Clinical characteristics and outcomes of *Pseudomonas aeruginosa* bacteremia in febrile neutropenic children and adolescents with the impact of antibiotic resistance: a retrospective study

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**Abstract**

**Background:** Although the proportion of *Pseudomonas aeruginosa* infections has reduced after the introduction of antibiotics with anti-pseudomonal effects, *P. aeruginosa* bacteremia still causes high mortality in immunocompromised patients. This study determined the clinical characteristics and outcomes of *P. aeruginosa* bacteremia and the antibiotic susceptibilities of strains isolated from febrile neutropenic patients.

**Methods:** Thirty-one febrile neutropenic children and adolescents with underlying hematologic/oncologic disorders diagnosed with *P. aeruginosa* bacteremia between 2011 and 2016 were enrolled in the study. Their medical records were retrospectively reviewed to evaluate the demographic and clinical characteristics. Antibiotic susceptibility rates of the isolated *P. aeruginosa* to eight antibiotic categories (anti-pseudomonal penicillin, anti-pseudomonal penicillin and β-lactamase inhibitor combination, anti-pseudomonal cephalosporin, monobactam, carbapenem, aminoglycoside, fluoroquinolone, and colistin) were also determined. Among the investigated factors, risk factors for mortality and infections by a multidrug-resistance (MDR) strain were determined.

**Results:** Thirty-six episodes of *P. aeruginosa* bacteremia were identified. The mean age of the enrolled patients was 9.5 ± 5.4 years, and 26 (72.2%) episodes occurred in boys. Acute myeloid leukemia (41.7%) and acute lymphoblastic leukemia (33.3%) were the most common underlying disorders. The 30-day mortality was 38.9%, and 36.1% of the episodes were caused by MDR strains. The deceased patients were more likely to experience breakthrough infection (*P* = 0.036) and bacteremia (*P* = 0.005) due to MDR strains when compared with the patients who survived. The survived patients more likely received appropriate empirical antibiotic therapy (*P* = 0.024) and anti-pseudomonal β-lactam and aminoglycoside combination therapy (*P* = 0.039) compared with the deceased patients. The antibiotic susceptibility rates of the isolated *P. aeruginosa* strains were as follows: piperacillin/tazobactam, 67.6%; meropenem, 72.2%; and amikacin, 100%.

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Conclusions: Mortality due to *P. aeruginosa* bacteremia remained at 38.9% in this study, and more than one-third of the isolated strains were MDR. In this context, empirical antibiotic combination therapy to expand the antibiotic spectrum may be a strategy to reduce mortality due to *P. aeruginosa* bacteremia in febrile neutropenic patients.

Keywords: *Pseudomonas aeruginosa*, Antibiotic resistance, Multidrug resistance, Neutropenia, Child

Background

*Pseudomonas aeruginosa* was the most common infectious pathogen in patients with hematologic/oncologic disorders during the 1960s and 1970s; *P. aeruginosa* infections also showed higher mortality rates compared with other bacterial infections [1, 2]. After the introduction of antibiotics with anti-pseudomonal effects in the 1970s and the increased frequency of Gram-positive bacterial infections in the 1980s, the proportion of *P. aeruginosa* infections in immunocompromised patients was reduced. In our hospital, 8.3% of bacteremia episodes diagnosed in children with febrile neutropenia (FN) between 2010 and 2014 were caused by *P. aeruginosa* [3]. However, *P. aeruginosa* is still the third most common Gram-negative cause of bacteremia in FN patients, after *Klebsiella pneumoniae* and *Escherichia coli* [3, 4]. In addition, *P. aeruginosa* bacteremia resulted in approximately 30% mortality in patients with underlying hematologic/oncologic disorders in the 2000s [5–7].

Although multidrug-resistance (MDR) *P. aeruginosa* infections have been increasing since 2000s [4], empirical monotherapy with an anti-pseudomonal β-lactam agent has been recommended for the treatment of FN in patients with underlying hematologic/oncologic disorders [8]. However, the prediction of severe infections due to MDR *P. aeruginosa* strains and an empirical antibiotic combination therapy to broaden the antibiotic spectrum for those patients may improve the prognosis. Nevertheless, the clinical characteristics and outcomes of *P. aeruginosa* bacteremia and risk factors for MDR strain infections have been reported more rarely in children than in adults [7, 9, 10], with only a few recent studies on *P. aeruginosa* bacteremia in FN children [11, 12].

The present study investigated the recent characteristics and outcomes of *P. aeruginosa* bacteremia in FN children and adolescents with underlying hematologic/oncologic disorders and assessed the antibiotic susceptibilities of the *P. aeruginosa* isolates. Risk factors for a grave outcome and infections due to MDR strains were also evaluated.

