks of 3-4 mg/L
  - For HDEI dosing in gram-negative infections, redose when tobramycin/gentamicin $C_{tr}$ <1 mg/L or amikacin $C_{tr}$ <4 mg/L (ideally undetectable)
- **Follow any changes in flow rate as this could significantly impact clearance**

Concentrations

- Two random serum concentrations will be obtained 4 and 12 hours after completion of the 1st dose.
- Determine appropriate maintenance dose based upon calculated PK parameters (**ensure CRRT uninterrupted between concentrations**)

Factors that may lead to changes in amount of drug removed

- Changes in ultrafiltration rate
- Dialysis interrupted (i.e. filter clotted, particularly overnight)
- Alterations in existing renal function (ARF vs CRF)

## Acute Kidney Injury or Unstable Renal Function

- Two concentrations must be drawn ≥ 1 half-life apart so current renal function must be considered to determine when to order levels.
  - This may require the standard 12-hour level to be delayed to 18 hrs, 24 hrs, etc.
  - Consider passing off ordering of the second level to the primary pharmacist if CRRT is likely or it is unclear when it should be drawn.
- Of course, if renal function is actively changing, the utility of the calculated PK parameters are limited.

# PEDIATRIC (NON-CF) AMINOGLYCOSIDE GUIDELINES

| **Pediatric HDEI Dosing (gentamicin, tobramycin)**<br>Assume Vd = 0.3 - 0.35 L/kg<br>*Dosing based on dosing body weight* | |
|---|---|
| **Age** | **Dosage** |
| ≥3 months* to <2 years | 9.5 mg/kg/dose IV q24 |
| 2 to <8 years | 8.5 mg/kg/dose IV q24h |
| ≥8 years | 7.5 mg/kg/dose IV q24h |
| *Amikacin (general dosing): 20 to 30 mg/kg/dose IV q24h* | |

*Children aged ≥3 months corrected according to gestational age (i.e. PMA ≥52 weeks)

## Rationale for HDEI Dosing in Pediatric (Non-CF) Patients:

High dose extended interval (HDEI) dosing (e.g., "once daily") is the preferred method by which to dose aminoglycosides in pediatric patients. HDEI dosing optimizes the concentration-dependent killing of aminoglycosides while simultaneously reducing the associated risk of nephrotoxicity. One meta-analysis of 24 randomized control trials in pediatric patients demonstrated a significant reduction in clinical or microbiological failures with HDEI dosing, when compared to conventional dosing of amikacin.

**Time Undetectable:** There is no clinical data to support the historic concern that a prolonged duration of undetectable aminoglycoside concentration, even when exceeding the anticipated post-antibiotic effect, may compromise efficacy.

**Inclusion Criteria:** All pediatric patients ordered aminoglycosides for prophylaxis, empiric therapy, or documented infection. Aminoglycosides are usually indicated as synergistic or adjunctive therapy with other antibiotics as double coverage for gram-negative infections.

**Exclusion Criteria:**
1. Patients with ascites
2. Patients with burns on >20% of total body surface area
3. Pregnant patients
4. Patients with unstable renal function
5. Patients with CrCl <60 mL/min or receiving renal replacement therapy
6. Patients with Gram positive bacterial endocarditis
7. Patients with cystic fibrosis (CF) – please refer to specific guidelines for CF patients
8. Patients who received a one-time dose of aminoglycoside for open fracture prophylaxis (Please see Open Fracture Prophylaxis Guidelines)

## Therapeutic Drug Monitoring Goals for HDEI Dosing:

| Monitoring Parameter | Gentamicin/Tobramycin | Amikacin |
|---|---|---|
| Peak (mg/L) | > 12 mg/L (ideal is 20 to 30 mg/L) | 20-40 mg/L |
| Trough (mg/L) | ≤ 0.3 mg/L | ≤ 4 mg/L |
| AUC (mg*hr/L) | ≥80-125 mg*hr/L | N/A |

Approved by the AST committee and P&T June 2022

## Monitoring:

**Initial Dose**: two concentrations (ordered as "random" concentrations) will be obtained:

1. ***1st* concentration** will be drawn ***~2 hours*** after completion of the ***1st dose***.

