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# Use of Ceftazidime-Avibactam in Infants and Children

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On March 18, 2019, the Food and Drug Administration (FDA) extended approval for ceftazidime-avibactam to pediatric patients 3 months of age and older for the treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole and the treatment of complicated urinary tract infections (cUTI) including pyelonephritis.[1] Ceftazidime-avibactam was first approved in 2015 for adults with cIAI and cUTI, and was subsequently approved for the treatment of hospital-acquired or ventilator-associated pneumonia in February 2018.[2,3] A recent systematic review and meta-analysis confirmed its utility in cIAI and cUTI in adults, with results similar to those achieved with carbapenems in susceptible organisms, while offering an effective agent for patients with carbapenem-resistant Gram-negative infections.[4]

## Mechanism of Action

Avibactam is the first in a new class of synthetic beta-lactamase inhibitors that also has activity against carbapenemases.[2-4] It protects ceftazidime, a third generation cephalosporin with antipseudomonal activity, from being degraded by beta-lacatamases and extended-spectrum beta-lactamases (ESBLs), including TEM, SHV, CTX-M, *Klebsiella pneumoniae* carbapenemases (KPCs), AmpC, and some oxacillinases (OXA). The combination has also been shown to have *in vitro* activity against *Pseudomonas aeruginosa* in the presences of some AmpC beta-lactamases. It is generally ineffective against bacteria producing metallo-beta-lactamases, but has been successful in the treated New Delhi metallo-beta-lactamase (NDM-1) producing strains of *K. pneumoniae* and *Morganella morganii* when used in combination with aztreonam.

## Spectrum of Activity

Ceftazidime-avibactam, in combination with metronidazole, is indicated for the treatment of cIAI in infants and children caused by susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytocia*, *Proteus mirabilis*, *Enterobacter cloacae*, *Citrobacter freundii* complex, and *P. aeruginosa*. It is also approved as single-agent therapy for use in pediatric patients with cUTI due to *E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii* complex, *Proteus mirabilis*, and *P. aeruginosa*.[2]

The International Network for Optimal Resistance Monitoring (INFORM) surveillance program has provided a useful overview of the real-world experience with ceftazidime-avibactam.[5] In a recent paper from INFORM data collected from 26 medical centers in six countries in Latin America between 2012 to 2015, Enterobacteriaceae isolates were highly susceptible to ceftazidime-avibactam, with inhibition of 99.6% to 100% of isolates carrying serine beta-lactamases (ESBLs, AmpC cephalosporinases, and carbapenemases including KPC). Ceftazidime-avibactam inhibited 87.4% of all *P. aeruginosa* isolates, including 89.5% of carbapenem non-susceptible strains in which no beta-lactamase could be identified.

A recent assessment of INFORM surveillance data from 82 medical centers in the United States gathered from 2011 to 2015 included 53,381 Gram-negative organisms that had been tested against ceftazidime-avibactam, including 8,461 isolates from children.[6] Ceftazidime-avibactam inhibited more than 99.9% of all Enterobacteriaceae at the $\leq$ 8 mcg/mL break point and was highly active against ESBL-positive strains of *E. coli* and *K. pneumonia*. Only one isolate was non-susceptible, an isolate of *Enterobacter aerogenes* with an MIC value of 16 mcg/mL. Ceftazidime-avibactam inhibited 99% of *P. aeruginosa* isolates, including the few strains that were non-susceptible to ceftazidime alone, meropenem, or piperacillin-tazobactam. This level of activity did not vary among the age groups tested or over time.

## Bacterial Resistance

While the results of the INFORM surveillance program are promising, there are already reports

of resistance to ceftazidime-avibactam. The resistant strains identified to date have been most frequently the result of an amino acid substitution at or near the omega loop of the KPC enzyme.[4,7] In an early release from *The Journal of Antimicrobial Chemotherapy*, Hemarajata and Humphries described resistance occurring after use of ceftazidime-avibactam in a patient with end-stage renal and liver disease on dialysis while awaiting liver transplantation.[7] On hospital day 35, the patient was placed on cefepime and vancomycin for ventilator-associated pneumonia. Three days later, a KPC-2 producing strain of *K. pneumoniae* was identified and treatment was changed to ceftazidime-avibactam and gentamicin. Twelve days later, *K. pneumoniae* was again isolated from a blood culture. This isolate contained a single L169P mutation in the KPC-2 enzyme which significantly reduced susceptibility to ceftazidime-avibactam and necessitated a change to meropenem for another 13 days until clinical cure was achieved.

