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**Original Article**

# Better Outcome of Off-Label High-Dose Ceftazidime in Hemato-Oncological Patients with Infections Caused by Extensively Drug-Resistant *Pseudomonas Aeruginosa*

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract.** ***Background*: *P. aeruginosa* sepsis in immunocompromised patients is a serious complication of cancer treatment, especially in the case of an Extensively Drug Resistant (XDR) pathogen.**
**The aim of the study is to evaluate the efficacy of high-dose ceftazidime in the treatment of XDR *P. aeruginosa* infection and to compare it with the conventionally treated cohort in hemato-oncological patients.**
***Methods:* We identified 27 patients with XDR *P. aeruginosa* infection during the 2008-2018 period, 16 patients served as a conventionally treated cohort with an antipseudomonal beta-lactam antibiotic in standard dose (cohort A), and 11 patients were treated with high-dose ceftazidime (cohort B). Most of the patients were neutropenic and under active treatment for their cancer in both cohorts.**
***Results:* Mortality and related mortality were statistically significantly better for cohort B than cohort A; it was 18.2% and 9.1% for cohort B and 68.8% and 68.8% for cohort A, respectively. More patients in cohort A needed mechanical ventilation and renal replacement therapy, 75% and 50% for cohort A and 27.3% and 9.9% for cohort B, respectively. It corresponded well with the worst sequential organ failure score (SOFA) in cohort A compared to cohort B, 16 versus 7, respectively. Reversible neurotoxicity was seen only in two patients in cohort B.**
***Conclusion:* Ceftazidime in high doses is a very potent antibiotic (ATB) for treating XDR *P. aeruginosa* infections in neutropenic cancer with acceptable toxicity.**

**Keywords:** Ceftazidime; Neutropenia; XDR *P. aeruginosa* infection.

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**Introduction.** Hemato-oncological patients in active treatment are at high risk of opportunistic infection, especially during their stay in the intensive care unit. Their propensity to infections is caused not only by neutropenia but also by the treatments, which frequently are immunosuppressive and produce organ damage. In

recent years an increase in antimicrobial resistance, especially in Gram-negative bacilli, has been repeatedly described.[1-3] These infections caused by multidrug-resistant pathogens are burdened by a very high mortality rate.[3-5] With multidrug-resistant pathogens, the probability of inadequate antibiotic coverage is much higher than in susceptible pathogens, which further increases the mortality rate of these patients.[5-8]

Pseudomonas aeruginosa (*P. aeruginosa*) is one of the most life-threatening bacterial infections in an immunosuppressed host.[3] It frequently develops as a breakthrough infection, often MDR or even extensively drug-resistant (XDR).[9-11] Colonization with MDR P. aeruginosa is another well-described factor leading to a higher infection rate.[12-14] It causes severe and difficult-to-treat infections with reported mortality rates of 43% and 63% in MDR and XDR pathogens, respectively.[3,5,6,15-17] Moreover, *P. aeruginosa* is prone to high hospital transmission, and the water supply system often serves as a reservoir of these MDR pathogens.[18,19]

Ceftazidime is one of the most potent antipseudomonal cephalosporins with a very acceptable side effect profile compared to other cephalosporins.[20,21] The most clinically relevant toxicity is central nervous system impairment.[22,23] It manifests itself both neurologically and psychiatric way and includes encephalopathy, convulsion, confusion, myoclonus, hallucinations, coma, epilepsy, tremor, drowsiness, disorientation, and agitation in decreasing order. Most of these disorders are linked to renal insufficiency.[24] The pathophysiological explanation is a decreased inhibitory of gamma-aminobutyric acid and increased excitatory amino acid release.[25] Ceftazidime has been described as time-dependent pharmacokinetics with a pharmacokinetic/pharmacodynamic target for critical patients with 100% plasma concentration time above minimal inhibitory concentration (MIC).[26] It is probably even better when plasma drug concentration is 4 times higher for 100% time than MIC.[27]

In this study, we wanted to describe the effect of higher-dose ceftazidime in the treatment of XDR *P. aeruginosa*, which occasionally occurs in our intensive care unit and causes clinically very severe and hard-to-treat infections. Historically, our patients experienced intolerably high mortality with these infections, so despite the higher risk of toxicity, we started to use high-dose ceftazidime treatment for these patients. Here, we want to describe our experience compared to a historical cohort.

