

Original Article



Clinical Efficacy and Safety of Arbekacin against Pneumonia in Febrile Neutropenia: A Retrospective Study in Patients with Hematologic Malignancies

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ABSTRACT

Background: Arbekacin (ABK) is an aminoglycoside that exhibits anti-methicillin-resistant *Staphylococcus aureus* (MRSA) and anti-*Pseudomonas aeruginosa* activities. Therefore, for patients with febrile neutropenia (FN) and concurrent pneumonia suspected to be caused by MRSA, ABK may be sufficiently effective even as a single agent.

Materials and Methods: Patients with hematologic malignancies treated with ABK who met the following criteria were included: 1) fever during neutropenia or functional neutropenia, 2) FN complicated by pneumonia, and 3) possible infection by antimicrobial-resistant Gram-positive cocci.

Results: This study encompassed 22 episodes involving 19 patients, of which, 15 (68.2%) were successfully treated with ABK. Of the nine episodes showing inadequate response to other anti-MRSA drugs, eight were successfully treated with ABK. Grade 2 or worse adverse events included acute kidney injury (13.6%) and increased transaminase levels (9.1%).

Conclusion: The present study demonstrated that ABK is effective and safe in patients with FN and concurrent pneumonia caused by antimicrobial-resistant Gram-positive cocci. ABK may also be effective in patients who are unresponsive to other anti-MRSA drugs. Therefore, ABK may be beneficial in the treatment of pneumonia caused by antimicrobial-resistant Gram-positive cocci in patients with FN.

Keywords: Febrile neutropenia; Pneumonia; Hematologic malignancy; Methicillin-resistant *Staphylococcus aureus*; Staphylococcal infection

INTRODUCTION

Febrile neutropenia (FN) is a problematic adverse event during chemotherapy with cytotoxic anticancer agents that may lead to life-threatening infections [1, 2]. In particular, patients with hematologic malignancies have a high risk of FN because neutropenia is exacerbated and prolonged by intensive cytotoxic chemotherapeutic agents.

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Conflict of Interest

No conflict of interest.

Author Contributions

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FN is typically caused by Gram-positive cocci, such as coagulase-negative staphylococci (CNS) and *Staphylococcus aureus*, and Gram-negative bacilli, such as *Pseudomonas aeruginosa* [2]. Specifically, untreated *P. aeruginosa* infections are associated with a high mortality rate of 40.0% [3, 4]. Thus, high-risk patients require hospitalization for intravenous empirical antibiotic therapy with broad-spectrum anti-pseudomonal β -lactam agents [2]. Furthermore, combination therapy with aminoglycosides may be considered when FN is complicated by septic shock and pneumonia. However, combination therapy with anti-methicillin-resistant *S. aureus* (MRSA) drugs may be considered for antimicrobial-resistant Gram-positive cocci infections [2].

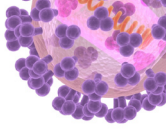
The frequency of FN caused by MRSA and methicillin-resistant CNS (MRCNS) has been increasing recently because of the generalized use of central venous catheters [2, 5]. For this reason, the early application of anti-MRSA agents, such as vancomycin (VAN), linezolid (LZD), or daptomycin (DAP), is more commonly considered, particularly if the patient's blood is positive for MRSA or MRCNS as per the Infectious Diseases Society of America (IDSA) guidelines [2]. However, these anti-MRSA drugs are not always appropriate for FN with pneumonia. For instance, the minimum inhibitory concentrations (MICs) of VAN and teicoplanin (TEC) against MRSA strains have gradually been increasing worldwide [6-8]. Several reports have shown that the high MIC (>2 $\mu\text{g/mL}$) of VAN is associated with treatment failure and increased mortality among patients with MRSA infections [9, 10]. CNS strains with reduced susceptibility to TEC have also been documented [11-13]. Furthermore, DAP is not indicated for the treatment of MRSA pneumonia because of its inactivation by surfactants present in the lungs. In contrast, LZD, which efficiently penetrates into the lungs, is the recommended first line of treatment for MRSA pneumonia [14, 15]. Meanwhile, because LZD is a bacteriostatic agent, it can be insufficient in neutropenic patients. A postmarketing survey revealed the significantly decreased efficacy of LZD in patients with hematologic malignancies [16]. Thus, the use of these conventional anti-MRSA drugs in the treatment of MRSA pneumonia in neutropenic patients is concerning. Nevertheless, arbekacin (ABK), an aminoglycoside with bactericidal activity against MRSA, may offer a solution.

