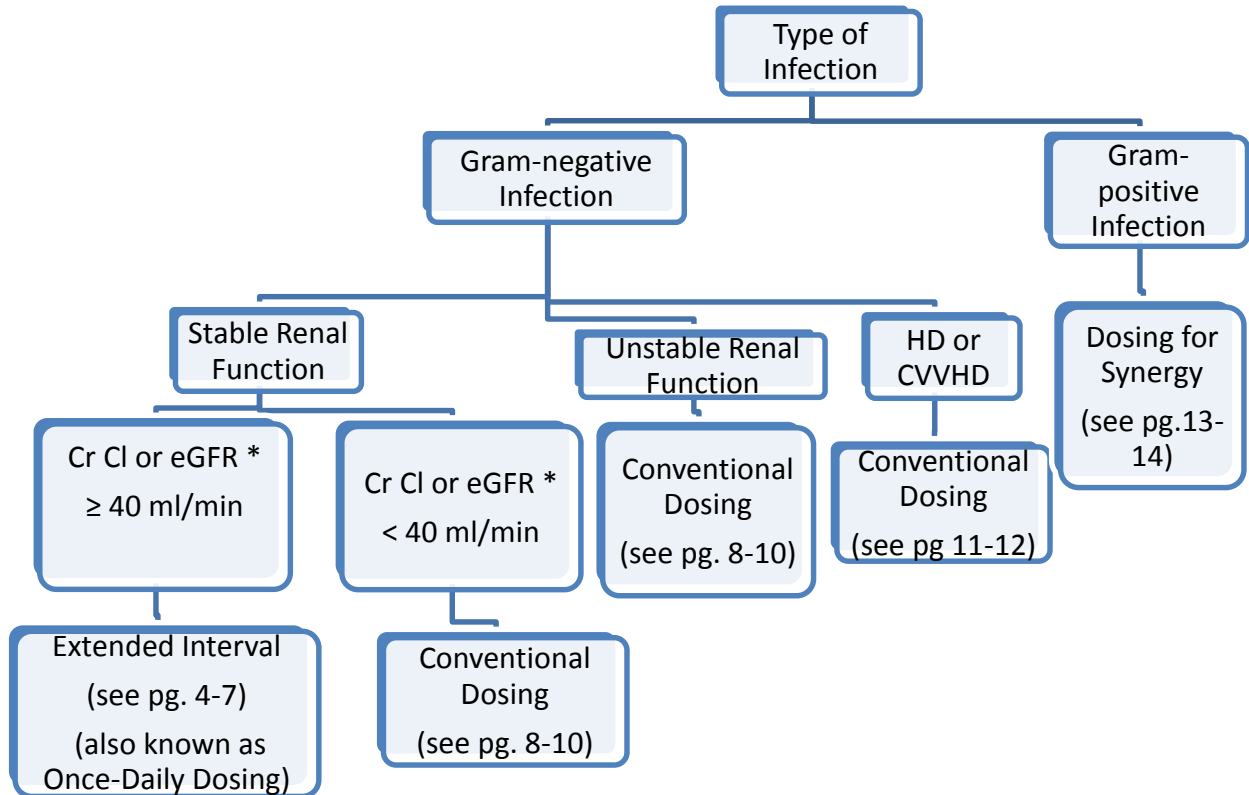


Aminoglycoside Dosing and Monitoring Guidelines for Adult Patients at Stony Brook University Hospital

Algorithm for initial Aminoglycoside dosing



* eGFR is normalized to BSA 1.73m². Convert normalized eGFR (ml/min/1.73m²) to individualized eGFR (ml/min) by multiplying eGFR (ml/min/1.73m²) with Patient's BSA and divided by 1.73.

Both estimated Cr Cl by Cockcroft-Gault equation and eGFR by CKD-EPI equation provide reasonable estimates for aminoglycoside dosing.

However, due to the limitations of these estimating equations, it would be prudent for clinicians to apply clinical judgment when interpreting either estimates (Cr Cl or eGFR) in elderly patients, patients at the extremes of muscle mass and patients with unstable serum creatinine levels.

If the 2 estimates (Cr Cl and eGFR) lead to different dosing regimens, it would be advisable for clinicians to incorporate risk versus benefit assessment in determining the aminoglycoside dosing regimen.

