Adult Aminoglycoside guidelines for UWMC and HMC

1.Calculate desired dosing weight (DDW)

***Ideal body weight (IBW) (male) = 50 + [2.3 x Ht (inches>60)]; IBW (female) = 45.5 + [2.3 x Ht (inches>60)]**

- ☐ DDW = IBW, unless underweight, overweight/obese or have cystic fibrosis.
- ☐ Underweight [Total Body Weight (TBW) < IBW]: DDW = TBW
- ☐ Overweight/Obese or Pregnant (TBW > 20% of IBW): DDW = IBW + 0.4 (TBW-IBW) = adjusted body weight
- ☐ Cystic Fibrosis: DDW = TBW unless obese, then use adjusted body weight

2.Choose clinical indication and method Aminoglycosides not recommended if on concurrent neuromuscular blockers

- ☐ Gram-negative infections (i.e. sepsis, pneumonia, osteomyelitis, intra-abdominal infections):
  - **(a) Preferred option: High-dose Extended Interval Dosing (See #3)**
    - (i) Exclusion: Burns >20% of BSA, Cystic Fibrosis, Age <12, Ascites, Morbid Obesity (BMI >40)[1], CrCl <20ml/min, Hemodialysis
  - **(b) Alternative option: Traditional Pharmacokinetic Dosing (See #4)**
- ☐ Gram-positive infections (i.e. synergy for endocarditis): gentamicin only
  - **(c) Preferred option: Traditional Pharmacokinetic Dosing (See #4)**
  - **(d) Alternative option: Consolidated Interval Dosing (See #5)**
    - (i) Consider for streptococcal endocarditis (native or prosthetic) in patients with CrCl > 60 ml/min: 3mg/kg/daily
- ☐ Hemodialysis: (See #6)
- ☐ Cystic Fibrosis (See #7)
- ☐ Tuberculosis and non-tuberculosis

3.High dose extended interval dosing (Hartford Nomogram)

- ☐ Gentamicin or tobramycin: use 7mg/kg
  - Consider 5 mg/kg/day for UTI, > 65yo, pregnant women or single dose prophylaxis
- ☐ Amikacin: use 15mg/kg (For more resistant organisms, clinicians may opt for 20mg/kg)
- ☐ Select interval based on CrCl (ml/min) ≥ 60 = q24h 40-59 = q36h 20-39 = q48h <20 = Use traditional dosing
- ☐ Serum concentration monitoring (drawn 6-14hrs after start of infusion)
  - Draw single level after 1st or 2nd dose if expected duration >5 days. Do not draw peak and trough levels.
  - Once targeted level achieved, recheck levels weekly (6-14 hour level) unless changing renal function, then check level sooner.
- ☐ Alter dose interval (not the dose) to that indicated in nomogram zone.

Level must be drawn 6-14 hours after start of infusion to use nomogram

- ✓ Hartford nomogram only valid for 7mg/kg of gentamicin and tobramycin.
- ✓ For amikacin, divide measured level by 2, then plot this value on nomogram.
- ✓ For other dosing regimens, the resultant level should be multiplied by a factor equal to 7 mg/kg divided by the dose/kg (Example: If a patient is receiving 5 mg/kg/day and the 10h post-dose level was 2 mcg/mL, multiply the level by 1.4 (7/5) to get a level of 2.8 mcg/mL. This adjusted level is the one you would plot on the Hartford nomogram.
- ✓ If level falls ABOVE q48h line, order qday levels till trough <1 mcg/mL for gentamicin and tobramycin (< 5 mcg/mL for amikacin) and change to traditional dosing or other abx.
- ✓ If level UNDETECTABLE within 6-14hrs, calculate individualized PK parameters and change to traditional dosing or other abx.

