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Clinical Usefulness of Arbekacin

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Arbekacin is a broad-spectrum aminoglycoside used to treat methicillin-resistant *Staphylococcus aureus* (MRSA). Arbekacin has antibacterial activities against high-level gentamicin-resistant *Enterococci*, multidrug-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* et al. Here, we reviewed *in vitro* data on arbekacin in *Staphylococci* and Gram-negative microorganisms. We also reviewed clinical studies for clinical efficacy and microbiologic efficacy data in patients with identified MRSA and suspected MRSA infections. The overall clinical efficacy ranged from 66.7% to 89.7%. The microbiologic efficacy rate ranged from 46.2% to 83%. In comparative studies between arbekacin and glycopeptides, arbekacin was similar to other glycopeptides with respect to clinical and microbiological efficacy rates. Combination trials with other antibiotics suggest that arbekacin will be a promising strategy to control *Enterococcus* spp. multi-drug resistant *P. aeruginosa*. The major adverse reaction was nephrotoxicity/hepatotoxicity, but patients recovered from most adverse reactions without any severe complications. Based on these results, arbekacin could be a good alternative to vancomycin/teicoplanin in MRSA treatment. Finally, therapeutic drug monitoring is recommended to maximize clinical efficacy and decrease nephrotoxicity.

Key Words: Arbekacin; Methicillin-resistant *Staphylococcus aureus*; Glycopeptides; Alternative; Antibiotics

Introduction

Arbekacin sulfate was discovered in 1972 and is a derivative of dibekacin. It is classified as a kanamycin family aminoglycoside [1]. It has been used in Japan since 1990 to treat sepsis and pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA). It has been available in Korea since 2000 [1]. Arbekacin is not inactivated by aminoglycoside-inactivating enzymes and shows concentration-dependent and long lasting post-antibiotics effects [2-5]. Arbekacin has broad antimicrobial activities not only against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, but also against Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [6-8].

Unlike in Japan, for the last 15 years, Korean physician have been unfamiliar with the use of arbekacin as an anti-MRSA agent. We think the main causes of this unfamiliarity among Korean physicians are as follows; first, there are several excellent anti-MRSA agents available, including vancomycin, teicoplanin, linezolid and tigecycline. Second is the fear of nephro-

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toxicity. Third is a mistrust of anti-MRSA agents such as arbekacin. However, the vancomycin minimal inhibitory concentration (MIC) against MRSA is increasing. The vancomycin resistant enterococci incidence is still increasing and is already a problem for public health. For these reasons, alternative anti-MRSA agents are urgently needed in Korea.

To date, clinical efficacy/safety studies related with arbekacin have been reported in Japan, but clinical studies have been limited in Korea due to the lack of usage [9-15]. These studies showed that arbekacin has similar efficacy to glycopeptides and could be a good alternative anti-MRSA agents.

In vitro studies of arbekacin

1. Antibacterial activity against MRSA and methicillin-resistant coagulase-negative staphylococci (MRCNS)

Arbekacin showed *in vitro* activity against *S. aureus* and coagulase-negative Staphylococcus [16, 17]. The results of antibacterial activity assays from several studies using anti-MRSA drugs against MRSA and MRCNS clinical isolates are shown in Table 1. In several studies performed in Korea, the MIC_{90} of arbekacin against MRSA clinical isolates was less than 4 μg/mL [16-18], and that against MRCNS was less than 2 μg/mL [16, 17]. Wie et al. evaluated the *in vitro* activities of aminoglycosides (arbekacin, gentamicin, and amikacin) against 278

Table 1. *In vitro* antibacterial activity against aerobic bacteria reported in several studies performed in Korea

Ref	Organism	MIC (μg/mL)	Antibacterial agent						
			Arbekacin	Gentamicin	Amikacin	Ciprofloxacin	Vancomycin	Teicoplanin	Quinupristin/ Dalfopristin
[16]	MSSA (n = 271)	MIC_{50}	0.25	0.25	2	ND	1	ND	ND
		MIC_{90}	0.5	32	4	ND	1	ND	ND
		Range	0.06 to 2	0.125 to 256	0.5 to 32	ND	0.5 to 2	ND	ND
[16]	MSCNS (n = 129)	MIC_{50}	0.25	2	2	ND	1	ND	ND
		MIC_{90}	0.5	32	8	ND	2	ND	ND
		Range	0.015 to 2	0.125 to256	0.125 to 16	ND	0.25 to 2	ND	ND
[18]	MRSA (n = 328)	MIC_{50}	1	ND	ND	ND	1	4	1
		MIC_{90}	1	ND	ND	ND	2	8	1
		Range	0.06 to 2	ND	ND	ND	0.5 to 2	0.06 to 16	0.25 to 1
[16]	MRCNS (n = 122)	MIC_{50}	0.5	32	8	ND	1	ND	ND
		MIC_{90}	2	256	128	ND	2	ND	ND
		Range	0.03 to 32	0.125 to 256	0.125 to 256	ND	0.25 to 2	ND	ND
[17]	*Escherichia coli* (n = 30)	MIC_{50}	1	0.5	2	<0.03	ND	ND	ND
		MIC_{90}	1	16	4	32	ND	ND	ND
		Range	0.25 to 16	<0.12 to 64	0.5 to 32	<0.03 to 64	ND	ND	ND
[17]	*Klebsiella pneumoniae* (n = 30)	MIC_{50}	2	1	4	0.06	ND	ND	ND
		MIC_{90}	>128	>128	128	32	ND	ND	ND
		Range	0.5 to >128	0.5 to >128	1 to 128	<0.03 to 128	ND	ND	ND
[17]	*Citrobacter freundii* (n = 15)	MIC_{50}	1	1	2	0.12	ND	ND	ND
		MIC_{90}	16	128	32	4	ND	ND	ND
		Range	0.5 to >128	0.5 to >128	1 to >128	<0.03 to 8	ND	ND	ND
[17]	*Acinetobacter baumannii* (n = 15)	MIC_{50}	1	2	8	0.25	ND	ND	ND
		MIC_{90}	>128	>128	>128	128	ND	ND	ND
		Range	0.5 to >128	0.5 to >128	0.5 to >128	0.06 to >128	ND	ND	ND
[17]	*Pseudomonas aeruginosa* (n = 29)	MIC_{50}	2	2	8	0.25	ND	ND	ND
		MIC_{90}	64	>128	>128	32	ND	ND	ND
		Range	0.5 to 64	0.5 to >128	1 to >128	0.06 to >128	ND	ND	ND

ND, not done; MSSA, methicillin-susceptible *Staphylococcus aureus*; MSCNS, methicillin-susceptible coagulase negative *Staphylococcus* species; MRSA, methicillin-resistant *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase-negative *Staphylococcus* species; MIC_{50}, minimal inhibitory concentration for 50% of the organisms; MIC_{90}, minimal inhibitory concentration for 90% of the organisms.

