Pharmacokinetic and Pharmacodynamic Dose Optimization of Antibiotics (β-lactams, aminoglycosides, and ciprofloxacin) for the Treatment of Gram-Negative Infections – Adult – Inpatient/Emergency Department Clinical Practice Guideline

Note: Active Table of Contents – Click each header below to jump to the section of interest

Table of Contents
EXECUTIVE SUMMARY ................................................................. 3
TABLE 1. PK/PD OPTIMIZED DOSING REGIMENS .................................................... 4
TABLE 2. AMINOGLYCOSIDE DOSING STRATEGIES .............................................. 5
FIGURE 1. GENTAMICIN AND TOBRAMYCIN DOSING ............................................. 6
INTRODUCTION ......................................................................................... 7
SCOPE ........................................................................................................ 7
DEFINITIONS ............................................................................................ 7
METHODOLOGY .......................................................................................... 19
COLLATERAL TOOLS & RESOURCES .......................................................... 21
APPENDIX A. COMPATIBILITY INFORMATION ................................................. 22
APPENDIX B. MONTE CARLO SIMULATIONS ................................................ 24
APPENDIX C. ANTIBIOTIC ALTERNATIVES TO FLUOROQUINOLONES .......... 30
TABLE 1. RECOMMENDED ALTERNATIVE EMPIRIC REGIMENS – GENERAL CARE ................................................................................................................................. 30
TABLE 2. RECOMMENDED ALTERNATIVE EMPIRIC REGIMENS – INTENSIVE CARE MEDICINE ................................................................................................................................. 32
TABLE 3. RECOMMENDED ALTERNATIVE EMPIRIC REGIMENS – ABDOMINAL TRANSPLANT ................................................................................................................................. 34
APPENDIX D. TWO-POINT KINETIC CALCULATIONS FOR TRADITIONAL OR SYNERGY DOSING WITH GENTAMICIN AND TOBRAMYCIN 30-MINUTE INFUSIONS ................................................................................................................................. 36
REFERENCES ............................................................................................. 41
Content Experts:
Name: Lucas Schulz, PharmD, BCPS AQ-ID – Pharmacy Services
Phone Number: 608-890-8617
Email Address: L.Schulz2@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS – Pharmacy Services, Drug Policy Program
Phone Number: 608-263-1328
Email Address: PTrapskin@uwhealth.org

Guideline Authors:
Meagan Adamsick, PharmD – Pharmacy Services
Jeffrey Fish, PharmD, BCPS – Pharmacy Services
Lucas Schulz, PharmD, BCPS AQ-ID – Pharmacy Services

Workgroup Members:
Barry Fox, MD – Infectious Diseases
Joshua Vanderloo, PharmD, BCPS – Pharmacy Services, Drug Policy Program

Reviewers:
David Andes, MD – Infectious Diseases
Alex Lepak, MD – Infectious Diseases
Philip Trapskin, PharmD, BCPS – Pharmacy Services, Drug Policy Program
Marie Pietruszka, PharmD, BCPS – Pharmacy Services
Erin McCreary, PharmD, BCPS – Pharmacy Services
Katie Cinnamon, PharmD, BCPS – Pharmacy Services

Committee Approvals:
UW Health Antimicrobial Use Subcommittee: August 2018
UW Health Lab Practice Committee: September 2018
UW Health P&T Committee: September 2018
Executive Summary

Key Practice Recommendations

Pharmacokinetic/pharmacodynamics (PK/PD) principles should be used to optimize (improve efficacy and minimize toxicity) antimicrobial utilization when possible due to increasing antimicrobial resistance and the limited availability of novel antimicrobial agents.1-6 (UW Health Strong Recommendation, High Quality of Evidence)

1. The dosing of antibiotics for included patient populations should be based upon recommendations outlined in Table 1. In general, dosing regimens in Table 1 provide PK/PD optimized empiric therapy for high-MIC pathogens. When the MIC of the pathogen is known and is low, dose reductions should be completed to re-optimize antibiotic therapy. (UW Health Strong Recommendation, Low Quality of Evidence)

2. Patients EXCLUDED from this guideline:
   a. Cystic fibrosis patients
   b. Patients receiving antibiotic treatment for central nervous system infections.
   c. Pediatric patients

3. Patients in the ICU, receiving antibiotics for treatment of septic shock, should receive their first dose of antibiotic as a 30-minute infusion to reduce the time to a therapeutic concentration. (UW Health Strong Recommendation, Low Quality of Evidence)

4. Patients not in septic shock may or may not receive their first dose of antibiotic over 30 minutes and may have prolonged infusion started immediately. (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

5. Occasionally, dose optimization can achieve concentrations sufficient to treat organisms reported as resistant.7 This may be an alternative to more toxic antibiotics, such as colistin. Dosing of antimicrobials in this scenario should be done under the guidance of the Infectious Disease service via consult with an infectious disease pharmacist. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

6. Line Time/Incompatibility: Patients requiring significant intravenous access for other medications may receive standard intermittent infusions (30-60 minute) of β-lactam antibiotics to minimize antibiotic line time and drug incompatibility (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)
   a. These patients should be transitioned to prolonged infusion as soon as it is clinically appropriate. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

7. Empiric dosing of aminoglycosides occurs via three strategies: traditional dosing, extended interval dosing (EID), or synergy dosing.
   a. Refer to Table 2 and Figure 1 for aminoglycoside dosing recommendations by patient population.
   b. Aminoglycoside concentration monitoring should occur after five half-lives for synergy and traditional dosing. (UW Health Strong Recommendation, Low Quality of Evidence) This is usually between 24 and 36 hours after starting therapy.
   c. A single aminoglycoside concentration monitoring should occur between 6 and 14 hours after initiation of extended interval dosing. (UW Health Strong Recommendation, Low Quality of Evidence)
Table 1. PK/PD optimized dosing regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Est CrCL (mL/min)</th>
<th>Empiric</th>
<th>Definitive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sepsis, Septic Shock Indication</td>
<td>Non-sepsis^A Indication</td>
</tr>
<tr>
<td>Cefepime^C - 4hr infusion</td>
<td>&gt; 50</td>
<td>2 g IV Q8H</td>
<td>1 g IV Q6H</td>
</tr>
<tr>
<td></td>
<td>30 – 50</td>
<td>2 g IV Q12H</td>
<td>1 g IV Q8H</td>
</tr>
<tr>
<td></td>
<td>15 – 29</td>
<td>2 g IV Q24H</td>
<td>1 g IV Q12H</td>
</tr>
<tr>
<td></td>
<td>&lt;15 / HD</td>
<td>1 g IV Q24H</td>
<td>1 g IV Q24H</td>
</tr>
<tr>
<td>Piperacillin/ tazobactam - 4hr infusion</td>
<td>&gt; 20</td>
<td>4.5 g IV Q8H</td>
<td>3.375 g IV Q8H</td>
</tr>
<tr>
<td></td>
<td>&lt; 20</td>
<td>4.5 g IV Q12H</td>
<td>3.375 g IV Q12H</td>
</tr>
<tr>
<td>Meropenem^C - 3hr infusion</td>
<td>&gt; 50</td>
<td>500 mg IV Q6H</td>
<td>500 mg IV Q8H</td>
</tr>
<tr>
<td></td>
<td>26 – 50</td>
<td>500 mg IV Q8H</td>
<td>500 mg IV Q8H</td>
</tr>
<tr>
<td></td>
<td>10 – 25</td>
<td>500 mg IV Q12H</td>
<td>500 mg IV Q12H</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 / HD</td>
<td>500 mg IV Q24H</td>
<td>500 mg IV Q24H</td>
</tr>
<tr>
<td>Ciprofloxacin - 1hr infusion</td>
<td>&gt; 30</td>
<td>400 mg IV Q8H or 600 mg IV Q12H</td>
<td>400 mg IV Q12H</td>
</tr>
<tr>
<td></td>
<td>10 – 30</td>
<td>400 mg IV Q12H</td>
<td>400 mg IV Q12H</td>
</tr>
<tr>
<td></td>
<td>&lt;10 / HD</td>
<td>400 mg IV Q24H</td>
<td>400 mg IV Q24H</td>
</tr>
</tbody>
</table>

^A includes neutropenic fever
^B obesity is defined as BMI ≥40 OR actual body weight >120kg
^C patients with a concern for seizure disorders should receive prolonged infusions whenever clinically possible to minimize the risk of precipitating seizures

MIC – Minimum Inhibitory Concentration; HD – Hemodialysis
### Table 2. Aminoglycoside dosing strategies

<table>
<thead>
<tr>
<th>Dosing strategy</th>
<th>Patient population</th>
<th>Initial Dose (normal renal function)</th>
<th>Dosing weight</th>
<th>Goal peak/C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Goal trough/C&lt;sub&gt;min&lt;/sub&gt;</th>
<th>Timing of Concentration Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
<td>See Table 9</td>
<td></td>
<td>8-10 mcg/mL</td>
<td>&lt;1 mcg/mL (&lt;0.5 mcg/mL preferred)</td>
<td>See Table 9</td>
</tr>
<tr>
<td></td>
<td>• Neonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe burns (&gt; 20% body surface area)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anasarca</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ascites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Endocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extended Interval Dosing</strong></td>
<td>• Gram-negative infections</td>
<td>7 mg/kg&lt;sup&gt;A&lt;/sup&gt; for respiratory infections</td>
<td>(1) total body weight is less than ideal body weight, then use total body weight</td>
<td>Dosing per extended interval dosing nomograms</td>
<td>After first dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg/kg&lt;sup&gt;A&lt;/sup&gt; for all other infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Synergy</strong></td>
<td>• Enterococcal endocarditis and prosthetic staphylococcal endocarditis</td>
<td>1 mg/kg IV every 8 hours</td>
<td>(2) BMI &gt;30, then use adjusted body weight (see definitions)</td>
<td>3-4 mcg/mL</td>
<td>&lt;1 mcg/mL (&lt;0.5 mcg/mL preferred)</td>
<td>See Figure 1</td>
</tr>
<tr>
<td></td>
<td>• Streptococcal endocarditis</td>
<td>3 mg/kg every 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>A</sup> Multiply dose and drug concentration monitoring by a factor of three if using amikacin.
Figure 1. Gentamicin and Tobramycin Dosing

Gentamicin and Tobramycin Dosing Methods
(see full text for Amikacin information)

Traditional Dosing

What is the dosing approach?*

Synergy Dosing

Extended Interval Dosing

- CrCl >60 mL/min
  - 1.5-2 mg/kg every 8 hours
  - Trough 30-60 minutes before the 4th dose
  - Peak: 30-60 minutes after the end of the 30-minute infusion following the 3rd dose

