Scientific Publications

Global Journal of Medical Case Reports, 2023, 3, 754
www.scipublications.org/journal/index.php/gjmcr
DOI: 10.31586/gjmcr.2023.754

Case Series

Treatment by Ceftolozane/Tazobactam for *Pseudomonas Aeruginosa* Pneumonia Patients with or without Bacteremia

Masafumi Seki [1,2,*], Seigi Lee [2], Kokyo Sakurada [3], Yutaka Miyawaki [2], Ayumu Masuoka [4], Futoshi Kotajima [4]

[1] Division of Infectious Diseases and Infection Control, Saitama Medical University International Medical Center, Hidaka City, Saitama, Japan

[2] Division of Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka City, Saitama, Japan

[3] Division of Neurological Surgery, Saitama Medical University International Medical Center, Hidaka City, Saitama, Japan

[4] Respiratory Support Team, Saitama Medical University International Medical Center, Hidaka City, Saitama, Japan

*Correspondence: Masafumi Seki (sekimm@saitama-med.ac.jp)

Abstract: Background: *Pseudomonas aeruginosa* (*P. aeruginosa*) is one of the most common pathogens in hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP). Recently, ceftolozane/tazobactam (CTLZ/TAZ) has been used to treat pneumonia due to *P. aeruginosa*. **Case series**: Two cases of *P. aeruginosa* pneumonia treated by CTLZ/TAZ that had been initially treated by piperacillin/tazobactam (PIPC/TAZ) are presented. (Case 1): A 76-year-old man who underwent esophagectomy developed severe pneumonia caused by *P. aeruginosa* infection and received oxygen by high-flow nasal canula. PIPC/TAZ was started, and he improved 10 days later. PIPC/TAZ was switched to sulbactam/ampicillin, but on day 14, his respiratory condition worsened, and septic shock developed. *P. aeruginosa* was isolated from his blood, and CTLZ/TAZ was started because the isolated *P. aeruginosa* showed resistance to PIPC/TAZ. Although he recovered on Day 28, and CTLZ/TAZ was switched to levofloxacin, his condition worsened again, and *P. aeruginosa* resistant to CTLZ/TAZ was isolated from his blood on day 32. Finally, he died of septicemia and renal failure. (Case 2) A 51-year-old woman who underwent surgery for a brain tumor developed VAP due to *P. aeruginosa* and was treated by PIPC/TAZ. Her pneumonia improved, but pneumothorax developed, and she was therefore switched to CTLZ/TAZ on day 7. Her pneumonia improved smoothly without bacteremia 10 days later. **Conclusions:** These data and cases suggest that CTLZ/TAZ was effective for severe *P. aeruginosa* pneumonia although the isolated *P. aeruginosa* was resistant to PIPC/TAZ. However, the duration of CTLZ/TAZ administration may need to be considered for pneumonia cases with bacteremia due to *P. aeruginosa*.

Keywords: Blood Stream Infection, Ceftolozane/Tazobactam (CTLZ/TAZ), Piperacillin/Tazobactam (PIPC/TAZ), *Pseudomonas aeruginosa*

How to cite this paper:
Seki, M., Lee, S., Sakurada, K., Miyawaki, Y., Masuoka, A., & Kotajima, F. (2023). Treatment by Ceftolozane/Tazobactam for *Pseudomonas Aeruginosa* Pneumonia Patients with or without Bacteremia: Ceftolozane/tazobactam for Pseudomonas aeruginosa pneumonia. *Global Journal of Medical Case Reports*, *3*(1), 5-11. Retrieved from https://www.scipublications.com/journal/index.php/gjmcr/article/view/754