ABK is a bactericidal antibiotic with high activity against Gram-negative bacilli as well as MRSA and MRCNS [17-20]. Currently, the drug is approved for treating MRSA infections in Japan, Korea, and India. Among the anti-MRSA agents, only ABK exhibits such a broad antibacterial spectrum. Thus, ABK can be expected to have sufficient antimicrobial activity even in neutropenic patients. In clinical practice, the combination of ABK with β -lactams or monobactams has shown a synergistic effect on multidrug-resistant *P. aeruginosa* and MRSA [21-23]. Additionally, Miura et al. [24] observed that the combination of ABK and broad-spectrum β -lactams was effective even in patients who had FN, along with hematologic malignancies. Therefore, we retrospectively evaluated the efficacy of ABK in patients with FN and concurrent pneumonia, with MRSA being the suspected causative agent.

MATERIALS AND METHODS

1. Patients

We conducted a retrospective chart review on patients with hematologic malignancies who were treated with ABK between April 2010 and March 2017 at the Gunma Prefectural Cancer Center. Patients who met the following criteria were included: 1) became febrile as a result of neutropenia or functional neutropenia, 2) FN complicated by pneumonia, and 3) possibility



of infection by antimicrobial-resistant Gram-positive cocci. The third criterion was applicable for patients meeting any of the following conditions: possibility of catheter-related infection; detection of Gram-positive cocci in culture (blood, sputum, bronchial lavage fluid, and catheter tip); or continued fever despite effective antimicrobial treatment against Gram-negative bacilli, including *P. aeruginosa*. Pneumonia was defined as fever (axillary temperature of $\geq 37^{\circ}\text{C}$) and positive C-reactive protein (CRP) in patients with new or worsening infiltrative shadows noted on chest X-rays or computed tomography images at least 48 hours after admission [25]. Neutropenia was defined according to the IDSA guidelines [2] as an absolute neutrophil count (ANC) of <500 cells/ mm^3 or an ANC that is expected to decrease to <500 cells/ mm^3 during the next 48 hours. In addition, the definition of functional neutropenia was “hematologic malignancy that results in qualitative defects (*i.e.*, impaired phagocytosis and killing of pathogens) in circulating neutrophils.” Fever was defined as an axillary temperature of $\geq 37.5^{\circ}\text{C}$ or an oral temperature of $\geq 38.0^{\circ}\text{C}$, as per the common definition in Japan [26].

2. Ethics statement

The study protocol was approved by the ethics committee of the Gunma Prefectural Cancer Center (no. 405-29017). The requirement for informed consent was waived owing to the retrospective nature of the study. However, the opportunity to refuse participation through an opt-out method was guaranteed.

3. Data collection

ABK was deemed to be effective in treating pneumonia by the attending physicians if fever reduced and CRP levels or abnormal chest imaging showed improvements [25]. Because the FN guideline states that “appropriate antibiotics should continue for at least the duration of neutropenia (until ANC is >500 cells/ mm^3) or longer if clinically necessary,” the efficacy was determined at the end of treatment [2]. If antimicrobial agents are considered effective, these can be continued. Patients who did not meet the abovementioned criteria or who relapsed immediately after treatment completion were considered to have shown inadequate response to antimicrobial agents. Changes in the laboratory data before and after ABK administration were assessed. The values at the closest time points before and after ABK administration were used. The Common Terminology Criteria of Adverse Events (version 5.0) was used to grade the severities of kidney and liver dysfunction as adverse events [27].

