Stanford Health Care Aminoglycoside Dosing Guideline

I. DETERMINING DOSE AND CREATININE CLEARANCE:

1. Use of total body weight (TBW) in underweight and non-obese patients is widely accepted. Use of ideal body weight (IBW) for determining the mg/kg/dose may also be considered. For obese patients (total body weight > 20% over Ideal body weight), dosage requirement may best be estimated using an adjusted body weight (ABW) of: IBW + 0.4 (TBW - IBW).[1]

   IBW (male) = 50 kg + (2.3 x height in inches > 60 inches)
   IBW (female) = 45 kg + (2.3 x height inches > 60 inches)

2. Calculate creatinine clearance with the Cockcroft-Gault equation using an ideal body weight (IBW) or an adjusted body weight (ABW) if the patient is obese

$$\text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW}}{\text{SCr} \times 72} \quad (\times 0.85 \text{ for females})$$

II. AMINOGLYCOSIDE DOSING STRATEGIES

A. Gram negative infections

1. High-dose Extended-Interval Therapy

Rationale:

- **Aminoglycoside bactericidal activity is concentration dependent.**[2,3] The higher the peak/MIC ratio, the greater the rate and extent of bacterial kill. The pharmacodynamic goal is to maximize drug concentration at the site of infection. Optimum bactericidal activity for the aminoglycosides is achieved when the exposure concentration is approximately 8 to 10 times the MIC
- **Aminoglycosides exhibit a post-antibiotic effect (PAE).**[2,4–6] PAE ranges of 0.5 to 8-hours have been reported. Factors influencing the PAE include: height of the preceding AMG peak, in-vivo > in-vitro, shortened by neutropenia, and extended in the presents of beta-lactams
- **Saturable aminoglycosides uptake in renal tubule cell and inner ear.**[7] This suggests that higher peaks do not result in greater risk of toxicity. A single dose of aminoglycoside results in significantly lower renal cortical tissue concentration compared to the same total dose administered through a continuous infusion or in divided doses.[8,9] . Modeling data suggests that thrice-daily administration is associated with nephrotoxicity that occurs more rapidly, with greater intensity, and for longer duration, as compared to once-daily aminoglycoside.[10] Clinical data and experience suggests that high-dose extended interval may be less nephrotoxicity compared to traditional regimens.[11,12]
- **Adaptive resistance of gram-negative bacilli to aminoglycosides.**[13,14] Also known as the first exposure effect, this refers to the down-regulation of aminoglycoside uptake into bacterial cell follow the initial exposure of the organism to the drug, thus making the organism refractory to the bactericidal action of subsequent doses. A longer dosing interval can be achieved with once-daily dosing, which allows for a drug-free period in which the bacteria are not exposed to an aminoglycoside and therefore preserve antibacterial activity.[15]
- **Decrease emergence of resistant subpopulation**. Bacterial regrowth following an animal dose of aminoglycoside was prevented by regimens in which the peak drug concentration was at least eight folders higher than the MIC. It is thought that

The **Hartford Nomogram** method utilizes high-dose, once daily dosing to optimize the peak/MIC ratio in most clinical situations by administering a dose of **7mg/kg** of either gentamicin or tobramycin. The **Urban & Craig Nomogram** is another method of extended-interval therapy utilizing **5 mg/kg** of gentamicin or tobramycin in patients without renal dysfunction. For patients with **cystic fibrosis exacerbation** the Cystic Fibrosis consensus guidelines recommend extended interval dosing with **10 mg/kg** once daily.

Exclusion Criteria:

- Renal insufficiency (CrCl <30 mL/min or rapidly declining renal function)
- Pregnancy
- Synergy for gram-positive infections
- Ascites
- Burns (>20%)

2. Conventional / Traditional Dosing

Tradition dosing includes reduced doses and more frequent administration of aminoglycosides using pharmacokinetic parameters to determine dose and frequency to achieve target peak and trough values.

