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Nosocomial *Pseudomonas putida* Bacteremia: High Rates of Carbapenem Resistance and Mortality

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Previously, *Pseudomonas putida* was considered a low-virulence pathogen and was recognized as a rare cause of bacteremia. Recently, however, multidrug-resistant and carbapenem-resistant *P. putida* isolates have emerged, causing difficult-to-treat nosocomial infections in seriously ill patients. Currently, the outcome of multidrug-resistant or carbapenem-resistant *P. putida* bacteremia remains uncertain. Here, we report 18 cases of *P. putida* bacteremia with high rates of carbapenem resistance and mortality. From January 2005 through December 2011, all cases of nosocomial *P. putida* bacteremia were identified and analyzed at Chonnam National University Hospital and Chonnam National University Hwasun Hospital. Electronic medical records were reviewed retrospectively. Four (22%) and five (23%) of 18 *P. putida* isolates were resistant to imipenem and meropenem, respectively. Common primary infection sites were central venous catheter (7, 39%), pneumonia (5, 28%), and cholangitis (2, 11%). Fourteen (78%) patients had indwelling devices related to the primary site of infection. The 30-day mortality rate was 39% (7/18): 40% (2/5) in patients with carbapenem-resistant *P. putida* bacteremia vs. 38% (5/13) in patients with carbapenem-susceptible *P. putida* bacteremia. Nosocomial *P. putida* bacteremia showed high resistance rates to most potent β-lactams and carbapenems and was associated with high mortality rates.

Key Words: *Pseudomonas putid; Carbapenems; Drug resistance*

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INTRODUCTION

Pseudomonas putida, of the fluorescent group of *Pseudomonas* species, as well as other nonfermenting Gram-negative organisms frequently found in the environment (e.g., *Acinetobacter, Burkholderia,* and *Stenotrophomonas* species), were previously thought to be of low pathogenicity.[1] Over the last three decades, however, these have been increasingly encountered as significant human pathogens. Because *P. putida* can colonize moist and inanimate hospital surfaces, it causes nosocomial infections, especially in immunocompromised patients and in patients possessing medical devices or catheters.[2,3] Outbreaks of bloodstream infection associated with contaminated fluids have also been reported.[4-7]

Despite the fact that this organism causes healthcare-related infections, clinical data on *P. putida* infections are lacking owing to the rarity, relatively lower virulence, and higher antimicrobial susceptibility of *P. putida* compared with other *Pseudomonas* species, especially *Pseudomonas aeruginosa*.[2,8-10] However, recently, the emergence of multi-drug-resistant (MDR) and carbapenem-resistant *P. putida* has become a cause for concern.[11-15] The outcome of MDR *P. putida* bacteremia has not been extensively investigated. Here, we report carbapenem resistance rates and outcomes of 18 *P. putida* bacteremia cases treated in a tertiary care hospital.

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MATERIALS AND METHODS

1. Study design and patient selection

Patients with *P. putida* bacteremia from January 2005 to December 2011 at Chonnam National University Hospital (1,000 beds) and Chonnam National University Hwasun Hospital (700 beds) were identified through a review of the clinical microbiology laboratory records. Only the first bacteremic episode for each patient was included in the analysis. Nosocomial bacteremia was defined as the isolation of one or more positive blood cultures in a patient occurring 48 hours after admission. Data collected from electronic medical records included age, gender, underlying disease, comorbid conditions, prior receipt of any type of antibiotics within the previous 30 days, primary sites of infection, antibiotic regimens and duration, and 30-day mortality. The following comorbid conditions were also documented at the time of infection: neutropenia, prior surgery within the previous 3 months, and presence of medical devices or catheters.