Methods

**Patients and study design**

Among children and adolescents hospitalized in the Department of Pediatrics of Seoul St. Mary’s Hospital (Seoul, Republic of Korea) between 2011 and 2016, FN children and adolescents <19 years of age with underlying hematologic/oncologic disorders diagnosed with *P. aeruginosa* bacteremia were enrolled in the present study. Seoul St. Mary’s Hospital is a university-affiliated tertiary teaching hospital that has a separate 46-bed ward for children and adolescents with hematologic/oncologic disorders. A mean of 1400 children and adolescents are admitted to the ward and 60–80 allogeneic and autologous hematopoietic cell transplantations are performed annually. This study was performed as a retrospective observational study: the medical records of the enrolled patients were retrospectively reviewed in order to investigate their demographic data, including sex and age. The clinical data included the type and status of the underlying disorders, the therapy administered for treatment of the underlying disorders preceding bacteremia, the presence of focal infections, the type and appropriateness of administered antibiotic agents for FN and bacteremia, and the occurrence of complications and death. In addition, the antibiotic susceptibilities of the isolated *P. aeruginosa* strains were also investigated.

For the whole study population, two comparisons were performed. Firstly, the enrolled patients were divided into survived and deceased groups based on mortality within 30 days after the development of *P. aeruginosa* bacteremia, and a comparison was performed between the two groups in order to identify factors associated with mortality. Secondly, the whole study population was divided into MDR and non-MDR groups based on the antibiotic susceptibilities of the *P. aeruginosa* isolates, and another comparison was performed between the two groups in order to determine the risk factors of MDR strain infections.

**Microbiological tests**

Blood samples for the culture studies were collected from a peripheral vein and each lumen of the central venous catheter. Each 1–3 mL blood sample was immediately inoculated into a culture bottle (BD BACTEC™ Peds Plus Culture Vial, Becton Dickinson, Sparks, MD, USA), and transferred to the laboratory. An automated system (BACTEC™ FX, Becton Dickinson) was used for culturing; the bacterial identification and antibiotic susceptibility tests of the *P. aeruginosa* isolates were also performed using an automated system (VITEK®2, bioMérieux, Hazelwood, MO, USA). The antibiotics used...
for the susceptibility tests included piperacillin (anti-
psuedomonal penicillin), piperacillin/tazobactam and
ticarcillin/clavulanate (anti-psuedomonal penicillin and
β-lactamase inhibitor combination), ceftazidime and
cefepime (anti-psuedomonal cephalosporin), aztreonam
(monobactam), meropenem and imipenem (carba-
penem), gentamicin and amikacin (aminoglycoside),
ciprofloxacin (fluoroquinolone), and colistin.

Definitions
Neutropenia was defined as an absolute neutrophil
count <500/mm³ or an expected absolute neutrophil
count <500/mm³ within 2 to 3 days on the day when
fever developed [13]. Fever was defined as axillary or
tympanic membrane temperatures above 37.5 °C or
38.0 °C, respectively [13].

P. aeruginosa bacteremia was diagnosed when at least
one of the blood sample cultures was positive for P.
aeruginosa. If P. aeruginosa bacteremia was diagnosed
within 1 month after the diagnosis of a previous P. aere-
ginosa bacteremia in the same patient, the bacteremia
episode was excluded from the present study with an as-
sumption of undertreated previous bacteremia. Poly-
microbial infection was defined as the presence of bacteria
other than P. aeruginosa identified from blood samples
collected on the same day or as other viral or fungal
infections identified during the bacteremia period. Ser-
um galactomannan levels were measured twice a
week during each neutropenic period, and a multiplex
polymerase chain reaction assay for respiratory viruses
was performed in patients with respiratory symptoms.
For patients complaining of diarrhea during antibiotic
therapy, a Clostridium difficile toxin assay was per-
formed. Breakthrough infection was defined as the
diagnosis of P. aeruginosa bacteremia in a patient who
had been receiving antibiotic agents with anti-
pseudomonal effects for more than 2 days. Empirical
antibiotic therapy was considered appropriate if the
identified P. aeruginosa strain was susceptible to at least
one of the empirical antibiotic agents administered
within 24 h of the development of FN.