MRSA clinical isolates and 122 MRCNS clinical isolates [9]. In that study, the MIC_{90} of arbekacin against MRSA was 1 μg/mL, while the MIC_{90} values of amikacin and gentamicin were 32 μg/mL and 128 μg/mL, respectively. The MIC_{90} of arbekacin against MRCNS was 2 μg/mL, and it was more potent than that of amikacin (MIC_{90} 128 μg/mL) and gentamicin (MIC_{90} 256 μg/mL) [16]. The *in vitro* activity of arbekacin against MRSA was similar to that of vancomycin [9-11] and was more potent than that of teicoplanin [18, 19].

In addition, the combination of arbekacin and vancomycin showed *in vitro* synergistic effects against gentamicin-resistant MRSA isolates [20]. You et al. studied the *in vitro* synergistic activity of the combination of vancomycin and arbekacin against 13 gentamicin-resistant MRSA isolates. The MICs of arbekacin against these 13 isolates ranged from 0.5 to 2.0 μg/mL, and the MICs of vancomycin ranged from 0.5 to 2.0 μg/mL. The combination of vancomycin and arbekacin produced *in vitro* synergistic activity against 12 of 13 MRSA strains [20].

2. Antibacterial activities against hetero-VISA

Matsumoto et al. reported that arbekacin was effective in a patient with MRSA that had low sensitivity to vancomycin (MIC 2 μg/mL for both arbekacin and vancomycin) [1]. They suggested that arbekacin might be useful against bacterial strains with low sensitivity to vancomycin. Arbekacin-based combinations showed synergistic effects against vancomycin-intermediate resistant *S. aureus* (VISA) [21, 22]. Lee et al. evaluated the *in vitro* synergic effect of arbekacin-based combinations against 7 hetero-VISA strains using time-kill assays. Vancomycin, rifampin, ampicillin-sulbactam, teicoplanin, and quinupristin-dalfopristin were tested in combination with arbekacin at the MIC of each antibiotic. In their study, the combination of arbekacin and vancomycin showed synergistic activity against 7 of 7 hetero-VISA isolates, the combinations of arbekacin and teicoplanin and ampicillin-sulbactam were synergistic against 4 of 7 hetero-VISA isolates, and the combination of arbekacin and rifampin was synergistic against 3 of 7 hetero-VISA isolates. However, the combination of arbekacin and quinupristin-dalfopristin was not synergistic in any of the tested hetero-VISA strains [21]. Moreover, the combination of arbekacin and vancomycin at half the MIC concentration of each antibiotic showed synergistic activity against 4 of 7 hetero-VISA isolates. In another study, the combination of arbekacin with daptomycin showed *in vitro* synergistic activity against glycopeptide intermediate-resistant *S. aureus* [22]. This combination has an additional benefit of reduced nephrotoxicity since daptomycin has been shown to provide a protective effect on renal proximal tubular cells exposed to an aminoglycoside [23].

3. Antibacterial activities against high-level gentamicin-resistant *Enterococci*.

The combination of ampicillin and arbekacin showed *in vitro* and *in vivo* synergistic activities against high-level gentamicin-resistant enterococci [24, 25]. Kak et al. reported *in vitro* synergistic activity for the combination of ampicillin and arbekacin against vancomycin and high-level gentamicin-resistant *Enterococcus faecium* [24]. They tested the *in vitro* synergistic activity against 13 clinical isolates. All 13 *E. faecium* isolates were resistant to ampicillin (MIC ranged from 32 μg/mL to 256 μg/mL), and the MIC of arbekacin ranged from 4 to 32 μg/mL. The combination of ampicillin and arbekacin produced *in vitro* synergistic elimination of 8 of 13 strains. In another study, Kak et al. studied the efficacy of the combination of ampicillin and arbekacin in an experimental rabbit model of aortic-valve endocarditis caused by ampicillin-susceptible and high-level gentamicin-resistant *Enterococcus faecalis* [25]. They compared the efficacy of a combination of ampicillin and arbekacin with the efficacy of ampicillin alone and of ampicillin and gentamicin together. In this study, the animals received the antibiotic (s) for 5 days and were sacrificed 12 hours after the final dose of antibiotic. The efficacy of the treatments was compared using the mean bacterial count (log_{10} CFU per gram of vegetation). The combination of ampicillin and arbekacin more significantly reduced the mean bacterial vegetation count than ampicillin alone or ampicillin plus gentamicin (the mean log_{10} CFU of bacteria per gram of vegetation for ampicillin plus arbekacin, ampicillin plus gentamicin, and ampicillin alone were 4.82, 5.98, and 6.29, respectively).

4. Antibacterial activities against *P. aeruginosa*

Although the number of cases was small, in one study, arbekacin showed an efficacy rate of 100% against *P. aeruginosa* [26]. The MIC_{90} of arbekacin against *P. aeruginosa* has been shown to be 1~4-fold lower than those of other aminoglycosides (amikacin and gentamicin) and meropenem [16, 19, 27, 28]. The arbekacin-based combinations showed synergic effects against multidrug-resistant *P. aeruginosa* (MDRP) [7, 29, 30]. Araoka et al. evaluated the *in vitro* synergic activity of the combination of aztreonam and aminoglycosides (arbekacin,

amikacin, or gentamicin) against 47 MDRP strains using the break-point checkerboard plate method [20]. They found that the combined effect of aztreonam plus arbekacin against MDRP was higher than that of aztreonam plus other aminoglycosides (gentamicin and amikacin). Moreover, arbekacin decreased the MIC of aztreonam in a dose-dependent manner. In particular, the combined effect of aztreonam plus arbekacin was more effective against metallo-β-lactamase (MBL)-producing *P. aeruginosa* than against MBL non-producers [7, 30]. In another study, Nakamura et al. evaluated the *in vitro* synergic activity of the combination of meropenem and arbekacin against 50 *P. aeruginosa* isolates [21]. In that study, only two *P. aeruginosa* isolates were resistant to meropenem (MIC ranged from 0.05 to 12.5 μg/mL). The combination of meropenem and arbekacin was effective against 49 of 50 *P. aeruginosa* strains, including meropenem-resistant strains. The MIC_{90} of meropenem was reduced from 3.13 μg/mL to 0.78 μg/mL when used in combination with arbekacin.