Pharmacokinetics

Ceftazidime-avibactam exhibits linear pharmacokinetics.[2] Less than 10% of the administered dose is bound to serum proteins. It is excreted by the kidneys, with 80-90% of the dose eliminated as unchanged drug. Approximately 50% of the dose is excreted within 2 hours of dose administration. Elimination is decreased in patients with renal impairment, requiring dosage adjustment to avoid drug accumulation and toxicity.

The pharmacokinetic profile of ceftazidime-avibactam was evaluated as part of a phase 1 safety and tolerability study conducted in 32 children.[8] Patients were divided into four cohorts: 1 (12 years to up to 18 years of age), 2 (6 years up to 12 years), 3 (2 years up to 6 years), and 4 (3 months up to 2 years). A single dose was given over 2 hours: 2 grams for cohort 1 and 50 mg/kg up to a maximum of 500 mg in cohorts 2-4. Mean maximum plasma ceftazidime concentrations ($C_{max}$) for the four cohorts were 79.8 mg/L (CV% 41.8), 81.3 mg/L (17.8), 80.1 mg/L (14.7), and 91.7 mg/L (19.6), respectively. Additional parameters were only evaluated in the two older cohorts. Area under the concentration-time curve (AUC) results were also similar to adult values, with a mean of 230.6 hr•mg/L (30.7) in cohort 1 and 221.2 hr•mg/L (17.4) in cohort 2. Mean elimination half-lives for the two cohorts were 1.7 hours (range 0.9-2.8 hours) and 1.6 hours (0.9-1.8 hours). Likewise, avibactam $C_{max}$ was similar across all four cohorts: 15.1 mg/L (52.4), 14.1 mg/L (23.1), 13.7 mg/L (22.4), and 16.3 mg/L (22.6). Values for avibactam AUC in cohorts 1 and 2 were 36.4 hr•mg/L (33.6) and 34.8 hr•mg/L (22.6), and half-lives for groups 1 and 2 were 2.0 hours (2.9-2.6 hours) and 2.1 hours (1.9-2.4), respectively.

Clinical Experience

There have been only limited reports of ceftazidime-avibactam use in infants, children, and adolescents prior to the FDA approval for pediatric patients. In 2018, Tamma and colleagues at Johns Hopkins Hospital described their experience treating a 2-month-old infant with a refractory infection.[9] The patient was a previously full-term infant with a congenital diaphragmatic hernia that had been surgically repaired at 2 weeks but remained hospitalized for respiratory support. At 2 months, she developed fevers and hypotension requiring vasopressors and was started on cefepime and vancomycin empirically. Cultures grew Gram-negative rods that were subsequently speciated as *Burkholderia cepacia* complex (Bcc). Treatment was changed to intravenous trimethoprim-sulfamethoxazole and daily blood cultures were continued.

Ceftazidime was added on day 6 of the infection for persistent bacteremia. The ceftazidime MIC at that time was 8 mcg/mL. With continued bacteremia in spite of removing all central IV catheters, the ceftazidime was changed to a continuous infusion on day 12. Four days later, ceftazidime was replaced with extended infusion meropenem and the trimethoprim-sulfamethoxazole continued. On day 32 of positive blood cultures, treatment was changed to ceftazidime-avibactam 50 mg/kg (40 mg/kg ceftazidime and 10 mg/kg avibactam) as an extended infusion over 8 hours and given every 8 hours. Antimicrobial sensitivity testing had revealed that the Bcc was highly sensitive to ceftazidime-avibactam, with a zone of inhibition of 33 mm (with the breakpoint for susceptibility defined as > 18 mm) and an MIC of 2 mcg/mL. Within 24 hours of initiating the change in therapy, the patient had her first negative blood culture. She was treated for an additional 6 weeks without further issues and remained infection-free at 10-month follow-up. Genomic sequencing of the Bcc isolate revealed a Pen-like beta-lactamase.