- CrCl 40-59 mL/min
  - 1.5-2 mg/kg every 12 hours
  - Trough 30-60 minutes before the 3rd dose
  - Mid-point (random) concentration 10-12 hours after the 2nd dose
  - Allow 2 hours post-dialysis, then draw level
  - Peak: 30-60 minutes after the end of the 60-minute infusion following the 2nd dose

- CrCl <40 mL/min
  - 2 mg/kg load, then 1.5 mg/kg every 24 hours or longer
  - Mid-point (random) concentration 10-12 hours after the 2nd dose
  - Allow 2 hours post-dialysis, then draw level

- Hemodialysis
  - 2 mg/kg load, then 1.5 mg/kg post-dialysis

- Patient Excluded from EID:
  - Pregnant patients
  - Neonates
  - Severe burns (>20% BSA)
  - Anasarca
  - Ascites
  - Cystic Fibrosis
  - Meningitis
  - Endocarditis
  - CrCl <20 mL/min
  - Unstable renal function

- Infection type dictates weight-based dose
  - Pneumonia: 7 mg/kg Gentamicin or Tobramycin once
  - All other infections: 5 mg/kg Gentamicin or Tobramycin once

- Concentration: 6-14 hours after the START of the 60-minute infusion

- Use appropriate nomogram to determine dosing frequency

Synergy Dosing

- CrCl >50 mL/min
  - 1 mg/kg Q8H Gentamicin or Tobramycin
  - Trough 30 minutes before the 4th dose
  - Goal: <1 mcg/mL
  - Peak: 30-60 minutes after the end of the 60-minute infusion following the 3rd dose

- CrCl <50 mL/min
  - 1 mg/kg Q12H or Q24H Gentamicin or Tobramycin
  - Q12H Regimen:
    - Trough 30-60 minutes before the 3rd dose
    - Goal: <1 mcg/mL
  - Q24H Regimen:
    - Trough 30 minutes before the 2nd dose
    - Goal: <1 mcg/mL
  - Peak: 30-60 minutes after the end of the infusion of the 2nd dose

* Dosing weight:
  - Use IBW unless TBW<IBW then use TBW.
  - If BMI >30 mg/m², then use AdjBW.

Abbreviations:
- IBW = Ideal Body Weight
- TBW = Total Body Weight
- AdjBW = Adjusted Body Weight
**Introduction**
As a result of continuously developing antimicrobial resistance and a paucity of novel antimicrobial development, new dosing strategies have been proposed to optimize the pharmacodynamics of existing antimicrobials. Antimicrobial activity can be separated into two broad categories: time-dependent or concentration-dependent killing. Time-dependent antimicrobials demonstrate maximum efficacy when the percent of time above the minimum inhibitory concentration (%T>MIC) is optimized. In contrast, the efficacy of concentration-dependent antimicrobials is dependent on the ratio of the area under the concentration-time curve and the minimum inhibitory concentration (AUC/MIC) or concentration/MIC ratio. 

**Scope**

**Intended Users:** Physicians, advanced practice providers, pharmacists, and nurses

**Objectives:**
The objective of this guideline is to improve the use of antibiotic agents with activity against Gram-negative organisms by optimizing the pharmacokinetic and pharmacodynamics antibiotic characteristics through prolonged infusion, extended interval dosing, appropriate drug concentration monitoring, or dose modification based on minimum inhibitory concentration.

**Target Population:** All adult patients requiring antimicrobial therapy with piperacillin/tazobactam, meropenem, cefepime, gentamicin, tobramycin, amikacin or ciprofloxacin should receive PK/PD optimized therapy with the following exclusions:

a. Individuals with cystic fibrosis are excluded from this guideline. These patients may receive intermittent or prolonged infusions of β-lactam antibiotics at the discretion of the primary team.

b. Patients with documented or suspected central nervous system (CNS) infection are excluded from this guideline due to the higher peak antibiotic concentrations required for CNS penetration.

c. Patients under the age of 18 years are excluded from this guideline. These patients may receive intermittent or prolonged infusions of β-lactam antibiotics at the discretion of the pediatric primary team.

**Clinical Questions Considered:**
- How should we appropriately manage prolonged infusion of piperacillin/tazobactam, cefepime, and meropenem?
- What methods of aminoglycoside dosing are appropriate for what patient populations; including extended interval, synergy, and traditional dosing of aminoglycoside antibiotics?
- How should ciprofloxacin be dose-reduced based on a pathogen MIC?

**Definitions**
1. **Total body weight (TBW):** actual total mass of the patient in kilograms.
2. **Body mass index (BMI):** BMI = TBW/(height (m²))
3. **Ideal body weight (IBW):**
   - Males IBW = 50 kg + 2.3 kg for each inch over 5 feet in height
   - Females IBW = 45.5 kg + 2.3 kg for each inch over 5 feet in height
4. **Adjusted body weight (AdjBW):** AdjBW = IBW + (0.4 x [TBW – IBW])
5. **Lean body weight (LBW):**
   - Males LBW = (9270 x TBW)/(6680 + 216 x BMI)
   - Females LBW = (9270 x TBW)/(8780 + 244 x BMI)
6. **MIC:** minimum inhibitory concentration
7. **EID:** extended interval dosing
8. **Empiric therapy:** Selection of antimicrobials based on clinical presentation prior to culture results
9. **Definitive therapy:** Deescalation of antimicrobial selection to narrower spectrum based on specific pathogen-directed treatment with culture and sensitivity results or with no culture results after 72 hours
Recommendations

General Recommendations
Pharmacokinetic/pharmacodynamic (PK/PD) principles should be used to optimize (improve efficacy and minimize toxicity) antimicrobial utilization when possible due to increasing antimicrobial resistance and limited availability of novel antimicrobial agents.1-8 (UW Health Strong Recommendation, High Quality of Evidence)

1. Consider administering antimicrobials with short half-lives that exhibit time-dependent antimicrobial activity (e.g. β-lactam agents) by prolonged infusion because this dosing strategy results in an increased likelihood of successful antimicrobial activity, (UW Health Strong Recommendation, High Quality of Evidence) shorter hospital stays, and reduced mortality.5-6,11-13 (UW Health Strong Recommendation, Low Quality of Evidence)

1.1. Providing some β-lactam antimicrobials by prolonged infusion can reduce hospital costs and reduce the total daily dose of drug administered without compromising antimicrobial efficacy.3,14

1.2. A prospective, randomized, open-labeled controlled trial evaluated prolonged infusions (referred to as continuous infusion in the publication) versus intermittent 30-minute infusions of several beta-lactam antibiotics.13 Seventy patients were randomized to each group. The study showed statistically significant differences in clinical cure (39 patients vs. 24 patients, 95% CI: -0.4 to -0.1, p=0.011), and 100% PK target attainment on day 3 (55 patients vs 37 patients, 95% CI: -0.4 to -0.1, p<0.001).

1.3. A retrospective study of 121 patients was conducted at a surgical/medical ICU after implementing prolonged infusions of piperacillin/tazobactam and meropenem.12 The study showed statistically significant decreases in ventilator days (16.8 days to 9.6 days, 95% CI: -12.4 to -2.4), ICU length of stay (15.3 days to 10.7 days, 95% CI: -8.3 to -1.4), and hospital length of stay (30.9 days to 22.4 days, 95% CI: -18.7 to -1.2) between the intermittent infusion and the prolonged infusion group. There was also a decrease in mortality in the prolonged infusion group (20.7% to 12.4%, OR 0.54 (95% CI 0.18-1.66)) that did not reach statistical significance. The use of the prolonged infusion was also associated with an estimated $10,000 drug cost savings for the 54 patients included in the prolonged infusion group.

2. When administering β-lactam agents as a prolonged infusion, the difference in time to a therapeutic concentration between intermittent and prolonged infusions is not considered to be clinically significant for non-critically ill patients.15-17 Therefore, a ‘loading’ dose administered over 30 minutes is not recommended for all patients, but should be given in patients with sepsis and septic shock. (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

2.1. Patients in the ICU, who are receiving antibiotics for treatment of septic shock, should receive the first dose as a 30-minute infusion. (UW Health Weak/Conditional Recommendation, Low Quality of Evidence) Subsequent doses should be given as prolonged infusion.18,19 (UW Health Strong Recommendation, Low Quality of Evidence)

2.2. Non-ICU patients may or may not receive the first dose as a 30-minute infusion. The time to f/T>MIC is not expected to be clinically significant in the non-ICU patient.

3. Consider administering concentration-dependent antimicrobials with a post-antibiotic effect (e.g. aminoglycosides) at a high dose and with extended dosing interval because this dosing strategy results in an increased likelihood of successful antimicrobial activity and a lower incidence of adverse drug events.20,21 (UW Health Weak/Conditional Recommendation, Low Quality of Evidence). Additionally, high-dose extended interval dosing has been shown to reduce hospital costs and total daily dose of drug administered without compromising antimicrobial efficacy.20,22 (UW Health Strong Recommendation, Low Quality of Evidence)

4. Occasionally, dose optimization can achieve concentrations sufficient to treat organisms reported as resistant.7 This may be an alternative to more toxic antibiotics, such as colistin. Dosing of antimicrobials in this scenario should be done under the guidance of an Infectious Disease consult and an infectious disease pharmacist. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

4.1. Monte Carlo simulations of various patient populations are listed in Appendix A. These may be used to help select alternative dosing regimens. When selecting a dose, the goal should be to achieve at least 90% probability of target attainment (y-axis) at the expected or reported minimum inhibitory concentration (MIC) value (x-axis).

5. Line Time/Incompatibility
5.1. Patients requiring significant intravenous access for other medications may receive standard intermittent infusions (30-60 minutes) of β-lactam antibiotics to minimize antibiotic line time and drug incompatibility. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

5.2. These patients should be transitioned to prolonged infusion antibiotics as soon as it is clinically appropriate. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

**β-lactam Antibiotics**

Beta-lactam antibiotics, including piperacillin/tazobactam, cefepime, and meropenem, all exhibit time-dependent killing. Prolonged and continuous infusions of β-lactams increase the fraction of time when the antibiotic concentration exceeds an organism’s MIC and, as a result, the antibiotic’s efficacy is improved. Prolonged infusions have beneficial effects over continuous infusions including not needing a dedicated line/catheter and usually using a lower total daily dose. Prolonged infusions do not appear to increase risk of acute kidney injury (AKI) compared to intermittent infusions.

**Piperacillin/Tazobactam Recommendations and Evidence**

1. Administration of piperacillin/tazobactam by four-hour prolonged infusion is recommended for most patients; exceptions include patients receiving therapy for meningitis and patients with line-time issues. Dosing should be based on Table 3 (UW Health Strong Recommendation, High Quality of Evidence)

<table>
<thead>
<tr>
<th>Estimated CrCL (mL/min)</th>
<th>Standard Dosing</th>
<th>Obesity A Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>3.375 g IV Q8H</td>
<td>4.5 g IV Q8H</td>
</tr>
<tr>
<td>&lt; 20 / HD</td>
<td>3.375 g IV Q12H</td>
<td>4.5 g IV Q12H</td>
</tr>
</tbody>
</table>

A Obesity defined in most studies as a BMI >40 or weight >120 kg

2. Administering piperacillin/tazobactam by prolonged infusion results in shorter hospital stays and reduced mortality. Decreased mortality, improved outcomes, and reduced length of stay were observed in a meta-analysis of severely ill patients.