5. Antibacterial activities against other Gram-negative bacilli

The results of antibacterial activity assays of antibiotics against clinical isolates of Gram-negative bacilli from several studies are shown in Table 1. The MIC_{90} of arbekacin against *Escherichia coli* (*E. coli*) and *Citrobacter freundii*, 1 μg/mL and 16 μg/mL, were 2-4 fold and 8-16 fold lower than those of amikacin and gentamicin, respectively. However, the MIC_{90} values of arbekacin against other species of Gram-negative bacilli, 64->128 μg/mL, were similar to those of other aminoglycosides [16]. Recently, Sader et al. reported the *in vitro* activity of arbekacin against *Acinetobacter baumannii* clinical isolates [22]. Their study showed that 65% of tested isolates were susceptible to arbekacin (MIC ≤ 4 μg/mL), and arbekacin was the most potent aminoglycoside tested (gentamicin, tobramycin, and amikacin) against *A. baumannii*. Moreover, 58.0% of imipenem-resistant *A. baumannii* isolates (MIC_{50}, 8 μg/mL, and MIC_{90}, 32 μg/mL) were inhibited at ≤ 8 μg/mL [27]. Zapor et al. evaluated the *in vitro* activity of arbekacin against 200 *A. baumannii-calcoacetics* clinical isolates [8] and found that the MICs of arbekacin ranged from 0.5 μg/mL to > 64 μg/mL (the median MIC was 2 μg/mL), and a total of 86.5% of isolates were susceptible to arbekacin (MICs of < 4 μg/mL). Moreover, they evaluated the *in vitro* combination effects of arbekacin and other antibiotics against *A. baumannii-calcoacetics* using the broth microdilution checkerboard method. The combination with arbekacin and carbapenems (meropenem and imipenem) showed *in vitro* synergistic effects [8].

Clinical usage of arbekacin

1. Arbekacin single therapy

There have been some data reported relating to arbekacin single therapy for the treatment of MRSA confirmed or suspected infection (Table 2). Arbekacin has concentration-dependent antibacterial activity, and the peak serum concentration and trough concentration of arbekacin have been investigated as indicators of efficacy and adverse reactions, respectively.

There are prospective data evaluating the relationship between serum concentration and the clinical efficacy/safety of arbekacin [26]. Patients with pneumonia or sepsis who were identified or suspected to be infected with MRSA were included in the study. The clinical efficacy rate was 77.8% at <5 mg/kg, 87.5% at ≥5 to <6, 100% at ≥6, and the overall efficacy rate was 89.7% (26/29). This study showed that higher C_{peak} values at the final therapeutic drug monitoring (TDM) and higher doses produced greater clinical efficacy. With respect to the bacteriologic effect, the eradication or decreased rate of MRSA was 69.2%. The eradication or decreased rate for *P. aeruginosa* was 100%. Overall, they recommended that the dosage regimen of arbekacin be set at 5-6 mg/kg or higher and adjusted to achieve C_{peak} at 10-15 ug/mL or higher to achieve greater clinical efficacy.

In another study, the efficacy and safety of once-daily high dose arbekacin sulfate therapy for MRSA were assessed [12]. A total 13 patients (10 pneumonia, 3 sepsis) who were suspected to be MRSA infected were enrolled. The total clinical efficacy rate was 66.7% (66.7% sepsis/66.7% pneumonia). The bacterial eradication-reduction rate was 62.5% (50% sepsis/66.7% pneumonia).

A multi-center clinical study of arbekacin 200 mg q.d. in patients with MRSA infection was performed to evaluate the therapeutic effect of arbekacin [11]. A total of 14 MRSA pneumonia cases were included in the efficacy evaluation, and 19 patients were studied in the safety evaluation. The clinical efficacy rate was 71.4%, and the bacteriological efficacy was 46.2%, which was slightly lower than that reported by others [9, 12, 26].

There is also one interesting older study on the clinical effects of arbekacin on MRSA infections after gastrointestinal surgery [9]. MRSA-infected patients with pneumonia, entero-

colitis, urinary tract infection, intra-abdominal infection, other wound infection, or biliary tract infection were included in the study to evaluate the clinical and microbiologic efficacy of arbekacin. Among the 85 patients evaluated, the clinical efficacy was 85% (pneumonia 84%, intra-abdominal infection 79%, enterocolitis 82%, urinary tract infection (UTI) 100%, wound infection 100%, and hepatobiliary infection 100%), and the microbiological efficacy rate was 83%.

There has been only one study of efficacy and safety of arbekacin for MRSA in the neonatal intensive care unit [10]. Infants treated with arbekacin for MRSA or central nervous system infection were enrolled. In that study, the efficacy rate was as high as 79.3%. Based on this study, arbekacin may also be used in infants along with TDM.