2. Microbiological tests

The VITEK II automated system (bioMérieux Inc., Marcy l'Etoile, France) provided microbiological identification and antimicrobial susceptibility testing by use of a standard identification card. Strains showing "intermediate" antimicrobial susceptibility testing were considered resistant. The antimicrobial agents tested included piperacillin, piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, imipenem, meropenem, tobramycin, amikacin, levofloxacin, ciprofloxacin, and colistimethate. An MDR strain was defined as a strain resistant to three or more of the five categorized classes.[16]

RESULTS

1. Clinical features and outcomes in patients with *P. putida* bacteremia

During the study period, 24 patients with nosocomial *P. putida* bacteremia were identified. Among these, five cases of *P. putida* bacteremia were clustered and removed from this report. In addition, one more case was excluded because the *P. putida* blood isolate was considered as contamination. The patient had no systemic inflammatory signs when the blood was obtained and the *P. putida* was isolated in only one pair of blood cultures. The clinical features and outcomes of the remaining 18 patients with *P. putida* bacteremia are summarized in Table 1. The mean age (±standard deviation) of the patients was 56±20 years. Solid tumor was the most common underlying disease (n=8, 44%), followed by traumatic intracranial hemorrhage (n=2, 11%). Eight patients (44%) had undergone an operation within the previous 3 months, and two patients (11%) had experienced neutropenia. Sixteen patients (89%) had been administered antibiotics within 1 month prior to *P. putida* bacteremia. The most common primary site of infection was the central venous catheter (n=7, 39%), followed by ventilator-associated pneumonia (n=4, 22%) and the biliary tract (n=2, 11%). Fourteen cases (77%) were device-related infections (central venous catheter 7, endotracheal tube 4, biliary stent 1, indwelling urinary catheter 1). Polymicrobial infection was found in five (28%) cases.

The 30-day mortality rate was 39% (7/18): 40% (2/5) in patients with carbapenem-resistant *P. putida* bacteremia vs. 38% (5/13) in patients with carbapenem-susceptible *P. putida* bacteremia. Three of 7 patients who died (43%) had received inappropriate antibiotics compared with 2 of 11 survivors (19%; p=0.326).

2. Antibiotic resistance in *P. putida* nosocomial isolates

The rate of resistance of 18 *P. putida* blood isolates to antibiotics is shown in Table 2. Four (22%) and five (28%) isolates of the 18 *P. putida* isolates were resistant to imipenem and meropenem. MDR strains were found in 28% of *P. putida* isolates. None of the *P. putida* isolates was resistant to colistimethate.

DISCUSSION

Infections caused by *P. putida* are relatively rare and are generally restricted to immunocompromised patients and patients with invasive medical devices in place.[8] Excluding pediatric and outbreak cases due to transfusion of contaminated blood or fluid, *P. putida* bacteremia is rarely reported. To date, Anaissie et al. reported six oncology patients with *P. putida* bacteremia[17] and Yang et al. reported eight cases in Taiwan.[18] Recently, five cases of *P. putida* bacteremia were reported in Japan.[2] This study likely contains the largest number of *P. putida* bacteremia cases in the literature to date.

Among the 18 cases reported here, 77% were device-related infections, and 56% of the cases were in an immunocompromised state (e.g., solid tumor, hematologic malignancy, liver cirrhosis). The clinical features present in our study were similar to those seen in previous studies.[2,8]

In previous reports, clinical isolates of *P. putida* showed high susceptibility to various antibiotics. For example, Fass et al. reported 100% susceptibility of 15 *P. putida* clinical isolates to ciprofloxacin and tobramycin and 87% to imipenem and piperacillin/tazobactam.[19] However, carbapenem-resistant *P. putida* isolates from the urinary tract, tracheal aspiration, and areas other than blood are increasingly being reported.[11,20] This carbapenem-resistance mechanism was known to be related with metallo-β-lactamase (MBL) production. In Korea, 12 imipenem-resistant isolates of *Pseudomonas* species other than *P. aeruginosa* were collected by the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program in 2005. Among them, eight (67%) isolates were MBL-producing pathogens, all of which were identified as *P. putida*.[21] In our study, 4 (22%) and 5 (28%) isolates of the 18 *P. putida* isolates were resistant to imipenem and meropenem. In the same period, 171 *P. aeruginosa* blood isolates were col-

TABLE 1. Clinical characteristics and outcomes of 18 patients with *P. putida* nosocomial bacteremia