3. Providing piperacillin/tazobactam by prolonged infusion can reduce hospital costs and reduce the total daily dose of drug administered to the patient without compromising antimicrobial efficacy.

4. Patients who are obese (BMI > 40 or weight >120 kg) are candidates for prolonged infusion piperacillin/tazobactam therapy.

4.6. Providers may consider administering 4.5 g piperacillin/tazobactam over four hours every eight hours in the obese population (BMI >40 or weight >120 kg) to increase the likelihood of target attainment (UW Health Strong Recommendation, Moderate Quality of Evidence)

5. Patients receiving prolonged infusion in the ICU for treatment of septic shock should receive the first dose as a 30-minute infusion. Subsequent doses should be given as prolonged infusion. (UW Health Strong Recommendation, Low Quality of Evidence)

5.6. Increased piperacillin-tazobactam doses of 4.5 g by prolonged infusion in patients with sepsis improves clinical cure rates and better target attainment. (UW Health Weak/Conditional Recommendation, Low Quality of Evidence)

5.6.1. Prolonged infusion piperacillin-tazobactam in this patient population may reduce duration of therapy and provide cost savings.

6. The differences between intermittent and prolonged infusions in the time to achieve therapeutic concentrations of piperacillin/tazobactam are not considered to be clinically significant for the non-critically ill patient. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

**Meropenem Recommendations and Evidence**

1. Administration of meropenem by three-hour prolonged infusion is recommended for most patients; exceptions include patients receiving therapy for meningitis and patients with line-time issues. Dosing should be based on Table 4. (UW Health Strong Recommendation, High Quality of Evidence)
Table 4: Prolonged Infusion Meropenem (infuse over 3 hours)

<table>
<thead>
<tr>
<th>Estimated CrCL (mL/min)</th>
<th>Initial/Empiric Dosing</th>
<th>Dose Reduction for Definitive Therapy</th>
<th>Obesity Dosing for Definitive Therapy^A</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>500 mg IV Q6H</td>
<td>500 mg IV Q8H</td>
<td>500 mg IV Q8H</td>
</tr>
<tr>
<td>26-50</td>
<td>500 mg IV Q8H</td>
<td>500 mg IV Q8H</td>
<td>500 mg IV Q8H</td>
</tr>
<tr>
<td>10-25</td>
<td>500 mg IV Q12H</td>
<td>500 mg IV Q12H</td>
<td>500 mg IV Q12H</td>
</tr>
<tr>
<td>&lt; 10 / HD</td>
<td>500 mg IV Q24H</td>
<td>500 mg IV Q24H</td>
<td>500 mg IV Q24H</td>
</tr>
</tbody>
</table>

^A Obesity defined in most studies as a BMI >40 or weight >120 kg

2. Administering meropenem by prolonged infusion results in a longer time above the MIC that correlates with efficacy in carbapenem-class antibiotics. (UW Health Strong Recommendation, High Quality of Evidence)

3. Providing meropenem by prolonged infusion can reduce hospital costs and reduce the total daily dose of drug administered to the patient without compromising antimicrobial efficacy. 

4. Patients who are obese (BMI >40) are candidates for prolonged infusion meropenem therapy.

4.1. A Monte Carlo simulation of meropenem dosing in morbidly obese patients (weight 152 ± 31 kg, BMI 54.7 ± 8.6) predicts a target attainment (40% time above MIC) of 92% for 500 mg meropenem given as a prolonged infusion over three hours every eight hours with the organism MIC of 4 mg/L. The target attainment for the same dose and duration infused over 0.5 hours is 68%. Target attainment for 500 mg meropenem given as a prolonged infusion over three hours every six hours is 92% whereas the same dose and duration infused over 0.5 hours is 76%. For organisms with a meropenem MIC ≤2mg/L, the likelihood of target attainment is greater than 95% for 500 mg prolonged infusion meropenem dosed either every six or every eight hours, greater than 93% for 500 mg intermittent infusion meropenem dosed every eight hours, and greater than 90% for 500 mg intermittent infusion meropenem dosed every six hours. Pharmacokinetic values were calculated based on samples obtained from nine morbidly obese patients treated with either 500 mg meropenem infused over 0.5 hours every six hours or 1 g meropenem infused over 0.5 hours every six hours. 

5. A Monte Carlo simulation for an estimated creatinine clearance of 40 mL/min (500 mg Q6H), 30 mL/min (500 mg Q8H), and 17 mL/min (500 mg Q12H) (George Drusano MD, personal communication). The results in Table 5 show percent of patients with meropenem concentrations greater than MIC for 40% of the dosing interval.

Table 5: Simulated probability of target attainment at various renal functions for meropenem

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Est. CrCL = 40 mL/min</th>
<th>Est. CrCL = 30 mL/min</th>
<th>Est. CrCL = 17 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>99%</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>4</td>
<td>92%</td>
<td>88%</td>
<td>75%</td>
</tr>
</tbody>
</table>

6. Patients receiving prolonged infusion in the ICU for the treatment of septic shock should receive the first dose as a 30-minute infusion. Subsequent doses should be given as prolonged infusion. (UW Health Strong Recommendation, Low Quality of Evidence)

7. The differences between intermittent and prolonged infusions in the time to achieve therapeutic concentrations of meropenem are not considered to be clinically significant in the non-critically ill patient. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

7.1. The median time to attain a therapeutic unbound concentration of meropenem (>4 mg/L) is approximately 30 minutes when 500 mg meropenem is administered over three hours.

7.2. A recent Monte Carlo simulation using population data from healthy volunteers demonstrated that it took 12 minutes to achieve concentration exceeding the MIC of a resistant Pseudomonas isolate (MIC 2 mcg/mL).

8. Dose Reduction

8.1. Patients who have no organism cultured after 72 hours of meropenem therapy OR who have an organism recovered with an MIC to meropenem that is ≤2 mcg/mL, should receive a dose reduction based on Table 4 (above). (UW Health Strong Recommendation, Low Quality of Evidence)
8.2. Patients who have an organism recovered with an MIC to meropenem that is >2 mcg/mL are not eligible for a dose reduction and should not be dose reduced unless their renal function changes. *(UW Health Strong Recommendation, Low Quality of Evidence)*

**Cefepime Recommendations and Evidence**

1. Administration of cefepime by four-hour prolonged infusion is recommended for most patients; exceptions include patients receiving therapy for meningitis and patients with line-time issues. Dosing should be based on Table 7. *(UW Health Strong Recommendation, Low Quality of Evidence)*

2. Patients with a concern for seizure disorders should receive prolonged infusions whenever clinically possible to minimize the risk of precipitating seizures.

### Table 7: Prolonged Infusion Cefepime (infuse over 4 hours)*

<table>
<thead>
<tr>
<th>Estimated CrCL (mL/min)</th>
<th>Empiric Dosing (ICU/Sepsis/Septic Shock)</th>
<th>Empiric Dosing (General Medicine and Neutropenic Fever)*B</th>
<th>Dose Reduction Based on Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>2 g IV Q8H</td>
<td>1 g IV Q6H</td>
<td>1 g IV Q6H</td>
</tr>
<tr>
<td>30-50</td>
<td>2 g IV Q12H</td>
<td>1 g IV Q8H</td>
<td>1 g IV Q8H</td>
</tr>
<tr>
<td>15-29</td>
<td>2 g IV Q24H</td>
<td>1 g IV Q12H</td>
<td>1 g IV Q12H</td>
</tr>
<tr>
<td>&lt;15 / HD</td>
<td>1 g IV Q24H</td>
<td>1 g IV Q24H</td>
<td>1 g IV Q24H</td>
</tr>
</tbody>
</table>

*A Patients with a concern for seizure disorders will receive prolonged infusions whenever clinically possible to minimize the risk of precipitating seizures

*B May consider using ICU dosing in obese (BMI ≥40) regardless of patient’s current location or service

3. Administering cefepime by prolonged infusion results in a longer time above the MIC that correlates with efficacy in cephalosporin-class antibiotics.5

4. Administering cefepime by prolonged infusion can result in shorter hospital stays, reduced hospital costs, and reduced mortality.36 Prolonged infusion cefepime demonstrated similar efficacy and outcomes to intermittent cefepime infusions in a small pilot study of patients with febrile neutropenia.37

4.1. A retrospective pre/post study compared patients with lab-confirmed Gram-negative bacteremia or pneumonia treated with 2 g cefepime given every eight hours (adjusted for renal function) as a 0.5 hour (pre-) or four hour (post-) infusion. There were no differences in length of stay, hospital costs, or mortality. However, in a pre-defined subgroup analysis of patients with lab-confirmed *P. aeruginosa* infection, overall mortality (20% vs. 3%, *p* = 0.03) and ICU median length of stay (18.5 vs. 8 days, *p* = 0.04) were significantly reduced in the prolonged-infusion group. Median length of stay (14.5 vs. 11 days, *p* = 0.36), median hospital costs ($51,231 vs. $28,048, *p* = 0.13) favored the prolonged infusion group, but did not reach statistical significance. After adjusting for significant confounders (APACHE-II score, admission to the ICU), the authors calculate an odds ratio of in-hospital death of 16.7 for intermittent infusion (95% CI: 1.57-949.35).

5. Patients who are obese are candidates for prolonged infusion cefepime therapy. Due to the apparent increased clearance of cefepime in obese patients, providers may consider using ICU dosing (2 g cefepime infused over four hours every 8 hours) in this population regardless of location or service, particularly if the organism MIC is ≥4 mg/L.38

6. Patients receiving prolonged infusion in the ICU, for treatment of septic shock, should receive the first dose as a 30-minute infusion. Subsequent doses should be given as prolonged infusion.*16,19 (UW Health Strong Recommendation, Low Quality of Evidence)

7. The differences between intermittent and prolonged infusions in the time to achieve therapeutic concentrations of cefepime are not considered to be clinically significant for non-critically ill patients.17 *(UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)*

8. The mean time to attain a therapeutic unbound concentration of cefepime (> 4 mg/L) is approximately 30 minutes when 1 g cefepime is administered over four hours.17

9. Dose Reduction

9.1. All patients from whom no organism is isolated after 72 hours of cefepime therapy OR for whom a non-*Pseudomonas* organism is isolated should receive a dose reduction based on Table 7 (above) regardless of patient’s location in the hospital. *(UW Health Strong Recommendation, Low Quality of Evidence)*
9.2. All patients from whom a *Pseudomonas* organism is recovered will be maintained at (or escalated to) 2 g every 8 hours infused over 4 hours (adjusted based on renal function) until cefepime is discontinued regardless of the patient's location in the hospital.