In Korea, Hwang et al. performed drug use evaluation studies on arbekacin [31] and found that, in patients with MRSA, the total clinical efficacy was 67.4%. Miura et al. reported on the clinical efficacy and safety of arbekacin in patients with hematological malignancies [32]. In their study, 38 patients with various hematological malignancies were treated by arbekacin. A total of 54 infectious or febrile cases were evaluated. Among them, one case had MRSA pneumonia, and nine patients had bacteremia. The efficacy rates of arbekacin against febrile neutropenia, pneumonia, cellulitis, and neutro-

Table 2. Clinical efficacy and safety of arbekacin sulfate in patients with MRSA

Ref	Year	Sex	Clinical status	Organisms detected	Clinical efficacy rate	Microbiologic efficacy rate	Adverse reactions
[9]	1994	NA	Pneumonia (n = 37) Enterocolitis (n = 22) UTI (n = 1) Intra-abdominal infection (n = 14) Wound infection (n = 6) Biliary tract infection (n = 5)	MRSA (n = 85)	Total 85% Pneumonia 84% Intra-abdominal infection 79% UTI 100% Enterocolitis 82% Wound infection 100% Hepatobiliary infection 100%	Total 83% Pneumonia 87% Intra-abdominal infection 79%	NA
[10]	2003	29 infants	Sepsis (n = 4) Pneumonia (n = 17) NEC (n = 3) Others[a] (n = 4)	MRSA (n = 27) MRCNS (n = 2) Others[b]	Total[c] 79.3% Sepsis 75.0% Pneumonia 82.4% Others 75.0%	None	NA
[11][d]	2008	M/F; 15/4	Pneumonia (n = 14)	MRSA (N = 14)	Total 71.4%	Total 46.2%	Subjective symptoms 15.8% Abnormal laboratory finding 36.8%
[31]	2012	M/F; 64/39	SST (n = 66) OM (n = 14) Sepsis (n = 8) Pneumonia (n = 5) Others (n = 10)	MRSA (n = 78) MRSE (n = 13) MRSC (n = 4)	Total 67.4%	None	NA
[12]	2012	M/F; 10/3	Sepsis (n = 3) Pneumonia (n = 10)	MRSA	Total 66.7% Sepsis 66.7% Pneumonia 66.7%	Total 62.5% Sepsis 50.0% Pneumonia 66.7%	Total 38.5%
[26]	2013	M/F; 16/13	Sepsis (n = 8) Pneumonia (n = 21)	MRSA (n = 22) MRSA/PAE (n = 4) MRSA/ABA (n = 2) MRSA/PAE/ABA (n = 1)	Total 89.7% <5 mg/kg; 77.8% ≥5 to <6; 87.5% ≥6; 100%	MRSA 69.2% *P. aeruginosa* 100%	<5 mg/kg; 33.3% ≥5 to <6; 12.5% ≥6; 8.3%

MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; UTI, urinary tract infection; MRCNS, methicillin-resistant coagulase-negative *Staphylococcus* species; SST, skin and soft tissue infection; OM, osteomyelitis; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MRSC, methicillin-resistant *Staphylococcus capitis*; PAE, *Pseudomonas aeruginosa*; ABA, *Acinetobacter baumannii*.

[a]Ventriculitis (n = 1), cellulitis (n = 1), submandibular glanditis (n = 1), funisitis (n = 1), staphylococcal exanthematous disease (n = 1).

[b]3 coagulase-negative staphylococcus, 2 *Enterococcus faecalis*, 3 *P. aeruginosa*, 1 Klebsiella, Enterobacter, Serratia, Acinetobacter.

[c]6 cases of ABK only, 23 combinations (ampicillin/sulbactam 100% vs. other combination 64.3%, $P < 0.05$).

[d]Clinical/bacteriologic analysis (n = 14), adverse reactions (n = 19).

penic colitis were 82%, 57%, 100%, and 100%, respectively. The bacterial efficacy in the nine patients with bacteremia was 88.9% (8/9).

We evaluated the data from 7 clinical studies on the clinical and microbiologic efficacies in patients with identified and suspected MRSA infection. The overall clinical efficacy ranged from 66.7% to 89.7%. The microbiologic efficacy rate ranged from 46.2% to 83%.

2. Comparative study of arbekacin with glycopeptides in patients with MRSA

To date, there have been 5 comparative studies of arbekacin activity against MRSA with glycopeptides (Table 3). One study compared arbekacin with vancomycin and teicoplanin. Three other studies used vancomycin, and the fifth study used teicoplanin only [13-15, 33, 34].

Shimizu et al. collected clinical cases in which arbekacin, vancomycin, or teicoplanin were used at 50 medical facilities in Japan [33]. The total number of cases collected was 596 (arbekacin 479, vancomycin 93, teicoplanin 24). The results obtained from the arbekacin group vs. the vancomycin group vs. the teicoplanin group were as follows: the clinical efficacy rates were 74.7%/64.3%/30.8%, the bacteriological efficacy rates were 43.8%/35.1%/45.5%, adverse reactions were found in 5.3%/5.8%/13.0% of cases, and abnormal clinical laboratory values were found in 8.7%/8.0%/18.2% of cases, respectively. Arbekacin showed better clinical and bacteriological efficacy rates than the other 2 glycopeptides. The adverse reaction percentages were also lower than with the other 2 glycopeptides.

Hwang et al. reported on the usefulness of arbekacin in MRSA-infected patients who received arbekacin or vancomycin [13]. In their study, a total of 146 patients (sepsis/wound infections/pneumonia etc.) were enrolled to compare the clinical and bacteriological efficacy response rates. The clinical efficacy rate was not different between the two groups: arbekacin vs. vancomycin 65.3% vs 76.1%. The bacteriological efficacy rate was also not different between the two groups: arbekacin vs. vancomycin 71.2% vs. 79.5%. They concluded that arbekacin was not inferior to vancomycin and could be a good alternative to vancomycin in MRSA treatment.

The efficacy and safety of arbekacin were evaluated in comparison with vancomycin for the treatment of skin and soft tissue MRSA infections [14]. A total of 122 patients (63 arbekacin group vs. 59 vancomycin group) who received arbekacin/vancomycin for longer than 4 days were included in the study. Although the bacteriological efficacy rate (BER) with vancomycin was 10.1% higher than in the arbekacin group, there was

Table 3. Comparative study of arbekacin with glycopeptide in patients with MRSA infection

