

Drug Dosing in Pediatric Patients with Impaired Renal Function: Ceftazidime-Avibactam Case Example

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Introduction

- For drugs that are primarily renally excreted, impaired renal function typically alters drug pharmacokinetics (PK) to the extent that dosage modifications may be needed in adults
- To inform dosage adjustments in the labeling, PK is evaluated in adult patients with impaired renal function
- It is presumed that renal impairment may also impact the PK of these drugs in pediatric patients
- However, most drugs that are primarily renally excreted lack dosage recommendations in pediatric patients with impaired renal function due to challenges in obtaining PK data in this subpopulation

Objective

- Provide brief regulatory background on ceftazidime-avibactam
- Describe how extrapolation from adult data facilitated dosing recommendations for pediatric patients ≥ 2 years of age with impaired renal function

Regulatory Background

- Ceftazidime (CAZ) – β -lactam antibiotic
- Avibactam (AVI) – β -lactamase inhibitor
- Approved for multiple indications in adults
 - Complicated urinary tract infection (cUTI) including pyelonephritis
 - Complicated intra-abdominal infection (cIAI)
 - Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)
- CAZ and AVI are primarily excreted unchanged in urine (80-90%)
 - Dosage adjustments are needed in the setting of renal impairment

Estimated Creatinine Clearance (mL/min) ^a	Recommended Adult Dosage Regimen ^{b,c}
>50	2 g CAZ, 0.5 g AVI every 8 h
31 to 50	1 g CAZ, 0.25 g AVI every 8 h
16 to 30	0.75 g CAZ, 0.19 g AVI every 12 h
6 to 15	0.75 g CAZ, 0.19 g AVI every 24 h
<5	0.75 g CAZ, 0.19 g AVI every 48 h
<p>a As calculated using the Cockcroft-Gault formula</p> <p>b All doses of AVYCAZ are administered over 2 h</p> <p>c Treatment for cIAI is 5-14 days, and treatment for cUTI and HABP/VABP is 7-14 days.</p>	

Primary Evidence for Approval of Pediatric Dosage Regimens



- For cUTI, cIAI and HABP/VABP, disease course and response to treatment are considered sufficiently similar in adults and pediatrics to permit use of exposure matching to establish efficacy and support safety
 - Existing adult population PK model was updated with PK data from 3 pediatric studies
 - Simulated regimens that would achieve CAZ and AVI plasma systemic exposures (i.e., AUC) similar to the efficacious exposures attained in adults

Infection	Age Range	Recommended Dosage Regimen ^{a,b}
cIAI, cUTI including pyelonephritis, HABP/VABP	2 years to <18 years	50 mg/kg CAZ, 12.5 mg/kg AVI (up to a maximum of 2 g CAZ and 0.5 g AVI) every 8 h ^c
	6 months to <2 years	50 mg/kg CAZ, 12.5 mg/kg AVI every 8 h
	3 months to <6 months	40 mg/kg CAZ, 10 mg/kg AVI every 8 h
a All doses of AVYCAZ are administered over 2 h b Treatment for cIAI is 5-14 days, and treatment for cUTI and HABP/VABP is 7-14 days c Dosage adjustments are recommended for patients ≥ 2 years with $\text{eGFR} \leq 50 \text{ mL/min/1.73m}^2$ as calculated using the Schwartz bedside formula		

Question 1

What are the recommended dosage adjustments in pediatric patients ≥ 2 years of age with renal impairment?

Number of Enrolled Pediatric Patients Stratified by Age and BSA-normalized eGFR



Age (years)	BSA-normalized eGFR (mL/min/1.73m ²)				
	0-30	31-50	51-80	80-120	>120
0 to <0.5	0	0	1	2	2
0.5 to <1	0	1	4	3	2
1 to <2	0	0	7	3	2
2 to <6	0	0	4	4	8
6 to <12	0	1	9	23	17
12 to <18	0	0	6	25	3