Earlier this year, Hobson and colleagues at the Robert Debré Hospital in Paris reported the use of ceftazidime-avibactam in a 3-year-old girl with a refractory infection following chemotherapy for a relapse of acute lymphoblastic leukemia.[10] She presented with a fever and neutropenia, and was found to be bacteremic. Her initial culture grew a *K. pneumoniae* strain producing CTX-M-1. She was successfully treated with imipenem, but 8 days later was found to have a multidrug-resistant NDM-1-producing strain of *Morganella morganii*. The MIC values were > 256 mcg/mL for ceftazidime, 3 mcg/mL for meropenem, > 32 mcg/mL for imipenem, 4 mcg/mL for aztreonam, and 0.016 mcg/mL for ceftazidime-avibactam. The patient received aztreonam 100 mg/kg/day and ceftazidime-avibactam 150 mg/kg/day for 10

days, with resolution of the infection, negative cultures, and no further signs of relapse at 6-month follow-up.

The manufacturer conducted two controlled studies of ceftazidime-avibactam to support their request for FDA approval of a pediatric indication. Effectiveness in pediatric cIAI was demonstrated in a multicenter randomized, single-blind, active-comparator controlled trial of 83 patients ranging from 3 months to 18 years of age. Patients were randomized in a 3:1 ratio to receive either ceftazidime-avibactam and metronidazole or meropenem. Children and adolescents 2 to 18 years of age received a ceftazidime-avibactam dose of 62.5 mg/kg (50 mg/kg ceftazidime and 12.5 mg/kg of avibactam) up to a maximum of 2.5 grams, while infants 3 months up to 6 months of age were given a dose of 50 mg/kg (40 mg/kg ceftazidime and 10 mg/kg avibactam), infused over 2 hours every 8 hours in combination with metronidazole 20 mg/kg IV every 8 hours. Patients treated with meropenem were given a dose of 20 mg/kg IV every 8 hours. Patients were treated for 72 hours with their assigned study drug, but could then be switched to oral therapy to complete 7 to 15 days of treatment by the site investigator.

The majority of the patients in the study were being treated for a perforated appendix or a peri-appendiceal abscess. Mean age of the study patients was 11 years, with a range of 3 to17 years. There were no infants in the ceftazidime-avibactam group. Sixty-nine patients had at least one positive bacterial culture; 50 in the combination group and 19 in the meropenem group. The most common organisms were *E coli*, in 80% of patients, and *P. aeruginosa* in 33%. The test-of-cure visit was scheduled between 8 and 15 days after the last dose of the study drug. Clinical cure was defined as resolution of all acute signs and symptoms or improvement such that antibiotics were discontinued.

In the intention-to-treat population, 56 of 61 patients (91.8%) in the ceftazidime-avibactam plus metronidazole group and 21 of the 22 meropenem patients (95.5%) were categorized as having a clinical cure. Clinical cure rates in the patients with positive cultures were 45 of 50 patients (90%) in the combination group and 18of 19 patients (94.7%) in the meropenem group. In patients with *E. coli* infections, the clinical cure rates were 90.5% for ceftazidime-avibactam and 92.3% for meropenem. Clinical cure rates for *P. aeruginosa* were 85.7% and 88.9%, respectively. Although the results of this study have not been published, the results are available at www.ClinicalTrials.gov, NCT 02475733).

A subsequent multicenter single-blind active-comparator safety and tolerability study was conducted by the manufacturer in 95 infants, children, and adolescents from 3 months to 18 years of age with cUTI.[2] Patients were randomized to either ceftazidime-avibactam at the same doses as in the previous study or cefepime given at the standard recommended dose for age and weight. The median patient age was 4.2 years, with a range of 3.5 to 18 years. Most of the patients had been diagnosed with pyelonephritis, and 77 had at least one Gram-negative pathogen in the urine, with *E. coli* found in 92%. Clinical cure was defined in a manner similar to the earlier study. Microbiological cure was defined as eradication of the organism identified at the baseline urine culture. Clinical cure was reported in 48 of 54 (88%) of the ceftazidime-avibactam patients and 19 of the 23 cefepime patients (83%). Microbiological cure was seen in 43 (80%) and 14 (61%) patients in the two groups. Neither of the two tests was powered to determine a statistically significant difference in clinical efficacy.