**Aminoglycosides**

Aminoglycosides demonstrate rapidly bactericidal, concentration-dependent killing with a prolonged post-antibiotic effect. Administering a higher dose of gentamicin, tobramycin, or amikacin increases the maximum concentration to MIC ratio and improves efficacy. Administering a higher dose less frequently ("HEAT", high-dose extended-interval aminoglycoside therapy or "EID" extended interval dosing) takes advantage of the significant post-antibiotic effect, providing equivalent efficacy and minimizing AUC-associated toxicity.²⁰

Empiric dosing of aminoglycosides occurs via three strategies: (1) extended interval dosing (EID), (2) traditional dosing, and (3) synergy dosing. Refer to the following recommendations for appropriate patient populations, dosing weight, timing of concentration monitoring, and goal peak/trough concentrations.

**Aminoglycoside General Recommendations and Evidence**

1. Appropriate dosing weight should be used for all dosing schemes. *(UW Health Strong Recommendation, Low Quality of Evidence)*
   1.1. For all dosing regimens, use ideal body weight unless BMI > 30 or total body weight is below ideal body weight.
      1.1.1. If BMI is greater than 30 kg/m², use adjusted body weight.³⁹
      1.1.2. AdjBW = IBW + (0.4 x (TBW – IBW))
      1.1.3. Use total body weight if total body weight is below ideal body weight.³⁹
   1.2. In EID, altered volume of distribution and glomerular filtration in obese patients increases the risk of both supratherapeutic and subtherapeutic drug concentrations.⁴⁰
      1.2.1. A retrospective evaluation of morbidly obese patients (>190% IBW) receiving EID of gentamicin or tobramycin assessed the appropriateness of an adjusted body weight-based nomogram. Gentamicin concentrations obtained 16 hours after an infusion in this population were as follows: therapeutic (71%), subtherapeutic (13%), and supratherapeutic (16%). The authors correlate older age with an increased likelihood of supratherapeutic values (61.5 ± 12.3 [supratherapeutic] vs. 50.5 ± 12.4 [therapeutic], p=0.04).⁴⁰

2. **Synergy Dosing**

   2.1. Synergy dosing of aminoglycosides in conjunction with another antibiotic is recommended for treatment of enterococcal endocarditis⁴¹,⁴² *(UW Health Strong Recommendation, Low Quality of Evidence)* and may be considered for streptococcal endocarditis.⁴² *(UW Health Strong Recommendation, Low Quality of Evidence)*
      2.1.1. Empiric gentamicin or tobramycin synergy dose for a patient with a calculated creatinine clearance of greater than 50 mL/min is 1 mg/kg IV every 8 hours with subsequent dosing based on drug concentration monitoring.⁴²,⁴³ *(UW Health Strong Recommendation, Low Quality of Evidence)*
      2.1.2. Patients with a calculated creatinine clearance of ≤50 mL/min should receive 1 mg/kg dose at an interval of every 12 or 24 hours based on subsequent drug concentration monitoring⁴³ *(UW Health Strong Recommendation, Low Quality of Evidence)*
      2.1.3. An EID nomogram should not be used for synergy. *(UW Health Strong Recommendation, Very Low Quality of Evidence)*
      2.1.4. Empiric gentamicin synergy dosing of 3 mg/kg IV every 24 hours may be considered as an alternative dosing strategy for highly penicillin-susceptible viridans group streptococci or *Streptococcus gallolyticus (bovis)* if the patient has native-valve endocarditis. *(UW Health Strong Recommendation, Low Quality of Evidence)*
      2.1.4.1. Every 24-hour dosing may be appropriate when needed to facilitate discharge to a skilled nursing facility or to simplify antimicrobial administration in the home after aminoglycoside concentrations and patient-specific pharmacokinetics are assessed. *(UW Health Strong Recommendation, Very Low Quality of Evidence)*
2.1.4.2. Target concentrations for synergy dosing using 3 mg/kg IV every 24 hours have not been defined but can be estimated based on the volume of distribution for aminoglycosides.

2.1.4.2.1. Peak concentrations (drawn no sooner than 60 minutes after the end of the infusion) of 9-12 mcg/mL can be expected with this dosing scheme and the Cmin should be below 0.5 mcg/mL.39

2.1.4.2.2. A mid-point (random) concentration should be drawn no sooner than 3 half-lives (about 10-12 hours after the start of the infusion) for two-point pharmacokinetic calculations with the assistance of the clinical pharmacist.

2.2. Peak and trough aminoglycoside drug concentrations for synergy dosing using 1 mg/kg IV every 8, 12 or 24 hours should be drawn after three to five half-lives.39 (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

2.2.1. A peak aminoglycoside concentration does not need to be mathematically extrapolated to a Cmax given that the distributional phase is very short with low aminoglycoside doses given for synergy (UW Health Strong Recommendation, Low Quality of Evidence)

2.2.2. The peak should be drawn no sooner than 30 minutes after the end of the infusion to avoid the distribution phase.39 (UW Health Strong Recommendation, High Quality of Evidence)

2.2.3. Drawing the trough 60 minutes prior to the next dose is acceptable if needed to ensure a detectable concentration.39 (UW Health Strong Recommendation, High Quality of Evidence)

3. Extended Interval Dosing (EID)

3.1. Empiric EID should be considered for all eligible patients (UW Health Strong Recommendation, Low Quality of Evidence)

3.2. Patients excluded from empiric EID dosing and who should receive traditional dosing include45 (UW Health Strong Recommendation, High Quality of Evidence):

- pregnant patients
- neonates
- severe burns (>20% BSA)
- anasarca
- ascites
- cystic fibrosis
- meningitis
- endocarditis
- patients with a calculated creatinine clearance < 20 mL/min
- patients with unstable renal function

3.3. Administering aminoglycosides using a combination of a higher dose (compared to traditional dosing regimens) and an extended interval can result in increased likelihood of successful antimicrobial activity, reduced hospital costs, reduced total daily dose of drug administered to the patient without compromising antimicrobial efficacy, and lower incidence of adverse drug events.20-21

3.3.1. A 1997 retrospective cost analysis at the Mayo medical center assessed the relative costs of EID versus intermittent gentamicin dosing based on acquisition, preparation, and administration costs; therapeutic drug monitoring; and treatment of nephrotoxicity. The mean per-patient cost of 4.5 days of aminoglycoside therapy was $36.77 (EID) versus $87.32 (traditional dosing). Due to a reduced incidence of nephrotoxicity observed with the EID regimen (1.2% vs. 4%), the authors also concluded that there exist significant cost-savings in nephrotoxicity management costs (per-patient cost, $55 vs. $182, extended-interval vs. intermittent dosing).46

3.3.2. Parker and Davey provide an excellent review of direct and indirect savings of EID. The authors conclude that EID accrues fewer costs in: (1) product preparation and administration, (2) product wastage and (3) therapeutic monitoring. There are also indirect savings in delayed development of toxicity, reduced risk of litigation due to adverse drug events, fewer treatment failures and fewer venipuncture events.47
3.3.3. A mathematical model system analogous to a Monte Carlo simulation used patient data provided in other publications to create a representative model of aminoglycoside concentrations, antibacterial efficacy, nephrotoxicity, and ototoxicity. The authors conclude that EID reduced both onset and extent of nephrotoxicity and ototoxicity, but did not eliminate the need for therapeutic drug monitoring.48

3.4. Patients receiving EID therapy for the treatment of lower respiratory infections should receive a single dose of 7 mg/kg IV tobramycin or gentamicin calculated using appropriate body weight (see 1.11).45 If amikacin is selected, a 21 mg/kg dose should be used.45 (UW Health Strong Recommendation, High Quality of Evidence)

3.4.1. Although EID dosing does not require 2-point kinetics, 7 mg/kg in an appropriate patient population would yield a predicted peak of 20-25 mcg/mL with a trough < 1 mcg/mL for tobramycin and gentamicin.45 A 21 mg/kg amikacin dose would yield an expected peak of 40-60 mcg/mL and a trough <4 mcg/mL.45

3.5. Patients receiving EID therapy for all other indications should receive a single dose of 5 mg/kg IV tobramycin or gentamicin calculated using appropriate dosing weight (see 1.11.1). If amikacin is selected, a 15 mg/kg dose should be used. (UW Health Strong Recommendation, High Quality of Evidence)

3.5.1. Although EID dosing does not require 2-point kinetics, 5 mg/kg in an appropriate patient population would yield a predicted peak of 15-18 mcg/mL with a trough < 1 mcg/mL for tobramycin and gentamicin.45 A 15 mg/kg amikacin dose would yield an expected peak of 35-50 mcg/mL and a trough <4 mcg/mL.

4. Drug Concentration Monitoring for EID

4.1. A single drug concentration should be obtained between 6 and 14 hours after the start of the 60-minute aminoglycoside infusion. This drug concentration should be used with the appropriate nomogram below to determine the appropriate interval for subsequent doses.45 (UW Health Strong Recommendation, High Quality of Evidence)

4.2. If the drug concentration falls within the area designated as Q24h, Q36h, or Q48h according to the nomogram, then the interval should be Q24, Q36, or Q48 hours respectively. If the drug concentration falls on the line, then the longer dosing interval should be chosen.45
4.3. A subtherapeutic or supratherapeutic initial drug concentration indicates that the individual patient pharmacokinetic parameters are not consistent with the population studied for the nomogram. This patient should receive traditional dosing based on two-point pharmacokinetics.

4.3.1. If a supratherapeutic drug concentration occurs (i.e. above the upper limit of the nomogram), a second aminoglycoside concentration should be drawn and two-point pharmacokinetics should be drawn to determine the appropriate dose and interval via traditional dosing.39 (Class A, Low) See section 11.6.2

4.3.2. If a subtherapeutic concentration (< 2 mcg/mL for gentamicin/tobramycin or < 6 mcg/mL for amikacin) is obtained with the initial concentration, then two-point pharmacokinetics should be used to guide therapy.
4.3.3. The clinical pharmacist should investigate the possibility of a contaminated blood draw causing an initial concentration to fall outside of the nomogram.

4.4. If the patient is expected to have good clearance (young, critically ill patients), consider checking an early aminoglycoside concentration (<10 hours) to minimize the risk of finding an undetectable concentration.49,50

4.5. While EID dosing via the nomogram may be used, for these young, critically ill patients, two-point kinetics may be considered (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence).