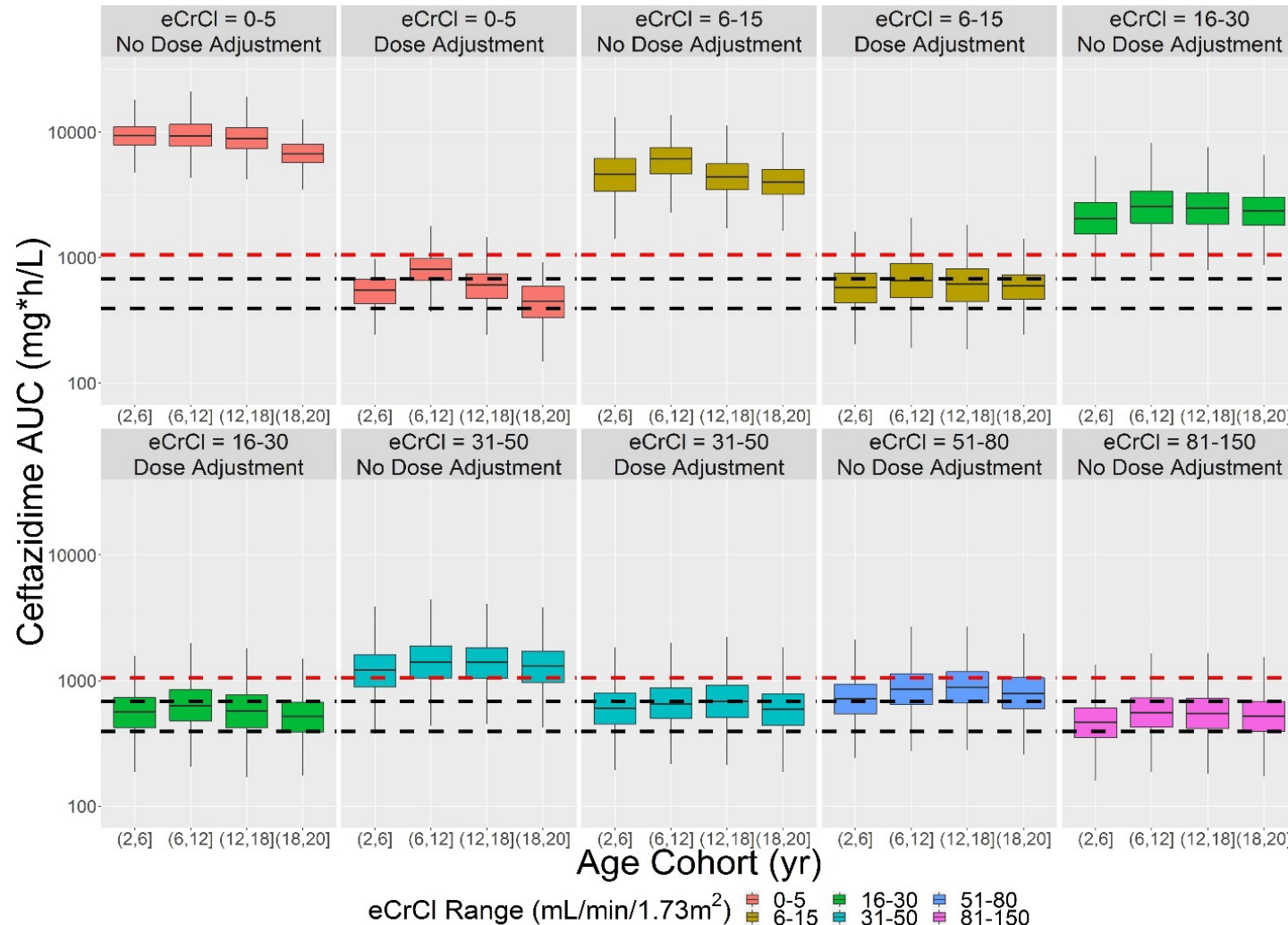
- Only 2 patients with CLcr ≤50 mL/min/1.73m²; effect of renal impairment on PK largely extrapolated from adults
- Population PK assumed similar proportional effects of renal impairment in adults and pediatric patients ≥2 years of age

Comparability of eGFR and Normalized CLcr



- Adult dosage adjustments for renal impairment were based on CLcr determined by Cockcroft-Gault equation
- Schwartz bedside formula was used to calculate eGFR in pediatric patients ≥ 2 years of age
- Bridged BSA-normalized eGFR and normalized CLcr (nCLcr) by showing eGFR and nCLcr to be reasonably similar using adult data