Ref	Year	Sex (ABK vs GLY)	CA	Clinical status	Clinical efficacy rate	Microbiological efficacy rate	Adverse reactions (ABK vs. GLY)
[33]	2003	ABK 479, VAN 93, TEI 24	VAN, TEI	Sepsis (n = 33) Pneumonia (n = 196) Others (n = 86)	ABK/VAN/TEI, 74.7%/64.3%/30.8%	ABK/VAN/TEI, 43.8%/35.1%/45.5%	ABK/VAN/TEI, 5.3%/5.8%/13.0%
[13]	2011	M/F; 43/30 vs. 43/30	VAN	Sepsis (n = 5) WC related (n = 45) Others[b]	ABK/VAN, 65.3%/76.1% (P = 0.157)	ABK/VAN, 71.2%/79.5% (P = 0.249)	15.1% vs 32.9% (P = 0.019)
[14]	2013	M/F; 42/21 vs. 36/23	VAN	SSTI	ABK/VAN; 67.2%/78.0% (P = 0.265)	ABK/VAN, 73.0%/83.1% (P = 0.264)	15.9% vs 49.2% (P = 0.001)
[34]	2015	M/F; 9/11 vs. 15/21	VAN	CSOM[c]	ABK/VAN, 90.0%/97.2% (P = 0.288)	ABK/VAN, 85.0%/97.2% (P = 0.125)	5.0% vs 33.3% (P = 0.020)
[15][a]	2016	M/F; 43/28 vs. 49/22	TEI	SST (n = 43) Pneumonia (n = 10) Otitis media (n = 8) Sepsis (n = 7) Others (n = 3)	ABK/TEI, 59.4%/69.1% (P = 0.257)	ABK/TEI, 72.9%/70.3% (P = 0.835)	18.3% vs 36.6% (P = 0.003)

[a]Skin and soft tissue infection (ABK vs. TEI; 60.6% vs. 63.5%), pneumonia (ABK vs. TEI; 14.1% vs. 16.9%), otitis media (ABK vs. TEI; 11.3% vs. 0%), sepsis (ABK vs. TEI; 9.8% vs. 14.1%), others (ABK vs. TEI; 4.2% vs. 5.6%).

MRSA, methicillin-resistant *Staphylococcus aureus*; ABK, arbekacin; GLY, glycopeptide; CA, comparative antibiotics; VAN, vancomycin; TEI, teicoplanin; WC, wound-and catheter-related infection; SSTI, skin and soft tissue infection; CSOM, chronic suppurative otitis media.

[b]Otitis media; n = 13, meningitis; n = 6, pneumonia; n = 29, peritonitis; n = 6, urinary tract infection, cellulitis, neutropenic fever; 1.

[c]Chronic suppurative otitis media (CSOM) without cholesteatoma (arbekacin vs. vancomycin 70.0% vs. 75.0%), CSOM with cholesteatoma (arbekacin vs. vancomycin 30.0% vs. 25.0%).

no statistical difference between the two groups (arbekacin vs. vancomycin 73.0% vs. 83.1%). However, adverse reactions were more frequently reported in the vancomycin group.

In another interesting study, arbekacin was used to treat chronic suppurative otitis media (CSOM) caused by MRSA [34]. In that study, 95 patients were diagnosed with MRSA-infected CSOM. Among these patients, 20 were treated with arbekacin and 36 received treatment with vancomycin. The clinical status was divided based on patients with cholesteatoma or without cholesteatoma. However, no statistically significant different was found between the two groups. Complications were more common in the vancomycin group than in the arbekacin group (vancomycin vs. arbekacin, 33.3% vs. 5.0%, P=0.020). The BERs of arbekacin and vancomycin were 85.0% and 97.2%, respectively. The BER of the vancomycin group was 12.2% higher than that of the arbekacin group, but this was not statistically significant (P = 0.125). The clinical efficacy rate (CER) of the arbekacin group was lower than that of the vancomycin group (vancomycin vs. arbekacin, 90.0% vs. 97.2%, P = 0.020), but this difference between the two groups was not significant. For these reasons, it was suggested that arbekacin could be a promising antibiotic for the treatment of CSOM caused by MRSA.

Recently, arbekacin was compared with teicoplanin for the treatment of MRSA infection [15]. A total of 235 patients received arbekacin (n = 108) or teicoplanin (n = 127). These patients were matched by age and sex and assigned to either the arbekacin (n = 71) or teicoplanin group (n = 71). Skin and soft tissue infections accounted for the majority of infections in the enrolled patients, and other similar clinical infectious diseases were included between the two groups (P = 0.262). The CER of the arbekacin group was lower than that of the teicoplanin group (arbekacin vs. teicoplanin, 59.4% vs. 69.1%), but this was not a statistically significant difference (P = 0.286). The BERs of the arbekacin and teicoplanin groups (arbekacin vs. vancomycin 72.9% vs. 70.3%) were not significantly different (P = 0.848).

In these comparative studies, arbekacin was not inferior to other glycopeptides in clinical efficacy or microbiological efficacy rate.

3. Clinical efficacy of arbekacin for combined infection with Gram-negative bacteria (GNB) and MRSA

In one interesting report, the efficacy of arbekacin against Gram-negative bacteria was investigated in patients from whom GNB were isolated during treatment for MRSA infection [6]. In their study, GNB inhibited by low MIC of amikacin or gentamicin were eradicated by the end of treatment with only arbekacin. These results suggest that arbekacin may be useful for controlling GNB during arbekacin treatment for an MRSA infection.

4. Combination therapy

The combined effect of aminoglycoside and monobactams against MDRP was studied using the break-point checkerboard plate assay [35]. A 63-year-old man with acute myelogenous leukemia experienced eye discharge and fever after cord blood transplant. His neutrophil count was 0/mm^3, and MDR *P. aeruginosa* was cultured in blood and eye discharge. He was treated with a combination of aztreonam and arbekacin and subsequently recovered from MDR *P. aeruginosa* bacteremia.

An additional case of pneumonia caused by a *Pseudomonas putida* producing metallo-beta-lactamase (MBL) was successfully treated with arbekacin with levofloxacin [36]. In Korea and Japan, most imipenem-resistant *P. aeruginosa* strains produce MBLs [37]. In Korea, 67% of imipenem-resistant bacteria isolated in 2005 expressed MBLs [37]. As in this case, combination therapy with arbekacin may effectively treat infections with MBL-producing *Pseudomonas* spp.

