Evaluation of the Use of Ceftolozane/Tazobactam for the Treatment of ESBL-producing Enterobacterales Infections Using International Data from SPECTRA (Study of Prescribing Patterns and Effectiveness of Ceftolozane/Tazobactam Real World Analysis)

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INTRODUCTION

- The incidence of severe infections caused by extended-spectrum β- lactamases- producing Enterobacterales (ESBL-E) is a rising concern worldwide owing to the successful dissemination of these species in both community and healthcare settings. Serious infections caused by these strains are usually treated with carbapenems; however this may potentially select for carbapenem resistant pathogens.
- Ceftolozane/tazobactam (C/T) is a novel β-lactam/β-lactamase inhibitor (BLBLI) combination, that has shown potent activity against gram-negative bacteria, and has been approved in >60 countries for complicated urinary tract infections, complicated intra-abdominal infections and hospital-associated and ventilator-acquired pneumonia. However, there is a paucity of data on outcomes of patients with severe ESBL-E infections treated with empiric or directed C/T. One recently published multicenter evaluation of C/T for ESBL-E infections in Italy (CEFTABUSE-II) demonstrated C/T to be an effective drug for treating different types of ESBL-E infections.
- The aim of this multinational study was to evaluate treatment patterns and outcomes associated with C/T use in the treatment of ESBL-producing Enterobacterales.

METHODS

- **SPECTRA Study**: SPECTRA is a multi-national, multicenter retrospective, study involving 32 hospitals in 6 countries (Australia, Austria, Germany, Italy, Spain, and United Kingdom). All adult, hospitalized patients who were treated with C/T during the study period (2016 - 2019) were eligible, regardless of indication for use. Since the study's primary and secondary objectives evaluate not only drug utilization, but outcomes associated with C/T exposure, a minimum exposure of 48 hours of C/T was required for inclusion in the study
- **Patients and Clinical Data:** In the study period from 2016 to 2019, the subset of SPECTRA enrolled patients with an ESBL positive Enterobacterales sterile site culture and treated with ≥ 48 hours of C/T were included. Because SPECTRA is a retrospective study, treatment of ESBL infections was at the discretion of the treating physician.

Table 1. Study Outcomes

Analysis	Outcomes
Clinical Outcomes	
Clinical Success	At the completion of treatment with C/T: • No additional gram negative antibacterial therapy required for a minimum of 48 hours targeted to index infection after a minimum of 48 hours of C/T, not including discharge antibiotics or de-escalation • No death attributed to Gram negative infection • Discharge (from hospital, ICU, step-down) • No need for re-operation of source infection control • Microbiological eradication
Clinical Failure	If at least one of the following apply during treatment with C/T: • Death attributed to Gram negative infection during index hospitalization • Therapy escalation (as defined below) • Positive culture of index infection organism after 7 days of treatment • Need for re-operation for source control
Indeterminate	Inability to classify as success or failure
Therapy Escalation	
Escalation therapy	Addition of gram negative therapy for at least 48 hours after at least 48 hours of initial Gram negative therapy (additional Gram-negative coverage or switch to a broader-spectrum drug class, including but not limited to polymyxins, carbapenems, and aminoglycosides
Escalation of therapy after C/T receipt	Additional therapy for at least 48 hours after 48 hours of C/T receipt
Mortality	
30-day Mortality (all-cause)	Death due to any cause, within 30 days of initiation of C/T
Readmission	
30-day Readmission	Readmission to the same hospital within 30 days after the last dose of C/T
Outcomes Related to Practice Pattern	
Infection type	Primary indication for C/T use
Empiric therapy	The timing of gram negative antimicrobial start relative to availability of susceptibility results. If Gram negative antimicrobial is initiated prior to receipt of susceptibility testing results or pathogen identification via rapid diagnostic tests, it was considered empiric
Definitive therapy	If gram negative antimicrobial is initiated after receipt of susceptibility testing results

- Variables were analyzed descriptively. Parametric and nonparametric tests were used as appropriate, depending on whether the data were normally distributed. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

- During the study period, 59 patients with 121 ESBL positive isolates within the SPECTRA study met criteria for ESBL infection and received C/T. The baseline characteristics are summarized in Table 2.
- Septic shock was observed in 14 (24%) patients; 29 (49%) were in the ICU at the onset of infection. The most common comorbid conditions were immunocompromised hosts (37%) and cardiac disease (32%). 29% of patients were transplant recipients, and 28% had a CrCl < 50 ml/min.

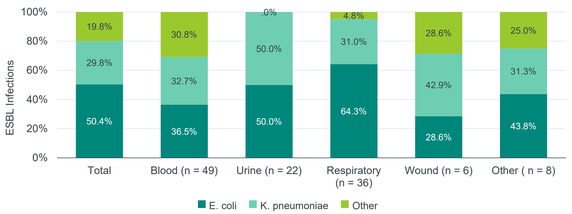
Table 2. Patient Demographic and Clinical Characteristics (N = 59)