Indication:

- Treatment of gram-negative infections and **NOT** a candidate for high-dose extended interval dosing therapy (see exclusion criteria above)

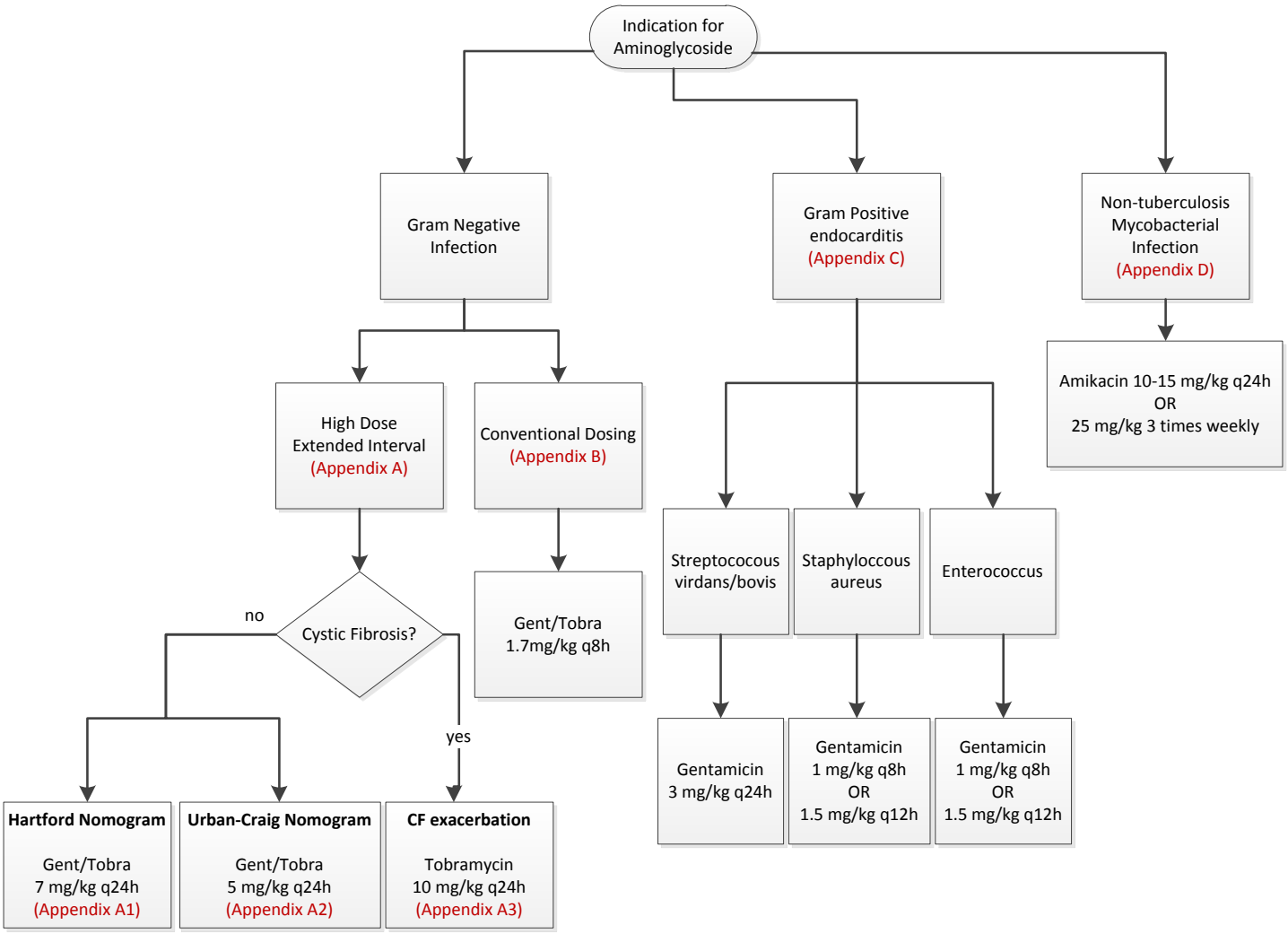
B. Gram positive-synergy

Synergy dosing is a low dose of aminoglycoside in conjunction with an antimicrobial agent that exhibits activity against the cell wall of Gram-positive bacteria (i.e. beta-lactams, glycopeptides) for the treatment of Gram-positive infections

C. Non-tuberculosis mycobacterium (NTM)

Treatment of NTM infections include combination therapy of either macrolides, clarithromycin, azithromycin, ethambutol, rifamycin and possibly an aminoglycoside. The decision to add an aminoglycoside depends on multiple factors including the extensiveness of disease, drug-refractory/resistant profile, and drug tolerance.

