Antibiotic Selection & Dose Optimization Guide for Pediatric Patients at least One Month of Age with Gram-Negative Infections

The purpose of this document is to serve as an antibiotic selection and dosing reference for clinicians who are providing care to pediatric patients with infectious diseases caused by particular Gram-negative pathogens (e.g., *Pseudomonas aeruginosa*, AmpC-producing Enterobacterales). These topics were purposefully identified due to the variety of antibiotic dosing recommendations available for pediatric patients; however, depending on the organism or site of infection, specific dosing regimens are required to optimize the pharmacokinetic and pharmacodynamic (PKPD) parameters of the bug-drug-site interaction.

This document provides dosing recommendations that pertain to the majority of pediatric patients receiving care at UNC Children's Hospital. The dosing regimens below are applicable to patients with normal renal function. As some antimicrobials have a range of dosing recommendations for those with renal dysfunction, these regimens below may serve as a guide for target dosing when making dose adjustments. These recommendations do not pertain to patients with cystic fibrosis (CF) due to their augmented clearance. Please refer to the CF Medication Dosing Guide for recommendations pertaining to the management of CF bronchopneumonia. For dosing recommendations regarding patients in the neonatal population up to corrected gestational age of 45 weeks, please refer to NeoFax.

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INFECTIONS CAUSED BY *PSEUDOMONAS AERUGINOSA*

Pseudomonas aeruginosa is a gram-negative pathogen that can cause infections in normal and immunocompromised hosts. This organism has the potential to be resistant to numerous first-line antibiotics due to the various mechanisms of resistance it may harbor. Optimizing the dosing of antipseudomonal antibiotics ensures the necessary PKPD parameters are met, improving microbiological and clinical outcomes. **Tables 1-2** below list a number of antibiotics that may have activity against *Pseudomonas aeruginosa*. Whenever patient-specific culture data is available for a patient's current infection, it is recommended to use these susceptibilities to further tailor antibiotics.

TABLE 1. General treatment options for infections caused by *Pseudomonas aeruginosa*

CLINICAL SCENARIO	PREFERRED ANTIBIOTIC(S) (listed in alphabetical order, not preference)
Cystitis	Aminoglycoside, aztreonam, ceftazidime, cefepime, meropenem, piperacillin/tazobactam Reserve use of ciprofloxacin or levofloxacin for patients with no other options.
Bloodstream infection, intra-abdominal infection, pneumonia, pyelonephritis, etc.	Aztreonam, cefepime, ceftazidime, ciprofloxacin, levofloxacin, meropenem, piperacillin/tazobactam
CNS involvement	Aztreonam, cefepime, ceftazidime, meropenem

TABLE 2. Dosing recommendations for empiric or targeted treatment of *Pseudomonas aeruginosa*

ANTIMICROBIAL	DOSING RECOMMENDATION	MAX DOSE	NOTES
Aminoglycosides	See separate Pediatric Aminoglycoside Dosing & Monitoring Guideline		
Aztreonam	40mg/kg/DOSE q8h	2000mg	Preferred therapy for patients with severe beta-lactam allergy
Ceftazidime	50mg/kg/DOSE q8h	2000mg	
Cefepime	50mg/kg/DOSE q8h	2000mg	More frequent dosing (i.e., q8h vs q12h) required to meet time-dependent PKPD goals for *Pseudomonas*
Ciprofloxacin	IV: 10mg/kg/DOSE q8h PO: 20mg/kg/DOSE q12h	400mg (IV) 750mg (PO)	More frequent IV dosing (i.e., q8h vs q12h) required to meet AUC:MIC PKPD goals for *Pseudomonas*
Levofloxacin	<5 years old: 10mg/kg/DOSE q12h ≥5 years old: 10mg/kg/DOSE q24h	750mg (IV/PO)	
Meropenem	20mg/kg/DOSE q8h	1000mg	Higher dosing required for CNS infections; see separate section
Piperacillin/ Tazobactam	100mg piperacillin/kg/DOSE q6h	4000mg piperacillin	More frequent dosing (i.e., q6h vs q8h) required to meet time-dependent PKPD goals for *Pseudomonas*

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INFECTIONS CAUSED BY AmpC-PRODUCING ENTEROBACTERALES (AmpC-E)

Beta-lactamase enzymes exist in a variety of forms, affecting different beta-lactams depending on their classification. AmpC belongs to the Ambler Class C beta-lactamases and is expressed to varying degrees by a number of gram-negative organisms, including Enterobacterales as well as some glucose non-fermenting gram-negative rods. While there are three main mechanisms of AmpC production, this section will focus on treatment options for organisms at moderate to high risk of expressing inducible AmpC resistance. Inducible AmpC resistance occurs when an organism harboring the *ampC* gene is exposed to particular beta-lactams that cause the bacteria to increase production of the AmpC beta-lactamase enzyme. Certain beta-lactams are considered either strong or weak inducers and/or good or poor substrates of AmpC (see **Table 3**). Good substrates of AmpC are easily broken down by the enzyme and are unlikely to be active against bacteria that have increased AmpC production. The concern for using beta-lactams that are considered good substrates in addition to being a strong or weak inducer is that resistance could develop during treatment (i.e., patient initially responds and then regresses).