Academic Editor:
Ravi Kumar Chittoria

Received: July 4, 2023
Accepted: August 31, 2023
Published: September 1, 2023

1. Background

Pseudomonas aeruginosa (*P. aeruginosa*) is a common nosocomial pathogen that often causes pneumonia in hospitalized patients [1, 2]. Due to the fact that *P. aeruginosa* is a virulent organism that is susceptible to only a limited number of antibiotic agents, infections caused by this organism are difficult to cure and often require combination therapy. Although the definition of multidrug-resistant *P. aeruginosa* (MDRP) has not been standardized internationally, it is defined as *P. aeruginosa* resistant to ceftazidime, ciprofloxacin, piperacillin, imipenem, and amikacin [3, 4]**.** In Japan, it is usually defined as *P. aeruginosa* resistant to carbapenems, such as imipenem or meropenem,

fluoroquinolones, and amikacin by the Japan Nosocomial Infections Surveillance (JANIS), a program of the Ministry of Health, Labour and Welfare [5]. The increasing resistance of *P. aeruginosa* is a growing threat to the clinical management of such infections [6].

Piperacillin/tazobactam (PIPC/TAZ) and ceftolozane/tazobactam (CTLZ/TAZ) are antibiotic regimens that combine a beta-lactamase inhibitor with an anti-pseudomonas agent, either penicillin or cephem, and their use for treating *P. aeruginosa* has increased, which has contributed to inhibiting carbapenem and fluoroquinolone overuse in Japan [7, 8]. Therefore, PIPC/TAZ and CTLZ/TAZ are named 'carbapenem-alternative drugs' and are recommended for *P. aeruginosa* pneumonia to decrease the emergence of carbapenem-resistant *P. aeruginosa* [8, 9]. However, the appearance of *P. aeruginosa* resistant to these two antibiotics is also a concern, and how to use these antibiotics, especially CTLZ/TAZ, may be controversial and unclear, because world-wide use of CTLZ/TAZ has recently started [8].

In this report, two cases of *P. aeruginosa* pneumonia are presented. Both cases had malignant tumors as the underlying diseases and were treated by PIPC/TAZ followed by CTLZ/TAZ after surgery. CTLZ/TAZ was effective, after PIPC/TAZ became ineffective. However, the first case had bacteremia and died, and CTLZ/TAZ-resistant *P. aeruginosa* was isolated after 14 days of treatment, and the second case without bacteremia survived after 10 days of treatment by CTLZ/TAZ.

These cases and the related study were approved as #2022-072 by the Institutional Review Board of Saitama Medical University International Medical Center on September 07, 2022 and registered as UMIN000047992, and the patients whose specimens were used provided written, informed consent to have their case details and any accompanying images published.

2. Cases

2.1. Case 1

A 76-year-old man with esophageal cancer underwent esophagectomy after chemotherapy for 2 months, but he developed hospital-acquired pneumonia (HAP) 6 days after the operation (Figure 1A). Infiltration shadows in both lung fields were found on chest X-rays, and arterial oxygen saturation (SpO_2) was 95% (O_2 10-L mask). *P. aeruginosa* was isolated, and TAZ/PIPC drip infusion 4.5 g three times per day and high-flow nasal canula (HFNC) management were started from this day (day 0). Laboratory data on day 0 were as follows: white blood cell (WBC) count, 14.56 x 10^3/μL, with 93.1% neutrophils, 3.3% lymphocytes, 3.4% monocytes, 0.1% eosinophils, and 0.1% basophils; platelet count, 13.2 × 10^4/μL; hemoglobin, 8.5 g/dL; blood urea nitrogen, 14.3 g/L; serum creatinine, 0.66 mg/dL; aspartate aminotransferase (AST), 21 U/L; alanine aminotransferase (ALT), 61 U/L; and C-reactive protein (CRP), 21.930 mg/dL.

After 10 days, his condition, including respiratory status, chest X-rays, and laboratory data, had improved, and PIPC/TAZ was switched to sulbactam/ampicillin (Figure 1B). However, on day 14, his respiratory condition, including chest X-ray, deteriorated, and septic shock developed (Figure 1C). Ventilator management and vasopressors were started. *P. aeruginosa* was isolated from the sputum and blood, and the isolated *P. aeruginosa* was found to show resistance to PIPC/TAZ (Table 1, left column). CTLZ/TAZ was started instead on day 28, and the pneumonia improved (Figure 1D). CTLZ/TAZ was then switched to levofloxacin, but his condition worsened again on day 32, and *P. aeruginosa* resistant to CTLZ/TAZ was isolated from his blood (Table 1, right column). Finally, he died due to septicemia and renal failure.