5. Inhalation therapy for pneumonia with MRSA/*P. aeruginosa*

Inhalational therapy for pneumonia is very limited so far. There has been only one arbekacin inhalational trial for pneumonia [38]. In their study, the investigators studied arbekacin inhalation for the treatment of pneumonia caused by *P. aeruginosa* and/or MRSA. A total of 6 patients were included in this study; two patients had multidrug-resistant *P. aeruginosa*, one had *P. aeruginosa* /MRSA, and the other 3 had *P. aeruginosa*. Arbekacin showed good clinical efficacy in all six patients. Based on these results, the investigators suggested the adoption of arbekacin inhalation therapy for pneumonia, especially in cases caused by multidrug-resistant Gram-negative organisms in situations where systemic therapy alone might result in failure or be inadequate or where intravenous access is not available because of systemic toxicity. In their study, they showed the possibility of the new therapeutic option of inhalation therapy for pneumonia caused by *P. aeruginosa* or MRSA.

Ochiai et al. reported on the clinical effect of arbekacin on

MRSA infections after gastrointestinal surgery [9]. In that study, arbekacin was administered by inhalation therapy or combined with intravenous treatment for respiratory tract infection after gastrointestinal tract surgery. The clinical effect of inhalation therapy or combined administration was seen in 3/5(60%) cases and 4/4 (100%) cases, respectively. The bacteriologic effect of inhalation therapy only and combined administration was seen in 3/4 (75%) cases and 6/6 (100%) cases, respectively.

Adverse reaction to arbekacin

To date, there have been no persistent, severe, or life threatening cases of arbekacin-related adverse reactions. The reported major adverse reactions to arbekacin were nephrotoxicity and hepatotoxicity (Table 4). Nephrotoxicity was an expected adverse reaction, and the rate of occurrence ranged from 0% to 23.1%. In one study, the estimated probabilities of arbekacin-induced nephrotoxicity were 2.5%, 5.2%, and 13.1% when the C_{min} values were 1, 2, and 5 ug/mL, respectively [4]. TDM will be needed to reduce arbekacin-induced nephrotoxicity. Hepatotoxicity was reported in 0.85% to 8.5% of cases. Gastrointestinal symptoms were rare, and the other reported adverse reactions were leukopenia, thrombocytopenia, skin rash, and drug-induced fever.

In Japan, a postmarketing surveillance review of arbekacin was performed [39]. In their study, the total rate of adverse reactions was 16.7% (35/210 cases). Adverse reactions consisted of nephrotoxicity, hepatotoxicity, electrolyte imbalance, skin rash, anemia, etc.

Therapeutic drug monitoring (TDM)

The therapeutic drug range of arbekacin is relatively narrow. Consequently, TDM is required to maximize efficacy and minimize adverse reactions [40]. In Japan, arbekacin is widely used for treating patients with MRSA, and TDM has been introduced into clinical practice. The Japanese Society of Che-

Table 4. Adverse reactions after use of arbekacin

Clinical adverse reactions	Yamamoto 2012 [12] (n = 13)	Hwang 2012 [31] (n = 0)	Shimizu 2003 [33] (n = 470)	Hwang 2012 [13] (n = 73)	Hwang 2013 [14] (n = 63)	Hwang 2015 [34] (n = 20)	Hwang 2016 [15] (n = 71)	Miura 2015 [32] (n = 54)	Matsumoto 2013 [26] (n = 29)
Nephrotoxicity	23.1%	7.8%	4.26%	6.8%	3.2%	0.0%	5.6%	11.1%	6.9%
Acute renal failure			1.91%						
Renal function decreased			1.28%						
Nephropathy			0.64%						
Creatinine increased			0.21%						
BUN increased			0.21%						
Hepatotoxicity	7.7%	7.8%	0.85%	4.1%	6.3%	5.0%	8.5%		6.9%
Gastrointestinal symptoms									
PMC								3.7%	
Diarrhea								3.7%	
Nausea								1.9%	
Ileus								1.9%	
Constipation									3.5%
Leukopenia				5.5%	3.2%	0.0%	4.2%	3.7%	
Thrombocytopenia			0.21%						
Skin rash			0.21%	0.0%	3.2%	0.0%	1.4%	9.3%	
Drug fever							1.4%		
EIP	7.7%								
Eighth nerve lesion			0.21%						

BUN, blood urea nitrogen; PMC, pseudomembranous enterocolitis; EIP, exacerbation of interstitial pneumonia.

motherapy developed clinical practice guidelines for TDM of arbekacin based on recent PK-PD studies aimed at achieving better clinical efficacy [40]. In their guidelines, the indications for TDM are as follows; 1. TDM is performed in patients who are likely to receive courses of arbekacin therapy administered at a dosing frequency of once daily for more than 4 days. 2. TDM should be planned from the start of arbekacin therapy in patients with serious infections, those receiving intensive dosing of arbekacin, those with impaired renal function/hemodialysis, or those with unstable (deteriorating or improving) renal function. TDM is also performed when adverse events occur or no favorable clinical response is obtained. 3. Clinical effects can be expected when the C_{max}/MIC ratio is 8 or higher, and a target C_{peak} of 15-20 ug/mL is recommended. 4. Trough concentrations >2 ug/mL are not recommended because of the risk of nephrotoxicity. However, TDM is not established at most hospitals in Korea. To increase the use of arbekacin in Korea, TDM should be established.