Blood sampling for therapeutic drug monitoring was performed only once: on days 3 - 5 after the initiation of ABK administration. C_{max} represents the maximum serum ABK concentration, and C_{peak} indicates the serum ABK concentration 30 - 60 minutes after administration. The serum ABK concentration was measured immediately before administration (trough) and 60 minutes after administration completion (C_{peak}) using a Nanopier[®] TDM ABK assay kit (Sekisui Medical Co., Ltd., Tokyo, Japan). The C_{max} of ABK was estimated using the Habekacin[®] TDM analysis software (Meiji Seika Pharma Co., Ltd., Tokyo, Japan). Values below the detection limit (0.5 $\mu\text{g}/\text{mL}$) were reported as 0.5 $\mu\text{g}/\text{mL}$. Sputum and blood cultures were performed before the administration of antimicrobial agents to identify the species. Bacterial species and MICs were determined using Pos Combo 3.1J panels (Beckman Coulter, Inc., Tokyo, Japan) in a Microscan[®] Walkaway 40 SI (Beckman Coulter, Inc., Japan).

4. Statistical analyses

The data were presented as median and range. The Wilcoxon signed-rank test was used to compare the pre- and post-ABK values. *P*-values <0.05 were considered statistically

significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28].

RESULTS

1. Patient demographics and characteristics

In this study, 30 episodes were treated with ABK. Of these, six did not involve pneumonia and one did not involve neutropenia; one episode of ABK discontinuation because of inappropriate use was reported by the antimicrobial stewardship team. All these eight episodes were excluded from the analysis. Finally, 22 episodes were included in the analysis. If the same patient underwent ABK treatment at various instances, each treatment period was considered as a different episode. Hence, this study reviewed 22 episodes involving 19 patients. **Table 1** shows the background information of the patients. Acute myeloid leukemia

Table 1. Patient characteristics

Characteristics	n
Number of cases	22
Sex, male/female	13/9
Age (years), median (range)	69 (21 - 78)
Disease diagnosis	
AML	11
Myelodysplastic syndrome	6
Acute lymphocytic leukemia	2
Myelofibrosis	2
Pancytopenia	1
Treatment	
AML (induction therapy)	9
AML (consolidation therapy)	1
Azacitidine	3
Gemtuzumab ozogamicin	2
Immunosuppressive drugs	2
Hydroxycarbamide	1
Best supportive care	4
Previous antimicrobial drugs	
Carbapenem	17
Cephem	16
Quinolone	14
Penicillin	13
Anti-MRSA drugs	11
Aminoglycosides	2
Others	6
Concomitant antimicrobial drugs	
Carbapenem	11
Quinolone	11
Cephem	9
Penicillin	5
Anti-MRSA drugs	2
Others	3
Neutropenia	
Neutropenia (<500/mm ³)	15
Functional neutropenia	7
Renal insufficiency before ABK therapy ^a	3
Usage of central venous catheter	
Yes	14
No	8

^aSerum creatinine levels of >1.1 mg/dL in men and >0.9 mg/dL in women were defined as renal insufficiency. AML, acute myeloid leukemia; MRSA, methicillin-resistant *Staphylococcus aureus*; ABK, arbekacin.

(n = 11) was the most common disease type in this cohort. Among the 22 episodes, 15 matched the definition for FN, whereas the remaining seven were classified as functional neutropenia. Central venous catheter was used in 14 episodes. Broad-spectrum antimicrobial agents with anti-*P. aeruginosa* activity, such as meropenem, were given before the administration of ABK in all of the episodes. The details of anti-MRSA drugs administered prior to ABK included five episodes of VAN, four episodes of LZD, and one episode each of TEC and DAP. However, since two different combinations of anti-MRSA drugs (VAN and LZD and DAP and LZD) were administered to two episodes, a total of nine episodes received anti-MRSA drugs before ABK administration. Antimicrobials administered before ABK were discontinued if they did not improve the symptoms of infection, such as improvement in fever, CRP levels, and abnormal chest imaging. The concomitant drugs in ABK were anti-pseudomonal agents in 19 (86.4%) and anti-fungals in 18 (81.8%) episodes.

2. Efficacy and safety of ABK

Of the 22 episodes that were analyzed, 15 (68.2%) were successfully treated with ABK. In particular, eight of the nine patients who showed inadequate response to other anti-MRSA drugs were successfully treated with ABK. The observed grade 2 or worse adverse events included acute kidney injury in three episodes (13.6%) and increased transaminase level in two episodes (9.1%) (Table 2). The two episodes in which ABK treatment was discontinued because of severe adverse events involved renal dysfunction and drug eruption. Although a patient with leukemia complained of dizziness, the treatment was continued because the symptom was found to be caused by central nervous system invasion of the leukemia cells.