Dosing Methods by Indication



Appendix A: High-Dose Extended-Interval Nomograms (Gram-negative infections)

Appendix A1: Hartford Nomogram[16]

Initial Dose:

- 7 mg/kg using actual body weight (Nomogram was developed and validated with actual body weight)
- If obese, use adjusted body weight if obese IBW + (0.4 [TBW – IBW])
- The dose of 7mg/kg is expected to achieve a C_{max} level of ~20 mg/L

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin
≥ 60 mL/min	7 mg/kg Q24H	15 mg/kg Q24H
40 – 59 mL/min	7 mg/kg Q36H	15 mg/kg Q36H
30 – 39 mL/min	7 mg/kg Q48H	15 mg/kg Q48H
20 – 29 mL/min	Not recommended	Not recommended
< 20 mL/min	Not recommended	Not recommended
Hemodialysis	Not recommended	Not recommended
CRRT	Not recommended	Not recommended

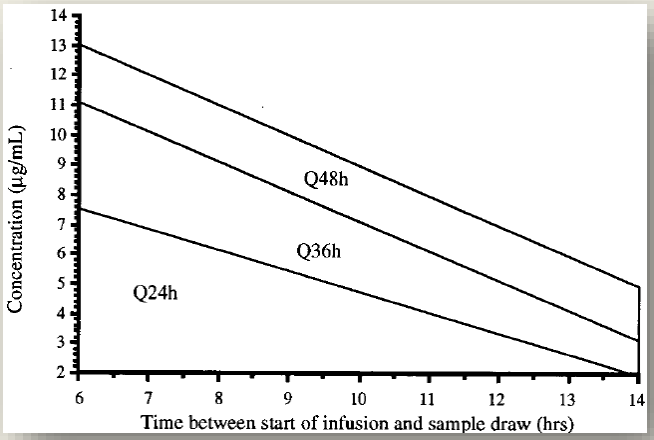
Monitoring:

Initial Monitoring

- Single level drawn 8-12 hours after first dose (from the start of infusion)
- Use nomogram to confirm/modify dosage interval
- Only applicable for 7 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance
  - Gentamicin/tobramycin (7 mg/kg/dose): Plot level on graph
  - Amikacin (15 mg/kg/dose): Divide level in half, then plot on graph

Follow up trough level testing

- Trough monitoring (30-60 minutes prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure
- Maintenance random levels should be monitored at least once weekly
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered



Appendix A2: Urban & Craig Nomogram

Initial Dosing:

- **Gentamicin/Tobramycin 5 mg/kg IV Q24H based on actual body weight**

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin
≥ 60 mL/min	5 mg/kg Q24H	15 mg/kg Q24H
40 – 59 mL/min	5 mg/kg Q36H	15 mg/kg Q36H
20 – 39 mL/min	5 mg/kg Q48H	15 mg/kg Q48H
< 20 mL/min	Not recommended	Not recommended
Hemodialysis	Not recommended	Not recommended
CRRT	Not recommended	Not recommended

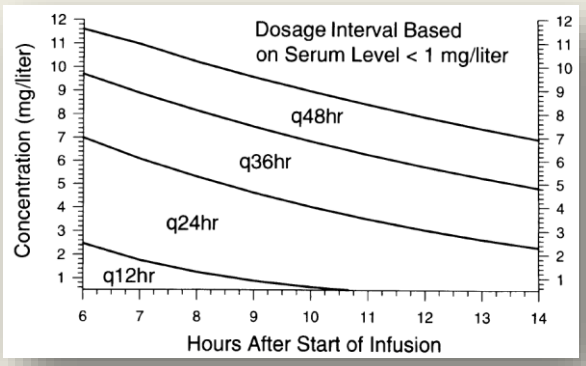
Monitoring:

Initial Monitoring

- Single level drawn 8-12 hours after the first dose.
- Use nomogram to confirm/modify dosage interval.
- Only applicable for 5 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance)
  - Gentamicin/Tobramycin 5 mg/kg/dose
  - Amikacin 15 mg/kg/dose

Follow up monitoring:

- Trough monitoring (30-60 minutes prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure
- Maintenance random levels should be monitored at least once weekly
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered



Appendix A3: Cystic Fibrosis Dosing[17]

Initial Dosing:

CrCl (mL/min)	Tobramycin	Amikacin
≥ 60 mL/min	10 mg/kg Q24H	20 mg/kg Q24H
40 – 59 mL/min	10 mg/kg Q36H	20 mg/kg Q36H
30 – 39 mL/min	10 mg/kg Q48H	20 mg/kg Q48H
20 – 29 mL/min	Not recommended	Not recommended
< 20 mL/min	Not recommended	Not recommended
Hemodialysis	Not recommended	Not recommended
CRRT	Not recommended	Not recommended

Monitoring:

Timing of Levels		
	Peaks	**Troughs**
Initial Level	30 minutes after 2nd dose	30-60 minutes before 2nd dose
Maintenance levels	• Weekly peaks/troughs for prolonged duration of therapy • Acute renal changes • Changes in dosing regimen	
Goal Levels		
Antibiotic	**Target Peak**	**Target Trough**
Gentamicin/Tobramycin	20 – 30 mcg/mL	< 1 – 2 mcg/mL
Amikacin	40 – 60 mcg/mL	< 4 – 8 mcg/mL

Appendix B: Conventional / Traditional Dosing (Gram-negative infections)

Initial Dosing:

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin
> 60 mL/min	1.7 mg/kg Q8H	5 – 7.5 mg/kg Q8H
40 – 59 mL/min	1.7 mg/kg Q12H	5 – 7.5 mg/kg Q12H
30 – 39 mL/min	1.7 mg/kg Q24H	5 – 7.5 mg/kg Q24H
20 – 29 mL/min	1.7 mg/kg Q24H	5 – 7.5 mg/kg Q24H
< 20 mL/min; AKI	2 mg/kg load, then dose by level	5 mg/kg load, then dose by level
Hemodialysis	2 mg/kg load, then 1.5 mg/kg post-HD; Redose for 4-hr post-HD level Cp<1 mg/L or pre-HD ▪ Cp < 1 mg/L (mild UTI) ▪ Cp < 2–3 mg/L (moderate-severe UTI) ▪ Cp < 3–5 mg/L (severe GNR infection)	5 – 7.5 mg/kg post-HD
CRRT	1.5 – 2.5 mg/kg Q24-48H	10 mg/kg load, then 7.5 mg/kg Q24-48H

Monitoring:

Timing of Levels			
Regimen Frequency	**Peaks**		**Troughs**
Q8H	30 minutes after 3rd dose		30 – 60 minutes before 4th dose
Q12H	30 minutes after 3rd dose		30 – 60 minutes before 3rd dose
Q24H	30 minutes after 2nd dose		30 – 60 minutes before 2nd dose
Q48H	30 minutes after 2nd dose		30 – 60 minutes before 2nd dose
Dose by level	30 minutes after 2nd dose		Redose when Cp < 1 mcg/mL
Hemodialysis	30 minutes after 2nd dose		4-hr post-HD level Cp < 1 mcg/mL or pre-HD levels (see initial dosing table)
CRRT	30 minutes after 2nd dose		30 – 60 minutes before 3rd dose
Goal Levels			
Antibiotic	**Indication**	**Target Peak**	**Target Trough**
Gentamicin/Tobramycin	Life-threatening infection Serious Infections Urinary tract infections	8 – 10 mcg/mL 6 – 8 mcg/mL 4 – 6 mcg/mL	< 1 – 2 mcg/mL
Amikacin	Life-threatening infection Serious Infections Urinary tract infections	25 – 30 mcg/mL 20 – 25 mcg/mL 15 – 20 mcg/mL	< 4 – 8 mcg/mL

Appendix C: Gram-Positive Synergy Dosing

Initial Dosing:

CrCL (mL/min)	Synergy Dosing (Gentamicin/Tobramycin)
> 60	1 mg/kg Q8H*
40-59	1 mg/kg Q12H
30-39	1 mg/kg Q24H
20-29	1 mg/kg Q24H
<20; AKI	Redose when Cp < 1 mg/L
Hemodialysis	1 mg/kg q48-72H; Redose for pre-HD or post-HD Cp <1mg/L
CRRT	1 mg/kg Q24H, then by level

*Streptococci, *Streptococcus gallolyticus (bovis)*, *Streptococcus viridans* endocarditis: optional dosing 3 mg/kg q24h for CrCl > 60 mL/min.
Staphylococci; Enterococcus spp (strains susceptible to PCN and gentamicin) endocarditis: optional dosing 3 mg/kg in 2 or 3 equally divided doses

Monitoring:

Timing of Levels		
Regimen Frequency	**Peaks**	**Troughs**
Q8H	30 minutes after 3rd dose	30 – 60 minutes before 4th dose
Q12H	30 minutes after 3rd dose	30 – 60 minutes before 3rd dose
Q24H	30 minutes after 2nd dose	30 – 60 minutes before 2nd dose
Q48H	30 minutes after 2nd dose	30 – 60 minutes before 2nd dose
Dose by level	30 minutes after 2nd dose	Redose when Cp < 1 mcg/mL
Hemodialysis	30 minutes after 2nd dose	Immediately *before* HD; Redose for pre-HD or 4-hr post-HD level: Cp < 1 mg/L
CRRT	30 minutes after 2nd dose	30 – 60 minutes before 3rd dose
Goal Levels		
Antibiotic	**Target Peak**	**Target Trough**
Gentamicin/Tobramycin	3 – 4 mcg/mL	< 1 mcg/mL

Appendix D: Non-TB Mycobacterial Infections

Guideline Recommendations:

ATS/IDSA Nontuberculous Mycobacterial Disease Guidelines[17]	**US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations[18]**
➢ 10 – 15 mg/kg Q24H ➢ user lower dose (10 mg/kg Q24H; max of 500 mg daily) in patients older than 50 years old and/or in patients whom long-term therapy (> 3 weeks) is anticipated ➢ Alt: 25 mg/kg three times weekly	➢ 10 – 30 mg/kg Q24H ➢ Alt: 15 mg/kg/day in two divided doses ➢ *Usually aiming for peak levels of 20– 30 mg/mL and trough levels of <5–10 mg/mL.

Initial Dose:

CrCL (mL/min)	Amikacin
≥ 60 mL/min	10 – 15 mg/kg Q24H
40 – 59 mL/min	10 – 15 mg/kg Q36H
30 – 39 mL/min	10 – 15 mg/kg Q48H
20 – 29 mL/min	Dose by level
< 20 mL/min	Dose by level
Hemodialysis	Dose by level
CRRT	Dose by level

Monitoring:

Timing of Levels		
	Peaks	**Troughs**
Initial Level	30 minutes after 2nd dose	30-60 minutes before 2nd dose
Maintenance levels	• Weekly peaks/troughs for prolonged duration of therapy • Acute renal changes • Changes in dosing regimen	
Goal Levels		
Regimen	**Target Peak**	**Target Trough**
10 – 15 mg/kg Q24H	20 – 30 mcg/mL	< 4 mcg/mL
25 mg/kg three times weekly	65 – 85 mcg/mL	< 4 mcg/mL

Note: There is no established PK/PD target for optimal microbiologic and clinical outcome. The above peak values are typically expected and therefore have been suggested TDM targets by national guidelines. The goal trough is to ensure drug clearance and minimize accumulation/toxicity.