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References

1. Matsumoto T. Arbekacin: another novel agent for treating infections due to methicillin-resistant *Staphylococcus aureus* and multidrug-resistant Gram-negative pathogens. Clin Pharmacol 2014;6:139-48.
2. Matsuhashi Y, Yamamoto H. The enzymatic mechanisms of resistance to aminoglycoside antibiotics in methicillin-cephem-resistant *Staphylococcus aureus*. Jpn J Antibiot 1988;41:523-9.
3. Aoki Y. Bactericidal activity of arbekacin against methicillin-resistant *Staphylococcus aureus*. Comparison with that of vancomycin. Jpn J Antibiot 1994;47:640-6.
4. Sato R, Tanigawara Y, Kaku M, Aikawa N, Shimizu K. Pharmacokinetic-pharmacodynamic relationship of arbekacin for treatment of patients infected with methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2006;50:3763-9.
5. Watanabe T, Ohashi K, Matsui K, Kubota T. Comparative studies of the bactericidal, morphological and post-antibiotic effects of arbekacin and vancomycin against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 1997;39:471-6.
6. Hamada Y, Tamura K, Koyama I, Kuroyama M, Yago K, Sunakawa K. Clinical efficacy of arbekacin for Gram-negative bacteria. J Infect Chemother 2011;17:876-9.
7. Nakamura I, Yamaguchi T, Tsukimori A, Sato A, Fukushima S, Matsumoto T. New options of antibiotic combination therapy for multidrug-resistant *Pseudomonas aeruginosa*. Eur J Clin Microbiol Infect Dis 2015;34:83-7.
8. Zapor MJ, Barber M, Summers A, Miller GH, Feeney LA, Eberly LE, Wortmann G. In vitro activity of the aminoglycoside antibiotic arbekacin against *Acinetobacter baumannii-calcoaceticus* isolated from war-wounded patients at Walter Reed Army Medical Center. Antimicrob Agents Chemother 2010;54:3015-7.
9. Ochiai M, Tanimura H, Noguchi K, Takifuji K, Konishi R, Ohkouchi N, Kouno N, Ohnishi H, Shimada K, Kasitani M, Fukiage O, Ura S, Jouhata K, Kobayashi Y, Dounishi H, Aoki Y. Clinical effect of arbekacin on MRSA infections after gastrointestinal surgery. Jpn J Antibiot 1994;47:837-43.
10. Suzuki K. Efficacy and safety of arbekacin for staphylococcal infection in the NICU. Pediatr Int 2003;45:301-6.
11. Aikawa N, Kohno S, Kaku M, Watanabe A, Yamaguchi K, Tanigawara Y. An open clinical study of arbekacin 200mg q.d. in patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA)-A clinical pharmacology study-. Jpn J Chemother 2008;56:299-312.
12. Yamamoto Y, Izumikawa K, Hashiguchi K, Fukuda Y, Kobayashi T, Kondo A, Inoue Y, Morinaga Y, Nakamura S, Imamura Y, Miyazaki T, Kakeya H, Yanagihara K, Kohno S. The efficacy and safety of high-dose arbekacin sulfate therapy (once-daily treatment) in patients with MRSA infection. J Infect Chemother 2012;18:241-6.
13. Hwang JH, Lee JH, Moon MK, Kim JS, Won KS, Lee CS. The usefulness of arbekacin compared to vancomycin. Eur J Clin Microbiol Infect Dis 2012;31:1663-6.
14. Hwang JH, Lee JH, Moon MK, Kim JS, Won KS, Lee CS. The efficacy and safety of arbekacin and vancomycin for the treatment in skin and soft tissue MRSA infection: preliminary study. Infect Chemother 2013;45:62-8.

15. Hwang JH, Lee JH, Kim JS, Hwang JH, Lee CS. Arbekacin as an alternative drug to teicoplanin for the treatment of MRSA infection. Yonsei Med J 2016 [in press].
16. Wie SH, Kang JH, Huh DH, Lee DG, Kim SI, Kim YR, Choi JH, Kim JH, Yoo JH, Hur JK, Shin WS, Kang MW. Antimicrobial activities of Arbekacin against clinical isolates of *Staphylococcus aureus* and coagulase-negative Staphylococcus species. Korean J Infect Dis 2001;33:254-60.
17. Lee J, Kim CK, Roh KH, Lee H, Yum JH, Yong D, Lee K, Chong Y. In vitro activity of arbekacin against clinical isolates of *Staphylococcus* species and gram-negative bacilli. Korean J Lab Med 2007;27:292-7.
18. Ha SH, Jeong SH, Jeong TS, Seo DY, Chang C, Nam HJ, Baek YW, Ji JH. Antimicrobial susceptibilites of glycopeptides, arbekacin and quinupristin/dalfopristin against *Staphylococcal aureus* isolates. Korean J Infect Dis 2001; 33:261-5.
19. Watanabe A, Yanagihara K, Matsumoto T, Kohno S, Aoki N, Oguri T, Sato J, Muratani T, Yagisawa M, Ogasawara K, Koashi N, Kozuki T, Komoto A, Takahashi Y, Tsuji T, Terada M, Nakanishi K, Hattori R, Hirako Y, Maruo A, Minamitani S, Morita K, Wakamura T, Sunakawa K, Hanaki H, Ohsaki Y, Honda Y, Sasaoka S, Takeda H, Ikeda H, Sugai A, Miki M, Nakanowatari S, Takahashi H, Utagawa M, Kobayashi N, Takasaki J, Konosaki H, Aoki Y, Shoji M, Goto H, Saraya T, Kurai D, Okazaki M, Kobayashi Y, Katono Y, Kawana A, Saionji K, Miyazawa N, Sato Y, Watanuki Y, Kudo M, Ehara S, Tsukada H, Imai Y, Watabe N, Aso S, Honma Y, Mikamo H, Yamagishi Y, Takesue Y, Wada Y, Nakamura T, Mitsuno N, Mikasa K, Kasahara K, Uno K, Sano R, Miyashita N, Kurokawa Y, Takaya M, Kuwabara M, Watanabe Y, Doi M, Shimizu S, Negayama K, Kadota J, Hiramatsu K, Morinaga Y, Honda J, Fujita M, Iwata S, Iwamoto A, Ezaki T, Onodera S, Kusachi S, Tateda K, Tanaka M, Totsuka K, Niki Y, Matsumoto T. Nationwide surveillance of bacterial respiratory pathogens conducted by the Surveillance Committee of Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases, and Japanese Society for Clinical Microbiology in 2009: general view of the pathogens' antibacterial susceptibility. J Infect Chemother 2012;18:609-20.
20. You I, Kariyama R, Zervos MJ, Kumon H, Chow JW. In-vitro activity of arbekacin alone and in combination with vancomycin against gentamicin- and methicillin-resistant *Staphylococcus aureus*. Diagn Microbiol Infect Dis 2000; 36:37-41.
21. Lee JY, Oh WS, Ko KS, Heo ST, Moon CS, Ki HK, Kiem S, Peck KR, Song JH. Synergy of arbekacin-based combinations against vancomycin hetero-intermediate *Staphylococcus aureus*. J Korean Med Sci 2006;21:188-92.
22. Akins RL, Rybak MJ. In vitro activities of daptomycin, arbekacin, vancomycin, and gentamicin alone and/or in combination against glycopeptide intermediate-resistant *Staphylococcus aureus* in an infection model. Antimicrob Agents Chemother 2000;44:1925-9.
23. Beauchamp D, Pellerin M, Gourde P, Pettigrew M, Bergeron MG. Effects of daptomycin and vancomycin on tobramycin nephrotoxicity in rats. Antimicrob Agents Chemother 1990;34:139-47.
24. Kak V, You I, Zervos MJ, Kariyama R, Kumon H, Chow JW. In-vitro synergistic activity of the combination of ampicillin and arbekacin against vancomycin-and high-level gentamicin-resistant Enterococcus faecium with the aph(2")-Id gene. Diagn Microbiol Infect Dis 2000;37:297-9.
25. Kak V, Donabedian SM, Zervos MJ, Kariyama R, Kumon H, Chow JW. Efficacy of ampicillin plus arbekacin in experimental rabbit endocarditis caused by an *Enterococcus faecalis* strain with high-level gentamicin resistance. Antimicrob Agents Chemother 2000;4:2545-6.
26. Matsumoto T, Hanaki H, Kimura T, Nemoto M, Higashihara M, Yokota H, Oda S, Akiyama N, Miyao N, Yoshida M, Yukioka T, Soma K, Ohyashiki K, Suzuki Y, Arai T, Ikegami K, Ichiwata T, Otsuka Y, Kobayashi M, Totsuka K, Sunakawa K; ABK Dose Finding Study Group. Clinical efficacy and safety of arbekacin sulfate in patients with MRSA sepsis or pneumonia: a multi-institutional study. J Infect Chemother 2013;19:128-37.
27. Sader HS, Rhomberg PR, Farrell DJ, Jones RN. Arbekacin activity against contemporary clinical bacteria isolated from patients hospitalized with pneumonia. Antimicrob Agents Chemother 2015;59:3263-70.
28. Rajenderan S, Balaji V, Anandan S, Sahni RD, Tansarli GS, Falagas ME. Determination of MIC distribution of arbekacin, cefminox, fosfomycin, biapenem and other antibiotics against gram-negative clinical isolates in South India: a prospective study. PLoS One 2014;9:e103253.
29. Katou K, Nakamura A, Kato T, Tonegawa K, Kutsuna T, Niwa T, Morita H, Itoh M. Combined effects of panipenem and aminoglycosides on methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in vitro. Chemotherapy 2005;51:387-91.
30. Araoka H, Baba M, Tateda K, Ishii Y, Oguri T, Okuzumi K, Oishi T, Mori S, Mitsuda T, Moriya K, Nakamori Y, Ohmagari N, Yamaguchi K, Yoneyama A; ABX Combina-