*Study design*: This was a retrospective observational study of our standard clinical practice in intensive care patients experiencing XDR *P. aeruginosa* infection.

**Methods.** All subsequent cancer patients who underwent intensive care unit during the years 2008-2018 were retrospectively reviewed, and patients with signs of sepsis and infection caused by XDR *P. aeruginosa* were included in this study. In addition, the patient charts were reviewed by two independent clinicians, AZ and JR.

Patients were included if they were confirmed with bloodstream infection, even if the origin of the infection was unknown. Organ infection patients were included only if clinical or radiological signs of infection and concurrent microbial samples from the affected organ confirmed XDR *P. aeruginosa* as a causal pathogen. Patients with sepsis treated with antipseudomonal antibiotics upon colonization with XDR *P. aeruginosa* and not confirmed by causative *P. aeruginosa* were excluded. We identified two groups of patients; first, the conventionally treated control group (cohort A) received a combination of antibiotics according to the clinical judgment of their clinicians with antipseudomonal potential (beta-lactam), and everyone received at least one susceptible antibiotic to XDR *P. aeruginosa*. All antibiotics were given in recommended doses. The second group (cohort B) received off-label ceftazidime 3 g every 6 hours as a prolonged 3-hour infusion with other susceptible antipseudomonal antibiotics (except for one patient with ceftazidime monotherapy). The choice of a dosing regimen was entirely within the attending physician's discretion and was decided after careful evaluation of prior dismal experiences with this type of infection. This decision was made as all "clinically safe" effective ATB for treating *P. aeruginosa* when resistant.

All clinical samples, including patients' blood cultures, were processed at the Department of Clinical Microbiology University Hospital Hradec Kralove. Blood samples were inoculated in aerobic and anaerobic bottles and, within 2 hours, placed into BACTEC blood culture system. All pathogens were identified by Maldi TOF (Bruker Daltonics, Germany). Antimicrobial susceptibility testing was performed by the disc diffusion method and the broth microdilution method (TRIOS, CZ, Lachema, CZ). Because patients were evaluated between 2008 and 2018, susceptibility tests for the ceftolozane/tazobactam and ceftazidime/avibactam were unavailable then. The results were interpreted according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the 2017 tables were chosen as the most relevant for interpreting the results.[28,29]

*P. aeruginosa* was considered XDR if bacterial isolates remained susceptible to only one or two relevant antimicrobial categories (aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, antipseudomonal penicillins with beta-lactamase inhibitors, polymyxins).[30] No molecular testing was done to evaluate possible mechanisms of resistance further. Neutropenia was defined as an absolute neutrophil count of < 500 cells/mm$^3$.

Mortality was defined as death within this single episode of infection; related mortality was considered

death before the resolution of symptoms or signs of infection not caused by the progression of the underlying malignancy. The sequential organ failure score (SOFA) was used to demonstrate the infection severity.[31,32]

Statistical analysis was performed using GraphPad Prism version 9 for Windows, GraphPad Software, La Jolla, CA, USA. Fisher's exact test was used for the comparison of categorical variables, and the T-test or the Mann-Whitney *U* test in the case of an abnormal distribution was used for continuous variables. All variables were considered statistically significant at $p<0.05$.

The study was approved by the Ethics Committee board (Ethics Committee, Hradec Kralove University Hospital) of our institution.

**Results.** We were able to identify 27 patients. 16 patients treated during the years 2008-2015 serve as conventionally treated cohort A. Cohort B consists of 11 patients treated during the years 2015-2018.

