Ceftolozane/tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections in Immunocompromised Patients: A Multi-Center Study.

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INTRODUCTION

Multidrug-resistant (MDR) gram-negative bacterial infections are a serious and growing public health threat not only due to their virulence but in part due to limited treatment options. Ceftolozane/tazobactam (TOL-TAZ) is a novel cephalosporin antibiotic combined with a known beta-lactamase inhibitor that has activity against some extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and multidrug-resistant *Pseudomonas aeruginosa* (MDRPA). It was approved for the treatment of complicated intra-abdominal infections in combination with metronidazole and complicated urinary tract infections.
Published data are growing on its clinical pharmacology, spectrum of activity, pharmacokinetics/pharmacodynamics, clinical efficacy and safety. Case reports of successful treatment of pneumonia and bloodstream infections have been reported however there is limited published experience concerning immunocompromised patients treated with TOL-TAZ for highly antibiotic resistant Pseudomonas infection.

OBJECTIVE

To describe outcomes of immunocompromised patients treated with TOL-TAZ for MDRPA infections.

METHODS

This is a retrospective, multi-center observational study of adult patients (≥18 years) with an immunocompromised state (active malignancy or solid-organ transplant on immunosuppressive therapies) at 20 academic medical centers from June 2016 to February 2018. All involved researches used the Research Electronic Data Capture (RedCap) database at Temple University Hospital for data collection.

The patients included had microbiologically confirmed MDRPA isolated in culture from any source and received TOL-TAZ for at least 24 hours. MDRPA was defined as resistant to ≥1 agent in ≥3 classes of antibiotics. All patients received treatments as determined appropriate by the treating clinicians.

30-day survival, in-hospital mortality as well as the rates of microbiologic cure and clinical success were assessed. Clinical success was defined as resolution of signs and symptoms present on diagnosis. Microbiological cure was defined as the presence of a repeat negative culture after initiation of treatment. It was presumed if repeat cultures were not taken but the patients had clinical success.

RESULTS

Table 1: Demographics & Characteristics of 65 Study Patients

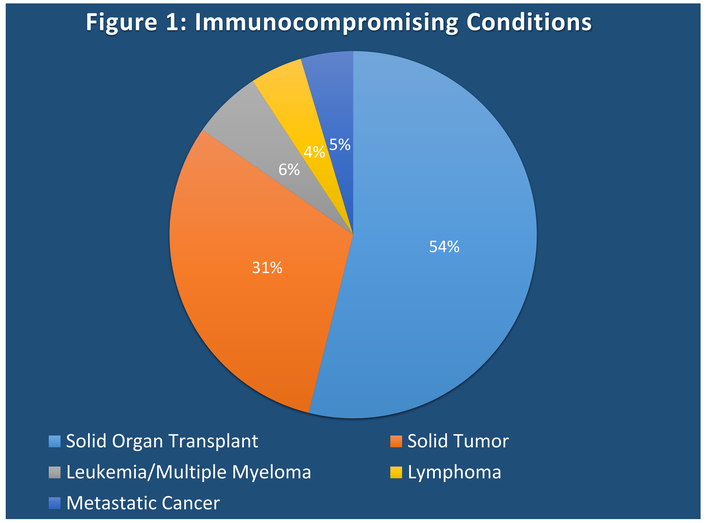
Male, n/N (%)	38/65 (58.4)
Age (median, IQR)	64 (20-87)
Charlson Comorbidity Index (median, IQR)	6 (1-12)
APACHE II score (median, IQR)	20 (4-41)
Admitted to ICU, n/N (%)	37/65 (56.9)
Hospital day index infection diagnosed (median, IQR)	17 (0-265)
Hospital day TOL-TAZ started (median, IQR)	19 (0-284)
Treated with concomitant anti-Pseudomonal agents n/N (%)	15/65 (23.1)
TOL-TAZ susceptible isolates, n/N (%)	35/37 (94.6)