Table 1. Antibiotic susceptibilities for the isolated *Pseudomonas aeruginosa* of Case 1

	Day 14		Day 32	
	MIC	**S/I/R**	**MIC**	**S/I/R**
AZT	>16	R	8	S
PIPC	>64	R	16	S
PIPC/TAZ	>64	R	16	S
IPM	2	S	0.5	S
MEPM	0.5	S	0.5	S
CAZ	>16	R	>16	R
CFPM	16	I	16	I
CTLZ/TAZ	≦1/4	S	≦8/4	R
AMK	≦4	S	≦4	S
GM	≦2	S	≦2	S
MINO	>8	R	>8	R
LVFX	1	S	>4	R
CPFX	0.25	S	4	R
ST	80	R	>80	R

Abbreviations: MIC; minimum inhibitory concentration, S/I/R; susceptible/intermediate/resistant, AZT; aztreonam, PIPC; piperacillin, PIPC/TAZ; piperacillin/tazobactam, CAZ; ceftazidim, CFPM; cefepime, CTLZ/TAZ; ceftolozane/tazobactam, IPM; imipenem, MEPM; meropenem, MINO; minocycline LVFX; levofloxacin, CPFX; ciprofloxacin, AMK; amikacin, GM; gentamycin, ST; sulfamethoxazole/trimethoprim.

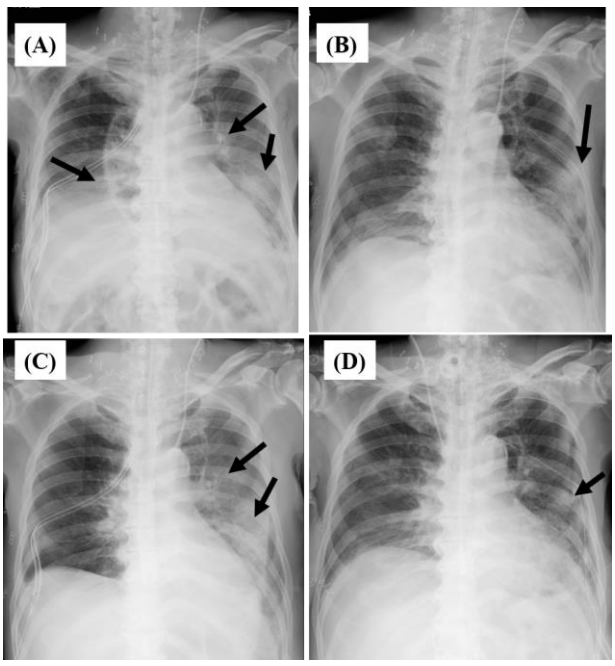

Figure 1. Chest X-rays of the case 1 patient. Infiltration shadow is seen in both lung fields on day 0 (A). The shadows are improved on piperacillin/tazobactam on day 10 (B). The shadows have worsened again on day 14 (C), but have almost disappeared on day 28 (D). Arrows indicate abnormal shadows on chest X-ray, such as infiltration shadows.

2.2. Case 2

A 51-year-old woman received a tracheotomy because of tracheobronchial injury following surgery for a brain tumor, and PIPC/TAZ was used to treat the isolated P. aeruginosa, which showed good susceptibility to most antibiotics (Table 2, left column). Seven days later, she developed ventilator-associated pneumonia (VAP) and then pneumothorax. Chest X-ray and computed tomography (CT) showed a massive infiltration shadow in the right lower lung field after expansion by drainage (Figure 2A and B). Laboratory data on that day (day 0) were as follows: white blood cell (WBC) count, 7.93 x 103/μL, with 82.0% neutrophils, 15.5% lymphocytes, 1.6% monocytes, 0.1% eosinophils, and 0.8% basophils; platelet count, 23.1 × 104/μL; hemoglobin, 7.9 g/dL; blood urea nitrogen, 18.3 g/L; serum creatinine, 0.29 mg/dL; aspartate aminotransferase (AST), 62 U/L; alanine aminotransferase (ALT), 117 U/L; and C-reactive protein (CRP), 12.963 mg/dL. Since the isolated P. aeruginosa became resistant to TAZ/PIPC (Table 2, right column), she was switched to CTLZ/TAZ. Ten days later (day 10), she recovered, and her chest X-ray and CT were improved (Figure 2C and D). Her pneumonia improved smoothly without bacteremia.