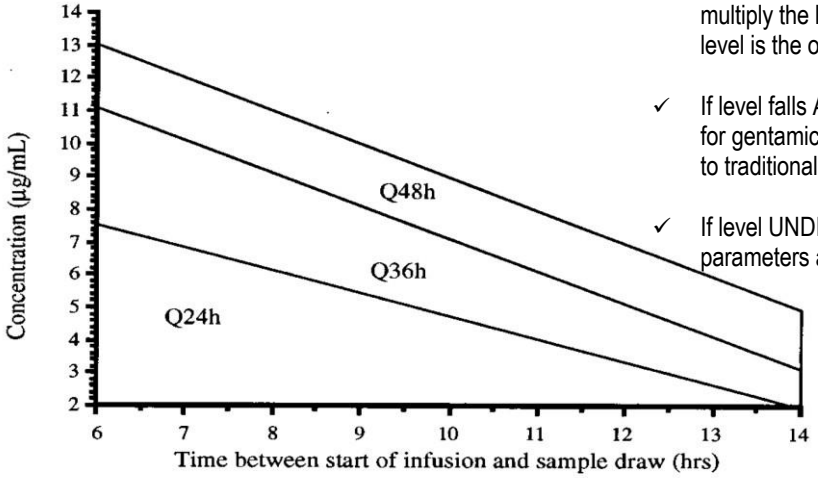

FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

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4.Traditional pharmacokinetic method

- **a.** Calculate dosing weight (see #1)
- **b.** Select dose from Table 1 or 2.
- **c.** Serum concentration monitoring.
  - Trough level: immediately prior to the 3rd dose.
  - Peak level: 30 min after the end of the infusion of the 3rd dose.
  - Once dose and renal function stable check peak and troughs at least weekly.

Table 1: Recommendations for Traditional Dosing gentamicin or tobramycin (Use DESIR ED DOSING WEIGHT)

CrCl	Conventional/Traditional dosing for GNR	Synergy for gram positive infections (gentamicin only)
>80 ml/min	1.7mg/kg IV q8H	1 mg/kg q8H
50-80 ml/min	1.7 mg/kg IV q12H	1 mg/kg IV q12H
20- 49 ml/min	1.7 mg/kg q24H	1 mg/kg IV q24H
< 20 ml/min (or rapidly changing renal function)	2mg/kg load, then dose by level	1 mg/kg load, then dose by level
Hemodialysis	2mg/kg load, then dose post HD, see #6	1mg/kg load, then dose post HD, see #6
CRRT	3 mg/kg load, then check level in 24 hours	1mg/kg load, then check level in 24 hours

Table 2: Recommendations for Traditional Dosing amikacin (Use DESIRED DOSING WEIGHT)

(Not applicable to nontuberculous mycobacteria infections see #8)

CrCl	Conventional/Traditional dosing for GNR	Synergy for gram positive infections
>80 ml/min	5mg/kg IV q8H	NA
50-80 ml/min	7.5 mg/kg IV q12H	NA
20-49 ml/min	7.5 mg/kg q24H	NA
< 20 (or rapid changing renal function)	7.5mg/kg load, then dose by level	NA
Hemodialysis	7.5 mg/kg load, then dose post HD, see #6	NA
CRRT	10 mg/kg load, then check level in 24 hours	NA

Table 3: Target peak/trough serum concentrations

	Gentamicin or tobramycin			Amikacin
Dose	**1mg/kg q8-24h**	**3mg/kg daily**	**1.7 mg/kg q8-24h**	**5-7.5 mg/kg q8-24h**
Target Peak* (mcg/ml)	3-5	Not necessary	5-10	20-35
Target Trough (mcg/ml)	<1	<1	<1	< 5

***Target a peak concentration of 8-10mcg/ml or 30-35mcg/ml for gentamcin/tobramycin or amikacin respectively for pneumonia or multidrug resistant infections.**

5.For patients with streptococcal endocarditis (native or prosthetic) with CrCl > 60 ml/min: 3mg/kg/daily.

- **a.** Give gentamicin 3mg/kg IV q24h
- **b.** Serum concentration monitoring:
  - Trough level should be drawn 30 minutes before dose. Targeted trough concentration should be undetectable. Draw single level after 1st or 2nd dose if expected duration >5 days, and weekly afterwards.
  - Peak levels are not recommended
  - If Scr increases, consider changing to traditional dosing or discontinuing the drug

6.Dialysis

Intermittent Dialysis

- **a.** Loading dose as above, Table 1 or Table 2.
- **b.** Maintenance dose:
  - Gentamicin or tobramycin: Redose at 1-1.5mg/kg AFTER HD (ONLY ON HD days) if POST-HD level <1 mcg/ ml
  - Amikacin: Redose at 3-5mg/kg AFTER HD if POST-HD serum concentration <5 mcg/mL
- **c.** Serum concentration monitoring:
  - POST-HD level: obtain post-HD levels at least 2hrs AFTER HD to allow for re-distribution
  - PRE-HD level: use PRE-HD level to estimate POST-HD level for subsequent dosing recommendation. Assume 50% of drug removed by 4 hour HD session. Example: PRE-HD level of 3.2 mcg/mL infers a POST-HD level of 1.6 mcg/mL