2. ***2nd* concentration** will be drawn ***~8 hours*** after completion of the ***1st* dose**.
   **NOTE:** The concentration at 8 hours post-infusion will vary based on renal function.

- Patients with normal renal function will usually have a "drug-free" period with an undetectable trough concentration ≤ 0.3 mg/L of gentamicin/tobramycin.
- For patients with trough concentration > 0.3 mg/L, renal function should be monitored closely and risks of nephrotoxicity and ototoxicity evaluated carefully.
- If the serum concentration after a HDEI dose requires > 48 hours to decline to <1mg/L, then conventional dosing may be warranted.
- Avoid tobramycin and gentamicin $C_{max}$ concentrations exceeding 40 mg/L

**Subsequent Doses:** The goal of the monitoring concentrations after the 1st dose is to verify that the drug is eliminated appropriately before the 2nd dose and to establish the dosing interval. Dosing intervals should be adjusted to achieve troughs **≤ 0.3 mg/L for gentamicin/tobramycin and ≤ 4mg/L for amikacin (ideally undetectable though).**

- Appropriate dosing intervals include every 24, 36, or 48 hours
- Scr/BUN should be measured at baseline and every 24 hours if aminoglycoside continued beyond 48 hours per NINJA criteria.

## Calculate Parameters:

1) Calculate k:

$$k = \frac{Ln\,(C1_{random}/C2_{random})}{T'}$$

$C1_{random}$ = 1st random ~2hrs after dose
$C2_{random}$ = 2nd random ~8hrs after dose
T' = time between $C1_{random}$ and $C2_{random}$

2) Calculate t½:

$$t_{1/2} = \frac{0.693}{k}$$

3) Calculate $C_{tr}$ at 24 hours:

$$C_{tr} = C2_{random} * e^{-kt'}$$

t' = time between $C2_{random}$ and $C_{tr}$
Goal for tobramycin/gentamicin <0.3 mg/L
Goal for amikacin <4 mg/L
(Ideally, $C_{tr}$ will be undetectable at 24 hours)

If 24hr $C_{tr}$ ≤ goal, continue q24hr dosing
If 24hr $C_{tr}$ > goal, extend dosing interval to q36 or 48 hrs. If >48 hrs required, then switch to conventional dosing or use lower dose.

4) Calculate $C_{max}$ (back to end of infusion)

$$C_{max} = C1_{random}/e^{-kt'}$$

t' = time between $C1_{random}$ and $C_{max}$

5) Calculate Volume of Distribution (Vd):

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})}$$

MD = maintenance dose
t = infusion time (e.g., 0.5hr)
τ = dosing interval

6) Calculate AUC

$$AUC = \frac{TDD}{k*Vd}$$

TDD = total daily dose

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**Follow-up monitoring if HDEI therapy is continued for > 7 days:**

- A trough concentration should be obtained weekly to check for drug accumulation and assess risk of nephrotoxicity
- Consider targeting a peak of 8 to 10 times the MIC to achieve optimal bactericidal activity.
- Dosing should be based clinically by site/severity of infection, causative organism (especially MDR gram-negative infections), immunocompetence, etc.
- Scr/BUN should also be monitored every 24 hours per NINJA criteria to assess for any changes in renal function and risk of nephrotoxicity. Concomitant nephrotoxic drugs should be avoided.
- Ototoxicity should be monitored closely and routine audiology exams should be performed in patients with repeated aminoglycoside exposure. Although previously thought to be related to peak concentrations, recent animal models suggest that aminoglycoside-induced ototoxicity is related to AUC (total cumulative exposure). Ototoxicity results from damage to the vestibular and cochlear portions of the eighth cranial nerve. **Auditory symptoms include tinnitus, roaring, ringing, or "buzzing" in the ears, and varying degrees of hearing impairment**. **Vestibular symptoms include nausea, vomiting, dizziness, vertigo, nystagmus, oscillopsia, and ataxia. A feeling of fullness in the ears and tinnitus are early signs of ototoxicity.** Hearing loss may be irreversible, but patients usually retain normal conversational hearing. Other ototoxic drugs (e.g., furosemide) should be avoided if possible.