Complete demographic and baseline data are in **Table 1**.

All these patients were treated for a wide range of hematologic diseases, except one on high-dose chemotherapy for testicular cancer. Infection complications occurred mainly during active treatment, but three patients were in the follow-up phase after allogeneic stem cell transplantation; one patient with progressive chronic lymphocytic leukemia was just planned to receive immunotherapy. Most patients were neutropenic during treatment; neutropenia was present in 14 pts (87.5%) and 7 pts (63.6%) in cohorts A and B, respectively. Their initial SOFA score was comparable, with a median of 5.5 (4-12) and 5 (2-9) in cohorts A and B, respectively. However, the SOFA score deteriorated during treatment due to non-survivor patients, the worst SOFA score was in the range 5-22 (median 16) and 2-17 (median 7) in cohorts A and B, respectively, and this reached statistical significance (p 0.008). In the course of infection, a statistically significant superior number of cohort A patients required mechanical ventilation and renal replacement therapy due to the deleterious effect of progressive sepsis. Mechanical ventilation and renal replacement therapy were administered to 12 patients (75.0%), three patients (27.3%) (p 0,022) and eight patients (50,0%), one patient (9.1%) (p 0.0417) in cohort A and cohort B, respectively. The most common source of infection was pneumonia (10 patients) and soft tissue inflammation (9 patients), six patients developed septic shock, and two patients suffered from intraabdominal sepsis. Details are described in **Table 1** and **Table 2**.

All isolates of *P. aeruginosa* were susceptible only to one aminoglycoside and colistin. All antibiotics from the other class of antipseudomonal antibiotics were resistant. Susceptibility to new antipseudomonal ATB was not tested, as the test nor new ATBs were yet available. The MICs of ceftazidime were: median 16 mg/l (8-64 mg/l) and 32 mg/l (16-128 mg/l) in cohort A and B, respectively, which was significantly different in favor of control Cohort A (p 0.0288). The details of the susceptibility tests are in **Tables 3 and 4**.

All patients, except one, were treated with a combination of antibiotics (one patient was treated with ceftazidime monotherapy in cohort B). However, significantly more patients in cohort A were treated even with the combination of 3 antipseudomonal antibiotics consisting of beta-lactam, aminoglycoside, and colistin. Data are shown in **Table 5**.

We experienced neurological complications after high-dose ceftazidime treatment in two patients. It was a

**Table 1.** Demographic and baseline data of the two patients' cohorts.

| Characteristics | Cohort A | Cohort B | *P* Value* |
|---|---|---|---|
| patients | 16 | 11 | |
| age (median) | 50-70 (61.0) | 23-69 (56.0) | 0.150 |
| sex male (%) | 6 (37.5) | 6 (54.6) | 0.452 |
| lymphoma, CLL (%) | 4 (25.0) | 1 (9.1) | 0.356 |
| acute leukemia (%) | 10 (62.5) | 9 (81.8) | 0.405 |
| primary myelofibrosis (%) | 2 (12.5) | 0 | 0.499 |
| testicular cancer (%) | 0 | 1 (9.1) | 0.407 |
| active treatment (%) | 13 (81.3) | 10 (90.9) | 0.624 |
| allogeneic transplantation (%) | 8 (50.0) | 5 (45.5) | >0.99 |
| pneumonia (%) | 5 (31.3) | 5 (45.5) | 0.687 |
| soft tissue inflammation (%) | 6 (37.5) | 3 (27.3) | 0.692 |
| intraabdominal sepsis (%) | 0 | 2 (18.2) | 0.157 |
| septick shock, unknown origin (%) | 5 (31.3) | 1 (9.1) | 0.350 |
| mechanical ventilation (%) | 1 (6.3) | 1 (9.1) | >0.99 |
| renal replacement therapy (%) | 0 | 0 | >0.99 |
| neutropenia (%) | 14 (87.5) | 7 (63.6) | 0.187 |
| SOFA score (median) | 4-12 (5.5) | 2-9 (5.0) | 0.246 |

*Fisher´s exact test. Abbreviations: CLL: chronic lymphocytic leukemia, SOFA: sequential organ failure assessment score.

