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Clinical outcomes with ceftolozane-tazobactam in patients with multi drug resistant (MDR) *Pseudomonas aeruginosa* bloodstream infections: a multi-center study

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UPDATED ABSTRACT

Background: Ceftolozane-tazobactam (TOL-TAZ) is a novel cephalosporin combination that is beneficial for the treatment of multidrug resistant (MDR) Pseudomonas infections. However, little data is available on the utility of TOL-TAZ for patients with bloodstream infections (BSIs) caused by this organism.
Methods: A retrospective, multicenter chart review was conducted at 12 hospitals to evaluate the utility of TOL-TAZ for MDR Pseudomonas BSIs from June 2016 to February 2018. Patients were included if they were over 18 years old with positive blood cultures for Pseudomonas aeruginosa and received TOL-TAZ for at least 24 hours. Patients were evaluated for in-hospital and 30-day mortality, as well as microbiologic and clinical cure.
Results:

Characteristic	Results (N=25)			
Male gender, n (%)	15 (60)			
Age, median (range)	60 (52-66)			
Charlson comorbidity index, median (IQR)	5 (4-7)			
APACHE II score, median (IQR)	19 (16.25-25.5)			
ICU, n (%)	15 (60)			
Organ transplant, n (%)	8 (32)			
Concomitant antibiotics used, n (%)	14 (56)			
Aminoglycoside, n/N (%)	8/14 (57)			
Fluoroquinolone, n/N (%)	5/14 (35)			
Polymyxin, n/N (%)	2/14 (14)			
Beta-lactam, n/N (%)	1/14 (7)			
Duration of TOL-TAZ, days (median, IQR)	13 (8-14)			
Susceptibility to TOL-TAZ, n/N tested (%)	19/20 (95)			
High dose (3g every 8 hours), n (%)	6 (24)			
Renal dose adjustment, n (%)	8 (32)			
Adverse events, n (%)	1 (4)			
Primary infection	30 day mortality, n/N (%)	In-hospital mortality, n/N (%)	Microbiologic success, n/N (%)	Clinical Success, n/N (%)
Primary bacteremia	1/7 (14)	0/7 (0)	7/7 (100)	6/7 (86)
Pneumonia	5/8 (63)	5/8 (63)	3/8 (38)	3/8 (38)
UTI	2/7 (29)	2/7 (29)	6/7 (86)	6/7 (86)
Intra-abdominal	0/4 (0)	0/4 (0)	4/4 (100)	4/4 (100)
Wound	1/1 (100)	1/1 (100)	0/1 (0)	0/1 (0)
30 day mortality, n (%)	7 (28)			
In hospital mortality, n (%)	6 (24)			
Microbiologic cure, n (%)	20 (80)			
Clinical success, n (%)	19 (76)			

Conclusions: In this multi-center evaluation of 25 patients from 12 health centers, mortality was seen at 30 days and at the end of stay in 28% and 24% of patients, respectively. Clinical and microbiologic success occurred in over 70% of patients. One patient developed *C. difficile* infection. The 7 patients with primary bacteremia had microbiologic success and survived their hospital stay. Two of 3 patients with pneumonia who survived received high dose TOL-TAZ. TOL-TAZ is an option for patients with MDR Pseudomonas bloodstream infections.

INTRODUCTION

Ceftolozane-tazobactam (TOL-TAZ) is a novel cephalosporin combination that is beneficial for the treatment of multidrug resistant (MDR) *Pseudomonas* infections. However, little data is available on the utility of TOL-TAZ for patients with bloodstream infections (BSIs) caused by this organism. One case report reported successful treatment of MDR *Pseudomonas* UTI and bacteremia with TOL-TAZ. Phase III studies showed good in vitro activity against *Pseudomonas*.

OBJECTIVES

- **Primary outcome:**
- 30-day and 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, multicenter chart review was conducted at 12 hospitals to evaluate the utility of TOL-TAZ for MDR *Pseudomonas* BSIs from June 2016 to February 2018. Patients were included if they were over 18 years old with positive blood cultures for *Pseudomonas aeruginosa* and received TOL-TAZ for at least 24 hours. Patients were evaluated for in-hospital and 30-day mortality, as well as microbiologic and clinical cure.