No	Age/ gender	Co-morbidities	Primary site of infection	ICU	Hospital days†	The number of positive blood culture	Indwelling device	Co-pathogen	Resistance to carbapenem	MDR	Antibiotics	Antibiotic appropria-teness	30-day outcome
1	24/male	Traumatic ICH	CVC	N	5	1	CVC, endotracheal tube, urinary catheter, chest tube		Resistant	Y	Colistimethate	Y	Survived
2	65/male	Bacterial meningitis	CVC	N	45	2	CVC, endotracheal tube		Resistant	Y	Pip-Tazo Amikacin	N	Survived
3	55/male	Esophagectomy d/t esophageal cancer	CVC	N	36	2	CVC, endotracheal tube, urinary catheter	*P. aeruginosa*	Resistant	N	Meropenem	N	Died
4	60/female	ALL, neutropenia	CVC	N	12	5	CVC, endotracheal tube, urinary catheter		Resistant	Y	Meropenem	N	Died
5	19/male	Traumatic ICH	Pneumonia (VAP)	N	15	1	Endotracheal tube, urinary catheter	*P. aeruginosa*	Susceptible	N	Imipenem	Y	Survived
6	38/female	Ectopic pregnancy 11 weeks	Unknown	Y	0*	1	None		Resistant	Y	Imipenem	NA‡	Survived
7	52/male	Esophagectomy, RUL resection d/t esophageal cancer	Pneumonia (VAP)	Y	4	4	CVC, endotracheal tube, urinary catheter, chest tube	*P. aeruginosa* *C. freundii*	Susceptible	N	Pip-Tazo	Y	Survived
8	25/male	Traumatic lung contusion	CVC	N	2	7	CVC, endotracheal tube, urinary catheter, chest tube		Susceptible	N	Pip-Tazo	Y	Survived
9	77/female	Cholangiocarcinoma	Biliary tract	Y	3	1	-		Susceptible	N	Ciprofloxacin	Y	Survived
10	42/female	Liver cirrhosis, Varix bleeding	CVC	Y	2	2	CVC, Urinary catheter		Susceptible	N	Ceftizoxime	N	Survived
11	80/male	Gastrectomy d/t gastric cancer	Urinary catheter	Y	9	3	Urinary catheter		Susceptible	N	Ciprofloxacin	Y	Survived
12	75/male	Cardiac arrest IHD, HTN, DM	Pneumonia (VAP)	N	11	4	Endotracheal tube, urinary catheter		Susceptible	N	Ciprofloxacin	Y	Survived
13	65/female	Small bowel resection, total colectomy d/t SMA infarction	Peritonitis	N	9	1	CVC, endotracheal tube, urinary catheter, peritoneal drainage	*P. aeruginosa*	Susceptible	N	Imipenem	Y	Survived
14	66/female	Pleomorphic leiomyosarcoma Neutropenia	Necrotizing fasciitis	N	1*	1	-		Susceptible	N	Pip-Tazo Ciprofloxacin	Y	Died
15	66/male	Esophagectomy d/t esophageal cancer	Pneumonia (VAP)	N	5	4	Endotracheal tube, urinary catheter, chest tube		Susceptible	N	Meropenem	Y	Died
16	79/male	Cholangiocarcinoma	Biliary tract	Y	25	1	Biliary stent	*P. aeruginosa*	Susceptible	Y	Imipenem	Y	Died
17	77/male	RUL lobectomy d/t lung cancer	CVC	N	20	3	CVC, endotracheal tube, urinary catheter, chest tube		Susceptible	N	Imipenem	Y	Died
18	39/male	Acute alcoholic hepatitis	Pneumonia	Y	3	2	Urinary catheter		Susceptible	N	Ceftriaxone	N	Died

*Transferred from other hospitals, admitted more than 48hours before the transfer, †Duration from admission to *P.putida* isolation in blood, ‡Not appraisable, this strain was resistant to meropenem but susceptible to imipenem. ICU: intensive care unit, MDR: multidrug resistance, ICH: intracranial hemorrhage, CVC: central venous catheter, Y: yes, N: no, Pip-Tazo: Piperacillin/tazobactam, d/t: due to, *P. aeruginosa*: *Pseudomonas aeruginosa*, ALL: acute lymphoblastic leukemia, VAP: ventilator associated pneumonia, RUL: right upper lobe, *C. freundii: Citrobacter freundii*, UTI: urinary tract infection, IHD: ischemic heart disease, HTN: hypertension, DM: diabetes mellitus, SMA: superior mesenteric artery.