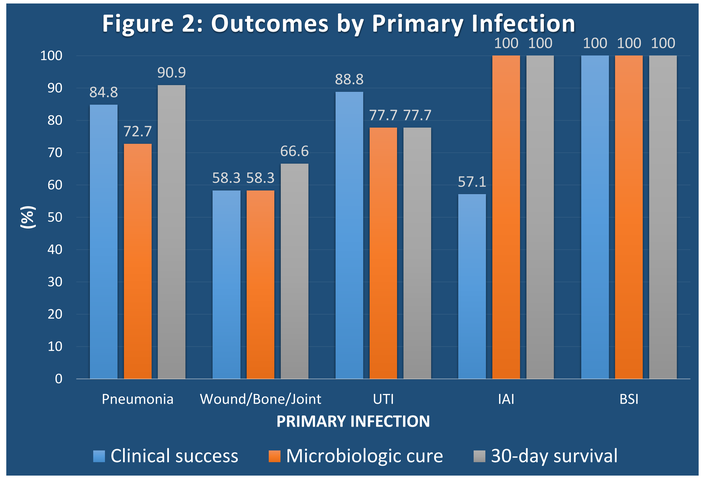
Table 2: TOL-TAZ Dosing

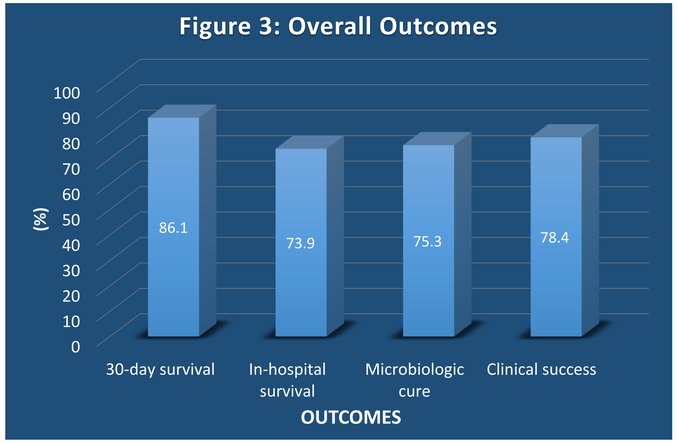
3g q8hrs, n (%)	23 (35.4)
1.5g q8hrs, n (%)	23 (35.4)
Renally adjusted <1.5g q8hrs, n (%)	19 (29.2)

Table 3: Concomitant Anti-Pseudomonal Agents

Aminoglycoside, n/N (%)	7/65 (10.8)
Fluoroquinolone, n/N (%)	4/65 (6.2)
Polymyxin, n/N (%)	3/65 (4.6)
Beta-lactam, n/N (%)	1/65 (1.5)







DISCUSSION

We present data on the use of ceftolozane/tazobactam in 65 patients with immunocompromising conditions treated in 20 different academic medical centers for MDRPA infections. The patients had a median APACHE II score of 20 (IQR 4-41) with 57% of the patients admitted to the ICU at the time TOL-TAZ was initiated. Out of the total number of isolates that were specifically tested against TOL-TAZ (N=37), we found 95% of the isolates were susceptible. TOL-TAZ dosing was equally divided between 3 dosing strata (table 2). At this time a comparison between renal adjustment dosing and outcomes was not made. While there were no equivalent patients treated with non-TOL-TAZ regimens, reported cure and survival rates in MDRPA infections following older treatments (immunocompromised or immunocompetent patients) have been substantially lower than those in this study.

CONCLUSIONS

In this cohort of 65 immunocompromised patients, 86.1% 30-day survival was achieved with rates of 78.4% (clinical success) and 75.3% (microbiologic cure). While not all patients considered to have clinical success achieved microbiologic cure, it is believed that the microbiologic persistence may have represented colonization in the absence of residual tissue invasion. Ceftolozane/tazobactam is effective in the treatment of MDRPA infections in immunocompromised patients.

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