Treatment of Carbapenem-Resistant Enterobacteriaceae Infections with Ceftazidime-Avibactam

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Introduction and Background

- CRE has been classified by CDC as one of the most urgent threats to public health, requiring immediate attention.
- CRE associated infections carry a high mortality rate estimated at >30-50%.
- Despite their questionable efficacy and well-known serious toxicity profiles, polymyxin-based antibiotics previously were the only available options against these deadly organisms.
- Most recently, a new therapeutic option has become available: ceftazidime-avibactam.
- We sought to describe outcomes from CRE infections treated with ceftazidime-avibactam.

Materials and Methods

- We retrospectively reviewed charts of 11 patients who were infected with CRE and received ceftazidime-avibactam for treatment between September 2015 to December 2016, at Keck Medical Center of USC.
- The patients were treated with standard dose ceftazidime-avibactam, 2.5 g IV every 8 hr with renal adjustment as recommended by the pharmaceutical manufacturer.
- Sixteen isolates from 11 patients were characterized as CRE based on resistance to meropenem (all MIC ≥ 16 µg/mL) and positive bla_{KPC} PCR.
- Ceftazidime-avibactam susceptibility testing was performed by E-test and/or disc diffusion for all patients.
- ST 258 and clade typing were done by multiplex PCR and capsular typing was performed by *wzi* sequence analysis.
- Clinical success was defined as clinical improvement, lack of recurrence, and survival in 90 days after CRE infection.
- Recurrence was defined by clinical signs of infection and recovery of CRE organism after ≥ 7 days of treatment.

Abbreviations:
CDC: US Centers for Disease Control and Prevention
CRE: Carbapenem-resistant *Enterobacteriaceae*
CRRT: continuous renal replacement therapy
MLST: Multilocus Sequence Typing
qSOFA: quick Sential Related Organ Failure Assessment
RIFLE: Risk, Injury, Failure, Loss, End Stage Renal Failure

Results

Table 1. Demographics

No of patients	11
Median (range) age	49 (35-89)
Female	73% (7/11)
Solid organ transplantation	27% (3/11)

Table 2. Clinical Data

Types of initial infections	
Intraabdominal infection (IAI)	7
Pyelonephritis	2
Skin and soft tissue infection (SSTI)	1
Primary bacteremia	1
Secondary bacteremia (4 from IAI and 1 from pyelonephritis)	5
Median (range) duration of treatment	15 (3-43) days
Antibiotics prior to ceftazidime-avibactam	100% (11/11)
Monotherapy	87% (9/11)
Dual therapy with colistemethate sodium	13% (2/11)
CRRT or hemodialysis during treatment	27% (3/11)
Incidents of renal toxicity by RIFLE	0
Overall clinical success	67% (7/11)
Intraabdominal infection	86% (6/7)
Pyelonephritis	50% (1/2)
Skin and soft tissue infection	0 (0/1)
Primary bacteremia	0 (0/1)
Secondary bacteremia	80% (4/5)
Median qSOFA score (range)	0 (0-2)
Predicted in hospital mortality	3%
30 day survival rate	82% (9/11)
90 day survival rate	73% (8/11)
Hospital mortality	27% (3/11)
CRRT or hemodialysis mortality	75% (3/4)
Clinical recurrence	18% (2/11)
CRE isolated after ≥ 7 days treatment	27% (3/11)

Table 3. Microbiological Data

Klebsiella pneumoniae	11/11
Susceptible to ceftazdime-avibactam	11/11
Decreased susceptibility after treatment course	1/11
Sequence type 258 (ST258)	11/11
bla_{KPC-2}	7/11
bla_{KPC-3}	4/11
Capsular type wzi-154	9/11
Capsular type wzi-29	2/11

Discussion and Conclusions

❖ In our patient population with CRE who were treated with ceftazidime-avibactam:

- *K. pneumonia* was the dominant *Enterobacteriaceae* isolated.
- The most common infections were intraabdominal infections followed by secondary bacteremia with majority related to intraabdominal infection.
- The overall mortality rate was 27% comparable to a prior description of CRE infection with ceftazidime-avibactam.
- All 3 fatalities occurred in patients requiring renal replacement therapy.
- Clinical recurrence was 18% at six weeks and 1 year following treatment both resulting in bacteremia.
- Decreased susceptibility was found in one case a year after completion of therapy in a patient with persistent colonization in urine cultures despite treatment.

❖ Additional research is needed to optimize use of ceftazidime-avibactam to treat CRE infections.

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