## Dosing and Monitoring in Bacterial Endocarditis:

- Viridans group *Streptococcus* or *Streptococcus gallolyticus (bovis)*
  - Once daily gentamicin 3 mg/kg/dose IV q24h
  - *No established goal peak concentration; ensure trough concentration remains <0.3 ug/mL*
- *Staphylococcus sp.* (prosthetic valve only) or *Enterococcus sp.*
  - Gentamicin 1 mg/kg/dose IV q8h
  - *Dose should be adjusted to achieve peak of 3-4 ug/mL and trough <1 ug/mL*

## Indications for Conventional Dosing in Pediatrics:

- Conventional dosing may be considered in patients with renal dysfunction who fail HDEI dosing or meet one of the HDEI exclusion criteria noted above.

| **Pediatric conventional dosing guidelines (gentamicin, tobramycin)**<br>Assume Vd = 0.3 - 0.35 L/kg | |
|---|---|
| **Age** | **Dosage** |
| Infants: ≥1 month <10 years | 2.5 mg/kg/dose IV q8h |
| Children: ≥10 –14 years | 1.7 to 2.5 mg/kg/dose IV q8h |
| Children: >14 years - adult | 1 to 2 mg/kg/dose IV q8h |
| *Amikacin (general dosing) : 5 to 10 mg/kg/dose IV q8h* | |

For pharmacokinetic assessment of conventional dosing, see Sawchuk-Zaske method above (page #113)

# NEONATAL GUIDELINES

| **Neonatal dosing guidelines (gentamicin, tobramycin)**<br>Assume Vd = 0.5 - 0.6 L/kg | |
|---|---|
| **Gestational Age** | **Dosage** |
| ≤ 29 weeks | ≤ 7 postnatal days: 5 mg/kg IV q48h<br>8 to 28 days: 4 mg/kg IV q36h<br>>28 postnatal days: 4 mg/kg IV q24h |
| 30 – 34 weeks | ≤ 7 postnatal days: 4.5 mg/kg IV q36h<br>> 7 postnatal days: 4 mg/kg IV q24h |
| ≥35 weeks | 4 mg/kg IV q24h |
| HIE<br>(Hypoxic Ischemic Encephalopathy) | 4 mg/kg IV q36h |

**Comments:**

- Don't confuse "once daily" dosing with every 24-hour dosing interval in neonates.
- Neonates require a longer dosing interval (decreased clearance) and larger mg/kg dose (increased volume).
- Concentrations (peak and trough) may not be warranted in all neonatal patients.
- If extended therapy is indicated (e.g., positive blood culture), concentrations (peak and trough) should be obtained with the 3rd dose.
- If urine output decreases < 1ml/kg/hr for at least 8 hours, concentrations are warranted.
- Goal concentrations usually: peak = 5 to 10 mg/L (indication: sepsis); trough < 1.5 mg/L.
- Dose may be infused as an IV push over 2 minutes (always check administration technique as possible source of error).

# HDEI DOSING FOR CYSTIC FIBROSIS PATIENTS (tobramycin):

**Inclusion Criteria:** Patients ≤35 years with an estimated $Cl_{cr}$ > 60 mL/min

## Exclusion Criteria:

1) Adult patients > 35 years of age with history of repeated aminoglycoside exposure (increased risk of nephrotoxicity)
2) Underlying renal dysfunction at presentation (important to obtain baseline SCr)
3) Patients that have received a lung transplant

| **Adult and pediatric cystic fibrosis (CF) patients dosing guidelines (tobramycin)**<br>Vd = 0.4 – 0.45 L/kg | |
|---|---|
| ***Age*** | ***Dosage*** |
| 1 month to 1 year | 2.5 to 3.3 mg/kg/dose IV q8h |
| ≥ 1 year to 12 years | 12 to 14 mg/kg/dose IV q24h |
| ≥ 12 years to adult | 10 to 12 mg/kg/dose IV q24h |
| *Amikacin: 30 to 35 mg/kg IV q24h* | |