The presence of focal infections was determined by
two independent pediatricians based on patients’ symp-
toms, physical examination and radiological findings.
Complications due to bacteremia included shock,
hypoxia, mechanical ventilation, and renal and hepatic
insufficiencies. Shock was defined when the patient
showed systolic blood pressure < 5th percentile for an
age-matched normal range despite fluid resuscitation or
received inotropic agents to maintain blood pressure
[14]. Hypoxia was defined when oxygen supplementation
was performed to maintain a SpO₂ > 90%. Renal insuffi-
ciency was defined as serum creatinine levels more than
twice those from before bacteremia [15]. Hepatic
insufficiency was defined as serum aspartate transamin-
ase or alanine transaminase levels more than twice
those from before bacteremia, with a serum total bili-
rubin ≥2.0 mg/dL and prothrombin time international
normalized ratio ≥ 1.5 [16]. All patients who died
within 30 days after the development of bacteremia
were included in the deceased group. The patients
who died of uncontrolled focal complications of P.
aeruginosa bacteremia were also included in the
deceased group regardless of the time of death.

The antibiotic susceptibility was determined based on
the Clinical and Laboratory Standards Institute 2010
recommendations. Among the automated antibiotic sus-
ceptibility test results, ‘intermediate’ and ‘resistance’ were
categorized as non-susceptible. Although isepamicin was
the most frequently administered aminoglycoside in the
enrolled patients, susceptibility tests for isepamicin were
not performed in our hospital. Therefore, antibiotic
susceptibility to isepamicin was determined based on the
results for amikacin. MDR was defined as P. aeruginosa
strains resistant to three or more of the eight recom-
manded antibiotic categories to be tested [17].

Statistical analysis
In the comparisons between patient groups, continuous
variables were compared using a Student’s t-test or a
Mann-Whitney test based on their normal distributions,
and categorical variables were compared using chi-
square tests. Statistical analyses were performed using
IBM SPSS Statistics for Windows, version 21.0 (IBM
Corporation, Armonk, NY, USA), with the statistical
significance defined as a two-tailed P value <0.05.

Results
Characteristics of patients diagnosed with P. aeruginosa
bacteremia
A total of 36 episodes of P. aeruginosa bacteremia were
diagnosed in the 31 FN children and adolescents during
the study period. Among them, three patients each expe-
rienced two episodes and one patient experienced three
episodes of P. aeruginosa bacteremia. The recurrent
episodes occurred a median of 7 weeks (range 4–
33 weeks) after the previous P. aeruginosa bacteremia.

The mean age of the enrolled patients was
9.5 ± 5.4 years, and 26 (72.2%) episodes occurred in boys
(Table 1). Acute myeloid leukemia (15, 41.7%) and acute
lymphoblastic leukemia (12, 33.3%) were most common
underlying disorders. Among 30 patients with underly-
ing malignancies, except for five patients with severe
aplastic anemia (SAA) and one patient with severe com-
bined immune deficiency, only eight (26.7%) patients
were in the complete remission or response of their
underlying malignancies. Accordingly, re-induction (13,
36.1%) and palliative (seven, 19.4%) chemotherapy were
Table 1 Characteristics of febrile neutropenic children and adolescents with *Pseudomonas aeruginosa* bacteremia

| Factor                                                | Number (%)          |
|-------------------------------------------------------|---------------------|
| Male sex                                              | 26 (72.2)           |
| Age (years), mean ± SD                                | 9.5 ± 5.4           |
| Underlying disorders                                  |                     |
| Acute myeloid leukemia                                | 15 (41.7)           |
| Acute lymphoblastic leukemia                          | 12 (33.3)           |
| Severe aplastic anemia                                | 5 (13.9)            |
| Neuroblastoma                                          | 2 (5.6)             |
| Lymphoma                                              | 1 (2.8)             |
| Severe combined immune deficiency                      | 1 (2.8)             |
| Remission state of underlying malignancy*             |                     |
| Complete remission                                     | 8 (26.7)            |
| Non-complete remission                                 | 22 (73.3)           |
| Administered therapy preceding bacteremia             |                     |
| Induction chemotherapy                                 | 2 (5.6)             |
| Re-induction chemotherapy                              | 13 (36.1)           |
| Consolidation chemotherapy                             | 6 (16.7)            |
| Autologous hematopoietic cell transplantation          | 1 (2.8)             |
| Allogeneic hematopoietic cell transplantation          | 4 (11.1)            |
| Palliative chemotherapy                                | 7 (19.4)            |
| None†                                                 | 3 (8.3)             |
| Central venous catheter                                |                     |
| Hickman catheter                                       | 27 (75.0)           |
| Subcutaneously implanted chemoport                     | 7 (19.4)            |
| None                                                   | 2 (5.6)             |
| Polymicrobial infection                                | 9 (25.0)            |
| Breakthrough infection                                 | 8 (22.2)            |
| Local infection                                        |                     |
| Gastrointestinal tract infection                       | 26 (72.2)           |
| Respiratory tract infection                            | 15 (41.7)           |
| Skin and soft tissue infection                         | 11 (30.6)           |
| Catheter site infection                                | 7 (19.4)            |
| Empirical antibiotic therapy                           | 2 (5.6)             |
| Empirical antibiotic therapy                           |                     |
| Piperacillin/tazobactam with aminoglycoside            | 16 (44.4)           |
| Meropenem                                              | 14 (38.9)           |
| Cefepime                                               | 3 (8.3)             |
| Cefepime with aminoglycoside                           | 2 (5.6)             |
| Meropenem with aminoglycoside                          | 1 (2.8)             |
| Empirical combination antibiotic therapy               | 19 (52.8)           |
| Appropriateness of empirical antibiotics               |                     |
| Overall                                                | 30 (83.3)           |
| β-lactam agents                                       | 24 (66.7)           |
| Fever duration (days), median (range)                  | 4 (1–53)            |
| Complications                                          | 17 (47.2)           |
| Hypoxia                                                | 14 (38.9)           |
| Shock                                                  | 13 (36.1)           |
| Mechanical ventilator care                             | 8 (22.2)            |
| Renal dysfunction                                      | 8 (22.2)            |
| Hepatic dysfunction                                    | 4 (11.1)            |
| Death                                                  | 14 (38.9)           |
| Multidrug-resistant strain infections                  | 13 (36.1)           |