Disclaimer

- The information contained is adapted from published pharmacokinetic and pharmacodynamics literature
- The information provided is not intended to replace sound clinical judgment
- This is not intended to be used for follow up when measured serum concentrations are available.
 - If measured serum concentrations are available, dosing should be based on indications, patient's PK parameters and optimal PK/PD target.
 - If assistance is needed, please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

General Information:

- Limiting the duration of aminoglycoside to 7 days or less, when possible, is highly recommended as aminoglycoside nephrotoxicity is correlated to the total renal accumulation of aminoglycoside
- Patients should be monitored for nephrotoxicity and ototoxicity (vestibular and cochlear)
- Monitoring of ototoxicity is recommended for prolonged duration of greater than 14 days. If it is clinically feasible and appropriate, monitor cochlear toxicity by audiometric function at baseline and during therapy
- In order to properly interpret and assess measured serum concentrations, the dose and sample time should be recorded accurately
- Creatinine Clearance calculation by Cockcroft-Gault equation:
 - Calculated Cr Cl (ml/min) for male = $\frac{(140-\text{Age}) \times \text{Ideal Body Weight}}{72 \times \text{Sr Cr}}$
 - Calculated Cr Cl (ml/min) for female = $0.85 \times \left(\frac{(140-\text{Age}) \times \text{Ideal Body Weight}}{72 \times \text{Sr Cr}} \right)$
 - Ideal Body weight (IBW): Male: 50 kg + 2.3 x (every inch above 60 inches)
Female: 45.5 kg + 2.3 x (every inch above 60 inches)

Questions to ask prior to the formulation of aminoglycoside dosing:

- 1. Has the patient received aminoglycoside in the recent past? If yes, dosing should take into consideration the severity of the current infection, current renal function, current optimal PK/PD target, prior dosing history and prior measured levels**
- 2. Does the Cr Cl or eGFR estimate reflect current clinical assessment? If no, use the more conservative estimate of renal function to formulate dosing**
- 3. What is the indication for aminoglycoside?**
 - a. For Gram Negative Infections:**
 - i. If Cr Cl or eGFR \geq 40 ml/min with stable renal function, use Extended Interval dosing**
 - ii. If Cr Cl or eGFR $<$ 40 ml/min or patients with unstable renal function, use conventional dosing**
 - iii. If patient is on Intermittent Hemodialysis (IHD) or Continuous Venovenous Hemodialysis (CVVHD), use conventional dosing**
 - b. For Synergy in Gram-positive infections (Staphylococcus, Streptococcus, Enterococcus), use Dosing for Gram Positive Synergy**

Aminoglycoside High Dose Extended Interval Method (Also known as Once-Daily Dosing)

Rationale for the use of Aminoglycoside High Dose Extended Interval Method

- Concentration dependent bactericidal effect
- Optimal Peak to MIC ratio ≥ 10
- Optimal AUC to MIC 75 -110
- Possibly less nephrotoxicity (Animal Studies and Clinical Studies)
- Similar efficacy as conventional dosing
- Reversal of adaptive resistance

Appropriate Patients

- Stable renal function
- Cr Cl or eGFR ≥ 40 ml/min
- Treatment for gram negative infections

Exclusions to Aminoglycoside High Dose Extended Interval Method

Synergy for Gram-positive infections

Pregnant patients

Burn patients (> 20% total body surface area)

Patients with ascites

Age < 16 years (SB Pediatric Pulmonary/Allergy Division uses tobramycin 10mg/kg once daily for Cystic Fibrosis patients)

Patients on renal replacement (hemodialysis, peritoneal dialysis, CVVHD)

Dosing for Aminoglycoside High Dose Extended Interval Method

Drug	Cr Cl or eGFR ≥ 60 ml/min	Cr Cl or eGFR 40 - 59 ml/min
Gentamicin Tobramycin	5- 7 mg /kg INT-Q24H <i>(round dose to the nearest 10mg)</i>	5-7 mg/kg INT-Q36 - 48H <i>(round dose to the nearest 10mg)</i>
Amikacin	15 -20 mg/kg INT-Q24H <i>(round dose to the nearest 50mg increment)</i>	15-20 mg/kg INT-Q36 -48H <i>(round dose to the nearest 50mg increment)</i>

