U.S. FOOD & DRUG ADMINISTRATION
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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

a As calculated using the Cockcroft-Gault formula
b All doses of AVYCAZ are administered over 2 h
c Treatment for cIAI is 5-14 days, and treatment for cUTI and HABP/VABP is 7-14 days.

Modified from Ceftazidime-Avibactam US Prescribing Information

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 eGFR ≤50 mL/min/$1.73m^2$ as calculated using the Schwartz bedside formula

Modified from Ceftazidime-Avibactam US Prescribing Information

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

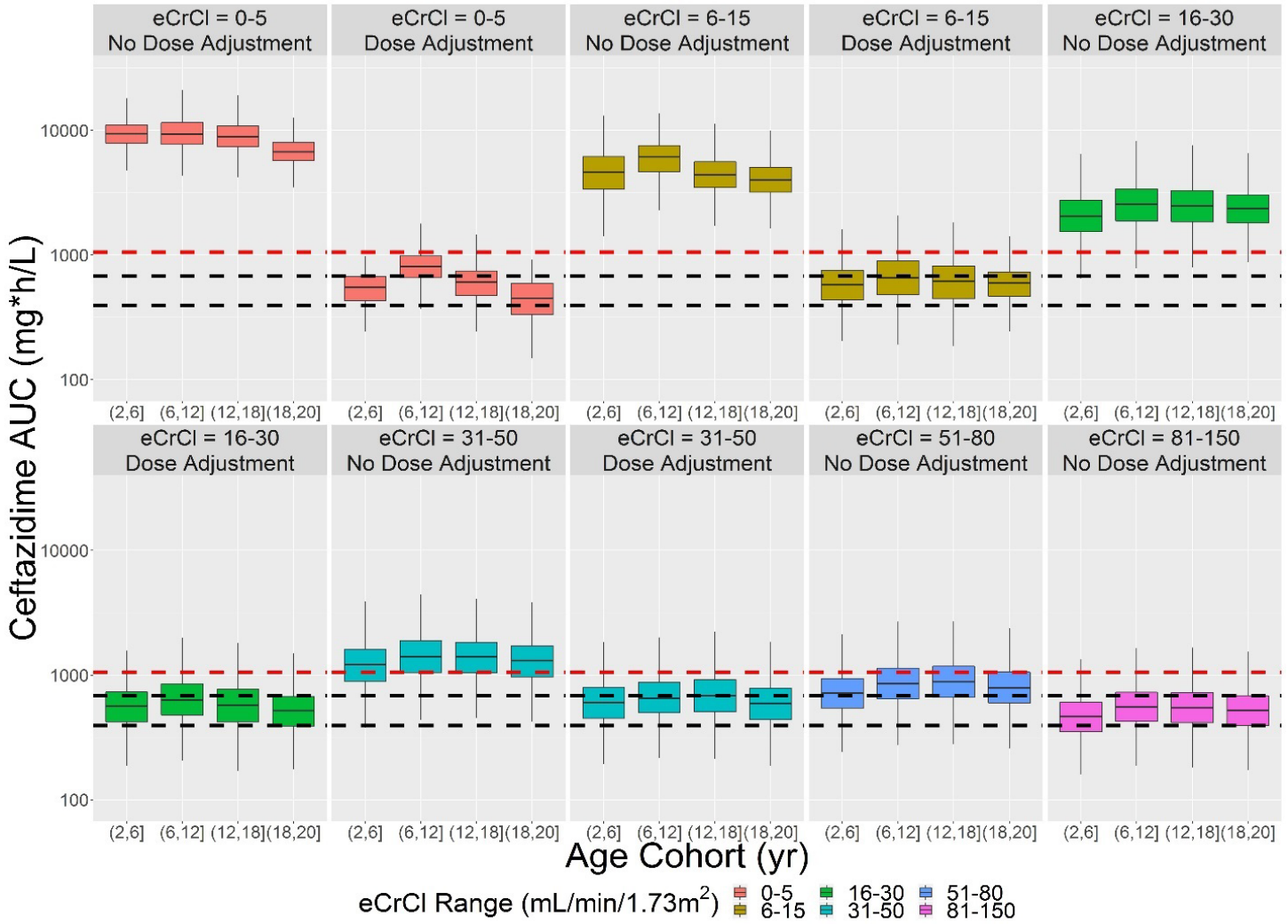
Age (years)	BSA-normalized eGFR (mL/min/1.73m^2)				
	0-30	**31-50**	**51-80**	**80-120**	**>120**
0 to <0.5	0	0	1	2	2
0.5 to <1	0	1	4	3	2
1 to <2	0	0	7	3	2
2 to <6	0	0	4	4	8
6 to <12	0	1	9	23	17
12 to <18	0	0	6	25	3

- Only 2 patients with CLcr ≤50 mL/min/1.73m^2; 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