SD, standard deviation

*Remission state of the underlying malignancy was determined in 30 children except those with non-malignant underlying disorders

†Three children with severe aplastic anemia had not received any therapy prior to the development of bacteremia

the most frequently administered therapies preceding bacteremia. Three (8.3%) episodes of bacteremia occurred in patients with SAA who had not received any immune suppression therapy or hematopoietic cell transplantsations. Polymicrobial infections were diagnosed in nine (25.0%) episodes; three (33.3%) of invasive pulmonary aspergillosis (IPA), two (22.2%) of *E. coli* bacteremia, and one each (11.1%) of *Enterobacter cloacae*, methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant coagulase-negative staphylococci bacteremia and *C. difficile*-associated diarrhea. Breakthrough infections were identified in eight (22.2%) episodes. Among them, seven (87.5%) episodes occurred in meropenem therapy, and one (12.5%) occurred in piperacillin/tazobactam therapy. Focal infections accompanied 26 (72.2%) episodes, most frequently as gastroenteritis (15, 41.7%) and respiratory tract infections (11, 30.6%). Piperacillin/tazobactam and isepamicin combination therapy (16, 44.4%) were most commonly administered as empirical antibiotic therapy. Empirical antibiotic therapy was appropriate for 30 episodes (83.3%); however, empirically administered β-lactam agents were appropriate for 24 episodes (66.7%). Complications occurred in 17 (47.2%) episodes; hypoxia (14, 38.9%) and shock (13, 36.1%) were most common. Fourteen (38.9%) patients died and were included in the deceased group.

The antibiotic susceptibility rates to amikacin, colistin, and ciprofloxacin were 100%, 100%, and 97.2%, respectively (Fig. 1). Piperacillin/tazobactam and cefepime, which have been most frequently used in our hospital as empirical antibiotics for FN patients, were effective against 67.6% and 88.9% of the *P. aeruginosa* isolates, respectively. The carbapenem susceptibility rate was 72.2%. MDR strains were identified in 13 (36.1%) episodes (Table 1). No strains were pandrug-resistant; however, three (8.3%) strains showed extensive drug resistance, in which they were susceptible to only one or two categories of antibiotics.

Clinical factors associated with mortality
Fourteen (38.9%) patients died a median of 5 days (range 0–43 days) after the development of bacteremia. Four (28.6%) patients died despite the resolution of *P. aeruginosa* bacteremia. Among these four patients, two died of uncontrolled IPA, and one died of uncontrolled relapse of acute leukemia. The remaining child died of uncontrolled intra-abdominal infection 43 days after the development of *P. aeruginosa* bacteremia.

The deceased patients experienced significantly more breakthrough infections compared with those of the survived group (*P* = 0.036, Table 2). In the survived group, two (9.1%) patients experienced breakthrough infections in meropenem therapy caused by meropenem-sensitive and meropenem-resistant strains, respectively.
Six (42.9%) patients in the deceased group experienced breakthrough infections. Four (66.7%) were during meropenem therapy, which had continued until the antibiotic susceptibility test findings were reported, and were infected with meropenem-resistant strains. Another deceased patient infected with a meropenem-resistant strain was also receiving meropenem therapy, and isepamicin was added on the day of fever. One deceased patient was receiving piperacillin/tazobactam therapy, which was changed to meropenem on the first day of fever; however, a meropenem-resistant strain was identified.