- For treatment of severe Gram-negative infections, dose recommended for gentamicin or tobramycin is 7 mg/kg and dose recommended for amikacin is 20mg/kg
- Use Total Body Weight (TBW) if Total Body Weight is less than 1.2 x Ideal Body Weight (IBW)
- Use Adjusted Body Weight if Total Body Weight is ≥ 1.2 x Ideal Body Weight (IBW)
 - Adjusted Body Weight = $IBW + 0.4 \times (TBW - IBW)$
 - IBW: Male: $50\text{kg} + 2.3 \times$ (every inch above 60 inches)
Female: $45.5 \text{ kg} + 2.3 \times$ (every inch above 60 inches)

Monitoring for Aminoglycoside High Dose Extended Interval Method

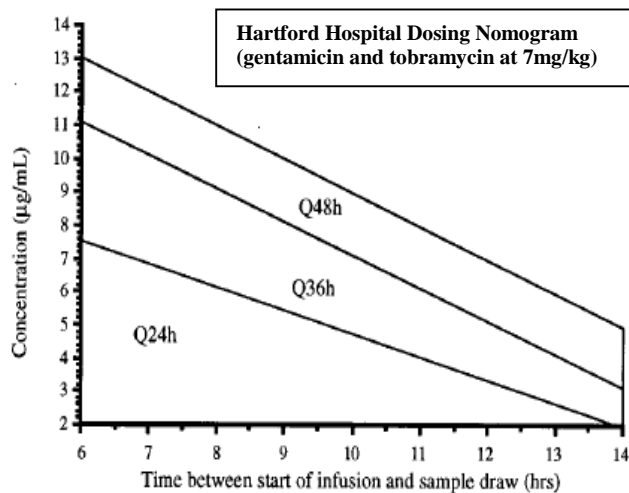
- Except for critically ill patients and elderly patients, there is no need to obtain serum concentration for monitoring if patient has stable renal function (Cr Cl or eGFR > 60 ml/min) and duration of therapy is going to be less than 3 - 5 days
- For High-Dose Extended Interval dosing method, monitoring can be done with any doses including the 1st dose since there is no accumulation of drug from one dose to the next
- For critically ill patients, it is recommended to be monitored by 2 random levels after the first dose to ensure early attainment of optimal PK/PD target (Method B)
- Monitor Bun/Cr every 1-3 days

Monitoring Methods:

1. Peak level Monitoring is not necessary. Gentamicin mean peak concentration of 18.7 mcg/ml (95% CI, 16.4 to 21 mcg/ml) was reported with dosing of 7mg/kg ¹

2. Method A - Monitor by Nomogram. See Instruction below

Gentamicin or Tobramycin 7mg/kg Extended Interval Dosing Method



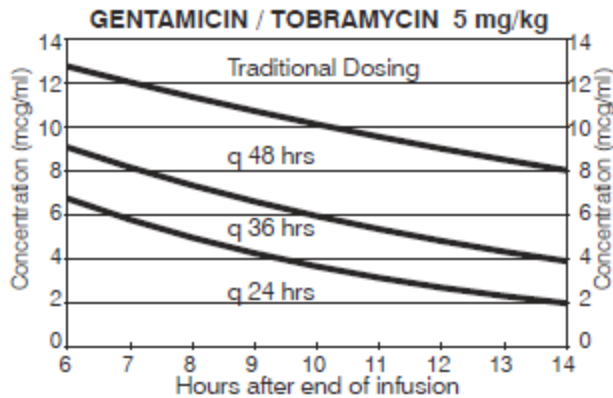
Hartford Hospital Nomogram¹ for Gentamicin/Tobramycin 7mg/kg:

- Obtain a random level 10 - 12 hours after dosing
- Plot the measured gentamicin or tobramycin levels against the corresponding time elapsed in hours from the start of infusion on the Hartford Nomogram
- If the level falls within “Q24h” area, the dosing frequency is INT-Q24h.
- If the level falls within “Q36h” area, the dosing frequency is INT-Q36h. Start new regimen 36 hours from the last dose and repeat a 10-12 hours post-dose random level.
- If the level falls within “Q48h” area, the dosing frequency is INT-Q48h. Start new regimen 48 hours from the last dose and repeat a 10-12 hours post-dose random level.
- If the plotted level falls on a division line, use the more extended dosing frequency
- If the plotted level falls on or above the upper limit line of q48h, Do NOT use High-Dose Extended Interval Dosing Method. Obtain a random level in 24 hours and contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

Monitoring after dosing frequency is confirmed:

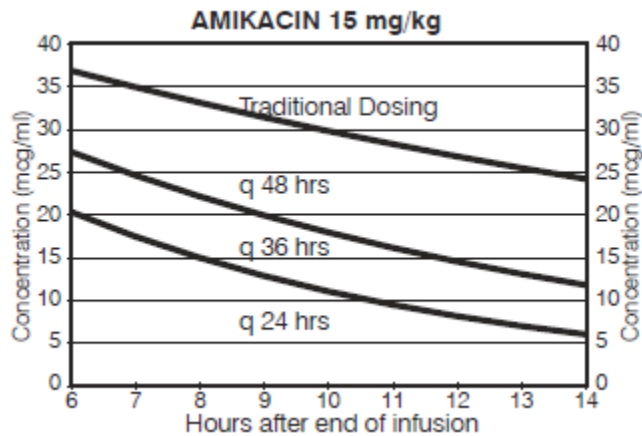
- *Monitor renal function*
- *If renal function is unchanged, recheck a random level 10-12 hours after dose every 5-7 days*
- *More frequent monitoring may be warranted in patients with higher risk for nephrotoxicity or unstable renal function*
- *Whenever decline in renal function is detected, reassess dosing frequency by a random level 10-12 hours after the dose*

Gentamicin or Tobramycin 5 mg/kg Extended Interval Dosing Method



Barnes-Jewish Hospital Nomogram²

Amikacin 15 mg/kg Extended Interval Dosing Method**



Barnes-Jewish Hospital Nomogram²

Monitoring after dosing frequency is confirmed:

- Monitor renal function
- If renal function is unchanged, recheck a random level 10-12 hours after dose every 5-7 days
- More frequent monitoring may be warranted in patients with higher risk for nephrotoxicity or unstable renal function
- Whenever decline in renal function is detected, reassess dosing frequency by a random level 10-12 hours after the dose

Use the Appropriate Barnes-Jewish Nomogram according to the dosing method. Instruction is the same for both Nomograms:

- Obtain a random level 10 - 12 hours after dosing
- Plot the measured gentamicin or amikacin levels against the corresponding time elapsed in hours from the start of infusion on the Barnes-Jewish Nomogram

**** if amikacin 20 mg/kg is used. Adjust the measured level with the following equation before plotting the level onto the Amikacin 15mg/kg Extended Interval Nomogram Level for the plot = Measured level x 0.75**

- If the level falls within "Q24h" area, the dosing frequency is INT-Q24h.
- If the level falls within "Q36h" area, the dosing frequency is INT-Q36h. Start new regimen 36 hours from the last dose and repeat a 10-12 hours post-dose random level.
- If the level falls within "Q48h" area, the dosing frequency is INT-Q48h. Start new regimen 48 hours from the last dose and repeat a 10-12 hours post-dose random level.
- If the plotted level falls on a division line, use the more extended dosing frequency
- If the plotted level falls on or above the upper limit line of q48h, Do NOT use High-Dose Extended Interval Dosing Method. Obtain a random level in 24 hours and contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

Monitoring for Aminoglycoside High Dose Extended Interval Method

Monitoring Methods (continued):

- 3. Method B- Monitored by 2 random Levels -1st random- 4 hours after the 1st dose, 2nd random level 12 hours after the 1st dose**
 - a. This requires user to be able to perform PK calculations to estimate $T_{1/2}$, peak level, trough level and optimal PK/PD target. Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.**
 - b. This monitoring method provides information to assess the attainment of optimal PK/PD target in critically ill patients who may have higher volume of distribution and/or higher clearance during the early sepsis phase**