**Comments (CF):**

- May consider more frequent dosing interval (i.e., q12hr, q18hr) based on the following considerations: half-life < 2 hours, time undetectable > 8 hours, or poor clinical response
- Q24hr is preferred in patients on concomitant nephrotoxins (e.g., vancomycin) or recent aminoglycoside exposure
- Larger Vd (0.4 to 0.45 L/kg) due to decreased body fat and increased clearance due to increased GFR
- For CF patients, levels are obtained after the 3rd day of therapy rather than after the 3rd dose, this allows for rehydration
- Concentrations should be obtained 2 and 8 hours post dose
- Usually require higher doses of tobramycin to achieve desired concentrations:
  - Peak ≥ 12 mg/L (ideal is 20 to 30 mg/L) or 8 to 10 x MIC
  - Trough <0.5 mg/L
  - AUC ≥ 80-125 mg*hr/L
- Monitor Scr, BUN, and UOP every 48h is encouraged while on aminoglycoside therapy; monitoring SCr/BUN should at a minimum be twice weekly for all patients
- Must be very cautious of nephrotoxicity and ototoxicity because of long-term and recurrent use
- Repeat concentrations are usually not obtained unless significant changes in dose are warranted (e.g., > 20%), available concentrations are not reliable (e.g., calculated Vd > 0.6 L/kg), changes in renal function or therapy is continued beyond 14 days
- Daily 10 mL/kg NS (rounded to nearest bag size) boluses are provided to pediatric patients on tobramycin or amikacin therapy for renal protection; assess fluid status and encourage increased oral intake and/or IV fluids since most patients are dehydrated on admission
- Patients with CF admitted for HDEI aminoglycoside therapy should have audiograms performed regularly
- Reference page #124 for recommendations on calculating patient specific PK parameters in CF patient

## Initial Dose:

- Dosing based on table above
- Alternative Dosing to Consider (based on exclusion criteria above):
  - > 35 years of age or underlying renal dysfunction on admit: 10 mg/kg tobramycin

        - Consider concentrations after **1st** dose to guide regimen
    - Lung Transplant Recipients: 7 mg/kg tobramycin, 15-20 mg/kg amikacin
        - Obtain concentrations after 1st dose to guide regimen at 4 and 12 hrs after dose

**Monitoring:** Two concentrations (ordered as "random" conc.) following the **3rd** day of therapy:

- 1st concentration will be collected **4 hours** after the dose is initiated in adult patients
    - Obtain 1st concentration **2 hours** after the dose is initiated in pediatric patients
- 2nd concentration will be collected **10 hours** after the dose is initiated in adult patients
    - Obtain 2nd concentration **8 hours** after the dose is initiated in pediatric patients
- Follow-up monitoring:
    - Draw tr concentration once weekly, goal $C_{tr} \leq$ 0.5 mg/L for tobramycin ($C_{tr} \leq$ 4 mg/L for amikacin). More frequent if concomitant nephrotoxic medications.
    - Repeat two-level pharmacokinetic assessment should be obtained following a dose adjustment of >20%, or following adjustment of the dosing interval secondary to changes in renal function