4.6. Patients who have a supratherapeutic concentration (i.e. above the upper limit of the nomogram) should be monitored with two-point kinetics51 (UW Health Strong Recommendation, Low Quality of Evidence)

4.6.1. As the aminoglycoside distribution phase in high-dose (e.g. 5 or 7 mg/kg) is prolonged due to high doses, timing of concentrations must be considered

4.6.1.1. The peak concentration should be drawn no sooner than 2.7 hours after the start of a 60-minute infusion

4.6.1.2. A midpoint (random) concentration should be drawn six to eight hours after the initial concentration

5. Traditional Aminoglycoside Dosing

5.1. Patients who are not eligible for EID and who are not receiving aminoglycosides for synergy should receive traditional aminoglycoside dosing, excepting cystic fibrosis patients. (UW Health Strong Recommendation, Very Low Quality of Evidence)

5.2. Empiric dosing and monitoring parameters are listed in Table 8.

5.2.1. Two peripheral aminoglycoside concentrations should be obtained to guide further therapy.52

Table 8. Traditional aminoglycoside dosing: empiric dosing and concentration monitoring

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>≥ 60 mL/min</th>
<th>40-59 mL/min</th>
<th>&lt;40 mL/min</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin or tobramycin</td>
<td>1.5-2 mg/kg every 8 hours</td>
<td>1.5-2 mg/kg every 12 hours</td>
<td>2 mg/kg load, then 1.5 mg/kg every 24 hours or longer</td>
<td>2 mg/kg load, then 1.5 mg/kg post-dialysis</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5-7.5 mg/kg every 8 hours</td>
<td>5-7.5 mg/kg every 12 hours</td>
<td>5-7.5 mg/kg every 24 hours or longer</td>
<td>7.5 mg/kg load, then 5-7.5 mg/kg post-dialysis</td>
</tr>
<tr>
<td>Trough</td>
<td>30-60 minutes before the 4th dose</td>
<td>30-60 minutes before the 3rd dose</td>
<td>Mid-point (random) concentration 10-12 hours following the 2nd dose</td>
<td>Allow 2 hours after the end of dialysis session for redistribution, then draw the trough</td>
</tr>
<tr>
<td>Peak (gentamicin/tobramycin)</td>
<td>30-60 minutes after the end of the 30 minute infusion following the 3rd dose</td>
<td>30-60 minutes after end of the 30 minute infusion following the 2nd dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak (Amikacin)</td>
<td>60-120 minutes after the end of the 60 minute infusion following the 3rd dose</td>
<td>60-120 minutes after the end of the 60 minute infusion following the 2nd dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2.2. Pharmacokinetic parameters should be calculated, including volume of distribution, Cmax, Cmin, elimination rate constant, and elimination half-life. (UW Health Strong Recommendation, Very Low Quality of Evidence)
5.2.3. Based on the pharmacokinetic calculations, the dose and dosing interval should be adjusted to meet the following parameters associated with efficacy for aminoglycosides\(^ {21,53}\) (UW Health Strong Recommendation, Low Quality of Evidence)

5.2.3.1. Peak to MIC ratio (peak:MIC) of 8-10 for pneumonia, meningitis, fever and neutropenia, Gram-negative bacteremia

5.2.3.1.1. Two-point kinetics must be used if higher peaks are needed.

5.2.3.2. Peak concentration 6-8 mcg/mL for abdominal infections, peritonitis, skin and soft tissue infections.

5.2.3.3. Peak concentration 4-6 mcg/mL for urinary tract infections

6. Drug Concentration Monitoring for Traditional Dosing

6.1. After the initial two-point pharmacokinetics are calculated, additional drug monitoring is not necessary if the expected duration of therapy is equal to or fewer than five days, unless the patient’s renal function changes. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

7. Drug Concentration Monitoring for Long-term Aminoglycoside Therapy

7.1. Traditional/synergy dosing: trough drug concentrations and creatinine should be monitored at least once weekly during prolonged therapy. (UW Health Strong Recommendation, High Quality of Evidence)

7.2. EID

7.2.1. Trough concentrations should be drawn 30-60 minutes before the dose and can be used to monitor for nephrotoxicity and drug accumulation in patients with extended course of EID therapy with every 24 hour interval.\(^ {39}\)

7.2.2. The target gentamicin/tobramycin trough concentration is less than 1 mcg/mL and less than 4-6 mcg/mL for amikacin for every 24-hour interval

7.2.2.1. A higher trough may indicate the need for two-point pharmacokinetics to monitor therapy

7.2.3. Monitoring EID at every 36 and 48-hour intervals has not been well defined.

7.2.3.1. Monitoring for change in renal function and checking a 6- to 14-hours post-dose concentration may be reasonable.

7.2.3.2. Monitoring a 24-hour concentration for two-point pharmacokinetics may be reasonable.

7.3. The target gentamicin and tobramycin trough is less than 0.5 mcg/mL for synergy dosing.

7.4. If therapeutic failure is suspected at any point after starting the course of therapy, two-point pharmacokinetics should be used to guide therapy

8. Audiology Testing for Long-term Aminoglycoside Therapy

8.1. For patients on long-term aminoglycoside therapy, consider baseline audiometry and subsequent monitoring for ototoxicity.\(^ {54}\)

Ciprofloxacin

Ciprofloxacin demonstrates optimal efficacy when the ratio of the AUC to the MIC is $\geq 125$.\(^ {4}\) A regimen of at least 400 mg IV ciprofloxacin given every 8 hours is necessary to reliably attain the desired AUC/MIC ratio when the organism MIC $>0.25$ mg/L. However, a regimen of 400 mg IV ciprofloxacin given every 12 hours is sufficient to reliably attain the desired AUC/MIC ratio when the organism MIC is $\leq 0.25$mg/L. In this situation, providing higher doses of ciprofloxacin or more frequent administration does not result in any additional benefit.\(^ {55}\) Therefore, a program of dose reduction dependent on an organism’s MIC is a reasonable way to minimize ciprofloxacin exposure without compromising antibacterial efficacy.

Ciprofloxacin Recommendations and Evidence

1. Pharmacokinetic- and pharmacodynamics-optimized ciprofloxacin dosing should be provided for all critically ill patients (UW Health Strong Recommendation, Low Quality of Evidence) and can be beneficial for non-critically ill patients (UW Health Strong Recommendation, Low Quality of Evidence) due to increasing rates of resistant organisms.

1.1. Pharmacokinetic data were calculated in a prospective observational study of 32 ICU patients receiving 400 mg ciprofloxacin every 12 hours. The resulting AUC was used to create models of
several simulated dosing intervals ranging from 400 mg ciprofloxacin every 12 hours to 400 mg ciprofloxacin every 3 hours. Target attainment of an AUC/MIC >125 was calculated with MICs ranging from 0.125 mg/L to 2 mg/L based on prevalence of that MIC in organisms recovered from the single study-site ICU over the previous two-year period. The probability of target attainment for 400 mg ciprofloxacin every 12 hours decreases dramatically from > 90% at MICs ≤0.25 mg/L to < 40% at MICs ≥0.5 mg/L. At an MIC of 0.5 mg/L, 400 mg ciprofloxacin every 8 hours has a probability of target attainment of 69% while 400 mg ciprofloxacin every 6 hours has a probability of target attainment of 91%.55

1.2. A Monte Carlo simulation (1000 subjects per arm) evaluated target attainment (AUC/MIC >123) in patients receiving ciprofloxacin to treat P. aeruginosa infection. The simulated regimens consisted of 400 mg ciprofloxacin every 12 hours, 400 mg ciprofloxacin every 8 hours, and a variable-frequency regimen that post-hoc would have attained AUC/MIC >123. The probability of target attainment was greater than 98% for all regimens at MIC ≤0.125 mg/L. At an MIC of 0.25 mg/L, 12-hour dosing had a probability of target attainment of 69% while 8-hour dosing target attainment was 77%. At 0.5 mg/L, 12-hour dosing had a probability of target attainment of 11% whereas 8-hour dosing target attainment was 38%.56

2. An internal review of organisms recovered from TLC during calendar year 2008 found 36 of 100 (36%) Gram-negative isolates with MIC sensitivities to ciprofloxacin ≥0.5 mg/L. The same review found 507 patients receiving 1674 total days of therapy with an average length of therapy of 3.3 days (range 0-63 days). Implementation of a dose reduction protocol reduced projected ciprofloxacin usage by 19% and resulted in a savings of $2,916 per year.

3. Initial/Empiric dosing:
   3.1. Patients with sepsis or septic shock or admitted to the ICU or obese should receive empiric ciprofloxacin dosed according to Table 9. (UW Health Strong Recommendation, Low Quality of Evidence)
   3.2. Patients admitted to the general medicine service without a severe infection may be considered for 1200 mg per day of ciprofloxacin empirically. (UW Health Weak/Conditional Recommendation, Low Quality of Evidence).

Table 9: Ciprofloxacin Dosing (infuse over 1 hour)

<table>
<thead>
<tr>
<th>Estimated CrCL (mL/min)</th>
<th>Initial/Empiric Dosing</th>
<th>Dose Reduction for Definitive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>400mg IV q8hrs or 600mg IV q12hrs</td>
<td>400mg IV q12hrs</td>
</tr>
<tr>
<td>10-30</td>
<td>400mg IV q12hrs</td>
<td>400mg IV q24hrs</td>
</tr>
<tr>
<td>&lt;10 / HD</td>
<td>400mg IV q24hrs</td>
<td>400mg IV q24hrs</td>
</tr>
</tbody>
</table>

4. Dose Reduction
   4.1. All patients from whom no organism is isolated after 72 hours or who have an organism recovered with an MIC to ciprofloxacin that is ≤0.25 mg/L are eligible for ciprofloxacin dose reduction based on Table 10. (UW Health Strong Recommendation, Low Quality of Evidence)
   4.2. Patients who have an organism recovered with an MIC to ciprofloxacin that is >0.25 mg/L should not be dose reduced and should continue to receive high-dose ciprofloxacin. (UW Health Strong Recommendation, Low Quality of Evidence)

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
**Methodology**

**Development Process**
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

**Methods Used to Collect the Evidence:**
The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

**Literature Sources:**
- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

**Time Period:** 2015-2018

**Search Terms on Pubmed:**
- Drug Administration Schedule, beta-lactams, AND infusions, intravenous
- Gentamicins, Tobramycin, Amikacin, AND Drug Administration schedule
- Obesity, Drug Administration Schedule, beta-lactams, AND infusions, intravenous
- Obesity, beta-lactams, AND infusions, intravenous
- Sepsis, beta-lactams, drug administration schedule, AND infusions, intravenous
- Sepsis, beta-lactams, AND infusions, intravenous

**Methods to Select the Evidence:**
Describe the inclusion/exclusion criteria used for selecting the literature; consider describing chosen variables such as language, study design, outcomes, and comparisons as appropriate.