Empirical antibiotic combination therapy was administered more frequently in the survived group than in the deceased group ($P = 0.039$). Empirical antibiotic therapy was appropriate for 95.5% and 64.3% of cases in the survived and deceased groups, respectively ($P = 0.024$); however, the appropriateness of the empirically administered $\beta$-lactam agents, except for combined aminoglycosides, did not differ significantly between the two groups.

Infections due to MDR strains were significantly more frequent in the deceased group than in the survived group ($P = 0.005$). Among the tested antibiotics, the susceptibility rates of piperacillin (86.4% vs. 35.7%, $P = 0.003$), aztreonam (68.2% vs. 14.3%, $P = 0.002$), and carbapenems (86.4% vs. 50.0%, $P = 0.026$) were significantly lower in the deceased group than in the survived group.

**Clinical factors associated with MDR *P. aeruginosa* infections**

Significantly more patients in the MDR group experienced breakthrough infections ($P < 0.001$) and had a Hickman catheter ($P = 0.034$, Table 3) compared with those in the non-MDR group. Although the type and frequency of combination empirical antibiotic agents did not differ significantly between the two groups, the appropriateness of empirical antibiotics was significantly lower in the MDR group than in the non-MDR group ($P = 0.001$). The occurrence rate of complications was not significantly different between the two groups; however, mortality was significantly higher in the MDR group than in the non-MDR group ($P = 0.005$).

**Discussion**

The present study investigated the clinical characteristics and outcomes of *P. aeruginosa* bacteremia in FN children and adolescents. Mortality due to *P. aeruginosa* bacteremia remained high in the 2010s, and more than one-third of the isolated *P. aeruginosa* strains were MDR.

The mortality among immunocompromised patients with *P. aeruginosa* bacteremia was approximately 70% in the 1960s and 1970s [1, 2, 18], which decreased to 20–25% in the 1990s with the use of anti-pseudomonal antibiotics [18, 19]. However, the mortality in the 2000s was 20–39%, similar to that in the 1990s [5–7, 11], and 38.9% of FN children and adolescents with *P. aeruginosa* bacteremia died in the present study. This recent slowdown in improving outcomes in *P. aeruginosa* bacteremia patients might be associated with increasing prevalence of antibiotic-resistant strains. MDR *P. aeruginosa* comprised 1.6–8.2% of the identified *P. aeruginosa* strains until the early 2000s [20, 21]; however, the proportion of MDR strains increased to 30.7–71.1% in the late 2010s [5, 6, 11]. In Korea, 11.3% of *P. aeruginosa* bacteremia cases diagnosed in hospitalized children,
Table 2  Comparison of characteristics between the survived and deceased groups