Table 3. Beta-lactam inducers and substrates of AmpC beta-lactamase

	Strong Inducers of *ampC*	**Weak Inducers of *ampC***
Good Substrates of AmpC	Ampicillin, amoxicillin, cefazolin, cephalexin, cefoxitin	Ceftazidime, ceftriaxone, cefotaxime, piperacillin, aztreonam
Poor Substrates of AmpC	Imipenem	Cefepime, meropenem

RED: avoid use; YELLOW: generally avoid use but may have role in certain infections, like cystitis;
GREEN: appropriate options

Clinically relevant organisms that have a moderate to high risk of expressing inducible AmpC resistance include those within the acronym "HECK Yes" listed below. While there are other commonly pathogenic species within these genera (e.g., *Klebsiella pneumoniae, Citrobacter koserii*), inducible AmpC resistance is primarily found in the particular species listed.

Hafnia alvei
Enterobacter cloacae*
Citrobacter freundii*
Klebsiella aerogenes*
Yersinia enterocolitica

*These are the most commonly encountered species in clinical practice.

Cefepime or meropenem are generally preferred for treatment of systemic infections caused by AmpC-E. In the setting of CNS involvement of the infection, meropenem is the preferred initial therapy; subsequent de-escalation to cefepime may be an option depending upon organism susceptibility and patient status. The role of piperacillin/tazobactam in treatment of systemic infections caused by AmpC-E is unclear due to the heterogeneity of available clinical outcomes data.[3-4,6,8] For these reasons, piperacillin/tazobactam generally is not recommended for serious infections caused by AmpC-E. In the setting that a patient is empirically started on piperacillin/tazobactam with clinical improvement and the causative pathogen is later found to be an AmpC-E, it may be reasonable to consider continuing on piperacillin/tazobactam.

If patients with localized infections, such as cystitis, are empirically started on ceftriaxone or piperacillin/tazobactam, they may be continued on such therapy when an AmpC-E is identified as the causative pathogen if the patient's clinical status is improving on that therapy. For the case of cystitis, the

success of these therapies may be due to the high concentration of beta-lactam present in the bladder, disallowing the emergence of AmpC-producing colonies. AmpC-E can also be treated with cefepime or meropenem.

Some infections involving AmpC-E may warrant IV antibiotics for the duration of therapy based on the susceptibility profile, type of infection, and patient preference. In the event that enteral therapy is appropriate, there are limited options for what are considered effective for infections caused by AmpC-E. Of note, **oral beta-lactams do not adequately cover AmpC-E** and should not be considered for transition to enteral administration. This leaves certain non-beta-lactam antibiotics as remaining options. See **Tables 4 & 6** for specific recommendations.

TABLE 4. General treatment options for infections caused by AmpC-E

CLINICAL SCENARIO	PREFERRED ANTIBIOTIC(S) (listed in alphabetical order, not preference)
Cystitis	Aminoglycoside, ceftriaxone*, fosfomycin†, nitrofurantoin, piperacillin/tazobactam*^, TMP/SMX Reserve use of ciprofloxacin or levofloxacin for patients with no other PO options.
Bloodstream infection, intra-abdominal infection, pneumonia, pyelonephritis, etc.	Cefepime, ertapenem, piperacillin/tazobactam†, meropenem
CNS involvement	Cefepime, meropenem (preferred)

*For low burden infections like cystitis, third generation cephalosporins or piperacillin/tazobactam may be appropriate; see text for details.
†Use with caution. Fosfomycin has demonstrated *in vitro* activity against AmpC-E; however, clinical outcomes data are lacking.
^Piperacillin/tazobactam may be effective in specific scenarios; see text for details.