**Methods Used to Formulate the Recommendations:**
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

**Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:**
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 3).
Figure 3. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

**GRADE Ranking of Evidence**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

**GRADE Ratings for Recommendations For or Against Practice**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>

**Cost Analysis:**

No cost analysis was performed.

**Recognition of Potential Health Care Disparities:** No health care disparities identified.
Collateral Tools & Resources
The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Order Sets & Smart Sets
- Empiric – Anti-infective Treatment – Adult – Supplemental order set [6474]
- Piperacillin/tazobactam 3.375 g prolonged infusion panel [282151]
- Piperacillin/tazobactam 4.5 g prolonged infusion panel [296661]
- Meropenem prolonged infusion panel [282152]
- Cefepime 1 g prolonged infusion panel [309481]
- Cefepime 2 g prolonged infusion panel [296728]

Guidelines
- Continuous Renal Replacement Therapy – Adult – Inpatient Clinical

Protocols
- Antimicrobial Dosing Based on Pharmacokinetic/Pharmacodynamic Principles – Adult – Inpatient [9]
- Therapeutic Medication Blood Concentration Monitoring – Adult/Pediatrics – Inpatient/Emergency Department [31]
### Appendix A. Compatibility Information

**Piperacillin/Tazobactam Compatibilities**

<table>
<thead>
<tr>
<th>Compatible</th>
<th>Incompatible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Voriconazole</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Dexmethasone</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Dexametomidine</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Droxycycline</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Drotrecogin</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Gancyclovir</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Insulin</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Labetalol</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td></td>
</tr>
<tr>
<td>Potassium Phosphate</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Sodium Phosphate</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>TNA</td>
<td></td>
</tr>
</tbody>
</table>
### Meropenem Compatibilities

<table>
<thead>
<tr>
<th>Compatible</th>
<th>Incompatible</th>
<th>No Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Acyclovir</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Amphotericin (all formulations)</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Diazepam</td>
<td>Calcium</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Doxycycline</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Fenoldopam</td>
<td>Cisatracurium</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Metronidazole</td>
<td>Droperidol</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Mannitol</td>
<td>Drotrecogin</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Ondansetron</td>
<td>Esmolol</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Pantoprazole</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Sodium Bicarbonate</td>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Labetalol</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium Chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cefepime Compatibilities

<table>
<thead>
<tr>
<th>Compatible</th>
<th>Incompatible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B. Monte Carlo Simulations
The data contained in Appendix A is the supporting evidence for prolonged infusion β-lactams. Occasionally, dose optimization can achieve concentrations sufficient to treat organisms reported as resistant. This may be an alternative to more toxic antibiotics, such as colistin. Dosing of antimicrobials in this scenario should be done under the guidance of Infectious Disease consult and infectious disease pharmacist. (UW Health Weak/Conditional Recommendation, Very Low Quality of Evidence)

Monte Carlo simulations of various patient populations are listed in below and sorted by drug. These may be used to help select alternative dosing regimens. When selecting a dose, the goal should be to achieve at least 90% probability of target attainment (y-axis) at the expected or reported minimum inhibitory concentration (MIC) value (x-axis).

Piperacillin/tazobactam Monte Carlo simulations:
The probability of achieving 50% unbound time above the MIC (fT>MIC evaluated as a cumulative fractional response where probability of target attainment was calculated at several MICs, adjusted by the prevalence of that MIC among 470 representative *P. aeruginosa* isolates and summated) and based on a 5000-subject Monte Carlo simulation was as follows:

<table>
<thead>
<tr>
<th>Infusion Type, Dosage</th>
<th>Daily Dose of Piperacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 g</td>
</tr>
<tr>
<td>Continuous (over 24 hrs)</td>
<td></td>
</tr>
<tr>
<td>10.125 g</td>
<td>82.3%</td>
</tr>
<tr>
<td>13.5 g</td>
<td>—</td>
</tr>
<tr>
<td>18 g</td>
<td>—</td>
</tr>
<tr>
<td>20.25 g</td>
<td>—</td>
</tr>
<tr>
<td>22.5 g</td>
<td>—</td>
</tr>
<tr>
<td>Prolonged</td>
<td></td>
</tr>
<tr>
<td>3.375 g over 4 hrs q8h</td>
<td>83.3%</td>
</tr>
<tr>
<td>4.5 g over 4 hrs q8h</td>
<td>—</td>
</tr>
<tr>
<td>4.5 g over 3 hrs q6h</td>
<td>—</td>
</tr>
<tr>
<td>Intermittent (over 30 min)</td>
<td></td>
</tr>
<tr>
<td>3.375 g q6h</td>
<td>—</td>
</tr>
<tr>
<td>4.5 g q6h</td>
<td>—</td>
</tr>
<tr>
<td>3.375 g q4h</td>
<td>—</td>
</tr>
</tbody>
</table>

Probability of target attainment at doubling minimum inhibitory concentration dilutions for piperacillin/tazobactam regimens containing piperacillin 12 g/day (Left). Low CFR (top/right) is due to a high incidence of isolates with piperacillin/tazobactam MICs ≥16 mcg/mL (bottom/right).18,19

Monte Carlo simulation for the following regimens: (A) 4 g piperacillin administered over 30 min or 4 h every 8 h as well as for 30 min or 3 h every 6 h; (B) 3 g piperacillin administered over 30 min or 4 h every 8 h as well as for 30 min or 3 h every 6 hrs.15
Parallel first-order/Michaelis-Menten mathematical models for prolonged infusion piperacillin. Lines represent the median, 5th-percentile, and 95th-percentile of unbound piperacillin concentrations at steady state for piperacillin (3 g) administered for 4 h. Open circles represent observed piperacillin plasma concentrations.15
Meropenem Monte Carlo Simulations

Probability of PK-PD target attainment (40% T>MIC) by MIC for various meropenem dosing regimens.\(^6^0\)

The probability of achieving 40% unbound time above the MIC (fT>MIC) evaluated as a cumulative fractional response where probability of target attainment was calculated at several MICs, adjusted by the prevalence of that MIC among 8096 representative \(P.\ aeruginosa\) isolates and summated and based on a 2000-subject Monte Carlo simulation was as follows.\(^6^1\)

<table>
<thead>
<tr>
<th>Infusion time, h</th>
<th>Dose (mg)</th>
<th>500 mg</th>
<th>1 g</th>
<th>2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
<td>72.5</td>
<td>82.5</td>
<td>94.4</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>76.0</td>
<td>85.1</td>
<td>91.2</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>82.6</td>
<td>89.1</td>
<td>94.4</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>87.9</td>
<td>93.4</td>
<td>96.7</td>
</tr>
</tbody>
</table>

Mean simulated steady-state free meropenem concentration-time profile based on final population pharmacokinetic parameters for 1g as a 0.5-hour infusion (solid line) and as a 3-hour infusion (dashed line). Please note that these values are for 1g meropenem, not for 500mg.\(^6^0\) The 40-48h represents a sampling after steady state was achieved. Residual meropenem is 3mcg/mL at time of infusion and 8mcg/mL 30 minutes into the 3-hour infusion, analogous to a 5mcg/mL increase if the patient weren't at steady-state.
Cefepime Monte Carlo Simulations

Probability of target attainment (PTA) at 60% \( f_T > \text{MIC} \) for six prolonged infusion regimens of cefepime at specific minimum inhibitory concentrations (MICs). The dotted line indicates a PTA ≥ 90%.\(^{17}\)

The probability of target attainment (50% time > MIC of 4 mg/L) based on a 5000-subject Monte Carlo simulation is shown below.\(^{62}\) All regimens tested achieved target attainment when the cefepime MIC was ≤ 4 mg/L. Cefepime scenarios tested included: 2g infused over 30 minutes every 6 hours, 2g infused over 30 minutes every 8 hours, 2g infused over 30 minutes every 12 hours, 2g infused over 3 hours every 6 hours, 2g infused over 3 hours every 8 hours, 1g infused over 30 minutes every 8 hours, 1g infused every 30 minutes over 12 hours, 2g daily continuously, 4g daily continuously and 6g daily continuously.

A separate Monte Carlo simulation (5000 subjects) evaluated target attainment (60% \( f_T > \text{MIC} \) of 8 mg/L) of six different prolonged infusion cefepime regimens.\(^{17}\) Probability of target attainment was > 90% for the following regimens: 2g cefepime infused over four hours every 8 hours, 1g cefepime infused over three hours every 6 hours and 2g cefepime infused over three hours every 6 hours. Regimens that did not achieve target attainment include: 1g cefepime infused over four hours every 8 hours, 1g cefepime infused over four hours every 12 hours and 2g cefepime infused over four hours every 12 hours. When the MIC is increased to 16 mg/L, the probability of target attainment was > 90% for 2g cefepime infused over four hours every 8 hours and 2 g cefepime infused over three hours every 6 hours. Organism-specific target attainment at an MIC of 8 mg/L are:\(^{17}\)

a. *E. coli*: All regimens listed above had a probability of target attainment > 96.9%.
b. *K. pneumoniae*: All regimens listed above had a probability of target attainment > 90.9% except for: 1g cefepime infused over four hours every 12 hours (88.6%).
c. *Enterobacter* spp.: All regimens listed above had a probability of target attainment > 95.0%.
d. *S. marcescens*: All regimens listed above had a probability of target attainment > 98.6%.
e. *Citrobacter* spp.: All regimens listed above had a probability of target attainment > 97.1%.
P. aeruginosa: All regimens listed above had a probability of target attainment > 92.7% except for: 1g cefepime infused over four hours every 12 hours (73.8%), 2g cefepime infused over four hours every 12 hours (87.1%) and 1g cefepime infused over four hours every 8 hours (88.6%).

A third Monte Carlo simulation (5000 subjects) evaluated target attainment (50% $f_T > \text{MIC}$) of different intermittent and prolonged infusion cefepime regimens. This target attainment is a cumulative fractional response where probability of target attainment was calculated at several MICs, adjusted by the prevalence of that MIC in a recently-collected large (>1000) population of organisms and summated. Organism-specific target attainment is as follows:

a. E. coli target attainment: 1g infused over 30 minutes every 12 hours (96.4%), 2g infused over 30 minutes every 12 hours (97.0%), 2g infused over 30 minutes every 8 hours (97.6%).

b. K. pneumoniae target attainment: 1g infused over 30 minutes every 12 hours (93.6%), 2g infused over 30 minutes every 12 hours (95.0%), 2g infused over 30 minutes every 8 hours (95.9%).

c. A. baumanii target attainment: 2g infused over 30 minutes every 12 hours (52.9%), 2g infused over 30 minutes every 8 hours (60.9%), 2g infused over 3 hours every 8 hours (64.0%).

d. P. aeruginosa target attainment: 2g infused over 30 minutes every 12 hours (83.6%), 2g infused over 30 minutes every 8 hours (90.1%), 2g infused over 3 hours every 8 hours (93.2%).