| Factor                                      | Survived group | Deceased group | P value |
|---------------------------------------------|----------------|----------------|---------|
| Male sex                                    | 13 (59.1)      | 13 (92.9)      | 0.054   |
| Age (years), mean ± SD                      | 9.2 ± 5.3      | 10.0 ± 5.7     | 0.663   |
| Underlying disorders                        |                |                | 0.294   |
| Acute myeloid leukemia                      | 12 (54.5)      | 3 (21.4)       |         |
| Acute lymphoblastic leukemia                | 6 (27.3)       | 6 (42.9)       |         |
| Severe aplastic anemia                     | 3 (13.6)       | 2 (14.3)       |         |
| Neuroblastoma                               | 1 (4.5)        | 1 (7.1)        |         |
| Lymphoma                                    | 0 (0.0)        | 1 (7.1)        |         |
| Severe combined immune deficiency           | 0 (0.0)        | 1 (7.1)        |         |
| Remission state of underlying malignancya  |                |                | 0.199   |
| Complete remission                          | 7 (36.8)       | 1 (9.1)        |         |
| Non-complete remission                     | 12 (63.2)      | 10 (90.9)      |         |
| Administered therapy preceding bacteremia  |                |                | 0.123   |
| Induction chemotherapy                      | 2 (9.1)        | 0 (0.0)        |         |
| Re-induction chemotherapy                   | 8 (36.4)       | 5 (35.7)       |         |
| Consolidation chemotherapy                  | 6 (27.3)       | 0 (0.0)        |         |
| Autologous hematopoietic cell transplantation| 0 (0.0)        | 1 (7.1)        |         |
| Allogeneic hematopoietic cell transplantation| 2 (9.1)        | 2 (14.3)       |         |
| Palliative chemotherapy                     | 2 (9.1)        | 5 (35.7)       |         |
| Noneb                                       | 2 (9.1)        | 1 (7.1)        |         |
| Central venous catheter                     |                |                | 0.318   |
| Hickman catheter                            | 17 (77.3)      | 10 (71.4)      |         |
| Subcutaneously implanted chemoprot          | 3 (13.6)       | 4 (28.6)       |         |
| None                                        | 2 (9.1)        | 0 (0.0)        |         |
| Polymicrobial infection                     | 4 (18.2)       | 5 (35.7)       | 0.267   |
| Breakthrough infection                      | 2 (9.1)        | 6 (42.9)       | 0.036   |
| Local infection                             | 15 (68.2)      | 11 (78.6)      | 0.706   |
| Gastrointestinal tract infection            | 9 (40.9)       | 6 (42.9)       | 0.908   |
| Respiratory tract infection                 | 4 (18.2)       | 7 (50.0)       | 0.067   |
| Skin and soft tissue infection              | 5 (22.7)       | 2 (14.3)       | 0.681   |
| Catheter site infection                     | 2 (9.1)        | 0 (0.0)        | 0.511   |
| Empirical antibiotic therapy                |                |                | 0.008   |
| Piperacillin/tazobactam with aminoglycoside | 13 (59.1)      | 3 (21.4)       |         |
| Meropenem                                   | 4 (18.2)       | 10 (71.4)      |         |
| Cefepime                                    | 3 (13.6)       | 0 (0.0)        |         |
| Cefepime with aminoglycoside                | 2 (9.1)        | 0 (0.0)        |         |
| Meropenem with aminoglycoside               | 0 (0.0)        | 1 (7.1)        |         |
| Empirical combination antibiotic therapy    | 15 (68.2)      | 4 (28.6)       | 0.039   |
| Appropriateness of empirical antibiotics    |                |                |         |
| Overall                                     | 21 (95.5)      | 9 (64.3)       | 0.024   |
| β-lactam agents                             | 16 (72.7)      | 8 (57.1)       | 0.471   |
| Fever duration (days), median (range)       | 2 (1–53)       | 4 (1–14)       | 0.713   |
| Complications                               |                |                |         |
| Hypoxia                                     | 4 (18.2)       | 13 (92.9)      | <0.001  |
| Shock                                       | 2 (9.1)        | 12 (85.7)      | <0.001  |
| Mechanical ventilator care                  | 3 (13.6)       | 10 (71.4)      | <0.001  |
| Renal dysfunction                           | 2 (9.1)        | 6 (42.9)       | 0.036   |
| Hepatic dysfunction                         | 1 (4.5)        | 7 (50.0)       | 0.003   |
| Multidrug-resistant strain infections       | 4 (18.2)       | 9 (64.3)       | 0.005   |

SD, standard deviation

*aRemission state of underlying malignancy was determined in 30 children except those with non-malignant underlying disorders
bThree children with severe aplastic anemia had not received any therapy prior to the development of bacteremia
Table 3  Comparison of characteristics between the MDR and non-MDR groups