## Therapeutic Range:

- Tobramycin:
    - Peak >12 mg/L (ideal is 20 to 30 mg/L) or ≥ 8 to 10 x MIC (e.g., if MIC 2 mg/L would target peak of 16-20 mg/L)
    - Trough ≤ 0.5 mg/L
        - If 10 hour concentration is ≤ 1 mg/L, consider increasing dose to 15 mg/kg/day or shorten dosing interval (i.e. 7-8 mg/kg IV q12hrs)
        - If estimated trough level prior to next dose is >0.5 mg/L, calculate new dose to achieve trough ≤ 0.5 mg/L
        - Repeat trough concentrations indicated if changes are made to the dose based on initial levels, creatinine/urine output changes, concomitant nephrotoxic medications are present, or if therapy is continued an additional 7 days.
    - AUC ≥80 mg*hr/L
        - Previous studies in adult CF patients have demonstrated the benefit of utilizing AUC to monitor total drug exposure to IV aminoglycosides, as AUC reflects both drug concentration and clearance, allowing for individualized dosing.
        - Utilization of AUC, in combination with peak, may result in enhanced efficacy while mitigating risk of nephrotoxicity.
- Amikacin:
    - Peak > 30 mg/L (or ≥ 8 x MIC)
        - For *Pseudomonas aeruginosa* target a peak of 80 to 120 mg/L
    - Trough ≤ 4 mg/L
- Vd: 0.4 to 0.45 L/kg: Important to calculate Vd, if estimated Vd > 0.6 L/kg, consider repeating two-level pharmacokinetics before making a dose adjustment
- Time Undetectable: 4 to 8 hours
    - Although not correlated with efficacy, it has been suggested that patients with CF likely have a shortened post-antibiotic effect, warranting consideration of maintaining time undetectable between 4-8 hours.
    - Clinical judgement, in combination with consideration of renal function, prior aminoglycoside exposure, and patient's clinical status should be utilized to guide dose adjustment based on time undetectable,

## Calculating Parameters:

*Equations are for both adult and pediatric patients with cystic fibrosis*

1. Calculate k:

$$k = \frac{Ln\ (C1_{random}/C2_{random})}{T'}$$

$C1_{random}$ = 1st random ~4hrs after dose (adults); ~2hrs after dose (pediatrics)
$C2_{random}$ = 2nd random ~10hrs after dose; ~8hrs after dose (pediatrics)
T' = time between $C1_{random}$ and $C2_{random}$

2. Calculate t½:

$$t_{1/2} = \frac{0.693}{k}$$

3. Calculate $C_{tr}$ at 24 hours (or 12 hours, depending on dosing interval):

$$C_{tr} = C2_{random} * e^{-kt'}$$

t' = time between $C2_{random}$ and $C_{tr}$
Goal for tobramycin ≤0.5 mg/L
Goal for amikacin ≤4 mg/L

If 24hr $C_{tr} \leq$ goal continue q24hr dosing
If 24hr $C_{tr}$ > extend dosing interval to q36 or 48 hrs. If >48 hrs required, then switch to conventional dosing or use lower dose (3mg/kg tobramycin or 7.5mg/kg amikacin)

4. Calculate $C_{max}$ (back to end of infusion):

$$C_{max} = C1_{random}/e^{-kt'}$$

t' = time between $C1_{random}$ and $C_{max}$

5. Calculate Vd:

$$Vd = \frac{\frac{MD}{t}(1-e^{-kt})}{k(C_{max})(1-e^{-k\tau})}$$

MD = maintenance dose
t = infusion time (e.g., 0.5hr)
τ = dosing interval

6. Assess $AUC_{24}$ for goal of ≥ 80 mg*hr/L for tobramycin

$$AUC = \frac{TDD}{k * Vd}$$

TDD = total daily dose

7. Calculate time undetectable for a q24hr regimen to help determine if post antibiotic effect is maintained:

$$t(hr) = \frac{\ln(0.5/C2_{random})}{-k}$$

$C2_{random}$ time = 10 hours post dose initiation if drawn appropriately

$$time\ undetectable = 24 - (t + C2_{random}\ time)$$

Goal: <8 hrs with concentration <0.5 mg/L. If time undetectable >8 hours consider increasing dose to 15 mg/kg/day or shorten dosing interval (i.e. 7-8 mg/kg IV q12hrs)*.
*Clinical judgement, in combination with consideration of renal function, prior aminoglycoside exposure, and patient's clinical status should guide dose adjustment based on time undetectable

Approved by the AST committee and P&T June 2022

- If a dose adjustment is warranted, use the following equations to calculate a new maintenance dose and anticipated peak, trough, and AUC.