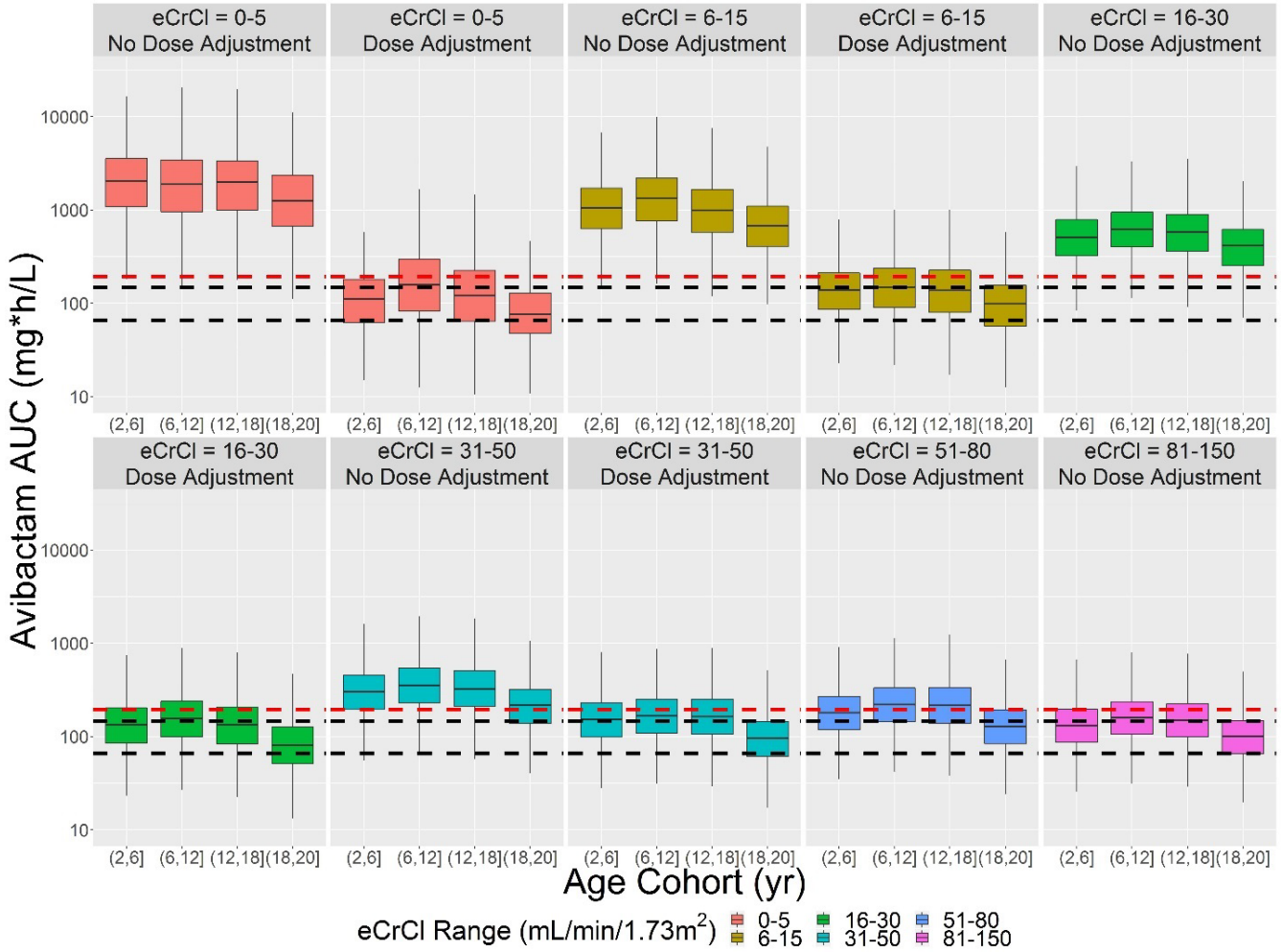
Simulated CAZ AUC Stratified by Renal Function with and without Dosage Adjustments



--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

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Question 2

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

Characterization of CLcr 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

Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.

Acknowledgements

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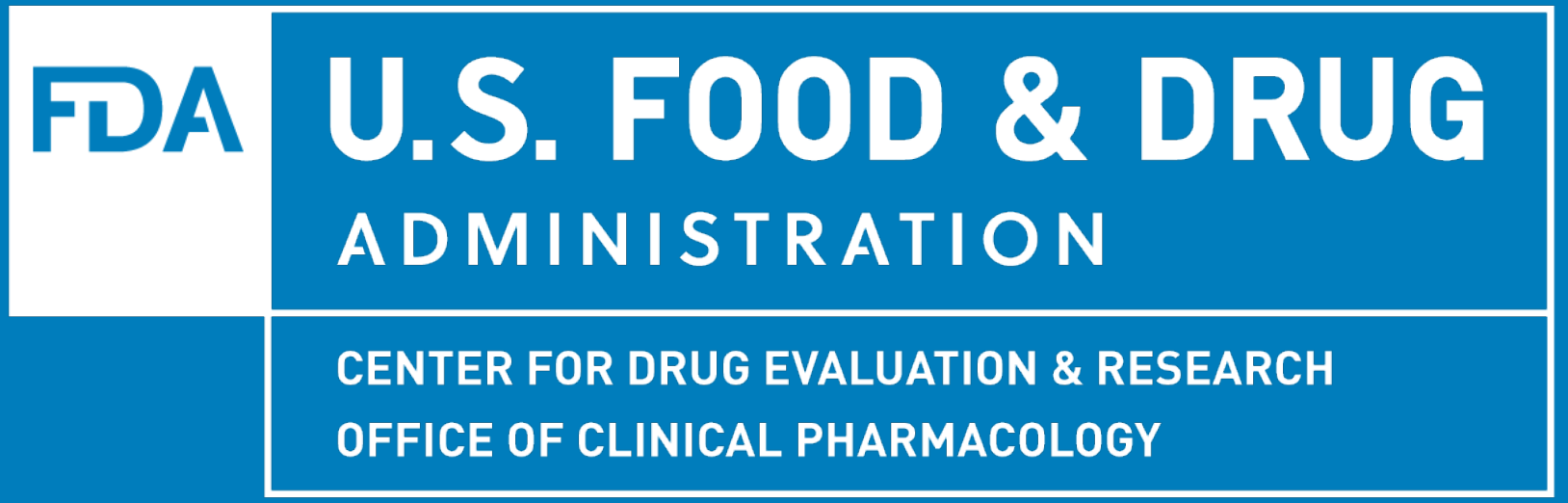
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