TABLE 5. Dosing recommendations for empiric or targeted treatment of infections caused by AmpC-E

ANTIMICROBIAL	DOSING RECOMMENDATION	MAX DOSE	NOTES
Aminoglycosides	See separate Pediatric Aminoglycoside Dosing & Monitoring Guideline		
Cefepime	50mg/kg/DOSE q8h	2000mg	Preferred therapy for majority of non-CNS infections caused by AmpC-producing bacteria
Ceftriaxone	50mg/kg/DOSE q24h	2000mg	If used empirically, only to be continued in patients with cystitis who respond promptly to therapy. See text for more details.
Ciprofloxacin	IV: 10mg/kg/DOSE q12h PO: 10-15mg/kg/DOSE q12h	400mg (IV) 750mg (PO)	Standard dosing applies for non-pseudomonal infections
Ertapenem	<12 yo: 15mg/kg/DOSE q12h ≥12 yo: 1000mg q24h	500mg (<12 yo)	More frequent dosing required for younger kids based on increased drug clearance

Levofloxacin	<5 years old: 10mg/kg/DOSE q12h ≥5 years old: 10mg/kg/DOSE q24h	750mg (IV/PO)	Standard dosing applies for non-pseudomonal infections
Meropenem	20mg/kg/DOSE q8h (non-CNS) 40mg/kg/DOSE q8h (CNS)	1000mg (non-CNS) 2000mg (CNS)	Preferred therapy for CNS infections caused by AmpC-producing bacteria. Higher dosing required for CNS infections
Nitrofurantoin	Macrodantin: 5-7mg/kg/**DAY** q6h Macrobid: 100mg q12h	100mg	Use for cystitis only. Standard dosing applies.
Piperacillin/ Tazobactam	100mg piperacillin/kg/DOSE q6h	4000mg piperacillin	May be considered in specific scenarios. Recommend Peds ID consult and/or discussion with ID pharmacist if choosing this.
Trimethoprim/ Sulfamethoxazole	UTI: 6-12mg TMP/kg/**DAY** q12h (IV/PO) Non-UTI: 8-12 mg TMP/kg/**DAY** q8-12h (IV/PO)	160mg (UTI) 320mg (non-UTI)	UTI includes cystitis and pyelonephritis. Not first-line for invasive infections such as bacteremia. *Consider* max total daily dose of 960mg TMP.

TABLE 6. Options for transition IV to PO when treating infections caused by AmpC-E

ENTERAL OPTIONS TO AVOID	PREFERRED ENTERAL OPTIONS (listed in alphabetical order, not preference)
Orally available beta-lactams do NOT provide adequate coverage of infections caused by AmpC-E	Cystitis: fosfomycin†, nitrofurantoin, TMP/SMX Fosfomycin & nitrofurantoin should NOT be used for treatment of systemic infections, including pyelonephritis Reserve use of ciprofloxacin or levofloxacin for patients with no other enteral options.
	Other infections: ciprofloxacin, levofloxacin, TMP/SMX

†Use with caution. Fosfomycin has demonstrated *in vitro* activity against AmpC-E; however, clinical outcomes data are lacking.

INFECTIONS CAUSED BY ESBL-PRODUCING ENTEROBACTERALES (ESBL-E)

Extended spectrum beta-lactamases (ESBLs) are additional examples of enzymes that break down beta-lactams. ESBLs in particular target most penicillins and cephalosporins, in addition to aztreonam. Carbapenems, however, usually retain activity against organisms harboring ESBLs. Non-beta-lactam antibiotics, like fluoroquinolones, aminoglycosides, and trimethoprim/sulfamethoxazole (TMP/SMX), are not affected by ESBL production; however, organisms that harbor ESBL genes often also carry genes conferring resistance to these other options.

While any gram-negative organism has the potential to contain ESBL genes, the more common microbes include *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca,* and *Proteus mirabilis*. Ceftriaxone resistance in these organisms has served as a surrogate marker of ESBL production. In other words, a Gram-negative organism, like *E coli*, demonstrating ceftriaxone resistance should be treated as a presumed ESBL-producing strain of *E coli*. The following recommendations found in **Tables 7-8** pertain to infections caused by ESBL-producing *E coli, K pneumoniae, K oxytoca,* and *P mirabilis*.

TABLE 7. General treatment options for infections caused by ESBL-E

CLINICAL SCENARIO	PREFERRED ANTIBIOTIC(S) (listed in alphabetical order, not preference)
Cystitis	Aminoglycoside, cefepime*, fosfomycin†, nitrofurantoin, piperacillin/tazobactam*, TMP/SMX Reserve use of ciprofloxacin or levofloxacin for patients with no other options.
Bloodstream infection, intra-abdominal infection, pneumonia, pyelonephritis, etc.	Ciprofloxacin, ertapenem, levofloxacin, meropenem
CNS involvement	Meropenem

*Cefepime or piperacillin/tazobactam may be appropriate in specific scenarios; see text for details.
†Use with caution. Fosfomycin may be used as an alternative for ESBL *E coli*; however, data for other ESBL-E suggest increased failure rates compared to nitrofurantoin.