Appendix E: PK Calculations

Aminoglycoside Pharmacokinetic Parameters

PK parameter	Value
Bioavailability (F)	-Water soluble -Poorly lipid soluble -Poor oral absorption
Volume of Distribution	0.25 L/kg (0.1 – 0.5 L/kg)
Fraction unbound in plasma	> 0.95
Clearance • Normal renal function • Functionally anephric • Hemodialysis	 Same as CrCL 0.0043 L/kg/hr 1.8 L/hr
t ½ • normal renal function • functionally anephric	 2 – 3 hours 30 – 60 hours

Abbreviations
IBW = ideal body weight
ABW = actual body weight
DBW = dosing body weight
kel = elimination rate constant
Vd = volume of distribution
τ = dosing interval
t = time of infusion
t_{before} = time between blood draw and start of infusion
t_{end} = time from end of infusion to blood draw
$t_{1/2}$ = half-life
C_{max} = peak serum level at steady-state
C_{min} = trough serum level at steady-state
SCr = serum creatinine

Initial Dosing

1. Determine CrCL using Cockcroft-Gault	CrCL (mL/min) = $\frac{(140 - age) \times IBW}{SCr \times 72}$ (x 0.85 for females)
2. Estimate elimination rate constant (Ke) based on PK kinetics	Ke = (0.003 x CrCl) + 0.01
3. Estimate half-life (t ½)	$t\,½ = \frac{0.693}{ke}$
4. Calculate Volume of distribution (Vd) using ABW or AdjBW	Gentamicin/Tobramycin = 0.25 L/kg Amikacin = 0.3 L/kg
5. Infusion time	Gentamicin/Tobramycin = 30 minutes Amikacin = 30 minutes; 60 minutes if doses > 15 mg/kg
6. Estimated dosing interval based on goal levels Ctr = Cmin = desired trough Cpeak = Cmax = desired peak Ti = infusion time	$T = \left(\frac{Ln (C\,max / C\,min)}{Ke}\right) + ti$ OR Estimated (T) = 3 x t ½
7. Maintenance dose (MD):	$MD = \frac{[(K_e) \times (VD) \times (ti) \times (C_{peak}\ desired) \times (1 - e^{-Ke\,T})]}{[(1 - e^{-Ke\,ti})]}$ OR MD = (Cpeak desired) x VD

Individualized Dose Revisions

1. Determine elimination rate constant Use levels within the same dosing interval	$K\ (hr^{-1}) = \frac{\text{(Ln peak/trough)}}{\Delta \text{ time between levels}}$ OR $k = \frac{\ln (Cmax/Cmin)}{\tau - (t + t_{end} + t_{before})}$
2. Determine actual Cmax (if level not drawn at correct time;1 hour after the start or 30 minutes after completion of infusion)	$Cmax_{actual} = \frac{Cmax}{e^{-k(tend)}}$
3. Determine half-life	$t\ ½ = \frac{0.693}{k}$ Dosing interval for traditional dosing method = ~ 3-4 times the half-life
4. Time to achieve goal trough level	Time to clearance = $\frac{\text{Ln (actual trough/ desired trough)}}{Ke}$
5. Estimate dosing interval ti = infusion time τ = interval	$\tau = \left[\frac{\text{Ln (Cmax/Cmin)}}{K}\right] + ti$ OR Estimated $\tau = 3 \times t½$
6. Determine Vd t1 = time from beginning infusion to Cpeak	$Vd\ (L) = \frac{\text{Dose}}{Cmax_{actual}\ (1 - e^{-k(tau)})}$ OR $Vd\ (L) = \frac{[(Dose/C_{peak})}{(1 - e^{-K\tau})]} \times e^{-Kt_1}$
7. New maintenance dose ti = infusion time τ = interval	$MD = \frac{[(k_e) \times (Vd) \times (ti) \times (C_{peak}\ desired) \times (1 - e^{-K\tau})]}{[\ (1 - e^{-K\ ti})\ ]}$ OR MD = (goal peak Cmax) x Vd

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Document Information

A. Original Author/Date
Emily Mui, PharmD, BCPS: 05/2012

B. Gatekeeper
Pharmacy
Stanford Antimicrobial Safety & Sustainability Program (SASS Program)

C. Review and Renewal Requirement
This document will be reviewed every three years and as required by change of law or practice

D. Revision/Review History
Emily Mui, PharmD: 05/2013, 08/2017

E. Approvals
Approved by Antimicrobial Subcommittee: 05/2012, 05/2013, 08/2017
Approved by P&T Committee: 05/2012, 05/2013, 09/2017