- 4. Method C – Monitoring by trough level provides information for minimizing the risk of nephrotoxicity but does not provide information for PK/PD target assessment:**
 - Trough should be checked 30 minutes prior to the next dose**
 - Target Gentamicin and Tobramycin Trough - < 0.3 mcg/ml (undetectable)**
 - Target Amikacin Trough - < 0.8 mcg/ml (undetectable)**

(Undetectable is defined as below the limit of quantification of the assay)

- 5. Dosing adjustment when Monitored by Trough**
 - i. If trough is above the target, extend dosing interval by 12 hours and recheck trough. If rechecked trough is still above target, use conventional dosing method.**
 - ii. If measured trough is within target and patient's renal function is stable, check trough once a week if duration of therapy > 7 days**
 - iii. More frequent monitoring may be warranted in patients with higher risk for nephrotoxicity or unstable renal function**

References

1. Nicolau DP., Freeman CD., Belliveau PP., et al. Experience with a One-Daily Aminoglycoside Program administered to 2,184 adult patients. AAC 1995;39:650-655
2. Editors Casabar E, Ritchie D, Bain B, Bailey T. Aminoglycosides. Barnes Jewish Hospital Tool Book 2014
3. Freeman CD., Nicolau DP., Belliveau PP., et al. Once-daily dosing of Aminoglycosides: review and recommendations for clinical practice. JAC 1997;36:677-686
4. Begg EJ., Barclay ML., Duffull SB. A suggested approach to once-daily aminoglycoside dosing. Br J Clin Pharmac 1995;39:605-609

Conventional Dosing

Use in patients with

- Cr Cl or eGFR < 40 ml/min and/or
- Unstable renal function

Conventional dosing interval of q24h should not be confused with patients receiving High Dose Extended Interval Method (Once-daily). The dose used in Conventional Dosing Method is reduced in order to attain the optimal PK/PD target in patients with decreased renal function

Target Peak and Trough at steady state for Conventional dosing

Gentamicin and Tobramycin		
Indications	Target Peak at steady state (mcg/ml)	Target Trough at steady state (mcg/ml)
Gram-negative Pneumonia	8-10	< 2
Severe Gram negative Infections	6-8	< 2
Urinary Tract Infections	4-6	<1

Amikacin		
Indications	Target Peak at steady state (mcg/ml)	Target Trough at steady state (mcg/ml)
Gram-negative infections	25 - 35	< 8

Conventional Dosing

Drug	Indication	Loading Dose	Maintenance dose based on Cr Cl or eGFR (ml/min)	
			20 - 39	≤ 19
Gentamicin Tobramycin <i>(round to the nearest 10mg)</i>	UTI	2 mg/kg	1.5 mg/kg INT-Q24H	Maintenance dose is determined by measured levels. Contact pharmacy (444-2680) and request designated pharmacist for PK assessment.
	Moderate -Severe Gram-negative infections	3 mg/kg	2 mg/kg INT-Q24H	Maintenance dose is determined by measured levels. Contact pharmacy (444-2680) and request designated pharmacist for PK assessment.
Amikacin <i>(round to the nearest 50mg increment)</i>	UTI	7.5 mg/kg	5 mg – 7.5 mg/kg INT- Q24H	Maintenance dose is determined by measured levels. Contact pharmacy (444-2680) and request designated pharmacist for PK assessment.
	Moderate -Severe Gram-negative infections	10-15 mg/kg	7.5 mg – 10 mg/kg INT- Q24H	Maintenance dose is determined by measured levels. Contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

- Use Total Body Weight if Total Body Weight is less than 1.2 x Ideal Body Weight (IBW)
- Use Adjusted Body Weight if Total Body Weight is ≥ 1.2 x Ideal Body Weight (IBW)
 - Adjusted Body Weight = IBW + 0.4 x (Total Body Weight – IBW)
 - IBW: Male: 50kg + 2.3 x (every inch above 60 inches)
Female: 45.5 kg + 2.3 x (every inch above 60 inches)