TABLE 8. Dosing recommendations for empiric or targeted treatment of infections caused by ESBL-E

ANTIMICROBIAL	DOSING RECOMMENDATION	MAX DOSE	NOTES
Aminoglycosides	See separate Pediatric Aminoglycoside Dosing & Monitoring Guideline		
Ciprofloxacin	IV: 10mg/kg/DOSE q12h PO: 10-15mg/kg/DOSE q12h	400mg (IV) 750mg (PO)	Standard dosing applies for non-pseudomonal infections
Ertapenem	<12 yo: 15mg/kg/DOSE q12h ≥12 yo: 1000mg q24h	500mg (<12 yo)	More frequent dosing required for younger kids based on increased drug clearance
Levofloxacin	<5 years old: 10mg/kg/DOSE q12h ≥5 years old: 10mg/kg/DOSE q24h	750mg (IV/PO)	Standard dosing applies for non-pseudomonal infections
Meropenem	Non-CNS: 20mg/kg/DOSE q8h CNS: 40mg/kg/DOSE q8h	1000mg (non-CNS) 2000mg (CNS)	**Preferred therapy** for systemic ESBL-E infections.

Nitrofurantoin	Macrodantin: 5-7mg/kg/**DAY** q6h Macrobid: 100mg q12h	100mg	Use for **cystitis** only. Standard dosing applies.
Piperacillin/ Tazobactam	100mg piperacillin/kg/DOSE q6h	4000mg piperacillin	May be considered in specific scenarios. Recommend discussing with Peds ID Consults and/or ID pharmacist if choosing this.
Trimethoprim/ Sulfamethoxazole	UTI: 6-12mg TMP/kg/**DAY** q12h (IV/PO) Non-UTI: 8-12 mg TMP/kg/**DAY** q8-12h (IV/PO)	160mg (UTI) 320mg (non-UTI)	UTI includes cystitis and pyelonephritis. Not first-line for invasive infections such as bacteremia. *Consider* max total daily dose of 960mg TMP.

CONSIDERATIONS FOR BETA-LACTAM AGENTS FOR TREATMENT OF SELECT HIGHLY DRUG-RESISTANT GRAM-NEGATIVE ORGANISMS

The following organisms are considered highly drug resistant to many first- and second-line therapies and thus require special attention:

CRAB: carbapenem-resistant *Acinetobacter baumannii*
CRE: carbapenem-resistant Enterobacterales
DTR-*P aeruginosa*: *Pseudomonas aeruginosa* with difficult-to-treat resistance
Stenotrophomonas maltophilia

In order to combat the evolving resistance among gram-negative organisms, newer beta-lactamase inhibitors in combination with novel and routine beta-lactams have been developed. Available options, dosing recommendations, and possible indications for these agents are listed in **Table 9**. While these agents may have coverage of infections caused by AmpC-E and ESBL-E, they should be reserved for treatment of more resistant pathogens, such as CRE and difficult to treat (DTR) *Pseudomonas aeruginosa.* **Consultation with Pediatric Infectious Diseases is strongly recommended for any patient who develops an infection warranting the use of one of these agents.** Of note, use of these agents requires approval from either the Pediatric ID consult service or the Pediatric Antimicrobial Stewardship pharmacist to be used inpatient.

TABLE 9. Dosing recommendations & possible indications for newer antibiotic agents

ANTIMICROBIAL	DOSING RECOMMENDATION	MAX DOSE	POSSIBLE INDICATIONS
Cefiderocol	No pediatric data currently available Adult: 2000mg q8h **infused over 3h**	2000mg	CRE, DTR-*P aeruginosa*, CRAB, *S. maltophilia*
Ceftazidime/ avibactam	<6 mo: 40mg ceftazidime/kg/DOSE q8h **infused over 2h** ≥6 mo: 50mg ceftazidime/kg/DOSE q8h **infused over 2h**	2000mg ceftazidime	CRE, DTR-*P aeruginosa*
Ceftolozane/ tazobactam	UTI: 20mg ceftolozane/kg/DOSE q8h **infused over 1-3h** Non-UTI: 40mg ceftolozane/kg/DOSE q8h **infused over 3h**	1000mg ceftolozane (UTI) 2000mg ceftolozane (non-UTI)	DTR-*P aeruginosa*
Imipenem/ cilastatin/ relebactam	15mg imipenem/kg/DOSE q6h **infused over 0.5h**	500mg imipenem	CRE, DTR-*P aeruginosa*
Meropenem/ vaborbactam	40mg meropenem/kg/DOSE q8h **infused over 3h**	2000mg meropenem	CRE

CRE: carbapenem-resistant Enterobacterales; DTR-*P aeruginosa*: difficult to treat resistant *Pseudomonas aeruginosa*; CRAB: carbapenem-resistant *Acinetobacter baumannii*; *S maltophilia*: *Stenotrophomonas maltophila*

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