3. Therapeutic drug monitoring

In this study, all episodes were treated with ABK once daily. Serum ABK concentration was measured in 19 (86.3%) of the original 22 episodes. C_{max} reached effective serum ABK concentrations (C_{max} : 9 - 20 $\mu\text{g/mL}$) in all the 19 episodes, whereas C_{min} decreased to <1 $\mu\text{g/mL}$ in 16 episodes (Table 3). Based on the blood ABK concentrations, the dosage was adjusted as follows: increased in six episodes (31.6%), decreased in two episodes (10.5%), and maintained in 11 episodes (57.9%). In some older patients or episodes where dose reduction-related adjustments were made, the ABK dose was less than the recommended

Table 2. Comparison of laboratory data and vital signs pre- and postadministration of arbekacin

	Pre (range)	Post (range)	P-value
Neutropenia (n = 15)			
WBC (/mm ³)	480 (110 - 29,260)	1,450 (670 - 7,960)	0.013
ANC (/mm ³)	100 (0 - 580)	345 (50 - 980)	0.035
Functional neutropenia (n = 7)			
WBC (/mm ³)	8,030 (2,440 - 37,200)	5,600 (1,520 - 49,190)	1.000
ANC (/mm ³)	2,260 (1,640 - 6,090)	3,630 (60 - 10,100)	0.938
Myeloblast (%)	69 (0 - 93)	1 (0 - 83)	0.498
All cases (n = 22)			
Hb (g/dL)	7.9 (6.2 - 9.5)	8.1 (7.0 - 11.0)	0.127
Plt ($\times 10^3/\text{mm}^3$)	19 (7 - 411)	21 (5 - 304)	0.709
Scr (mg/dL)	0.7 (0.3 - 1.6)	0.9 (0.4 - 4.0)	0.002
AST ^a (U/L)	15 (8 - 67)	24 (11 - 106)	0.018
ALT ^a (U/L)	21 (4 - 117)	21 (2 - 173)	0.244
CRP ^b (mg/dL)	11.0 (1.3 - 27.1)	2.2 (0.3 - 27.1)	0.027
Body temperature (°C)	38.1 (36.7 - 39.7)	37.2 (36.3 - 40.4)	0.006
Pulse counts (counts/min)	106 (82 - 134)	96 (71 - 142)	0.136

^aOne patient with increased AST and ALT levels.

^bCRP was measured in only 18 cases.

WBC, white blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; Plt, platelet; Scr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

Table 3. Administration method and serum ABK concentrations

Administration method (n = 22)	Median (range)
Dose (mg/day)	200 (125 - 300)
Dose (mg/kg/day)	3.4 (2.2 - 5.9)
Dosing period (days)	16 (6 - 51)
Serum ABK concentration (n = 19)	Median (range)
C _{trough} (mg/mL)	0.5 (0.5 - 2.3) ^a
C _{peak} (mg/mL)	9.1 (6.1 - 21.6)
Estimated C _{max} (mg/mL)	16.6 (9.6 - 39.0)

^aValues below the detection limit (0.5 µg/mL) were set as 0.5 µg/mL. ABK, arbekacin.

dose of 200 mg once daily. The serum ABK concentrations were not measured again after dose adjustment.

4. Bacterial examination

Sputum specimens were collected from the final 22 episodes in which treatment was continued. The most frequently isolated bacteria were MRCNS (68.2%, 15/22 isolates). MRSA was found in two specimens (Table 4). Gram-negative bacilli were detected in the remaining three specimens, two of which were *P. aeruginosa* strains and one was a multidrug-resistant *P. aeruginosa*. The MIC of ABK was <1 µg/mL in 95.0% of the MRSA and MRCNS strains (Table 5). On the other hand, the MIC of VAN was ≥2 µg/mL in 80.0% of the isolated staphylococci. All strains demonstrated high susceptibility to LZD. Blood cultures were also performed at 14 episodes. Two of the episodes were positive, one each for *P. aeruginosa* and *S. epidermidis*.