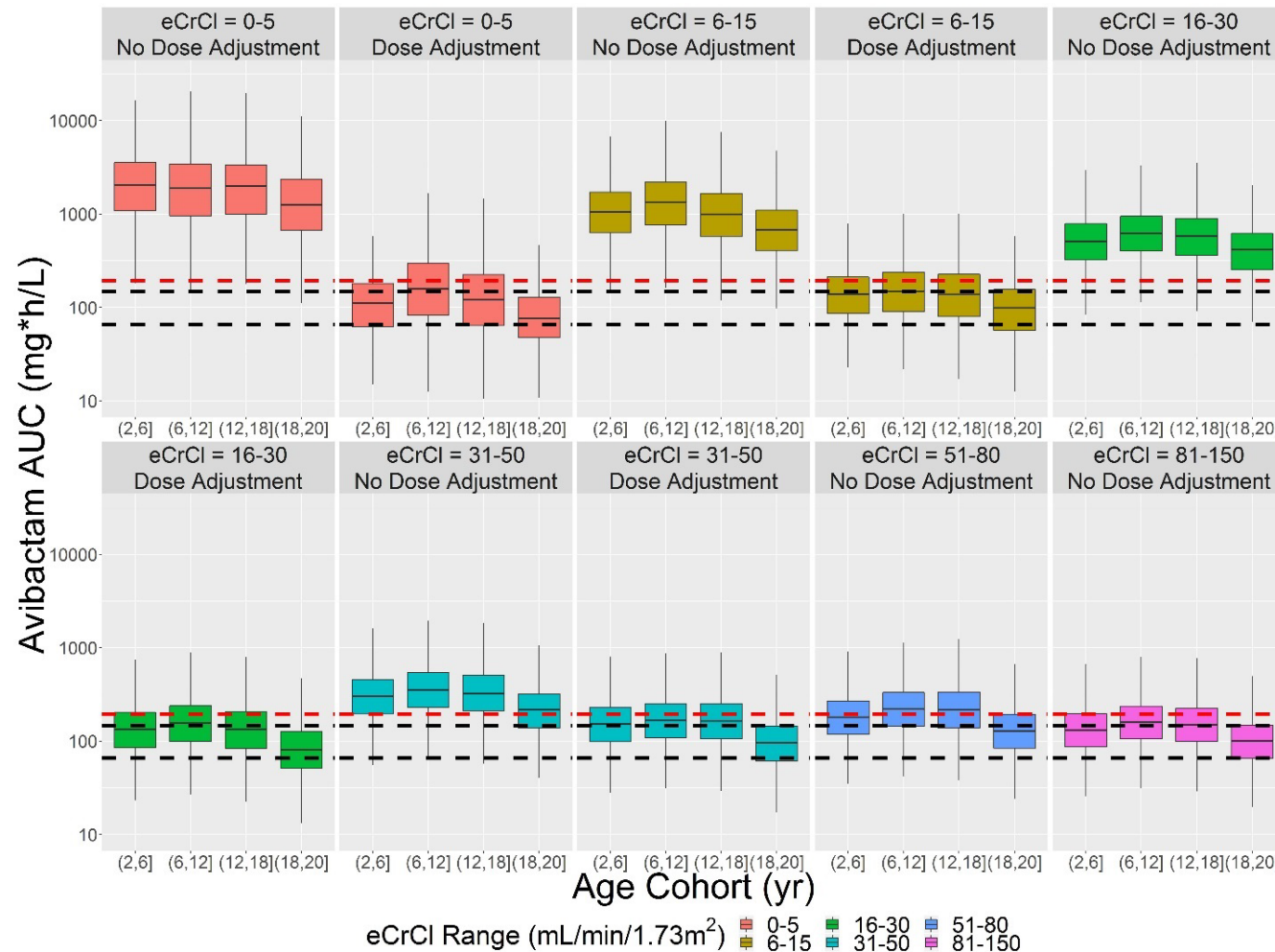
Simulated CAZ AUC Stratified by Renal Function with and without Dosage Adjustments



--Black dashed lines represent the 25th and 75th percentile of AUC in adult patients with normal renal function

--The red dashed line represents the 75th percentile of AUC in adult patients with mild renal impairment

Simulated AVI AUC Stratified by Renal Function with and without Dosage Adjustments



--Black dashed lines represent the 25th and 75th percentile of AUC in adult patients with normal renal function

--Red dashed line represents the 75th percentile of AUC in adult patients with mild renal impairment

Approved Pediatric Dosage Regimens with Adjustments for Renal Function

Age	Estimated Glomerular Filtration Rate (mL/min/1.73m ²) ^a	Recommended Dosage Regimen ^b
>2 years	>50	50 mg/kg CAZ, 12.5 mg/kg AVI every 8 h (up to a maximum of 2 g CAZ, 0.5 g AVI every 8 h)
	31 to 50	25 mg/kg CAZ, 6.25 mg/kg AVI every 8h (up to a maximum of 1 g CAZ, 0.25 g AVI every 8 h)
	16 to 30	18.75 mg/kg CAZ, 4.69 mg/kg AVI every 12h (up to a maximum of 0.75 g CAZ, 0.19 g AVI every 12 h)
	6 to 15	18.75 mg/kg CAZ, 4.69 mg/kg AVI every 24 h (up to a maximum of 0.75 g CAZ, 0.19 g AVI every 24 h)
	≤5	18.75 mg/kg CAZ, 4.69 mg/kg AVI every 48 h (up to a maximum of 0.7 5g CAZ, 0.19 g AVI every 48 h)
6 months to 2 years	Pediatric patients without renal impairment	50 mg/kg CAZ, 12.5 mg/kg AVI every 8 h
3 to 6 months		40 mg/kg CAZ, 10 mg/kg AVI every 8 h
a Calculated using the Schwartz bedside formula b All doses are administered over 2 h c Treatment for cIAI is 5-14 days, treatment for cUTI and HABP/VABP is 7-14 days		

Question 2

Why does the labeling lack dosage recommendations for pediatric patients <2 years of age with renal impairment?

Characterization of CL_{cr} in Pediatric Patients <2 Years of Age

- In pediatric patients <2 years of age, the Rhodin equation was used in the population PK model to describe GFR instead of the bedside Schwartz formula

$$-\frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}}$$

- Uses postmenstrual age (PMA) as covariate instead of eGFR and provides better model fit
- However, difficult to incorporate effect of changes in serum creatinine or eGFR along with effects of age-related kidney maturation
- Insufficient data to characterize renal impairment in children <2 years of age

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