Conventional Dosing - Monitoring

- **Monitor Bun/Cr every 1-3 days**
- **Obtain a random level 2 hours after the loading dose (a 2-hr post-dose random level is used because patients with significant renal impairment may have a longer distribution phase and PK analysis using one-compartment model is more appropriate to be performed after the distribution phase is completed)**
- **Obtain a 2nd random level 24 hours after the loading dose**
- **Contact pharmacy (444-2680) and request designated pharmacist for PK assessment.**
- **After maintenance dose is established and if patient's renal function is stable, check trough level once a week**
- **More frequent monitoring may be warranted in patients with higher risk for nephrotoxicity or unstable renal function**

Dosing for ESRD patients on Intermittent Hemodialysis (IHD)
(Assuming 3 times a week- 4 hours dialysis session)

Drug	Indication	Loading Dose	Maintenance dose
Gentamicin Tobramycin <i>(round to the nearest 10mg)</i>	Mild gram-negative infection	2 -3 mg /kg	1 -1.5 mg/kg after IHD <i>Subsequent maintenance dosage should be based on pre-dialysis target (see Monitoring section)</i>
	Moderate to Severe Gram-negative infection	2 - 3 mg/kg	1.5 -2 mg/kg after IHD <i>Subsequent maintenance dosage should be based on pre-dialysis target (see Monitoring section)</i>
Amikacin <i>(round to the nearest 50mg increment)</i>	All gram-negative infections	10 mg/kg	5 –7.5 mg/kg after IHD <i>Subsequent maintenance dosage should be based on pre-dialysis target (see Monitoring section)</i>

- Use Total Body Weight if Total Body Weight is less than 1.2 x Ideal Body Weight (IBW)
- Use Adjusted Body Weight if Total Body Weight is ≥ 1.2 x Ideal Body Weight (IBW)
 - Adjusted Body Weight = $IBW + 0.4 \times (Total\ Body\ Weight - IBW)$
 - IBW: Male: $50kg + 2.3 \times$ (every inch above 60 inches)
 Female: $45.5\ kg + 2.3 \times$ (every inch above 60 inches)

Monitoring

The rate and amount of drug removed are influenced by a variety of host and dialysis-related factors. Serum concentration monitoring is highly recommended for severe gram-negative infections.

- Obtain Peak 2 hours after loading dose (ESRD patients have a longer distribution phase)
- Obtain a pre-dialysis level (random for lab order) before the initiation of dialysis
- Target pre-dialysis level for re-dosing of gentamicin and tobramycin
 - Mild infection- < 2 mcg/mL
 - Moderate to Severe gram-negative infection - $< 3-5$ mcg/mL
- Target pre-dialysis level for re-dosing of amikacin
 - < 10 mcg/ml
- Check pre-dialysis level once a week after stable maintenance dose is established
- Dosing will need to be adjusted if intermittent hemodialysis is discontinued. Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

Dosing for patients receiving Continuous Venovenous Hemodialysis (CVVHD)

Drug	Gram-negative infection	
	Loading dose	Maintenance dose
Gentamicin Tobramycin (round to the nearest 10mg increment)	3 mg /kg <ul style="list-style-type: none"> • PK monitoring after loading dose is preferred • For less severe infections, PK monitoring can be done at steady state (Peak after 2nd and trough before 3rd maintenance dose) 	2 mg/kg INT-Q24h
	OR	
	5 mg /kg and must be followed with PK monitoring after loading dose	5 mg/kg INT-Q48h
Amikacin (round to the nearest 50mg increment)	10 mg/kg <ul style="list-style-type: none"> • PK monitoring after loading dose is preferred • For less severe infections, PK monitoring can be done at steady state (Peak after 2nd and trough before 3rd maintenance dose) 	7.5 mg/kg INT-Q24h
	OR	
	15 mg/kg and must be followed with PK monitoring after loading dose	15 mg/kg INT-Q48h

- Use Total Body Weight if Total Body Weight is less than 1.2 x Ideal Body Weight (IBW)
- Use Adjusted Body Weight if Total Body Weight is ≥ 1.2 x Ideal Body Weight (IBW)
 - Adjusted Body Weight = IBW + 0.4 x (Total Body Weight – IBW)
 - IBW: Male: 50kg + 2.3 x (every inch above 60 inches)
Female: 45.5 kg + 2.3 x (every inch above 60 inches)

Monitoring

The rate and amount of drug removed are influenced by a variety of host and dialysis-related factors. Serum concentration monitoring is highly recommended.