tion Therapy Study Group. In vitro combination effects of aztreonam and aminoglycoside against multidrug-resistant *Pseudomonas aeruginosa* in Japan. Jpn J Infect Dis 2012;65:84-7.
31. Hwang JH, Moon MK, Kim JS, Won KS, Lee CS. Drug use evaluation of arbekacin. J Kor Soc Health-Syst Pharm 2012;29:48-55.
32. Miura K, Nakagawa M, Takahashi H, Uchino Y, Kodaira H, Iriyama N, Sakagami M, Ohtake S, Kobayashi S, Hojo A, Kurita D, Kobayashi Y, Kusuda M, Hirabayashi Y, Hatta Y, Takei M. Clinical efficacy and safety of arbekacin for high-risk infections in patients with hematological malignancies. Int J Hematol. 2016;103:334-40.
33. Shimizu K AN, Tanigawara Y, Kaku M, Imae M, Nishizawa N, Nakamura H. Actual use of anti-MRSA drugs in Japan with the focus on arbekacin. Jpn J Chemother 2003;51: 717-30.
34. Hwang JH, Lee JH, Hwang JH, Chung KM, Lee EJ, Yoon YJ, Moon MK, Kim JS, Won KS, Lee CS. Comparison of arbekacin and vancomycin in treatment of chronic suppurative otitis media by methicillin resistant *Staphylococcus aureus*. J Korean Med Sci 2015;30:688-93.
35. Araoka H, Baba M, Takagi S, Matsuno N, Ishiwata K, Nakano N, Tsuji M, Yamamoto H, Seo S, Asano-Mori Y, Uchida N, Masuoka K, Wake A, Taniguchi S, Yoneyama A. Monobactam and aminoglycoside combination therapy against metallo-beta-lactamase-producing multidrug-resistant *Pseudomonas aeruginosa* screened using a 'breakpoint checkerboard plate'. Scand J Infect Dis 2010;42:231-3.
36. Iwashita Y, Enokiya T, Suzuki K, Yokoyama K, Yamamoto A, Ishikura K, Okuda M, Imai H. Arbekacin treatment of a patient infected with a *Pseudomonas putida* producing a metallo-beta-lactamase. J Intensive Care 2013;1:3.
37. Lee K, Park AJ, Kim MY, Lee HJ, Cho JH, Kang JO, Yong D, Chong Y; KONSAR group. Metallo-β-lactamase-producing *Pseudomonas* spp. in Korea: high prevalence of isolates with VIM-2 type and emergence of isolates with IMP-1 type. Yonsei Med J 2009;50:335-9.
38. Hamada Y SH, Hirai J, Yamagishi Y, Mikamo H. Evaluation of six cases of arbekacin inhalation for pneumonia. Jpn J Antibiot 2014;67:233-9.
39. Kawano H, Tanigawara Y. Postmarketing surveillance review of arbekacin sulfate in patients with therapeutic drug monitoring. Jpn J Ther Drug Monit 2010;27:55-71.
40. Okada K, Kimura T, Mikamo H, Kasahara K, Seki M, Takakura S, Tokimatsu I, Ohmagari N, Takahashi Y, Matsumoto K, Igarashi M, Kobayashi M, Hamada Y, Mochizuki T, Kimura M, Nishi Y, Tanigawara Y, Takesue Y; Japanese Society of Chemotherapy; Japanese Society of Therapeutic Drug Monitoring. Clinical practice guidelines for therapeutic drug monitoring of arbekacin: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. J Infect Chemother 2014;20:1-5.