**Table 2.** Outcome of patients and their characteristics during the treatment.

| Characteristics | Cohort A | Cohort B | *P* Value* |
|---|---|---|---|
| patients | 16 | 11 | |
| mortality (%) | 11 (68.8) | 2 (18.2) | 0.018 |
| related mortality (%) | 11 (68.8) | 1 (9.1) | 0.005 |
| worst SOFA (median) | 5-20 (16.0) | 2-17 (7.0) | 0.008 |
| mechanical ventilation (%) | 12 (75.0) | 3 (27.3) | 0.022 |
| renal replacement therapy (%) | 8 (50.0) | 1 (9.1) | 0.042 |
| length of stay (median) (%) | 3-76 (8.5) | 4-69 (16.0) | 0.235 |
| MIC of ceftazidime (median) | 16-64 (16.0) | 16-128 (32.0) | 0.029 |

*Fisher´s exact test. Abbreviations: MIC: minimal inhibitory, SOFA: sequential organ failure assessment score.

**Table 3.** Susceptibility testing results for *P. aeruginosa* pathogen in Cohort A.

| Cohort A | Amikacin | Gentamicin | Ceftazidim | Piperacillin Tazobactam | Meropenem | Colistin |
|---|---|---|---|---|---|---|
| **MIC break-point (susceptible ≤)**[29] | **8 mg/L** | **4 mg/L** | **8 mg/L** | **16 mg/L** | **2 mg/L** | **2 mg/L** |
| 1 | 1 | 8 | 16 | 128 | 32 | 0.25 |
| 2 | 1 | 64 | 16 | 32 | 32 | 0.25 |
| 3 | 2 | 32 | 16 | 128 | 32 | 0.5 |
| 4 | 64 | 64 | 32 | 128 | 32 | 0.25 |
| 5 | 8 | 32 | 32 | 64 | 16 | 2 |
| 6 | 0.5 | 64 | 16 | 32 | 32 | 0.5 |
| 7 | 1 | 64 | 32 | 128 | 128 | 0.5 |
| 8 | 1 | 32 | 16 | 64 | 16 | 1 |
| 9 | 0.5 | 64 | 32 | 256 | 32 | 2 |
| 10 | 4 | 64 | 16 | 32 | 8 | 1 |
| 11 | 2 | 64 | 16 | 256 | 8 | 1 |
| 12 | 32 | 4 | 64 | 64 | 32 | 1 |
| 13 | 4 | 16 | 16 | 128 | 32 | 0.5 |
| 14 | 32 | 4 | 16 | 64 | 32 | 0.5 |
| 15 | 2 | 64 | 32 | 128 | 16 | 0.25 |
| 16 | 4 | resistant | 32 | resistant | resistant | 0.25 |

Abbreviations: MIC: minimal inhibitory concentration

**Table 4.** Susceptibility testing results for *P. aeruginosa* pathogen in Cohort B.

| Cohort B | Amikacin | Gentamicin | Ceftazidim | Piperacillin Tazobactam | Meropenem | Colistin |
|---|---|---|---|---|---|---|
| **MIC break-point (susceptible ≤)**[29] | **8 mg/L** | **4 mg/L** | **8 mg/L** | **16 mg/L** | **2 mg/L** | **2 mg/L** |
| 1 | 64 | 32 | 16 | 32 | 16 | 2 |
| 2 | 32 | 4 | 32 | 32 | 16 | 1 |
| 3 | 64 | 16 | 128 | 128 | 16 | 0.5 |
| 4 | 32 | 16 | 32 | 64 | 16 | 2 |
| 5 | 8 | 32 | 32 | 64 | 8 | 2 |
| 6 | 4 | 32 | 32 | 128 | 8 | 2 |
| 7 | 8 | 4 | 32 | 64 | 16 | 1 |
| 8 | 4 | 32 | 32 | 128 | 8 | 1 |
| 9 | 2 | 8 | 16 | 128 | 16 | 2 |
| 10 | 4 | 64 | 32 | 128 | 16 | 0.5 |
| 11 | 16 | 16 | 64 | 128 | 16 | 4 |

Abbreviations: MIC: minimal inhibitory concentration.