Age, mean ± SD (median), years	61.0 ±15.3 (61.5)
Male sex, n (%)	40 (67.8%)
Weight, mean ± SD (median), kg	82.1 ±29.4 (75.0)
Previous healthcare exposure prior to hospitalization	15 (25.4%)
ICU at time of infection	29 (49%)
Underlying diseases	
Heart Disease	19 (32.2%)
Chronic Kidney Disease	16 (27.1%)
Acute Kidney Disease	9 (15.3%)
End Stage Renal Disease	5 (8.5%)
Requirement for Dialysis	6 (10.2%)
Chronic Pulmonary Disease	13 (22.0%)
Liver Disease	8 (13.6%)
Diabetes	20 (33.9%)
Other predisposing conditions	
Immunocompromised host	22 (37.0%)
Hematologic Malignancy	10 (17.0%)
Solid Tumor	2 (3.3%)
Transplant recipient	16 (28.8%)
Severity of clinical presentation	
SIRS	5 (8.5%)
Sepsis	20 (33.9%)
Septic shock	14 (23.7%)

Infection Characteristics

- Patients with a variety of different infection types were included and are summarized in Table 3. Blood was the most prevalent site cultured (41%), followed by respiratory (30%) and urine (18%). *E. coli* (50%) and *K. pneumoniae* (30%) were the most common pathogens.
- On average patients had 2 positive ESBL isolates; median 1; range 1-15. Most patients had the same infection site and ESBL pathogen, however 13 had multi-site ESBL pathogens identified and only 2 had polymicrobial ESBL pathogens.

Figure 1. Prevalence of ESBL Pathogens by Infection Site



Therapy Characteristics

- In most patients (71%), C/T was given as directed therapy (i.e., once culture results were available).
- C/T was given prior to culture results (i.e., as empiric therapy) in 17 (29%) patients, of which 77% had clinical success. C/T dose was 1.5 g in 49%.
- Only 2 of 10 patients with a respiratory source received the currently licensed 3 g dose, 1 additional patients with respiratory infection had dose increases to 3g after 4 days of 1.5g of therapy.

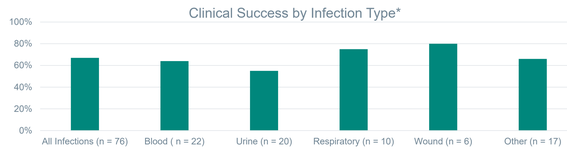
Table 4. Therapy Characteristics of Patients in SPECTRA with ESBL (N = 59)

Admission to antibiotic received, median (IQR), days	4 (0-16.5)
Admission date to C/T, median (IQR), days	19 (8-39)
Time from infection onset to C/T administration [median (IQR)], days Time from infection onset to C/T administration among those given definitive therapy [median IQR)]	3 (0-12.5) 7.5 (2.3-17.5)
Duration of C/T therapy [median (IQR)], days	9 (6-16.5)
Antibiotics before C/T treatment	
Received antibiotics before C/T for current infection, n (%)	42 (71.2%)
C/T Treatment	
Empiric C/T treatment	17 (28.8%)
High dose therapy, n (%)	5 (8.5)
3 g (or CrCL equivalent) for respiratory	2/10 (20%)
Infectious Disease Consult # of ID consults, median (IQR)	42 (74%) 3 (2-8)

Efficacy

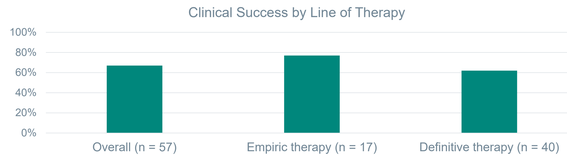
- Overall, clinical success was observed in 38/57 (67%) patients. Figure 2 stratifies clinical response of patients treated with C/T according to the site of infection. Clinical success occurred in 64% of patients with bacteremia, 55% with cUTI, and 75% with a respiratory infection.
- 30-day mortality was 12%; 4 of the 7 patients who died had multiple sites of infection with ESBL positive organisms. Readmissions occurred in 5%, of which 2 were infection related.

Figure 2. Outcomes of ESBL Infections by Infection Type by Patient



*Patients can have more than one site of infection, but same site only counted once even if multiple cultures collected for the patient

Figure 3. Outcomes of ESBL Infections by Line of C/T therapy



STUDY LIMITATIONS

- As this was an observational, retrospective study, we may not have been able to control for all measured and unmeasured variables that may have a clinical impact on patient outcome. Nevertheless, our series of ESBL Enterobacterales infections treated with C/T comprised, to our knowledge, the only multi-national real-life experience.
- C/T was mainly administered as second- or third-line therapy and the role of prior therapy on clinical outcome is unclear.
- Susceptibility testing was performed at each individual center and we do not have molecular analysis to determine the presence of enzymes associated with antibiotic resistance in the isolates.

CONCLUSIONS

- The role of newer non-carbapenem antibiotics in the treatment of severe ESBL infections is currently undefined.
- In a multinational patient database, ceftolozane/tazobactam was found to be effective in severe infections caused by ESBL-producing Enterobacterales.
- Prospective studies are needed to define further the role of ceftolozane/tazobactam in the setting of frequent drug-resistant Gram-negative pathogens.

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References: Bassetti M, Vena A, Giacobbe DR et al. Ceftolozane/tazobactam for treatment of severe ESBL-producing *Enterobacterales* infections: a multicenter nationwide clinical experience (CEFTABUSE II Study). Open Forum Infectious Diseases 2020; 7(5):ofaa139.

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