Contraindications, Warnings, and Precautions

Ceftazidime-avibactam is contraindicated in patients with known severe hypersensitivity to either component or other beta-lactam antibiotics.[2] Severe hypersensitivity reactions, including anaphylaxis and dermatologic reactions, have been reported after ceftazidime-avibactam use. Creatinine clearance should be evaluated daily in any patient with changing renal function or those at risk for worsening function due to illness. Patients with renal impairment are at greater risk for seizures from ceftazidime-avibactam accumulation and require close evaluation and dose adjustment. *Clostridium difficile*-associated diarrhea (CDAD) has been reported with ceftazidime-avibactam. Patients and their families should be aware of the need to report the development of diarrhea to their healthcare provider.

Adverse Effects

The most commonly reported adverse reactions with ceftazidime-avibactam in adults enrolled in clinical trials were diarrhea (8%), nausea (7%), and vomiting (5%).[2] In the children from 3 months up to 6 years of age participating in the pharmacokinetic, safety, and tolerability study described earlier, constipation, diarrhea, vomiting, a local infusion site reaction, increased serum transaminases, an elevated triglyceride level, and an increased gamma-glutamyl transferase level were each reported in one patient (3.1% for each reaction).[8] No adverse effects were reported in the patients 6 years of age or older.

Drug Interactions

Avibactam is a substrate of organic ion transporters 1 and 3 (OAT1 and OAT3) which might contribute to its uptake and excretion.[2] Probenecid is a potent OAT inhibitor and may

produce up to a 70% reduction in avibactam elimination when administered concomitantly.

Availability and Dosing Recommendations

Ceftazidime-avibactam (Avycaz®) is available in single-dose vials of 2.5 grams (2 grams ceftazidime and 500 mg avibactam).[2] The manufacturer's recommended dose in children 6 months up to 18 years of age with normal renal function is 62.5 mg/kg (equivalent to 50 mg/kg ceftazidime and 12.5 mg/kg avibactam), to a maximum of 2.5 grams, given every 8 hours. The dose should be infused over 2 hours. Patients 3 months up to 6 months of age should receive a dose of 50 mg/kg (40 mg/kg ceftazidime and 10 mg/kg avibactam) administered in the same manner. The recommended duration of treatment is 5 to 14 days for cIAI and 7 to 14 days for cUTI or pyelonephritis.

Dosing modifications for adults and children 2 years of age and older with renal impairment are included in prescribing information. In children with an estimated creatinine clearance of 31-50 mL/min/1.73 $m^2$ based on the Schwartz bedside formula, a dose of 31.25 mg/kg given every 8 hours is recommended, with a maximum dose of 1.25 grams. Patients with a clearance of 16-30 mL/min/1.73 $m^2$ should receive a dose of 23.75 mg/kg every 12 hours, with a maximum dose of 0.94 grams. Children with a clearance of 6-15 mL/min/1.73 $m^2$ should receive a dose of 23.75 mg once daily, and those with a clearance of 5 mL/min/1.73 $m^2$ or less should receive the same dose but given every 48 hours. Daily evaluation of serum creatinine levels should be used to identify changes in clearance to guide further dosing adjustments. Dosing adjustments are not yet available for children under 2 years of age with renal impairment. Ceftazidime-avibactam is cleared by hemodialysis and should be dosed after each hemodialysis session.

Ceftazidime-avibactam is compatible with a number of medications, including amikacin, azithromycin, aztreonam, daptomycin, dexmedetomidine, furosemide, gentamicin, heparin, magnesium sulfate, metronidazole, norepinephrine, phenylephrine, potassium phosphate, tobramycin, vasopressin, and vecuronium. More detailed information is available in the prescribing information.[2]

Summary

Ceftazidime-avibactam provides a new option for the treatment of infections caused by most beta-lactamase and carbapenemase-producing Gram negative bacteria. In clinical trials, it has been shown to be safe and effective in patients as young as 3 months of age with complicated intra-abdominal or urinary tract infections. While its benefits are clear, recent reports of the development of ceftazidime-avibactam resistance highlight the need for continued efforts to restrict its use to treatment of organisms known to be resistant to standard therapies.

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