| Factor                                    | Non-MDR group  | MDR group   | P value |
|-------------------------------------------|----------------|-------------|---------|
|                                           | (n = 23)       | (n = 13)    |         |
| Male sex                                  | 14 (60.9)      | 12 (92.3)   | 0.060   |
| Age (years), mean ± SD                    | 9.4 ± 5.7      | 9.8 ± 5.0   | 0.825   |
| Underlying disorders                      |                |             | 0.389   |
| Acute myeloid leukemia                     | 8 (34.8)       | 7 (53.8)    |         |
| Acute lymphoblastic leukemia               | 10 (43.5)      | 2 (15.4)    |         |
| Severe aplastic anemia                     | 3 (13.0)       | 2 (15.4)    |         |
| Neuroblastoma                              | 1 (4.3)        | 1 (7.7)     |         |
| Lymphoma                                   | 1 (4.3)        | 0 (0.0)     |         |
| Severe combined immune deficiency          | 0 (0.0)        | 1 (7.7)     |         |
| Remission state of underlying malignancy a|                |             | 0.682   |
| Complete remission                         | 6 (30.0)       | 2 (20.0)    |         |
| Non-complete remission                     | 14 (70.0)      | 8 (60.0)    |         |
| Administered therapy preceding bacteremia  |                |             | 0.454   |
| Induction chemotherapy                      | 2 (8.7)        | 0 (0.0)     |         |
| Re-induction chemotherapy                   | 9 (39.1)       | 4 (30.8)    |         |
| Consolidation/chemotherapy                 | 5 (21.7)       | 1 (7.7)     |         |
| Autologous hematopoietic cell transplantation| 0 (0.0)       | 1 (7.7)     |         |
| Allogeneic hematopoietic cell transplantation| 2 (8.7)       | 2 (15.4)    |         |
| Palliative chemotherapy                     | 3 (13.0)       | 4 (30.8)    |         |
| None b                                      | 2 (8.7)        | 1 (7.7)     |         |
| Central venous catheter                    |                |             | 0.034   |
| Hickman catheter                           | 14 (60.9)      | 13 (100.0)  |         |
| Subcutaneously implanted chemoport         | 7 (30.4)       | 0 (0.0)     |         |
| None                                       | 2 (8.7)        | 0 (0.0)     |         |
| Polymicrobial infection                     | 7 (30.4)       | 2 (15.4)    | 0.438   |
| Breakthrough infection                      | 1 (4.3)        | 7 (53.8)    | <0.001  |
| Local infection                            | 19 (82.6)      | 7 (53.8)    | 0.119   |
| Gastrointestinal tract infection            | 9 (39.1)       | 6 (46.2)    | 0.681   |
| Respiratory tract infection                | 8 (34.8)       | 3 (23.1)    | 0.708   |
| Skin and soft tissue infection             | 6 (26.1)       | 1 (7.7)     | 0.382   |
| Catheter site infection                     | 2 (8.7)        | 0 (0.0)     | 0.525   |
| Previous antibiotic therapy                | 18 (78.3)      | 12 (92.3)   | 0.385   |
| Empirical antibiotic therapy               |                |             | 0.078   |
| Piperacillin/tazobactam with aminoglycoside | 13 (56.5)     | 3 (23.1)    |         |
| Meropenem                                  | 6 (26.1)       | 8 (61.5)    |         |
| Cefepime                                   | 3 (13.0)       | 0 (0.0)     |         |
| Cefepime with aminoglycoside               | 1 (4.3)        | 1 (7.7)     |         |
| Meropenem with aminoglycoside              | 0 (0.0)        | 1 (7.7)     |         |
| Empirical combination antibiotic therapy   | 14 (60.9)      | 5 (38.5)    | 0.196   |
| Appropriateness of empirical antibiotics   |                |             |         |
| Overall                                    | 23 (100.0)     | 7 (53.8)    | 0.001   |
| β-lactam agents                            | 21 (91.3)      | 3 (23.1)    | <0.001  |
| Fever duration (days), median (range)      | 3 (1–53)       | 4 (1–32)    | 0.745   |
| Complications                              | 9 (39.1)       | 8 (61.5)    | 0.299   |
| Hypoxia                                    | 7 (30.4)       | 7 (53.8)    | 0.166   |
| Shock                                      | 7 (30.4)       | 6 (46.2)    | 0.474   |
| Mechanical ventilator care                 | 5 (21.7)       | 3 (23.1)    | 1.000   |
| Renal dysfunction                          | 4 (17.4)       | 4 (30.8)    | 0.422   |
| Hepatic dysfunction                        | 2 (8.7)        | 2 (15.4)    | 0.609   |
| Mortality                                  | 5 (21.7)       | 9 (69.2)    | 0.005   |

MDR, multidrug-resistant; SD, standard deviation

*aRemission state of underlying malignancy was determined in 30 children except those with non-malignant underlying disorders

*bThree children with severe aplastic anemia had not received any therapy prior to the development of bacteremia
including immune-competent and -compromised children, were caused by MDR strains in the 2000s [10]; however, 36.1% of P. aeruginosa bacteremia were caused by MDR strains in the present study. The appropriateness of empirical antibiotic therapy as well as infection due to MDR strains was associated with mortality in patients with P. aeruginosa bacteremia, a relationship that has been previously reported [5–7, 18, 22–25]. In sum, antibiotics to which MDR P. aeruginosa strains are susceptible should be administered empirically in order to improve the outcomes of immunocompromised patients with P. aeruginosa bacteremia. The P. aeruginosa antibiotic susceptibility rates in the present study were 100% to aminoglycosides and colistin and 97.2% to ciprofloxacin, which were higher than those to anti-pseudomonal β-lactam agents such as piperacillin/tazobactam and cefepime. Previous studies on P. aeruginosa bacteremia in children also reported higher antibiotic susceptibility rates to amikacin and fluoroquinolones compared with those of β-lactam agents [10, 11]. However, the use of fluoroquinolones has been restricted in children due to concerns of skeletal adverse effects, and empirical use of colistin may not be appropriate considering its nephrotoxicity and neurotoxicity [26]. Aminoglycosides are not effective as a single agent against Gram-negative bacterial infections including pseudomonal infections [22, 24, 27, 28]. As a result, anti-pseudomonal β-lactam agent and aminoglycoside combination therapy may be helpful to broaden the antibiotic coverage for MDR strains and consequently improve the outcomes of patients with P. aeruginosa bacteremia. In the present study, although the appropriateness of the empirical β-lactam agents did not differ significantly between the survived and deceased groups, the combination with aminoglycosides significantly increased the appropriateness of the empirical antibiotics in the survived group. However, the contribution of the β-lactam agent and aminoglycoside combination to antibiotic synergism, improved clinical outcomes, and suppressed the emergence of antibiotic resistance has not been confirmed [29–31]. Therefore, this antibiotic combination can be maintained for early (3 to 5 days) bacteremia, followed by targeted antibiotic therapy based on the antibiotic susceptibility results [23].