  1. Calculate new dosing interval ($\tau$) using your desired $C_{max}$ and $C_{tr}$:

$$\tau = \frac{\ln(C_{max\ desired}/C_{tr\ desired})}{k} + t + T$$

t = infusion time (usually 0.5 hrs)
T= time between end of infusion & $C_{max\ desired}$ (e.g, 0.5hr)
Consider a desired Cmax 15 to 25 mg/L and Ctr 0.5 mg/L for tobramycin

  2. Calculate new maintenance dose (MD):

$$MD = \frac{C_{max\,desired} V_d\ k\ (1-e^{-k\tau})t}{(1-e^{-kt})}$$

$\tau$ = dosing interval
t = infusion time (usually 0.5 hrs)

  3. Calculate the expected $C_{max}$ and $C_{tr}$ of the new MD

$$C_{max,predicted} = \frac{MD*(1-e^{-kt})}{k*Vd*t\ (1-e^{-k\tau})}$$

$\tau$= dosing interval
t = Infusion time

$$C_{tr,predicted} = C_{pk,predicted}\ x\ e^{-k(\tau-t)}$$

  4. Assess $AUC_{24}$ for goal of ≥ 80 mg*hr/L for tobramycin

$$AUC = \frac{TDD}{k*Vd}$$

TDD = total daily dose

# AMINOGLYCOSIDE DOSING DURING PREGNACY AND INTRAPARTUM

**Indications:**

- Rescue cerclage placement
- Chorioamnionitis
- Postpartum endometritis
- Prophylaxis in cephalosporin allergic patients for Cesarean section

**Inclusion Criteria:**

- Age ≥ 18 years old, or if deemed medically appropriate in younger patients
- Normal renal function (serum creatinine < 1.4mg/dL)
    - Obtain baseline serum creatinine in patients with increased risk for renal insufficiency if possible (pre-eclampsia, diabetes, underlying renal disease)

## Rescue Cerclage and Chorioamnionitis:

- Obtain CURRENT pregnancy weight and gestation of pregnancy. Calculate adjusted body weight if needed (if actual weight is > 25% above ideal accounting for ideal weight gain in pregnancy).
    - Ideal weight gain for pregnancy

| Pre-pregnancy Weight Category | Body Mass Index | Recommended Range of Total Weight Gain (kg) | Recommended First Trimester Weight Gain | Recommended Rates of Weight Gain in the 2nd/3rd Trimesters (kg/wk) |
|---|---|---|---|---|
| Underweight | < 18.5 | 12.5 -18 | 1.5 - 2 | 0.5 |
| Normal Weight | 18.5-24.9 | 11.5 - 16 | 1 – 1.5 | 0.45 |
| Overweight | 25-29.9 | 7 – 11.5 | 1 | 0.3 |
| Obese (All Classes) | ≥ 30 | 5 – 9 | 0 - 1 | 0.2 |

* Modified from Institute of Medicine (US) Weight Gain During Pregnancy: reexamining the guideline 2009; and ACOG Committee Opinion Number 548: Weight Gain During Pregnancy January 2013

- Utilize low dose conventional dosing of gentamicin
    - Target dose of 1.5-2mg/kg q8hr (actual or dosing body weight as appropriate)
    - ACOG 2017 recommendations: 2mg/kg initial dose followed by 1.5mg/kg IV q8hr
    - Round doses to 80mg or 120 mg if possible for rapid access by nursing
- Therapy continues for 24-48hrs post cerclage or 24hrs post maternal fever
- Obtain concentrations for therapy continuing for longer than 48hrs
- Used in conjunction with ampicillin, with the addition of clindamycin if cesarean section or complicated cerclage

## Postpartum Endometritis

**Dosing:**

1. Identify patient weight:
    - Obtain a postpartum body weight (PPBW) per nursing, calculate a dosing body weight if weight is > 25% above ideal body weight
    - If patient cannot be weighed, a PPABW can be calculated by subtracting ~5 kg from actual body weight at time of delivery of a term gestation
        - Approximately 2 kg is attributed to placental weight and fluids, and 3 kg for neonate)
        - If needed, may adjust the calculation if neonatal weight significantly varies from 3 kg.
    - One week post-delivery weight loss is ~8 kg
    - May need to calculate dosing body weight (DBW) if antepartum weight was significantly higher than ideal for gestation.