- PK Monitoring after loading dose - Obtain first random level 4 hours after the loading dose, and a second random level 16 hours after the loading dose (not at steady state). Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment
- PK Monitoring at steady state – Obtain Peak level 30 minutes after the infusion of the 2nd maintenance dose is completed and Trough level 30 minutes prior to the 3rd maintenance dose
- Check trough level once a week after stable maintenance dose is established
- More frequent monitoring is needed if patient is not receiving CVVHD on a daily basis
- Dosing will need to be adjusted if CVVHD is discontinued. Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

Dosing for Gram Positive Synergy

- The use of aminoglycosides other than gentamicin or streptomycin in combination with a cell wall active agents for synergy is not recommended due to the presence of resistance mechanisms against tobramycin and amikacin in many enterococci.

Gentamicin (round dose to the nearest 10mg)					
Cr Cl or eGFR ≥ 60 ml/min and age ≤ 65 y.o.	Cr Cl or eGFR 30 - 59 ml/min or Elderly (age > 65 y.o.)	Cr Cl or eGFR 20 - 29 ml/min	Cr Cl or eGFR ≤ 19 ml/min	Intermittent Hemodialysis (IHD)	CVVHD
1 mg/kg q8h	1 mg/kg q12h or 0.7mg/kg q8h	1 - 1.25 mg/kg q24h	1 – 1.25 mg/kg q48h	1mg /kg load, then 0.7mg/kg to 1mg/kg after each dialysis <i>(target for re- dose: pre-HD level < 2 mcg/ml)</i>	1mg/kg q24-36h

- Use Total Body Weight if Total Body Weight is less than 1.2 x Ideal Body Weight (IBW)
- Use Adjusted Body Weight if Total Body Weight is ≥ 1.2 x Ideal Body Weight (IBW)
 - Adjusted Body Weight = IBW + 0.4 x (Total Body Weight – IBW)
 - IBW: Male: 50kg + 2.3 x (every inch above 60 inches)
Female: 45.5 kg + 2.3 x (every inch above 60 inches)

Dosing for Gram Positive Synergy - Monitoring

Drug	Target Peak (mcg/ml)	Target Trough (mcg/ml)
Gentamicin	3-4	Less than 1.5

- No need to obtain serum levels for monitoring if the duration of therapy is going to be less than 3 - 5 days
- Monitor Bun/Cr every 1-3 days
- For q8-12h dosing frequency, obtain Peak level 30 minutes after the infusion of the 4th dose is completed and Trough level 30 minutes before the initiation of the 5th dose
- For q24h dosing frequency, obtain Peak level 30 minutes after the infusion of the 3rd dose is completed and Trough level 30 minutes before the initiation of the 4th dose
- For q48h dosing frequency, obtain a random level 2 hours after the first dose, and a second random level 24 hours after the first dose (not at steady state). Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.
- For Intermittent Hemodialysis patients, obtain pre- dialysis concentration (random)
- Target pre-dialysis level for re-dosing < 2 mcg/ml
- Check trough level once a week after stable maintenance dose is established
- More frequent monitoring if renal function is unstable
- Dosing may need to be adjusted if renal replacement therapy (IHD or CVVHD) is discontinued. Please contact pharmacy (444-2680) and request designated pharmacist for PK assessment.

References

1. Heintz BH., Matzke GR., Dager WE. Antimicrobial Dosing Concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 2009;29:562-577
2. Dager WE., King JH. Aminoglycosides intermittent hemodialysis: Pharmacokinetics with individual dosing. Ann Pharmacother 2006;40:9-14
3. Trotman RL., Williamson JC., Shoemaker DM, et al. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. CID 2005;41:1159-66
4. Beringer, P. and Winter, M. (2004) Aminoglycoside Antibiotics. In: Troy DB. ed. Basic Clinical Pharmacokinetics. Philadelphia: Lippincott Williams and Wilkins. pp 130-182
5. Leggett, James. Aminoglycosides. Principles and Practice of Infectious Diseases. Ed. Bennett JE, Dolin R, Blaser M. Publisher. Saunders. Eighth Edition 2015. Pg. 310-321