Table 4. Identified bacterial strains and their isolation sites

Bacterial strain	Isolation site			
	Sputum	Bronchoalveolar lavage fluid	Blood	Catheter
Gram-positive coccus, (%)				
<i>Staphylococcus epidermidis</i> (MRCNS)	36.4		7.1	100.0
<i>Staphylococcus haemolyticus</i> (MRCNS)	27.3	100.0		
<i>Staphylococcus hominis</i> (MRCNS)	4.5			
MRSA	9.1			
<i>Enterococcus faecalis</i>	4.5			
<i>Micrococcus</i> spp.	4.5			
Gram-negative bacillus, (%)				
<i>Pseudomonas aeruginosa</i>	4.5		7.1	
<i>Stenotrophomonas maltophilia</i>	4.5			
Episodes of tested	22 ^a	1	14	1

^aIn three episodes, different bacterial strains were identified from the same patient. MRCNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 5. Susceptibility of *Staphylococcus* strains to anti-MRSA drugs

Drug	MIC (µg/mL)	MRSA	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus haemolyticus</i>	<i>Staphylococcus hominis</i>	Total
Arbekacin	<1	2	9	7	1	19
	2		1			1
Vancomycin	1	2	1	1		4
	2		9	4	1	14
	4			2		2
Teicoplanin	<2	2	4	1	1	8
	4		4	2		6
	8		2	2		4
	>16			2		2
Linezolid	<2	2	10	7	1	20

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

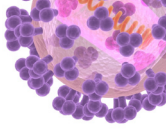
DISCUSSION

This retrospective study demonstrated 68.2% efficacy of ABK in treating pneumonia caused by antimicrobial-resistant Gram-positive cocci in patients with FN. Previous reports have shown that the efficacy of the drug in handling MRSA infection, including MRSA pneumonia, ranged from 65.0% to 95.0% [29-31]. Our results are consistent with these previous findings. Additionally, another study reported that the efficacy of ABK in managing patients with FN with hematologic malignancies was 82% and in patients of pneumonia in particular, the success rate was 57.0% [24]. In hematologic malignancies, the efficacy of vancomycin or teicoplanin combination therapy in patients with FN and pneumonia has been reported to range from 18.2% to 57.9% [32, 33]. Branimir et al. reported that the efficacy rates in LZD and VAN groups against pneumonia were 82.6% and 86.7%, respectively, in patients with FN with mainly hematologic malignancy [34]. However, the mean neutrophil count at treatment completion was 2,480/mm³ and 2,788/mm³, respectively, in that previous study, whereas the mean neutrophil count at treatment completion was <500/mm³ in the present study. In other words, in the study by Branimir et al., the number of patients whose neutrophil count had recovered to normal was higher. This might explain the high efficacy of LZD and VAN. These data indicate that the efficacy of ABK in patients with FN and hematologic malignancies is comparable to if not superior to those of VAN and TEC.

In terms of detailed treatment efficacy, ABK was effective in eight of nine patients treated with other anti-MRSA drugs prior to ABK. The drug susceptibility of bacteria detected in sputum showed that 95% of isolates had a low MIC for ABK (<1 µg/mL), whereas 80% of isolates had a high MIC for VAN (≥2 µg/mL). However, MRCNS was detected in most episodes (68.2%) in this study. Although high MIC of VAN has been reported to be associated with treatment failure in MRSA infections, the relationship between the MIC of VAN and MRCNS is unclear. Although LZD exhibited high susceptibility in all strains, it is a bacteriostatic agent and thus, may be insufficiently effective in neutropenic patients. For these reasons, we believe that ABK is effective in patients who do not respond to other anti-MRSA drugs. In addition, if the neutrophil count rises sufficiently, patients with FN will recover, even if the effect of antimicrobial agents is inadequate. The mean neutrophil count after ABK administration was <500/mm³, indicating that the reduction of infection was not due to an increase in neutrophil count but rather due to the efficacy of the drug.

Renal dysfunction and hepatic dysfunction are known major adverse events of ABK. In this study, grade 2 or higher acute renal failure (13.6%) and elevated transaminase levels (9.1%) were observed. The reported frequencies of renal dysfunction and hepatic dysfunction are 0.0 - 23.1% and 0.85 - 8.5%, respectively [35], which are comparable to the results of the present study.