TABLE 1: RESULTS

Characteristic	Results (N=25)
Male gender, n (%)	15 (60)
Age, median (range)	60 (52-66)
Charlson comorbidity index, median (IQR)	5 (4-7)
APACHE II score, median (IQR)	19 (16.25-25.5)
ICU, n (%)	15 (60)
Organ transplant, n (%)	8 (32)
Concomitant antibiotics used, n (%)	14 (56)
Aminoglycoside, n/N (%)	8/14 (57)
Fluoroquinolone, n/N (%)	5/14 (35)
Polymyxin, n/N (%)	2/14 (14)
Beta-lactam, n/N (%)	1/14 (7)
Duration of TOL-TAZ, days (median, IQR)	13 (8-14)
Susceptibility to TOL-TAZ, n/N tested (%)	19/20 (95)
High dose (3g every 8 hours), n (%)	6 (24)
Renal dose adjustment, n (%)	8 (32)
Adverse events, n (%)	1 (4)
Isolates susceptible to CAZAVI, n/N (%)	19/20 (95)

TABLE 2: OVERALL OUTCOMES

Outcome	Results (N=25)
30 day mortality, n (%)	7 (28)
In-hospital mortality, n (%)	6 (24)
Microbiologic cure, n (%)	20 (80)
Clinical success, n (%)	19 (76)

TABLE 3: OUTCOMES

Outcome	30-day mortality	In-hospital mortality	Microbiologic cure	Clinical success
Concomitant therapy, n/N (%)	6/14 (43)	4/14 (29)	11/14 (79)	10/14 (71)
ICU, n/N (%)	4/15 (27)	3/15 (20)	12/15 (80)	11/15 (73)
Infection Type, n/N (%)				
Primary Bacteremia	1/7 (14)	0/7 (0)	7/7 (100)	6/7 (86)
Pneumonia	5/8 (63)	5/8 (63)	3/8 (38)	3/8 (38)
Urinary tract	2/7 (29)	2/7 (29)	6/7 (86)	6/7 (86)
Intra-abdominal	0/4 (0)	0/4 (0)	4/4 (100)	4/4 (100)
Wound	1/1 (100)	1/1 (100)	0/1 (0)	0/1 (0)

SUMMARY OF RESULTS

Overall, 25 patients received TOL-TAZ for a *Pseudomonas* bloodstream infection. The source of bacteremia in 32% of cases was pneumonia, 28% had primary bacteremia. Over half of the patients were in the ICU at the time of receiving TOL-TAZ. In hospital mortality was 24%, 30-day mortality was 28%, 80% of patients had microbiological cure, and 76% had clinical success.
Mortality rates for each infection are listed. Mortality was highest for patients with pneumonia (63%). Mortality rates for patients in the ICU were low at 27 and 20% respectively for 30-day and in-hospital mortality. Patients who received concomitant therapy had a mortality rate of 29%.

OUTCOMES ANALYSIS

For 2 patients, the source of bacteremia was unclear between two sources. Each patient had a possible pneumonia source plus either a wound or UTI. The in-hospital and 30-day mortality rate for patients in the ICU was not significantly different than those not in the ICU. There was no significant difference between patients receiving concomitant therapy vs monotherapy with TOL-TAZ. Patients with pneumonia had significantly increased mortality compared to other sources of bacteremia (p=0.017). High dose TOL-TAZ was used in 2 of the patients with pneumonia. Four patients with pneumonia (63%) received concomitant therapy with an aminoglycoside IV or inhaled, or levofloxacin. There was no significant difference in mortality if patients with pneumonia received concomitant antibiotics. Patients with primary bacteremia and intra-abdominal sources had 100% microbiologic success, and no in-hospital mortality. One patient developed *C. difficile* infection. The 7 patients with primary bacteremia had microbiologic success and survived their hospital stay.

CONCLUSIONS

In this multi-center evaluation of 25 patients with MDR *Pseudomonas* infections from 12 health centers, mortality was seen in less than 30% of patients. Clinical and microbiologic success occurred in over 75% of patients. Overall, these patients were frequently in the ICU, had a median CCI of 5, and a median APACHE score of 19. With increasing rates of MDR *Pseudomonas* infections, TOL-TAZ is an option for patients with MDR *Pseudomonas* bloodstream infections. For patients with pneumonia as the source of their bacteremia, TOL-TAZ may not be optimal.

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