CVVH (continuous veno-venous hemofiltration commonly used at HMC)

- **a.** Loading dose as above, Table 1 or Table 2
  - CVVH recommendations assume ultrafiltration and dialysis flow rates of 1-2 L/hr and minimal residual renal function. Dosing

frequency will depend on ultrafiltration and dialysis flow rates, and subsequent vancomycin levels.

b. Maintenance dose
- Maintenance dose ranges from 1-2 mg/kg based on DDW if level <1 mcg/ml.
- Trough level can be drawn prior to the 2nd dose to assess drug clearance; important for unfamiliar or unknown CRRT settings.

SLED (Sustained low-efficiency dialysis, commonly used at UWMC)

a. Loading dose as above, Table 1 or Table 2.
- The duration of SLED can vary from 4 to 24 hours per day and thus can significantly alter drug clearance day to day. Patients may receive SLED sporadically; they may receive it on one day but not the next based upon need. See nephrology notes/discuss with primary team for planned duration of SLED for a given day.
- Anticipate a SLED run of about 8 hours to remove similar amounts of aminoglycoside as intermittent hemodialysis. Expect longer sessions to remove more drug, shorter to remove less drug.

b. Maintenance dose
- Maintenance dose ranges from 1-2 mg/kg based on DDW if level <1 mcg/ml.
- Serum aminoglycoside levels should be obtained at least 2 hours after the end of the dialysis session to allow for drug redistribution. For longer SLED runs (18-24 hours) it may be appropriate to check levels every 12-24 hours even if this is during the SLED session.
- Trough level can be drawn prior to the 2nd dose to assess drug clearance; important for unfamiliar or unknown CRRT settings.

7. Dosing for cystic fibrosis patients – see CF dosing appendix for specific guidelines

8. Tuberculosis or Non-tuberculosis mycobacteria dosing

a. See American Thoracic Society guidelines for appropriate dosing guidelines for amikacin and streptomycin.
b. Non-mycobacterial tuberculosis: Am J Respir Crit Care Med Vol 175. pp 367–416, 2007
c. Tuberculosis guidelines: MMWR 2003: 52: RR-11
d. Consult Stewardship

9. Toxicity and Monitoring (all patients)

a. **Nephrotoxicity**
i. Recommend SCr twice weekly and serum levels weekly (more often if unstable or changing renal function).
ii. Consider discontinuing aminoglycoside if baseline SCr rises by > 20%. Nephrotoxicity is mostly reversible if caught early.
iii. High dose extended interval dosing preferred due to potentially less nephrotoxicity

b. **Ototoxicity**
i. Recommend baseline a
ii. udiogram and weekly for anticipated duration >14 days.
iii. Damage usually permanent! Strong consideration to discontinue aminoglycoside if observed or suspected.
iv. Symptoms: Vestibular damage (loss of balance, vertigo, ataxia, nausea, vomiting). Assess daily when duration > 7 days. Cochlear damage results in high frequency hearing loss (requires audiometry to detect), or tinnitus.

10. If patients are discharged on an aminoglycoside, follow-up must be arranged to the Infectious Diseases clinic. Pharmacy is not responsible for managing outpatient therapy.

a. **Twice weekly Chem-7 must be ordered along with weekly serum concentrations.**
b. **All labs must be faxed to the ID clinic and pre-arranged with ID clinic staff.**

Footnotes:

1.NIH definition for obesity. Accessed at: http://www.nhlbi.nih.gov/health/health-topics/topics/obe/diagnosis, March 18th, 2015
Comments from stewardship: The once daily dosing will achieve the correct Cmax/MIC ratio in obese patients, but the changing Vd and increased clearance in obesity may not optimize post-antibiotic effect. In other words, the levels will be below MIC longer than in non-obese pts. Therefore, we prefer traditional dosing in morbid obese patients when feasible.