TABLE 2. Antibiotics susceptibilities of 18 *P. putida blood isolates*

	Piperacillin	Pip-Tazo	Ceftazidime	Aztreonam	Meropenem	Imipenem	Tobramycin	Amikacin	Ciprofloxacin	Levofloxacin	Cefepime	Colistin
1	R	R	R	R	R	R	I	S	R	R	R	S
2	R	R	R	R	R	R	R	R	R	R	R	S
3	S	S	S	R	I	I	S	S	S	S	S	S
4	R	R	R	R	R	R	R	R	R	R	R	S
5	S	S	S	S	S	S	S	S	S	S	S	S
6	I	I	I	R	I	S	R	S	S	S	S	S
7	S	S	S	S	S	S	S	S	S	S	S	S
8	S	S	S	R	S	S	S	S	S	S	S	S
9	S	S	S	S	S	S	S	S	S	S	S	S
10	S	S	S	S	S	S	S	S	S	S	S	-
11	S	S	S	R	S	S	S	S	S	S	S	-
12	S	S	S	I	S	S	S	S	S	S	S	S
13	S	S	S	R	S	S	S	S	S	S	S	S
14	S	S	S	S	S	S	S	S	S	S	S	S
15	S	S	S	R	S	S	S	S	S	S	S	S
16	I	R	I	I	S	S	S	S	S	S	R	S
17	S	S	S	R	S	S	S	S	S	S	S	-
18	S	S	S	R	S	S	S	S	S	S	S	S
Resistance* (total %)	5 (28)	5 (28)	5 (28)	13 (72)	5 (28)	4 (22)	4 (22)	2 (11)	3 (17)	3 (17)	4 (22)	0 (0)

*Strains showing "intermediate" antimicrobial susceptibility testing were considered resistant. Pip-Tazo: Piperacillin/tazobactam, R: resistance, I: intermediate, S: susceptible.

lected in the same hospitals (data not shown) and the antibiotics susceptibility was compared with that of the 18 *P. putida* isolates. The carbapenem-resistance rates did not differ significantly from those of *P. aeruginosa* blood isolates (28% vs. 23%; p=0.771). The resistance rate of other antibiotics was also similar (data not shown). However the aztreonam resistance rate of *P. putida* was significantly higher than that of *P. aeruginosa* (72% vs. 34%, p=0.001). These findings suggest that multidrug and carbapenem resistance is prevalent not only in *P. aeruginosa* bacteremia but also in *P. putida* bacteremia.

Unlike the well-known *P. aeruginosa* isolates, *P. putida* isolates were generally considered to have a low level of virulence and to be of little clinical significance.[10] A brief review of the literature revealed that the prognosis of *P. putida* bacteremia has been shown to be good, with 26 (93%) of 28 cases being cured.[2] However, in contrast to previous reports, the mortality rate in our patients with *P. putida* bacteremia was high. There are two possible explanations for this. The first is the higher rate of pneumonia as the primary site of infection in this study. The mortality rate in patients with pneumonia was high (40%; 2 of 5 patients) in this study, whereas previous studies reported that only 13% of the patients with *P. putida* infection had pneumonia.[8] The second is inadequate antimicrobial therapy in seriously ill patients. Three of 7 patients who died (43%) had received inappropriate antibiotics, compared with 2 of 11 survivors (19%; p=0.326). The higher rate of multi-drug and carbapenem resistance (28%) is presumed to affect the rate of inappropriate antibiotic therapy and high mortality, but further study with more cases is required to verify this relationship.

Our study had several limitations. First, organism identification was performed by using an automated system and was not confirmed by genotypic-based methods such as 16S rRNA gene sequencing. However, according to Jacquier et al., eight of nine *P. putida* isolates confirmed by 16S rRNA gene sequencing were identified accurately at the species level by using the VITEK II system and there was no misidentification.[22] In addition, previous studies have used automated systems for the identification of *P. putida*.[2,8] Thus, the VITEK II automated system is considered an acceptable tool for the identification of this organism. Second, the possibility of outbreak was excluded only by temporal relations of isolates, not by epidemiological tools such as pulsed-field gel electrophoresis. However, because there were no spatial or temporal relations between cases, we suggest that there is little possibility that outbreak cases were included in this study.

In conclusion, nosocomial infections of *P. putida* are highly resistant to the most potent β-lactams and carbapenems and can cause significant morbidity and mortality in infected patients. Thus, it is necessary to be aware of the fatality of nosocomial *P. putida* bacteremia and to consider the early initiation of appropriate antibiotic regimens.

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