Table 2. Antibiotic susceptibilities for the isolated *Pseudomonas aeruginosa* of Case 2

	Day 0		Day 7	
	MIC	**S/I/R**	**MIC**	**S/I/R**
AZT	8	S	16	I
PIPC	4	S	>64	R
PIPC/TAZ	≦4	S	>64	R
IPM	1	S	2	S
MEPM	0.25	S	0.5	S
CAZ	4	S	>16	R
CFPM	2	S	16	I
CTLZ/TAZ	≦1/4	S	≦2/4	S
AMK	≦4	S	≦4	S
GM	≦2	S	≦2	S
MINO	>8	R	>8	R
LVFX	1	S	1	S
CPFX	0.25	S	0.25	S
ST	80	R	80	R

Abbreviations: MIC; minimum inhibitory concentration, S/I/R; susceptible/intermediate/resistant, AZT; aztreonam, PIPC; piperacillin, PIPC/TAZ; piperacillin/tazobactam, CAZ; ceftazidim, CFPM; cefepime, CTLZ/TAZ; ceftolozane/tazobactam, IPM; imipenem, MEPM; meropenem, MINO; minocycline LVFX; levofloxacin, CPFX; ciprofloxacin, AMK; amikacin, GM; gentamycin, ST; sulfamethoxazole/trimethoprim.

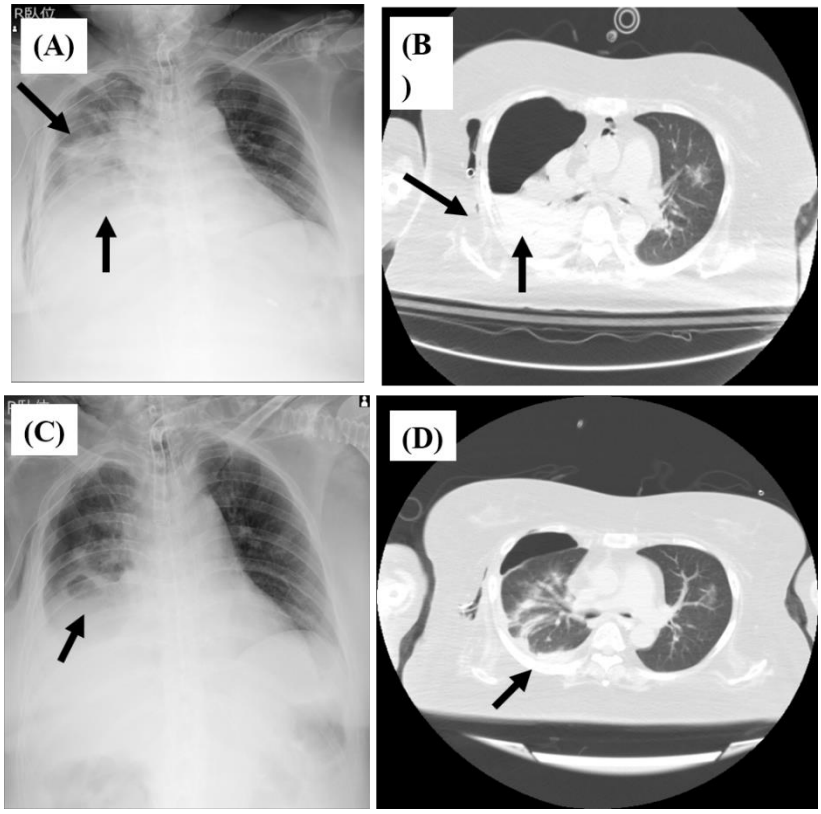

Figure 2. Chest X-ray (A and C) and CT (B and D) of the case 2 patient on day 0. Infiltration shadow is found in her right lower lung field (A and B). On day 10, these shadows are improved both on chest X-ray (C) and on CT (D). Arrows indicate abnormal shadows on chest X-ray and CT, such as infiltration shadows in the lungs.