**Table 5.** Representation of combination of antipseudomonal antibiotics.

| Characteristics | Cohort A | Cohort B | p value |
|---|---|---|---|
| **beta-lactam + aminoglycoside + colistin combination (%)** | **11 (68.8)** | **2 (18.2)** | **0.018** |
| beta-lactam + aminoglycoside combination (%) | 16 (100.0) | 9 (81.8) | 0.157 |
| beta-lactam + colistin combination (%) | 11 (68.8) | 3 (27.3) | 0.054 |

quantitative disorder of consciousness that did not lead to serious complications and lowering the dose of ceftazidime was sufficient to resolve the symptoms in both cases. No epilepsy was encountered. Both patients were evaluated for confusion even before ceftazidime, and septic encephalopathy was considered.

The mortality rate in both cohorts differed, 68.8% and 18.0% in cohorts A and B, respectively (p 0.0183). All patients died within 30 days except one patient from cohort A, who died 76 days after the onset of soft tissue

infection of the neck and pneumonia. The cause of death was a pulmonary abscess and multiple abscesses in the neck region caused by *P. aeruginosa* complicated by severe colitis. The pulmonary abscess was verified by pulmonary biopsy histologically and microbiologically. The patient underwent pulmonary resection and drainage of neck abscesses complicated by severe colitis; he died of septic shock with multiorgan failure. Related mortality was 68.8% and 9.1% in cohorts A and B, respectively (one patient died of the progression of leukemia) (p 0.047). Data in **Table 2**.

**Discussion.** This patient population with XDR P. aeruginosa infection in hemato-oncological patients is unique, and it is difficult to find comparable results in the literature. The most comparable data on the mortality rate of *P. aeruginosa* infections are from studies with MDR *P. aeruginosa*. The mortality rate in these studies varies. In the study by Zhao et al., it was 28.9% with MDR *P. aeruginosa* infection, even though 65.8% of the patients with MDR infection had inappropriate antibiotic coverage.[11] In the study conducted by Caselli et al., the mortality rate was slightly higher, 35.8%, and the highest mortality rate for MDR *P. aeruginosa* infections was reported by Trecarichi et al., which was 42.4%.[3,15] In these two studies, inappropriate treatment was not dated, so we do not know the percentage of patients adequately treated.[3,11,15] These results of mortality rates 28.9%, 35.8 and 42.4% are substantially better than the results in our cohort A (mortality 68,8%) and, on the other hand, substantially worse than in our cohort B (mortality 18.2%). If we compare the data only with MDR *P. aeruginosa* infection and inadequate antibiotic treatment, mortality was around 63%.[5] This result is already the same as in our group A. In our group A, the ATBs coverage should be considered adequate, as susceptible aminoglycosides and/or colistin were added to all patients. However, both ATBs should be used just as auxiliary ATBs, so this might be the reason for the high mortality rate in this group of highly immunocompromised patients. In one study of cancer patients with *P. aeruginosa* infection, the mortality rate of the XDR infection was 64%, the same rate as in our group A.[16] In contrast, our results with the mortality rate in group B (18,2%) are nearly comparable with the mortality rate of non-MDR *P. aeruginosa* infection. Previously reported mortality was 5.5% in the study by Zhao et al.[11] In the study by Trecarichi et al., it was 12.5%, and the same number was reported by Caselli et al.[3,15]

These results are in line with the recommendation that standard treatment for *P. aeruginosa* should be susceptible to beta-lactams. The results are very good, with expected mortality as low as 5.5%.[11,33] On the other hand, it supports our approach, in which we were able to overcome resistance by a higher dose of ceftazidime in the case of XDR infection and improve the bad prognosis in cancer patients. It is probably the result of an optimal blood level and time above the MIC achieved by a higher dose of ATB for a resistant pathogen.