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Pharmacokinetic Formulas

1. Elimination Rate Constant:

$$ke = \ln \frac{peak}{trough} \quad \Delta t = t_{tr} - t_{pk}$$
$$\Delta t$$

2. Half-life:

$$t_{1/2} = \frac{\ln 2}{ke}$$

3. Cmax (AKA "true peak"):

$$Cmax = \frac{Peak}{e^{-(ke * tpk)}}$$

4. Cmin (AKA "true trough"):

$$Cmin = (Trough) * (e^{-(ke * ttr)})$$

5. Volume of Distribution:

$$Vd = \frac{Dose}{ke * t_{inf}} * \frac{1-e^{-(ke * tinf)}}{Cmax-(Cmin * e^{-(ke * tinf)})}$$

6. Clearance:

$$Cl = (ke) * (Vd)$$

7. Desired Dosing Interval:

$$T = \ln \frac{Cmax}{Cmin} + t_{inf}$$
$$ke$$

8. Desired Maintenance Dose:

$$MD = (Cl)\ (t_{inf})\ (\text{desired Cmax}) * \frac{1-e^{-(ke * T)}}{1-e^{-(ke * tinf)}}$$

9. Predicted Cmax:

$$\text{Pred. Cmax} = \frac{MD}{Cl * t_{inf}} * \frac{1-e^{-(ke * tinf)}}{1-e^{-(ke * T)}}$$

10. Predicted Cmin:

$$\text{Pred. Cmin} = (\text{Pred. Cmax}) * (e^{-(ke * \Delta t)})$$
$$\Delta t = T - t_{inf}$$

Pred. Conc. at 1 hr (for CF patients):
$\text{Pred. C1hr} = (\text{Pred. Cmax}) * (e^{-(ke * 0.5)})$

11. Reported Peak (by lab):

$$\text{Reported pk} = (Cmax) * (e^{-(ke * tpk)})$$

12. Reported Trough (by lab):

$$\text{Reported tr} = (\text{Reported pk}) * (e^{-(ke * \Delta t)})$$
$$\Delta t = T - t_{inf}$$

Definitions:
T = dosing interval (hours)
t_{inf} = infusion time (hours)
t_{pk} = time from end of infusion until time peak drawn (hours)
t_{tr} = time between time trough drawn until next dose given (hours)
Cmax = maximum concentration at end of infusion
Cmin = minimum concentration prior to next dose

Infusion time at UWMC and HMC can be found in PharmNet.

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Case #1:
JH is a 36 yo female who is receiving tobramycin 140mg IV every 8 hours. Goal Cmax 8-10 mcg/ml, Goal Cmin < 2 mcg/ml.

Doses administered (assume all doses were infused over 30 minutes):

3/21 @ 0800

3/21 @ 1600 — 7.5 hours → 3/21 @ 2330, Trough 2.0 mcg/ml

3/22 @ 0000 - 0.5 hours → 3/22 @ 0030, Peak 7.7 mcg/ml

The following serum concentrations are contained:

ke = $\dfrac{\ln\left[\frac{7.7}{2.0}\right]}{(7.5 - 0.5)}$ = 0.193

t1/2 = $\dfrac{0.693}{0.193}$ = 3.59 hr

Cmax = 7.7 mcg/ml

Cmin = $(2.0) * (e^{-(0.193 * 0.5)})$ = 1.82 mcg/ml

Vd = $\dfrac{140}{0.193 * 0.5} * \dfrac{1 - e^{-(0.193 * 0.5)}}{7.7 - (1.82 * e^{-(0.193 * 0.5)})} = 1451 * \dfrac{0.092}{6.05}$ = 22.1 L

Clearance = (0.193) * (22.1) = 4.3

Maintenance Dose = (4.3) (0.5) (10.0) $* \dfrac{1 - e^{-(0.193*8)}}{1 - e^{-(0.193*0.5)}} = 21.5 * \dfrac{0.787}{0.092}$ = 184 Δ Tobramycin to 180 (rounded to nearest 10 mg)

Predicted Cmax w/ Q8 hour regimen = $\dfrac{180}{(4.3 * 0.5)} * \dfrac{1 - e^{-(0.193 * 0.5)}}{1 - e^{-(0.193 * 8)}} = 83.7 * \dfrac{0.092}{0.786}$ = 9.8 mcg/ml

Predicted Cmin w/ Q8 hour regimen = $9.8 * (e^{-(0.193)(7.5)})$ = 2.3 mcg/ml Cmin above desired goal, extend interval to Q12 hours

Predicted Cmax w/ Q12 hour regimen = $\dfrac{180}{(4.3 * 0.5)} * \dfrac{1 - e^{-(0.193 * 0.5)}}{1 - e^{-(0.193 * 12)}} = 83.7 * \dfrac{0.092}{0.903}$ = 8.5 mcg/ml

Predicted Cmin w/ Q12 hour regimen = $8.5 * (e^{-(0.193)(11.5)})$ = 0.92 mcg/ml

Recommend tobramycin 180mg IV Q12 hours

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Case #2
JH is a 36 yo female who is receiving tobramycin 140mg IV every 8 hours. Goal Cmax 8-10 mcg/ml, Goal Cmin < 2 mcg/ml.

