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Outcomes with ceftazidime/avibactam in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections: a multi-center study

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REVISED ABSTRACT

Background: Ceftazidime-avibactam (CAZAVI) is a cephalosporin-beta-lactamase inhibitor combination that is active against Enterobacteriaceae and Pseudomonas aeruginosa that is resistant to other agents, including carbapenems and late-generation cephalosporins. This purpose of this study is to describe the outcomes of patients receiving ceftazidime-avibactam for CRE infections.
Methods: A retrospective chart review was completed from March 2015 through August 2016 at 9 hospitals in the United States for adult patients who received ceftazidime/avibactam for a CRE infection. Patients were included if they received CAZAVI for at least 24 hours for a carbapenem-resistant Enterobacteriaceae. Dosage was chosen by providers at individual sites. The primary outcome was in-hospital mortality. Microbiologic and clinical outcomes were also evaluated. Microbiological success required a negative culture at the end of therapy. Clinical success was judged by improved symptoms, improved imaging where relevant, and defervesence.
Results: Overall, 60 patients received ceftazidime-avibactam for a CRE infection. *K. pneumoniae* was the causative pathogen in 80% of cases. Thirty eight percent of cases were bacteremia, 28% urinary tract, and 27% pneumonia. Over half of the patients were in the ICU at the time of receiving ceftazidime-avibactam. In hospital mortality was 32%, 53% of patients had microbiological cure, and 65% had clinical success.
Conclusions: In this severely ill population, ceftazidime/avibactam was an appropriate option for patients with multi-drug resistant organisms causing Enterobacteriaceae infections.

INTRODUCTION

Infections due to drug-resistant pathogens have become endemic in parts of the world, including the United States[1].Ceftazidime-avibactam (CAZAVI) is a cephalosporin-beta-lactamase inhibitor combination that is active against Enterobacteriaceae and *Pseudomonas aeruginosa* that is resistant to other agents, including carbapenems and late-generation cephalosporins[3,4]. In a sample of over 10,000 gram negative organisms, CAZAVI inhibited over 99% of Enterobacteriaceae tested, including carbapenem resistant strains. It was also active against over 80% of Pseudomonas strains, including ceftazidime non-susceptible strains[2]. The purpose of this study is to describe the outcomes of patients receiving ceftazidime-avibactam for CRE infections.

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OBJECTIVES

Primary outcome:
In-hospital mortality
Secondary outcomes:
Microbiologic and clinical success.

- Microbiological success required a negative culture at the end of therapy
- Clinical success was judged by improved symptoms, improved imaging where relevant, and defervesence.

METHODS

An IRB approved, retrospective chart review was completed from March 2015 through August 2016 at 9 hospitals in the United States for adult patients who received ceftazidime/avibactam for a CRE infection. Patients were included if they received CAZAVI for at least 24 hours for a carbapenem-resistant Enterobacteriaceae defined as having an MIC > 1 to meropenem or imipenem, or >0.5 to ertapenem. Dosage was chosen by providers at individual sites and patients were included if they were on concomitant antibiotics. The primary outcome was in-hospital mortality. Microbiologic and clinical outcomes were also evaluated. Susceptibility testing was performed where available.

SUMMARY OF RESULTS

Overall, 60 patients received ceftazidime-avibactam for a CRE infection. *K. pneumoniae* was the causative pathogen in 80% of cases. The primary infection type in 38% of cases was bacteremia, 28% urinary tract, and 27% pneumonia. Over half of the patients were in the ICU at the time of receiving ceftazidime-avibactam. In hospital mortality was 32%, 53% of patients had microbiological cure, and 65% had clinical success.
Mortality rates for each infection are listed. Mortality was highest for patients with pneumonia (56%), bone/joint (50%), and bacteremia (39%). Mortality rates for patients in the ICU neared 50%. Patients who received concomitant therapy (aminoglycosides, polymyxin B or colistin, tigecycline, carbapenems or other beta-lactams, or fluoroquinolones) had a mortality rate of 35%.

RESULTS: TABLE 1

Characteristic	Results (N=60)
Male gender, n(%)	36 (60)
Age (median, IQR)	60 (51-69)
Charlson Comorbidity Index (median, IQR)	4.5 (3-7)
Pitt Bacteremia Score (median, IQR)	2 (0-5)
ICU, n(%)	35 (59)
Moderate-severe renal disease, n(%)	19 (32)
Moderate-severe liver disease, n(%)	8 (13)
Primary organism, n(%)	
Klebsiella pneumoniae	48 (80)
Escherichia coli	5 (8)
Enterobacter spp.	4 (7)
Providencia stuartii	1 (2)
Serratia marcescens	1 (2)
Primary infection, n(%)	
Bacteremia	23 (38)
Urinary Tract	17 (28)
Pneumonia	16 (27)
Wound	8 (13)
Intra-abdominal	4 (7)
Bone/joint	2 (3)
Hospital day CRE infection diagnosed (median, IQR)	1 (1-15)
Hospital day CAZAVI started (median, IQR)	8 (5-22)
Patients receiving concomitant therapy for CRE, n/N(%)	
Aminoglycosides	11/26 (42)
Polymyxin	7/26 (27)
Tigecycline	6/26 (23)
Carbapenem	3/26 (12)
Fluoroquinolone	3/26 (12)
Isolates susceptible to CAZAVI, n/N (%)	35/36 (97)

TABLE 2: OUTCOMES

Outcome	Results (N=60)
In-hospital mortality, n(%)	19 (32)
Microbiologic cure, n(%)	32 (53)
Clinical success, n(%)	39 (65)

TABLE 3: OUTCOMES

Outcome	In-hospital mortality	Microbiologic cure	Clinical success
Concomitant therapy, n/N (%)	9/26 (35)	17/26 (65)	17/26 (65)
ICU, n/N (%)	16/35 (46)	16/35 (46)	18/35 (51)
Infection Type, n/N (%)			
Bacteremia	9/23 (39)	19/23 (82)	14/23 (61)
Urinary tract	2/17 (12)	7/17 (41)	15/17 (88)
Pneumonia	9/16 (56)	7/16 (44)	9/16 (56)
Wound	2/8 (25)	3/8 (38)	5/8 (63)
Intra-abdominal	1/4 (25)	3/4 (75)	3/4 (75)
Bone/joint	1/2 (50)	1/2 (50)	0/2 (0)

OUTCOMES ANALYSIS

The in-hospital mortality for patients in the ICU was significantly higher than those not in the ICU (46 vs 9%, p=0.0009). There was no significant difference between patients receiving concomitant therapy vs monotherapy with CAZAVI (35 vs 23%) or patients with bacteremia vs those with other infections (39 vs 21%).

CONCLUSIONS

This retrospective case series shows that ceftazidime-avibactam was an appropriate therapy for this critically ill population. Clinical success was observed in 65% of patients, microbiologic cure in 53% of patients, and in hospital mortality occurred in 32% of patients. Further studies evaluating the use of ceftazidime-avibactam in various infections are warranted.