Simulated steady-state concentration-time profile of cefepime 1g every 8 hours infused over 4 hours.
Ciprofloxacin Monte Carlo Simulations
Fractional attainment of AUC/MIC ≥ 125. Each ciprofloxacin dose was 400mg intravenous and the total daily dose of ciprofloxacin is displayed (i.e. 800mg represents 400mg ciprofloxacin every 12 hours, 1200mg represents 400mg ciprofloxacin every 8 hours, etc.)\textsuperscript{55}
Table 1. Recommended alternative EMPIRIC regimens – GENERAL CARE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empiric Therapy</th>
<th>Proposed New Empiric Therapy</th>
<th>Comments/Step Down Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis or Uncomplicated Urinary Tract Infection</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>Nitrofurantoin Fosfomycin Cefpodoxime</td>
<td>Do not treat asymptomatic bacteruria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Base on final culture results: nitrofurantoin, fosfomycin, TMP/SMX, cefpodoxime</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>No risk for MDRO: cefpodoxime or ceftriaxone</td>
<td>Ceftriaxone susceptibility predicts activity for cefpodoxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO: cefepime and vancomycinB</td>
<td>Tailor therapy based on final culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam: gentamicin OR TMP/SMX</td>
<td>Ceftriaxone susceptibility predicts activity for cefpodoxime</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis (SBP) prophylaxis</td>
<td>Ciprofloxacin</td>
<td>Oral therapy: TMP/SMX OR cefpodoxime Intravenous therapy: ceftriaxone</td>
<td>May transition to oral equivalent of empiric regimen OR to ciprofloxacin at discharge</td>
</tr>
<tr>
<td>Intra-abdominal infection – community or healthcare associated</td>
<td>Ciprofloxacin AND metronidazole</td>
<td>No risk for MDRO: • cefpodoxime AND metronidazole OR • ceftriaxone AND metronidazole</td>
<td>Base on final culture results, some examples of potential oral options: • cefpodoxime OR cefuroxime PLUS metronidazole • amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td></td>
<td>Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin</td>
<td>With risk factors for MDRO or severe community-acquired infection: • vancomycinB PLUS piperacillin/tazobactam OR • vancomycinB PLUS cefepime AND metronidazole</td>
<td>If final culture results require fluoroquinolone step down (e.g. <em>Pseudomonas</em>) single oral dose prior to discharge is acceptable</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Historical Empiric Therapy</td>
<td>Proposed New Empiric Therapy</td>
<td>Comments/Step Down Therapy&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------</td>
</tr>
</tbody>
</table>
| Community-acquired Pneumonia<sup>D</sup> | Moxifloxacin OR Levofloxacin | No risk factors for MDRO:  
• ceftriaxone PLUS doxycycline OR  
• ceftriaxone PLUS azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancomycin<sup>B</sup> PLUS aztreonam<sup>C</sup>  
If concern for atypical bacteria: ADD azithromycin | Potential oral options: cefpodoxime OR cefuroxime PLUS azithromycin OR doxycycline  
If no oral options, page 3333 for fluoroquinolone approval |
| Healthcare-associated Pneumonia<sup>D</sup> | Vancomycin PLUS Cefepime AND Ciprofloxacin | With risk factors for MDRO:  
vancomycin<sup>B</sup> PLUS cefepime  
If patient in septic shock: ADD tobramycin (Pending transfer to higher care level)  
If concern for atypical bacteria: ADD azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancocmycin<sup>B</sup> PLUS aztreonam<sup>C</sup>  
If concern for atypical bacteria: ADD azithromycin | Double coverage for <i>Pseudomonas</i> is not required in clinically stable, general care patient  
If no oral options, page 3333 for fluoroquinolone approval |
| Sepsis (without septic shock) of urinary origin/pyelonephritis | Vancomycin AND/OR ciprofloxacin | No risk factors for MDRO:  
ceftriaxone  
With risk factors for MDRO:  
vancocmycin<sup>B</sup> PLUS cefepime  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancocmycin<sup>B</sup> PLUS tobramycin |  |
| Septic Shock – unknown origin empiric coverage of <i>Pseudomonas</i> | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin | • Vancomycin<sup>B</sup> PLUS piperacillin/tazobactam PLUS tobramycin  
• Vancomycin<sup>B</sup> PLUS cefepime PLUS tobramycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancocmycin<sup>B</sup> PLUS aztreonam<sup>C</sup> PLUS tobramycin PLUS metronidazole |  |

<sup>A</sup> Base step-down therapy on culture results, if no oral step down therapy except fluoroquinolones exist, please page 3333 for approval or other options  
<sup>B</sup> Vancomycin therapy targeted to trough goal of 15-20 mcg/mL  
<sup>C</sup> Empiric aztreonam use is approved for 72 hours. Further therapy with aztreonam will require approval via 3333 pager or ID consult  
<sup>D</sup> If severe or immediate IgE-mediated beta-lactam allergy, please page 3333 for alternative options  
MDRO: Multidrug-resistant organism  
TMP/SMX: trimethoprim/sulfamethoxazole
## Appendix C. Antibiotic alternatives to Fluoroquinolones

From: [PK/PD Dose Optimization of Antibiotics for the Treatment of Gram-negative Infections – Adult – Inpatient Clinical Practice Guideline](mailto:CCKM@uwhealth.org)

Last Reviewed 9/2018; Last Updated 9/2018

Contact information: Lucas Schulz, PharmD, Phone Number: (608)890-8617, [LSchulz2@uwhealth.org](mailto:LSchulz2@uwhealth.org)

### Table 2. Recommended alternative EMPIRIC regimens – INTENSIVE CARE MEDICINE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empiric Therapy</th>
<th>Proposed New Empiric Therapy</th>
</tr>
</thead>
</table>
| **Septic Shock – unknown origin empiric coverage of** | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin                               | • Vancomycin\(^\text{A}\) PLUS piperacillin/tazobactam PLUS tobramycin OR  
• Vancomycin\(^\text{A}\) PLUS ceftepime PLUS tobramycin OR  
• Vancomycin\(^\text{A}\) PLUS meropenem PLUS tobramycin  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin\(^\text{A}\) PLUS aztreonam PLUS tobramycin PLUS metronidazole |
| **Pseudomonas**                                     |                                                                                          |                                                                                                                |
| **Community-acquired Pneumonia**                    | Moxifloxacin                                                                              | No risk factors for MDRO: ceftriaxone OR ampicillin/sulbactam  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin\(^\text{A}\) AND aztreonam  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin |
| **Healthcare-associated Pneumonia**                | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin                               | With risk factors for MDRO: vancomycin\(^\text{A}\) PLUS piperacillin/tazobactam OR ceftepime  
If patient in septic shock: ADD tobramycin  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin\(^\text{A}\) PLUS aztreonam  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin |
| **Sepsis (without septic shock) of urinary origin/pyelonephritis** | Vancomycin AND/OR ciprofloxacin                                                           | No risk factors for MDRO: ceftriaxone  
With risk factors for MDRO: vancomycin\(^\text{A}\) PLUS ceftepime  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin\(^\text{A}\) PLUS tobramycin |
| **Intraabdominal infection – with or without septic shock\(^\text{a}\)** | Ciprofloxacin AND metronidazole                                                           | No risk factors for MDRO:  
• ceftriaxone AND metronidazole OR  
• cefoxitin OR  
• piperacillin/tazobactam |
|                                                       | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin                               | With risk factors for MDRO:  
• vancomycin\(^\text{A}\) PLUS piperacillin/tazobactam PLUS tobramycin OR  
• vancomycin\(^\text{A}\) PLUS ceftepime PLUS tobramycin PLUS metronidazole OR  
• vancomycin\(^\text{A}\) PLUS meropenem with or without tobramycin |
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empiric Therapy</th>
<th>Proposed New Empiric Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to β-lactam: vancomycin(^A) PLUS aztreonam PLUS tobramycin PLUS metronidazole</td>
</tr>
</tbody>
</table>

\(^A\) Vancomycin therapy targeted to trough goal of 15-20 mcg/mL
\(^B\) Assess patient for risk factors for invasive candidiasis and need for empiric antifungal coverage

MDRO: Multidrug-resistant organism
## Appendix C. Antibiotic alternatives to Fluoroquinolones

From: [PK/PD Dose Optimization of Antibiotics for the Treatment of Gram-negative Infections – Adult – Inpatient Clinical Practice Guideline](#)

Last Reviewed 9/2018; Last Updated 9/2018

Contact information: Lucas Schulz, PharmD, Phone Number: (608)890-8617, LSchulz2@uwhealth.org

### Table 3. Recommended alternative EMPIRIC regimens – ABDOMINAL TRANSPLANT

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empirc Therapy</th>
<th>Proposed New Empiric Therapy</th>
<th>Comments/Step Down Therapy&lt;sup&gt;A&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis or Uncomplicated Urinary Tract Infection (non-renal transplant)</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>Nitrofurantoin</td>
<td>Base on final culture results: nitrofurantoin, fosfomycin, cefpodoxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fosfomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefpodoxime</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive urine culture in the deceased renal transplant donor</td>
<td>Ciprofloxacin &lt;sup&gt;ADD Vancomycin IF concern for Gram-positive organisms&lt;/sup&gt;</td>
<td>No risk factors for MDRO: ceftriaxone</td>
<td>Base on final culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to β-lactam: tobramycin or aztreonam&lt;sup&gt;B&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cystitis in renal transplant patient</td>
<td>Ciprofloxacin</td>
<td>ASYMPTOMATIC &lt;3 months post renal transplant</td>
<td>Base on final culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No treatment, unless associated rise in creatinine</td>
<td>Ceftriaxone susceptibility predicts activity for cefpodoxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SYMPTOMS present</td>
<td>If no oral options, page 3333 for fluoroquinolone approval</td>
</tr>
<tr>
<td>Pyelonephritis in renal transplant patient</td>
<td>Ciprofloxacin &lt;sup&gt;ADD Vancomycin IF concern for Gram-positive organisms&lt;/sup&gt;</td>
<td>No risk factors for MDRO: ceftriaxone</td>
<td>Base on final culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to β-lactam: tobramycin (while awaiting pathogen identification) OR aztreonam&lt;sup&gt;B&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Historical Empiric Therapy</td>
<td>Proposed New Empiric Therapy</td>
<td>Comments/Step Down Therapy&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
</tbody>
</table>
| Cholangitis in the historical liver transplant recipient                | Ciprofloxacin plus amoxicillin or moxifloxacin    | • Piperacillin/tazobactam plus metronidazole OR  
• Cefepime plus metronidazole  
For patients with IgE-mediated or severe reaction to β-lactam:  
• vancomycin (trough goal 10-20 mcg/mL) plus tobramycin OR  
• vancomycin (trough goal 10-20 mcg/mL) plus aztreonam | Cefpodoxime OR cefuroxime plus amoxicillin (Enterococcus coverage)  
If no oral options, page 3333 for fluoroquinolone approval |
| Intra-abdominal infection – Other community or healthcare associated      | Ciprofloxacin and metronidazole                   | No risk factors for MDRO: ceftriaxone and metronidazole                                    | Base on final culture results, some examples of potential oral options:  
• cefpodoxime OR cefuroxime plus metronidazole  
• amoxicillin/clavulanic acid  
If final culture results require fluoroquinolone step down (e.g. Pseudomonas) single oral dose prior to discharge is acceptable |
| Community-acquired Pneumonia<sup>D</sup>                                | Moxifloxacin OR levofloxacin                     | No risk factors for MDRO:  
• ceftriaxone plus doxycycline OR  
• ceftriaxone plus azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancomycin<sup>C</sup> plus aztreonam  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin | Potential oral options: cefpodoxime OR cefuroxime plus azithromycin OR doxycycline  
If no oral options, page 3333 for fluoroquinolone approval |
| Healthcare-associated Pneumonia<sup>D</sup>                             | Vancomycin plus cefepime AND ciprofloxacin       | With risk factors for MDRO: vancomycin<sup>B</sup> plus cefepime  
If patient in septic shock: ADD tobramycin (pending transfer to higher care level)  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancomycin<sup>B</sup> plus aztreonam<sup>C</sup>  
If concern for atypical bacteria or Legionnaires’ disease: ADD azithromycin | Double coverage for Pseudomonas is not required in clinically stable, general care patient  
If no oral options, page 3333 for fluoroquinolone approval |