ABK is a concentration-dependent drug, and the therapeutic window is C_{max} at 9 - 20 µg/mL [36]. Based on this definition, it could be stated that all patients in this study achieved the therapeutic C_{max} level. However, the Japanese therapeutic drug monitoring (TDM) guidelines recommend the use of C_{peak} (15 - 20 µg/mL) as the therapeutic index [37], only three episodes (13.6%) reached the therapeutic level. We speculate that the difference in blood sampling times for C_{peak} might have led to the huge discrepancy in the number of patients reaching the therapeutic levels when C_{max} or C_{peak} is used as the index. The Japanese TDM guidelines further recommend blood collection 30 minutes after administration completion; however, blood samples were taken 60 minutes after administration completion at our hospital. In



order to obtain an accurate C_{peak} , as defined by the Japanese TDM guidelines, our hospital needs to change the timing of blood sampling.

Dose escalation to reach the target C_{peak} raises the risk of renal dysfunction in patients with impaired renal function owing to the insufficient reduction of trough concentration. As per the TDM guidelines, prolonging the dosing interval to 48 hours in patients with impaired renal function is recommended for other aminoglycosides [37]. However, the efficacy of the 48-hour dosing interval has not been thoroughly investigated for ABK in neutropenic patients yet. Hence, further studies are necessary to clarify these issues.

CNS, commensal bacteria commonly found on the human skin, are the causative agents of typical opportunistic infections. CNS can cause various infections, such as catheter-related bloodstream infection (CRBSI), endocarditis, and postoperative and other wound infections. There is little evidence suggesting that CNS is a causative agent of pneumonia as the presence of CNS in sputum specimens is generally considered to reflect lung colonization or contamination. Interestingly, however, intratracheal administration of *S. haemolyticus* to immunocompromised mice has been shown to cause pneumonia [38]. This suggests that CNS is the causative agent of pneumonia in patients with neutropenia. In addition, the possibility that Gram-positive cocci or fungi are the causative organisms should be considered as there is no clinical improvement despite the adequate coverage of Gram-negative bacillus. CNS are the most common causative agents of CRBSI via central venous catheter [39]. Patients with hematologic malignancies are at a higher risk for CRBSI because central venous catheters are usually inserted during chemotherapy. Cook et al. [40] reported that six of seven device-related pulmonary emboli were caused by staphylococcal infections, three of which involved CNS. Since central venous catheters were used in 14 episodes (63.6%) in this study, isolated MRCNS could have possibly caused the concurrent pneumonia.

The main limitations of this study are its retrospective design, small number of episodes, and possibility of being influenced by other antimicrobial agents. Because ABK is not recommended by the guidelines for the management of FN [2, 26] and is not a first-line drug, it is only used when other anti-MRSA drugs respond inadequately. Therefore, the number of episodes was limited and prior administration of other antimicrobials could not be excluded in this study. Sometimes, pneumonia treatment in patients with FN with suspected GPC infection using VAN or LZD fails, although these agents are recommended in the guidelines. If other anti-MRSA drugs are not available for the patient, the patient is likely to have a fatal outcome. However, ABK treatment was successful in eight of nine patients with inadequate response to other anti-MRSA drugs. Therefore, although the number of episodes was small and whether ABK was really effective remained obscure, we believe that the study findings are worth reporting. Further studies are warranted to cover an extensive number of episodes and obtain more data to improve the accuracy of the analysis. Furthermore, prospective studies comparing ABK with other anti-MRSA agents such as VAN are necessary to validate the efficacy of the drug in neutropenic patients.

Our findings establish that ABK is an effective and safe treatment option for pneumonia caused by antimicrobial-resistant Gram-positive cocci in neutropenic patients with hematologic malignancies. This drug may also be considered for managing mixed infections by MRSA and *P. aeruginosa* and for the treatment of patients with FN who are at a high risk of infection with drug-resistant Gram-positive cocci. Because the empirical administration of anti-MRSA drugs is not recommended for patients with FN [2], the patients should be carefully selected for treatment

with ABK. Finally, although ABK is not covered in the IDSA guidelines because of its poor availability, our study findings indicate the potential value of this drug, which should be further evaluated by focusing on its unique pharmacologic properties.

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