2. Determine dose:
    - Gentamicin 2mg/kg IV q8hr conventional dosing OR Gentamicin Dose = 5 mg/kg (PPBW) IV q24hrs
    - Used in conjunction with ampicillin, with the addition of clindamycin if cesarean section

## Surgical prophylaxis in patients with severe beta lactam allergy undergoing cesarean section

### Dosing (ACOG 2018):

- Gentamicin 5mg/kg ABW x dose at time of procedure
    - Use dosing body weight if actual weight is > 25% above ideal body weight
- With clindamycin 900mg x 1 dose prior to surgery
    - May add azithromycin 500mg if previously in labor

### Monitoring:

- Gentamicin concentrations are NOT warranted unless the patient meets at least one of the following criteria:
    - Increased risk for renal insufficiency
    - Duration of gentamicin therapy is continued for > 48hours
    - Patient is not responding to antibiotic therapy or has persistent signs of infection
- If serum gentamicin concentrations are warranted
    - TWO GENTAMICIN CONCENTRATIONS should be obtained 4 AND 12 hours after the dose (order as “4 and 12 random gentamicin concentrations”)
    - A pharmacist will assess the concentrations and calculate the gentamicin trough (goal: <1mg/L) and recommend a new dosage if necessary.
- Additional monitoring:
    - If duration of aminoglycoside therapy continues > 3 days, suggest obtaining a BMP/RFP

If duration of aminoglycoside therapy continues > 7 days, suggest obtained a repeat gentamicin trough concentration to assess for accumulation

# DOCUMENTATION AND PRACTICE PROBLEMS

WRITE A CHART NOTE. Document pertinent clinical monitoring parameters, dose recommendations and estimated and/or calculated pharmacokinetic parameters in the medical record.

- Briefly describe the rationale of the drug and determine if warranted based on clinical and patient information.
- Document the current day of therapy and goal length of therapy (e.g., Day #2/14 vancomycin), and any concomitant antibiotics.
- Document the collect times of the reported concentrations and note if the samples were obtained appropriately. For example, if C1 was drawn late calculated the estimated $C_{max}$ if drawn correctly.
- Include the calculated PK parameters: K ($hr^{-1}$), t½ (hrs), Vd (L) and Vd (L/kg – DBW).
- Write a new dosage in mg and mg/kg-DBW/dose (e.g., vancomycin 1000 mg IV q12hrs, 15mg/kg/dose).
- When changing a dosage, include the start time of new dosing regimen with the order (*very helpful for the pharmacist entering the order and the nurse administering the drug*).
- Include a range for the predicted concentrations with the new dosage recommendation: (e.g., $C_{max}$ = 8-10mg/L; $C_{tr}$ <2mg/L, ~1mg/L).
- Include other pertinent information used to assess the patient: weight (ABW, IBW, DBW), height, Scr, Clcr, BUN, urine output, I/Os, cultures, Tmax, WBC, differential, allergies, and other nephrotoxic medications (e.g., furosemide, amphotericin, aminoglycosides).
- Refer to the sample note

**Pharmacy Therapeutic Drug Monitoring for AMG** **RE: Tobramycin Monitoring**

Height/Weight: Initial Weight: 90kg

HPI:
Patient is 50yo WM being treated with tobramycin 120mg IV q8hrs (1.45 mg/kg/dose) and piperacillin-tazobactam 4.5 gm IV q6hrs for nosocomial pneumonia based on positive sputum cultures for *Pseudomonas aeruginosa*. Current Tmax 102.5, WBC = 15K.