Doses administered (assume all doses were infused over 30 minutes):

3/21 @ 0800

3/21 @ 1600 — 7.5 hours → 3/21 @ 2330, Trough 2.0 mcg/ml

3/22 @ 0000 — 2.5 hours → 3/22 @ 0230, Peak 7.7 mcg/ml

The following serum concentrations are contained:

ke = $\frac{\ln\left[\frac{7.7}{2.0}\right]}{(7.5 - 2.5)}$ = 0.270

t1/2 = $\frac{0.693}{0.270}$ = 2.57 hr

Cmax = $\frac{7.7}{e^{-(0.270)(2.0)}}$ = 13.2 mcg/ml

Cmin = (2.0) * $(e^{-(0.270 * 0.5)})$ = 1.75 mcg/ml

Vd = $\frac{140}{0.270 * 0.5}$ * $\frac{1 - e^{-(0.270 * 0.5)}}{13.2 - (1.75 * e^{-(0.270 * 0.5)})}$ = 1037 * $\frac{0.126}{11.7}$ = 11.2 L

Clearance = (0.270) * (11.2) = 3.0

Maintenance Dose = (3.0) (0.5) (10.0) * $\frac{1 - e^{-(0.270*8)}}{1 - e^{-(0.270*0.5)}}$ = 15.0 * $\frac{0.885}{0.126}$ = 105 Δ Tobramycin to 100 (rounded to nearest 10 mg)

Predicted Cmax = $\frac{100}{(3.0 * 0.5)}$ * $\frac{1 - e^{-(0.270 * 0.5)}}{1 - e^{-(0.270 * 8)}}$ = 66.7 * $\frac{0.126}{0.885}$ = 9.5 mcg/ml

Predicted Cmin = 9.5 * $(e^{-(0.270)(7.5)})$ = 1.25 mcg/ml

Recommend tobramycin 100mg IV Q8 hours

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Appendix 1: Cystic fibrosis dosing protocol for aminoglycosides

Purpose: Ensure safe and efficacious dosing of tobramycin and amikacin for our CF patients.

Submitted by: Rupali Jain, PharmD

Approved by: Moira Aitken, MD; Medical Director for Cystic Fibrosis

Infectious Diseases Subcommittee: 12/6/2017

Tobramycin is an aminoglycoside antibiotic with broad gram-negative coverage; It is often combined with another antimicrobial for treatment for Cystic Fibrosis exacerbations related to *Pseudomonas aeruginosa.* The following dosing protocol is meant to optimize efficacy and reduce toxicity for tobramycin and amikacin. Although, amikacin is rarely used for CF exacerbations dosing recommendations are provided below. This dosing protocol is not applicable for mycobacterium infections. Gentamicin is never used for CF exacerbations therefore should be changed to tobramycin.

Dosing weight

CF patients often are low weight individuals;

1. Dosing weight should be determined by assessing the patient's current weight and height
2. Calculate Ideal body weight by using the formula:
    a. Males: IBW = 50kg + [2.3 x ht (inches above 60)]; females: 45.5kg + [2.3 x ht(inches above 60)]
    b. The measured weight of CF patients is often lower than the calculated IBW. If so, use measured weight (aka actual weight) for aminoglycoside dosing.
    c. If obese, use adjusted body weight [ABW > 20% of IBW): DDW = IBW + 0.4 (ABW-IBW)]
3. Assess patient for additional nephrotoxic agents.

Creatinine Clearance:

Due to the low weight and low muscle mass, Scr is often lower than non-CF individuals, and thus may over-estimate the CrCl. Calculate CrCl using Cockgraft and Gault, but understanding that it often over-represents renal function. A more accurate monitoring parameter is reviewing the baseline SCr and change over time.

Do not use this dosing protocol for patients with renal failure (i.e. hemodialysis or peritoneal dialysis)

Do not use this protocol for CF patients who are post-lung transplant UNLESS directed by Pulmonary Transplant and Infectious Disease teams.