The relationship between infections due to MDR strains and mortality of patients with P. aeruginosa bacteremia in the present study underscore the need to decrease the prevalence of MDR strains. Infections due to MDR P. aeruginosa were associated with recent use of carbapenems, ventilator care, and P. aeruginosa infection or colonization within the previous year [32, 33]. In Korean children, the primary risk factor for MDR P. aeruginosa bacteremia was admission to the intensive care unit within 2 months [10]; however, no patient in the present study had been admitted to the intensive care unit within 2 months before developing P. aeruginosa bacteremia. Almost all patients in the present study had received repeated anti-pseudomonal antibiotic therapy due to their underlying hematologic/oncologic disorders; therefore, recent use of anti-pseudomonal antibiotics was not significantly associated with MDR strain infections. However, the effect of recent antibiotic use on the MDR strain infections cannot be ignored, considering the relationship between breakthrough and MDR strain infections. Previous studies have reported that various β-lactam agents and fluoroquinolones were related to MDR P. aeruginosa infections [20, 30, 34]. In addition, the induction rate of antibiotic resistance in P. aeruginosa was affected by the type of previously administered antibiotics, and imipenem showed a higher rate of resistance induction compared with those of other antibiotic agents [30]. Accordingly, restriction of carbapenem use may reduce the emergence of MDR P. aeruginosa strains. Carbapenems have an additional antibiotic effect against extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae beyond other anti-pseudomonal β-lactam agents commonly used for FN patients. Our previous study, however, showed that a combination of empirical β-lactam agent and aminoglycoside instead of carbapenems did not cause unfavorable outcomes in FN patients with ESBL-producing E. coli and K. pneumoniae infections [35]. As a result, empirical anti-pseudomonal β-lactam and aminoglycoside combination therapy in FN patients may reduce carbapenem use and subsequently prevent the emergence of antibiotic resistance without worsening prognosis due to Gram-negative bacterial infections. In our hospital, anti-pseudomonal β-lactam and aminoglycoside combination therapy has been used as first-line empirical therapy for FN patients. However, carbapenems have been administered as a second-line empirical antibiotic agent for patients with persistent fever despite the first-line empirical antibiotic therapy until the recovery of neutropenia. Eventually, many patients might have received carbapenems for longer days than anti-pseudomonal penicillins or anti-pseudomonal cephalosporins during their hospitalization. Such prolonged use of carbapenems might cause the emergence of MDR P. aeruginosa strains in our hospital, and therefore, further efforts to shorten the duration of empirical carbapenem use should be performed.

The present study had several limitations. First, P. aeruginosa comprise about 10% of the pathogens identified in FN patients; thus, the number of FN patients with P. aeruginosa bacteremia was small. The increase in the number of enrolled patients may reveal additional factors related to mortality and MDR strain infections. A multicenter study is necessary to overcome this limitation; however, each hospital may have their own strategies for
In conclusion, *P. aeruginosa* bacteremia in FN children and adolescents exhibited continued high mortality in the 2010s, and MDR strain infections occurred more frequently than before. Mortality in patients with *P. aeruginosa* bacteremia was associated with MDR strain infections and the appropriateness of empirical antibiotic therapy. Therefore, ongoing surveillance for MDR *P. aeruginosa* infections and efforts to reduce MDR strains are necessary. In addition, anti-pseudomonal β-lactam agent and aminoglycoside combination therapy may be useful for empirical antibiotic therapy in FN patients to improve the appropriateness of empirical antibiotics.

### Abbreviations

ESBL: Extended-spectrum β-lactamase; FN: Febrile neutropenia; IPA: Invasive pulmonary aspergillosis; MDR: Multidrug-resistance; SAA: Severe aplastic anemia

### Acknowledgements

Not applicable.

### Funding

There was no funding source for the present study.

### Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

### Authors’ contributions

SBH, BC and JHK designed the study. HSK, BKP and SKK collected the data. BKP, SKK, JWL, DGL, NGC and DCJ analyzed the data and interpreted the analyzed data. HSK, BKP, SBH and DGL wrote the first draft. DGL, BC and JHK critically reviewed and revised the manuscript. HSK, SKK, SBH and DGL wrote the final draft. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Seoul St. Mary’s Hospital with waiver for informed consent (Approval number: KC16RIS0925).

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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Received: 21 March 2017 Accepted: 6 July 2017

**Published online:** 17 July 2017

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