<sup>A</sup> Base step down therapy on culture results, if no oral step down therapy except fluoroquinolones exist, please page 3333 for approval or other options  
<sup>B</sup> Empiric aztreonam use is approved for 72 hours. Further therapy with aztreonam will require approval via 3333 pager or ID consult  
<sup>C</sup> Vancomycin therapy targeted to trough goal of 15-20 mcg/mL  
<sup>D</sup> If severe or immediate IgE-mediated beta-lactam allergy, please page 3333 for alternative options  

MDRO: Multidrug-resistant organism
Appendix D. Two-point kinetic calculations for traditional or synergy dosing with gentamicin and tobramycin 30-minute infusions

Last Reviewed 9/2018; Last Updated 3/2017
Contact: Lucas Schulz, PharmD, BCPS, AQ-ID; LSchulz2@uwhealth.org or Marie Pietruszka, PharmD, BCPS; MPietruszka@uwhealth.org

Aminoglycoside Pharmacokinetic and Pharmacodynamic Properties

- Hydrophilic (volume of distribution approximates the volume of extracellular fluid)
- Rapidly bactericidal and concentration-dependent activity
- Post-antibiotic effect (bactericidal activity persists even after serum concentrations fall below minimum inhibitory concentration)
- Trough concentrations above target correlate to toxicities (e.g. ototoxicity, nephrotoxicity)
- Factors leading to faster drug clearance (e.g. dehydration, children)
  - \( \uparrow CL \) (renal function) \( \xrightarrow{\text{yields}} \) \( \uparrow k_e \)
  - \( \downarrow V_d \) (fluid volume) \( \xrightarrow{\text{yields}} \) \( \uparrow k_e \)
- Factors leading to slower drug clearance (e.g. edema, ascites, sepsis, obesity)
  - \( \downarrow CL \) \( \xrightarrow{\text{yields}} \) \( \downarrow k_e \)
  - \( \uparrow V_d \) \( \xrightarrow{\text{yields}} \) \( \downarrow k_e \)

Definitions for calculations (note: all times are in hours)
\[ t = \text{infusion time} \]
\[ t_1 = \text{time from } C_1 \text{ (trough) to start of infusion} \]
\[ t_2 = \text{time from end of infusion to } C_2 \text{ (peak)} \]
\[ \tau = \text{dosing interval} \]
\[ T' = (\tau - [t_1 + t_2]) \]
\[ C_1 = \text{measured concentration 30 minutes prior to the dose (lab reported value); represents trough} \]
\[ C_2 = \text{measured concentration 30 minutes after end of infusion (lab reported value); represents peak} \]
\[ C_{\text{max}} = \text{calculated peak (true peak); pharmacokinetic target at steady state} \]
\[ C_{\text{min}} = \text{calculated trough (true trough); pharmacokinetic target at steady state} \]
\[ K_e = \text{elimination rate constant (hr}^{-1}\text{)} \]
\[ V_d = \text{volume of distribution (reported in L or L/kg)} \]

References:
Selecting an appropriate initial gentamicin or tobramycin dosing regimen (to be infused over 30 minutes) based on desired PK target regimen (traditional dosing)\(^1,2\)

1. Choose an appropriate dosing weight
   a. Use ideal body weight unless total body weight is below ideal body weight, then use total body weight.
   b. If total body weight is greater than 20% in excess of ideal body weight, use adjusted body weight.
2. Calculate patient specific CrCL (in mL/min) using appropriate equation
3. Estimate \(k_e\)
   \[
   k_e = \left(\frac{0.00293}{\text{hr}} \times \text{CrCL}\right) + 0.014
   \]
4. Estimate \(t_{\frac{1}{2}}\)
   \[
   t_{\frac{1}{2}} = \frac{0.693}{k_e}
   \]
5. Estimate \(V_d\) using dosing weight established in Step 1
   - \(V_d\) (dehydration) = 0.20L/kg
   - \(V_d\) (normal and obesity) = 0.26L/kg
   - \(V_d\) (edema, ascites, CHF exacerbation)~0.35 L/kg
   ** NOTE: If both fluid overloaded and obese, use 0.26L/kg to avoid overestimating \(V_d\)
6. Calculate initial dosing interval \(\tau\)
   \[
   \tau = \ln\left(\frac{C_{\text{max desired}}}{C_{\text{min desired}}}\right) + t
   \]
   ** NOTE: If patient is HD-dependent, administer dose after each dialysis session. Round dosing interval to nearest 8, 12, 18, 24, 36, or 48 hours.
   See guideline for target \(C_{\text{max}}\) (peak) and \(C_{\text{min}}\) (trough) based on infection site
7. Calculate initial loading dose (based on desired \(C_{\text{max}}\), which is the PK peak target) and subsequent maintenance dose required to maintain desired target peak concentration
   - ** Loading Dose (mg) = \(\left(C_{\text{max}}\right) \times (V_d)\) \rightarrow Use only for life-threatening infections
   - ** Maintenance Dose (mg) = \(\left(C_{\text{max}}\right) \times (V_d) \times (1 - e^{-kt})\)
   ** NOTE: Consider aiming for the lower end of the PK range (\(C_{\text{max}}\)) for initial dose estimation for patients with BMI > 30 kg/m\(^2\) to avoid overestimating the dose required for this population. For example, aim for a peak of 8 mcg/mL for pneumonia instead of 10 mcg/mL.
8. Round calculated maintenance dose to nearest 10 mg or available stock bag dose, then recalculate the estimated \(C_{\text{max}}\) based on rounded dose
   \[
   \text{estimated } C_{\text{max}} = C_{\text{max desired}} \times \left(\frac{\text{rounded dose}}{\text{calculated dose}}\right)
   \]
9. Estimate \(C_{\text{min}}\) (trough) as a safety check
   \[
   \text{estimated } C_{\text{min}} = \text{estimated } C_{\text{max}} \times (e^{-kT})
   \]
   \(T = \text{estimated time between peak and trough (e.g. plug in 7 hours if the patient has an 8-hour dosing interval)}\)
Evaluating gentamicin and tobramycin steady state concentrations and making recommendations for dose adjustments (traditional or synergy dosing)\textsuperscript{1,2}

1. Verify administration time, duration of infusion (should be 30 minutes) and sampling time
2. Calculate patient-specific $k_e$
   \[
   k_e = \frac{\ln \left( \frac{C_2}{C_1} \right)}{T'}
   \]
3. Calculate patient specific $t\frac{1}{2}$ (using patient-specific $k_e$)
   \[
   t\frac{1}{2} = \left( \frac{0.693}{k_e} \right)
   \]
4. Calculate $C_{max}$ & $C_{min}$ (using patient-specific $k_e$)
   \[
   C_{max} = (C_2) \times (e^{k_e t_2}) \quad \quad C_{min} = (C_1) \times (e^{-k_e t_1})
   \]
5. Calculate patient-specific $V_d$ (using patient-specific $k_e$)
   \[
   V_d = \frac{(Dose/t) \times (1 - e^{-k_e t})}{[(C_{max} - (C_{min}e^{-k_e t})) \times (k_e)]}
   \]
6. Calculate new patient-specific dosing interval $\tau$ (using patient specific $k_e$)
   \[
   \tau = \left[ \frac{\ln \left( \frac{C_{max desired}}{C_{min desired}} \right)}{k_e} \right] + t + t_2
   \]
   **Note: Round dosing interval to nearest 8, 12, 18, 24, 36, or 48 hours.
7. Calculate new dose (using patient-specific $k_e$ and $Vd$)
   \[
   Dose = C_{max desired} \times V_d (1 - e^{-k_e t})
   \]
8. Dose check: Use calculated dose, patient specific $V_d$, patient specific $k_e$ and calculated dosing interval to verify expected $C_{max}$ (estimated peak) and $C_{min}$ (estimated trough) with the new dosing regimen
   \[
   C_{max} = \left( \frac{Dose}{V_d} \right) \times \left( \frac{1}{1 - e^{-k_e t}} \right) \quad \quad C_{min} = \left( \frac{Dose}{V_d} \right) \times (e^{-k_e t}) \times \left( \frac{1 - e^{-k_e t}}{1 - e^{-k_e t}} \right)
   \]
Graphical representations of steady-state aminoglycoside dosing regimens with adjustments:

**APPROPRIATE DOSE AND INTERVAL**

- Peak/MIC (10:1)
- MIC

**ELEVATED DOSE with NORMAL RENAL FUNCTION:**
- Both peak and trough elevated with correct interval for normal t½ and CL

Solution: hold dose until level < 0.5, reduce dose, keep same interval.
SUBTHERAPEUTIC DOSE with NORMAL RENAL FUNCTION:
Low peak AND level falls <0.5 for an extended period beyond the PAE.

SOLUTION: Increase dose, keep same interval.

APPROPRIATE DOSE but INTERVAL TOO SHORT:
Initial peak acceptable for t1/2 and CL BUT trough high with a prolonged t1/2.

Solution: Hold dose until trough < 0.5, keep same dose, increase interval.

APPROPRIATE DOSE but INTERVAL TOO LONG:
Peak acceptable for t1/2 and CL BUT level falls to < 0.5 for an extended period beyond the PAE.

Solution: Keep same dose, decrease interval.
References