3. Discussion

P. aeruginosa is a Gram-negative, aerobic, rod-shaped, polar-flagella bacterium, and an opportunistic pathogen responsible for VAP. VAP due to *P. aeruginosa* is usually multidrug-resistant and associated with severe infection and increased mortality, and it has been associated with higher rates of treatment failure, relapse, and death [10].

In this report, two cases of pneumonia, one HAP and one VAP, due to *P. aeruginosa* were presented. Both cases were treated by PIPC/TAZ first and then switched to CTLZ/TAZ treatment after 7-10 days because of relapse or exacerbation of the pneumonia. PIPC/TAZ is known as the penicillin to cover *P. aeruginosa* and is usually recommended for *P. aeruginosa* pneumonia, and a duration of treatment of 7-10 days may be appropriate [9]. Although it was previously recommended that antibiotics be continued for a minimum of 14–21 days to reduce the chance of relapse, the recent guidelines recommended a 7-day course of therapy for VAP, regardless of causative pathogen. To support their recommendation, the expert consensus panel performed a meta-analysis of studies comparing a short course (7–8 days) versus a long course (10–15 days) of therapy and found no differences in mortality or VAP recurrence [9, 11]. However, in the present cases, PIPC/TAZ-resistant *P. aeruginosa* was isolated after 7-10 days of therapy, which suggests that PIPC/TAZ might easily induce resistant bacteria in *P. aeruginosa* pneumonia.

Furthermore, CTLZ/TAZ was used after failure of the PIPC/TAZ therapy in the present two cases, with good clinical effectiveness according to the microbiological results that showed that the isolated *P. aeruginosa* was susceptible. Ceftolozane (CTLZ) is a β-lactam, novel cephalosporin antibiotic that exhibits broad-spectrum activity against *P. aeruginosa*, especially when combined with tazobactam (TAZ), a β-lactamase inhibitor, and it has been reported that 75% of carbapenem-resistant *P. aeruginosa* were susceptible

to CTLZ/TAZ, although 81% of the MDRP strains were resistant [12]. CTLZ/TAZ was thus non-inferior to meropenem (MEPM) in terms of both 28-day all-cause mortality and clinical cure at test of cure, and it has been used as a 'carbapenem-alternative antibiotic' to reduce the emergence of carbapenem-resistant bacteria from the perspective of antimicrobial stewardship [13, 14]. In fact, CTLZ/TAZ was effective, although the isolated *P. aeruginosa* became resistant to PIPC/TAZ, which has a similar spectrum to the carbapenem antibiotics, in the present cases. However, in case 1, the isolated *P. aeruginosa* also became resistant to CTLZ/TAZ after 14 days of treatment for pneumonia, and the patient showed bacteremia. In contrast, the case 2 patient completed the treatment for pneumonia without bacteremia within 10 days and ultimately survived. These data suggest that CTLZ/TAZ be used for *P. aeruginosa* pneumonia treatment within 7-10 days, the same as PIPC/TAZ and carbapenems to reduce the risk of the development of resistant strains and bacteremia.

P. aeruginosa and related pseudomonas strains were the second most common Gram-negative organisms in bloodstream infections among adult cancer patients, and one of the most common carbapenem-resistant isolates. Although the incidence of MDR Gram-negative blood stream infection (BSI) increased annually during 2015-2018, the mortality rate of Gram-negative BSI remains unchanged at about 20%; however, the mortality rate was significantly greater (35.4%) in those with resistant Gram-positive BSIs[15]. It was reported that the overall mortality rate was 21.5%. Early (7-day mortality) and late mortality (30-day mortality) rates were 10% and 3.4%, respectively. These data suggested that bacteremia was critical in *P. aeruginosa* infection, and we should take care not to induce bacteremia and resistant strains even when using novel antibiotics, including CTLZ/TAZ, and it might be better to complete the treatment for *P. aeruginosa* pneumonia within 7-10 days.