One can speculate that better survival in cohort B might have been caused by a beneficial effect of other ATBs added in combination. Actually, all of these patients were treated with a combination including aminoglycoside and colistin or both, except one patient in group B, who was on ceftazidime monotherapy. There were even significantly more patients covered by a combination of three anti-pseudomonas antibiotics in group A, probably due to deterioration of clinical condition as the course of infection was not under control.

However, a nice study with the new antibiotic ceftolozane/tazobactam supports the idea that higher MIC with the same antibiotics dosing leads to a worse outcome even in susceptible *P. aeruginosa*.[34] In this paper, mortality of the patients was higher with susceptible *P. aeruginosa* and the same dose of ATBs if the MIC > 2mg/L than MIC ≤ 2 mg/L; it was 41,2% and 16,2%, respectively.[34] Hypothetically this might further support our theory that during the treatment of life-threatening infections, we should pay more attention to the MIC of the pathogen. Accordingly, we should adjust the dose of antibiotics to aim for the ideal situation with 100% time of blood level above MIC, even in the resistant pathogen; this can lead to better outcomes for patients.

Ceftazidime is a relatively non-toxic antibiotic that can be used in a higher dose.[35,36] Despite the increased risk of toxicity, especially neurotoxicity, we decided to use a higher dose of ceftazidime in our patients. This decision followed a careful evaluation of historical results and experiences, mainly with soft tissue infection and pneumonia caused by this pathogen. The mortality rate of 68.75% was considered so huge that we decided to use not standard ceftazidime dosing, as no new ATBs were available at that time. We chose a uniform dose because drug monitoring for ceftazidime is not possible 24 hours per day/7, days per week at our institution and is not routinely recommended. We experienced toxicity in two patients, which seems to be an acceptable risk. Furthermore, these two patients suffered only from a quantitative disorder of consciousness, which did not result in any medical emergencies, such as the need for tracheal intubation. Lowering the dose of ceftazidime was sufficient for quick normalization of consciousness in both patients. In these two patients, a change in mental status was described even before ceftazidime and was probably caused by septic encephalopathy. We can speculate that this previous neurological abnormality might have contributed to ceftazidime toxicity, as was described previously.[22]

This study has some limitations; the sample size is small, the study is retrospective, and the data were

collected over an extended period. The biggest limitation is the sample size, where demonstrating superiority is very difficult. On the other hand, there is not only reduced mortality but also a worse SOFA score and a need for more mechanical ventilation in group A, and that seems very convincing to us. It is also very difficult to collect more patients because our institution's evaluation to use an off-label dose of ceftazidime was very strict. Despite these limitations, infection policy regarding bacterial infections was very similar during this time. No new ATBs were available, the dose of ATBs was unchanged then, and microbiological procedures were standardized throughout the period. A single change was made to off-label high-dose ceftazidime treatment in patients with risk of XDR *P. aeruginosa* sepsis. With the institution of this approach, the mortality rate decreased and enabled our patients to continue with further cancer treatment. On the other hand, we have seen some toxicity with our approach, but it was deemed acceptable concerning the severity of the infection.

An off-label dose of ceftazidime is no longer of use at our institution after the introduction of new antipseudomonal antibiotics and should not be considered if other susceptible ATBs can be available. The standard dose of susceptible ATBs is always prioritized over off label high dose regimen. Unfortunately, our institution has already experienced colonisation with resistant *P. aeruginosa* to all new antipseudomonal ATBs, including cefiderocol.

Still, the clinical implication of this study seems to be very important because the patients in cohort B performed well and achieved their cancer treatment, including planned allogeneic transplantation.

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