Drug levels/Labs-Comments:
Tobramycin concs drawn around 3rd dose on 9/2:
C2 = 2.2 mg/L at 07:30
Dose = 120 mg IV infused from 08:00 – 08:30
C1 = 7 mg/L at 09:00

Assessment of Concentrations: Previous doses administered on time & represent steady-state;
C1 & C2 drawn appropriately; Cmax is below recommended range for pneumonia (8-10mg/L) & Ctr above therapeutic range (<2mg/L). Renal function stable.

PK parameters: k = 0.18$hr^{-1}$; t½ = 3.9 hrs; Vd = 19.6L (0.24 L/kg)

Recommendations:
1. Suggest changing tobramycin to 160mg IV q12hrs (1.9 mg/kg/dose) to yield a Cmax ~8-10 mg/L & Ctr ~ 1mg/L; begin next dose at 20:00 today when conc. = 1mg/L; discussed with resident on primary team.
2. Not necessary to recheck Cmax & Ctr unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation.
3. Suggest checking Scr/BUN at least 2X/week to assess renal function.

XXXXXX, PharmD
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**Pharmacy Therapeutic Drug Monitoring for AMG Monitoring** **RE: Tobramycin**

Height/Weight: 177.8 cm, 58kg

HPI:
TY is a 21-year-old male (58 kg) with cystic fibrosis admitted for an acute pulmonary exacerbation. He was started on ceftazidime 8 grams as a continuous infusion and tobramycin 750 mg (12.9 mg/kg) IV every 24 hours. After the third day of therapy, 4 and 10-hour tobramycin levels were collected to assess efficacy and safety of the current regimen.

Drug levels/Labs-Comments:
Dose #3 was given on 3/7 at 1638 as a 30-minute infusion.
C1 = 9.8 mg/L, collected 3/7 at 2115
C2 = 1.4 mg/L, collected 3/8 at 0515

Assessment of concs: Previous doses administered on time & represent steady-state;

PK parameters: $k = 0.24 hr^{-1}$; $t_{½} = 2.9$ hrs; $C_{tr} = 0.09$ mg/L; $C_{max} = 25.9$ mg/L; Vd = 27.3 L (0.47 L/kg);
AUC = 114 mg.hr/L; time undetectable = 7.2 hrs

Recommendations:

1. Suggest continuing tobramycin 750 mg IV every 24 hours.
2. Not necessary to recheck Cmax & Ctr unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation.
3. Suggest checking Scr/BUN at least 2X/week to assess renal function.

XXXXXX, PharmD
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**Pharmacy Therapeutic Drug Monitoring for AMG Monitoring** **RE: Tobramycin**

Height/Weight: 90 cm; 19 kg

HPI:
DC is a 3yo, 19kg female admitted for febrile neutropenia. Service initiated Cefepime 1000mg IV q8h (rounded) and Tobramycin 160mg IV q24h.

Drug levels/Labs-Comments:
Dose #1 was given on 6/15 and was infused over 30 minutes (from 1745-1815)
C1 = 12 mg/L, collected on 6/15 at 2000
C2 = 2 mg/L, collected on 6/16 at 0152

PK parameters: $k = 0.305 hr^{-1}$; $t_{½} = 2.27$ hrs; $C_{tr} = 0.02$ mg/L; $C_{max} = 20.5$ mg/L; Vd = 7.25 L (0.38 L/kg);
AUC = 67 mg.hr/L

Recommendations:

1. Suggest increasing to tobramycin 190 mg IV every 24 hours to target AUC 80-120.
2. Not necessary to recheck Cmax & Ctr unless change in clinical status or renal function; if continue therapy > 7 days, would suggest recheck concentrations to assess for drug accumulation.
3. Suggest checking Scr/BUN daily if tobramycin continued beyond 48 hours.

XXXXXX, PharmD
Pager #

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