4. Conclusions

Two cases of *P. aeruginosa* pneumonia treated with PIPC/TAZ followed by CTLZ/TAZ were presented. The case 1 patient received prolonged treatment with PIPC/TAZ and CTLZ/TAZ, and the organism became resistant to both in sequential order. The patient had not only pneumonia, but also bacteremia, and finally died. The case 2 patient completed treatment with CTLZ/TAZ for *P. aeruginosa* pneumonia within the appropriate period and finally survived without bacteremia. We should take care to use broad-spectrum antibiotics appropriately, even though the drugs might be novel and effective, to avoid creating resistant strains and severe complications including bacteremia.

COI:

None

Acknowledgments

The authors would like to thank all healthcare staff, including physicians, pharmacists, nurses, and medical clinical microbiological technicians, for their kind support with respiratory management in Saitama Medical University International Medical Center.

References

[1] American Thoracic Society/Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*, 2005. 171: 388-416.

[2] Seki M, Mahida N, Yamagishi Y, Yoshida H, Tomono K, Nosocomial outbreak of multidrug-resistant Pseudomonas aeruginosa caused by damaged transesophageal echocardiogram probe used in cardiovascular surgical operations. *J Infect Chemother*, 2013.

[3] Harris A, Torres-Viera C,, Venkataraman L, DeGirolami P, Samore M, Carmeli Y. Epidemiology and clinical outcomes of patients with multiresistant Pseudomonas aeruginosa. *Clin Infect Dis* 1999. 28: 1128-1133.
[4] Mikura S, Wada H, Okazaki M, Nakamura M, Honda K, Yasutake T, et al. , Risk factors for bacteraemia attributable to Pseudomonas aeruginosa resistant to imipenem, levofloxacin, or gentamicin. *J Hosp Infect 2011*. 79: 267-268.
[5] Japan Nosocomial Infections Surveillance (JANIS) website. https://janis.mhlw.go.jp/. 2023.
[6] Miyoshi-Akiyama T, Tada T, Ohmagari N, Viet Hung N, Tharavichitkul P, Pokhrel BM, et al. Emergence and Spread of Epidemic Multidrug-Resistant Pseudomonas aeruginosa. *Genome Biol Evol*, 2017. 9(12): 3238-3245.
[7] Lodise TP Jr, Lomaestro B, Drusano GL, Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis*, 2007. 44(3): 357-63.
[8] Martin-Loeches I, Timsit JF, Kollef MH, et al , Clinical and microbiological outcomes, by causative pathogen, in the ASPECT-NP randomized, controlled, Phase 3 trial comparing ceftolozane/tazobactam and meropenem for treatment of hospital-acquired/ventilator-associated bacterial pneumonia. *J Antimicrob Chemother*, 2022. 77(4): 1166-1177.
[9] Kalil AC, Metersky ML, Klompas M, et al, Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*, 2016. 63(5): e61-e111.
[10] Bartlett JG, Breiman RF, Mandell LA, File TM Jr., Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis*, 1998. 26: 811-838.
[11] Albin OR, Kaye KS, McCreary EK, Pogue JM., Less Is More? Antibiotic Treatment Duration in Pseudomonas aeruginosa Ventilator-Associated Pneumonia. *Clin Infect Dis*., 2023. 76(4): 745-749.
[12] Kakehi A, Hagiya H, Iio K, et al, Susceptibility of ceftolozane/tazobactam against multidrug-resistant and carbapenem-resistant Pseudomonas aeruginosa. *New Microbiol*, 2023. 46(2): 213-215.
[13] Kollef MH, Nováček M, Kivistik Ü, et al, Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*, 2019. 19(12): 1299-1311.
[14] Doi Y. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. *Clin Infect Dis*, 2019. 69: S565-S575.
[15] Amanati A, Sajedianfard S, Khajeh S, et al. Bloodstream infections in adult patients with malignancy, epidemiology, microbiology, and risk factors associated with mortality and multi-drug resistance. *BMC Infect Dis*, 2021. 21(1): 636.