Starting dose:

1. Give Tobramycin 8mg/kg x dosing weight
    a. If using amikacin give 25 mg/kg x dosing weight
2. If the patient has received tobramycin/amikacin previously, look for previous doses in PharmNet or Epic (look for pharmacist note.) Use the same dose as previously prescribed, but use clinical judgement if changes in weight, serum creatinine, concomitant nephrotoxins, and/or if serum tobramycin levels were outside target range on the historical dosing.
3. Dose to be given IV over 1 hour every 24 hours.
4. Check 2 and 6 hour levels after the 1st or 2nd dose. Levels are to be drawn at 2 hours and 6 hours after the start of the infusion.
5. Tobramycin and amikacin levels are run at HMC. Order STAT to get rapid results.
6. Use CF powerplan to order levels
7. Instruct RN not to draw levels from the PORT, as this can provide false readings.

Assessment of levels:

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1. Use calculator to calculate a peak and trough (found on paige/change, under med specialities, CF)
2. **Primary goal: peak levels of 20-30 mcg/mL (tobramycin) and 35-50 mcg/mL (amikacin), trough undetectable**
3. Secondary goal for tobramycin: AUC: < 101 (tobramycin)
4. Amikacin does not have an AUC goal and therapy decisions should be made solely on peak and trough values.
5. Ensure levels are drawn according to time constraints above but if they are not drawn during these time constraints, enter them accordingly into the calculator. Any detectable level can be plugged into the calculator.
6. If any of the measured levels are undetectable, repeat the drug levels the next day.
7. If tobramycin trough is >1 mcg/ml (or amikacin level > 5 mcg/ml), discuss with pulmonary and medicine teams to determine if therapy should be continued due to risks of accumulation and nephrotoxicity. Depending on the magnitude of the level, the clinical pharmacist may consider increasing the interval to q36 or q48. Discuss with medicine or CF pharmacists.

Some pearls:

- If peak within goal and AUC at goal: keep same dose
- If peak within goal, but AUC higher than goal: Consider dose decrease especially if the AUC is well-above the goal (use clinical judgement); recheck levels within 2-3 days; Consider discussing with medicine or CF pharmacists.
- If peak above goal, but AUC at goal: reduce dose
- If peak above goal and AUC is above the goal: reduce the dose
- If peak below goal, but AUC at goal: increase dose modestly
- If peak below goal, and AUC higher than goal: Continue same dose; unlikely to happen, but consider rechecking levels or verify timing of lab draws with RN. Recheck the 2 and 6 hour levels the next day.
- If you are concerned that the levels do not make sense, please verify RN collection times and then contact the medicine/CF/ antimicrobial stewardship pharmacists to further discuss the case.
- The 2-hr and 6-hr levels do not need to be repeated daily if the numbers are within goal without toxicity and no other factors which would change the pharmacokinetics.
- If you are concerned about accumulation, use the calculated half-life to estimate current dosing interval. Also, consider checking a trough level before the next dose to evaluate clearance and validate dosing interval.
- Be vigilant in monitoring for other potentially nephrotoxic drugs, SCr, and dose timing/schedule,(i.e changes to Volume of distribution.) Also, keep in mind proper timing of the dose to anticipate transition to outpatient/home therapy and avoid stacking the dose when rescheduling.

Dose adjustments

1. Do **not** use calculator for new dose calculation, rather use proportions to determine new dose to obtain target tobramycin peak of 20-30 mcg/ml or amikacin peak of 35-50 mcg/mL
    a. Make sure to follow instructions in the calculator regarding data entry.
    b. Double check date and times for accuracy (especially when the two labs go into the next day). Use 24-hour time when plugging in the calculator for consistency.
2. In general, the maximum increase in the dose should not be more than 20% of original dose. (usually 10% change occurs). Some cases may require greater than 20% increase, so consider discussing the case with the Medicine or CF pharmacists. Consider the presence of concomitant nephrotoxins when making dosing adjustments.
3. Recheck levels the next day to verify dosing is correct.
4. Document your recommendations in the chart using the note template

Monitoring:

1. Once you have reached goal tobramycin/amikacin serum levels, check SCr daily and serum levels weekly while patient is hospitalized.
2. Outpatient therapy requires only twice weekly chem-7 and weekly 2 and 6 hour levels.
    a. Sign out to CF and home care pharmacists if patient will be discharged on aminoglycoside therapy
3. Provide counseling regarding signs and symptoms of ototoxicity (ataxia, tinnitus, etc) and nephrotoxicity.

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