Cleveland Clinic

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# Early Experience with Ceftazidime/avibactam at an Academic Medical Center and Affiliated Health System


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## Background

- Ceftazidime/avibactam (CAZ-AVI) is a novel combination cephalosporin/beta-lactamase inhibitor product
- Indications: complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI)
- *In vitro* activity against Ambler Class A (including KPC), Ambler Class C, and some Ambler Class D beta-lactamases
- Limited data evaluating use of CAZ-AVI for infections caused by KPC-producing carbapenem-resistant Enterobacteriaceae (CRE) and off-label indications

## Objectives

**Primary Objective:** Describe the utilization of CAZ-AVI throughout the Cleveland Clinic Health System

**Secondary Objectives:**
- Characterize CAZ-AVI dosing
- Describe the susceptibility of identified organisms to CAZ-AVI
- Describe the rate of clinical and microbiological cure in patients receiving CAZ-AVI

## Methods

**Study design**
- Retrospective case series including all patients that received CAZ-AVI from April 2015 – February 2016
- Cleveland Clinic Health System – 1400-bed tertiary academic medical center and 9 community regional hospitals

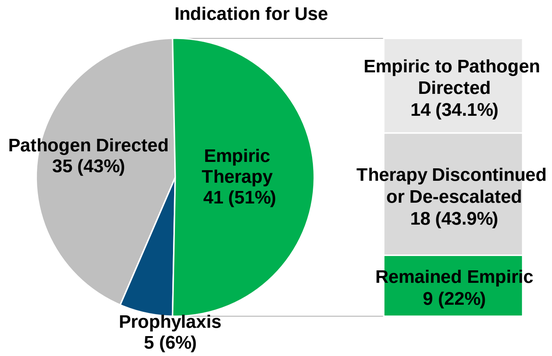
**Statistics**
- Chi-squared or Mann Whitney U, as appropriate

**Definitions**
- **Clinical cure:** complete resolution of index infection as evidenced by no further escalation of antimicrobial therapy or need for additional source control, in patients that received ≥ 72 hours of inpatient therapy
- **Clinical Failure:** not meeting criteria for clinical cure
- **Indeterminate Clinical Status:** unable to categorize patient as meeting clinical cure or clinical failure due to missing data or complex multi-source infections
- **Microbiological cure:** eradication of baseline pathogen in microbiologically evaluable patients

## Results

- 81 courses of CAZ-AVI prescribed over study period (total of 62 patients)
- **Baseline Characteristics**
  - Male, n (%): 50 (62)
  - Age (yr), mean ± SD: 62 ± 15
  - ICU admission, n (%): 41 (50.6)
  - Immunocompromised, n (%): 30 (37)
  - Length of stay (LOS), (d), median (IQR): 21(8-62)

### Primary Outcome: CAZ-AVI Utilization




### Source of Infection

| | |
|---|---|
| **Source of Infection, n (%)** | |
| Pneumonia | 23 (28.4) |
| Genitourinary | 19 (23.6) |
| Intra-abdominal | 12 (14.8) |
| Primary bacteremia | 9 (11.1) |
| Skin/soft tissue | 3 (3.7) |
| Bone and joint | 3 (3.7) |
| Endophthalmitis | 2 (2.4) |
| Endocarditis | 1 (1.2) |
| Febrile neutropenia | 1 (1.2) |
| Prophylaxis | 5 (6.2) |
| Source unknown | 3 (3.7) |
| **Concomitant Bacteremia, n (%)** | 24 (29.6) |
| **Source Control, n/N* (%)** | 20/28 (71.4) |

*Of patients where source control achievable

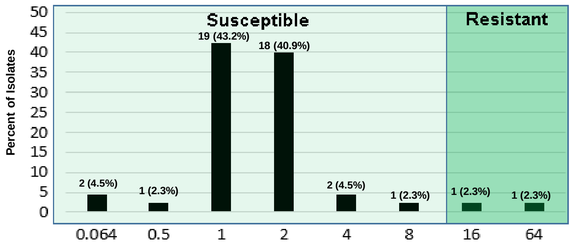
### CAZ-AVI Dosing

| | |
|---|---|
| **CAZ-AVI Initial Dose, n (%)** | |
| 2.5 g Q8h | 42 (51.9) |
| 1.25 g Q8h | 18 (22.2) |
| 0.94 g Q12h | 6 (7.4) |
| 0.94 g Q24h | 2 (2.5) |
| 0.94 g Q48h | 9 (11.1) |
| Nonstandard Dosing | 4 (4.9) |
| **IHD Dosing, n (%)** | N = 10 patients |
| 0.94 g Q24h | 2 (20) |
| 0.94 g Q48h | 8 (80) |
| **CRRT Dosing, n (%)** | N=11 patients |
| 1.25 g Q8h | 10 (90.9) |
| 0.94 g Q12 | 1 (9.1) |

### CAZ-AVI Susceptibility

| | |
|---|---|
| **Organism Isolated, n (%)** | N = 63 |
| K. pneumoniae | 39 (61.9) |
| K. oxytoca | 1 (1.6) |
| P. aeruginosa | 14 (22.2) |
| E. coli | 5 (7.9) |
| P. mirabilis | 3 (4.8) |
| S. maltophilia | 1 (1.6) |
| **Susceptibility to CAZ-AVI, n (%)** | |
| E. coli (n=3) | 2 (66.6) |
| K. pneumoniae (n=34) | 34 (100) |
| P. aeruginosa (n=9) | 8 (88.9) |
| CRE (n=39) | 39 (100) |

MIC Distribution to CAZ-AVI




### Outcomes

| | |
|---|---|
| **Clinical Cure, n /N* (%)** | 38/49 (77.6) |
| Monotherapy (n=20) | 18/20 (90) |
| Combination therapy (n=29) | 20/29 (69) |
| **Clinical Failure, n/N* (%)** | 8/49 (16.3) |
| Intra-abdominal | 3 |
| Pneumonia | 5 |
| **Indeterminate Clinical Status, n/N* (%)** | 3/49 (6.1) |
| **Microbiologic Cure, n/N (%)** | 37/41 (90.2) |
| **Microbiologic Failure, n/N (%)** | 4/41 (9.8) |
| Intra-abdominal | 2 |
| Bone and joint | 1 |
| Pneumonia | 1 |
| **Patient Disposition, n/N (%)** | |
| Completed Therapy In-Hospital | 35/81 (43.2) |
| Therapy Changed | 17/81 (21) |
| Discharged on CAZ-AVI | 15/81 (18.5) |
| Died on CAZ-AVI Therapy | 14/81 (17.3) |

*Of patients with CAZ-AVI susceptible infection, on therapy for ≥72 hours

### Combination Therapy vs. Monotherapy

| | Combination Therapy (n = 39) | Monotherapy (n = 42) | p-value |
|---|---|---|---|
| Age, years | 57 ± 15 | 67 ± 14 | 0.0033 |
| ICU Admission | 25 (64%) | 16 (38%) | 0.017 |
| LOS, days | 33 (10-71) | 15 (5-40) | 0.0598 |
| Source control | 7 (17.9%) | 13 (31%) | 0.175 |
| Clinical cure | 20/29 (69%) | 18/20 (90%) | 0.083 |
| Microbiologic cure | 24/25 (96%) | 13/16 (81.3%) | 0.120 |
| In-hospital mortality | 11 (28.2%) | 3 (7.1%) | 0.012 |

Data presented as n (%), median (IQR), or mean ± SD

## Conclusion

- In this case series, CAZ-AVI was successful in treating infection in both labeled and non-labeled indications as well as for infections caused by CRE
- The findings of this study justify further evaluation of CAZ-AVI in the treatment of these multi-drug resistant infections and off-label uses