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Arbekacin Activity against Contemporary Clinical Bacteria Isolated from Patients Hospitalized with Pneumonia

Helio S. Sader, Paul R. Rhomberg, David J. Farrell, Ronald N. Jones

JMI Laboratories, North Liberty, Iowa, USA

Arbekacin is a broad-spectrum aminoglycoside licensed for systemic use in Japan and under clinical development as an inhalation solution in the United States. We evaluated the occurrence of organisms isolated from pneumonias in U.S. hospitalized patients (PHP), including ventilator-associated pneumonia (VAP), and the *in vitro* activity of arbekacin. Organism frequency was evaluated from a collection of 2,203 bacterial isolates (339 from VAP) consecutively collected from 25 medical centers in 2012 through the SENTRY Antimicrobial Surveillance Program. Arbekacin activity was tested against 904 isolates from PHP collected in 2012 from 62 U.S. medical centers and 303 multidrug-resistant (MDR) organisms collected worldwide in 2009 and 2010 from various infection types. Susceptibility to arbekacin and comparator agents was evaluated by the reference broth microdilution method. The four most common organisms from PHP were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Enterobacter* spp. The highest arbekacin MIC among *S. aureus* isolates from PHP (43% methicillin-resistant *S. aureus* [MRSA]) was 4 μg/ml. Among *P. aeruginosa* isolates from PHP, only one had an arbekacin MIC of >16 μg/ml (MIC_{50} and MIC_{90}, 1 and 4 μg/ml), and susceptibility rates for gentamicin, tobramycin, and amikacin were 88.0, 90.0, and 98.0%, respectively. Arbekacin (MIC_{50}, 2 μg/ml) and tobramycin (MIC_{50}, 4 μg/ml) were the most potent aminoglycosides tested against *Acinetobacter baumannii*. Against *Enterobacteriaceae* from PHP, arbekacin and gentamicin (MIC_{50} and MIC_{90}, 0.25 to 1 and 1 to 8 μg/ml for both compounds) were generally more potent than tobramycin (MIC_{50} and MIC_{90}, 0.25 to 2 and 1 to 32 μg/ml) and amikacin (MIC_{50} and MIC_{90}, 1 to 2 and 2 to 32 μg/ml). Arbekacin also demonstrated potent *in vitro* activity against a worldwide collection of well-characterized MDR Gram-negative and MRSA strains.

Arbekacin is a broad-spectrum aminoglycoside licensed for systemic use in Japan, where it is largely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections (1–3). Arbekacin inhibits protein synthesis by binding both 50S and 30S ribosomal subunits, and it is highly stable to most aminoglycoside-modifying enzymes produced by *S. aureus* (4). The arbekacin spectrum of activity also includes *Enterobacteriaceae* species and nonfermentative Gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. (5–7).

Although arbekacin has demonstrated a broad spectrum of *in vitro* activity, it is licensed in Japan only for treatment of septicemia and pneumonia caused by MRSA. In the United States, arbekacin is under clinical development for the treatment of hospital-associated and ventilator-associated bacterial pneumonia (HABP/VABP) as an inhalation solution (development code ME1100) (8–10). We evaluated the frequency of occurrence of organisms causing pneumonia in hospitalized patients (PHP), including ventilator-associated pneumonias (VAP), in the SENTRY Antimicrobial Surveillance Program (United States, 2012), and the activity of arbekacin was assessed against selected isolates from PHP. In addition, we evaluated the activity of arbekacin against a global collection of well-characterized multidrug-resistant (MDR) strains from various infections sites.

MATERIALS AND METHODS

Frequency of occurrence of bacterial organisms from PHP. Consecutive unique bacterial isolates were cultured from patients with pneumonia in a prevalence sampling design. Isolates were collected from 25 medical centers distributed across all nine U.S. Census Regions in 2012 as part of the SENTRY Program (11). Each participant center was requested to collect 100 consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia. Only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted. The frequency of occurrence of organisms from patients with VAP and the frequency of those with pneumonia that was not ventilator associated (all cases excluding VAP) were separately analyzed.

Organisms from PHP tested against arbekacin. This collection includes isolates from the 25 U.S. medical centers that participated in the 2012 SENTRY Program (described above) as well as isolates from 37 additional U.S. medical centers. Thus, the isolates ($n = 904$) were collected from 62 U.S. medical centers in 2012, from patients hospitalized with bacterial pneumonia, including VAP. The most common specimen types were sputum (41.3%), tracheal aspirate (27.0%), bronchoalveolar lavage/wash (17.9%), and endotracheal tube (7.4%). Isolates were randomly selected and had patterns of susceptibility to key antimicrobial agents consistent with those observed in the SENTRY Program in the United States for 2012.

Resistant subsets tested against arbekacin. The organism collection ($n = 303$) comprised extended-spectrum-β-lactamase (ESBL)-producing *Escherichia coli* (33 isolates, including CTX-M [19 isolates]-, SHV [8 isolates]-, TEM [5 isolates]-, and OXA [1 isolate]-producing strains), ESBL/KPC-producing *Klebsiella pneumoniae* (78 isolates, including KPC-2/3

Received 18 November 2014 Returned for modification 1 March 2015
Accepted 15 March 2015

Accepted manuscript posted online 23 March 2015

Citation Sader HS, Rhomberg PR, Farrell DJ, Jones RN. 2015. Arbekacin activity against contemporary clinical bacteria isolated from patients hospitalized with pneumonia. Antimicrob Agents Chemother 59:3263–3270. doi:10.1128/AAC.04839-14.

Address correspondence to Helio S. Sader, helio-sader@jmilabs.com.

doi:10.1128/AAC.04839-14

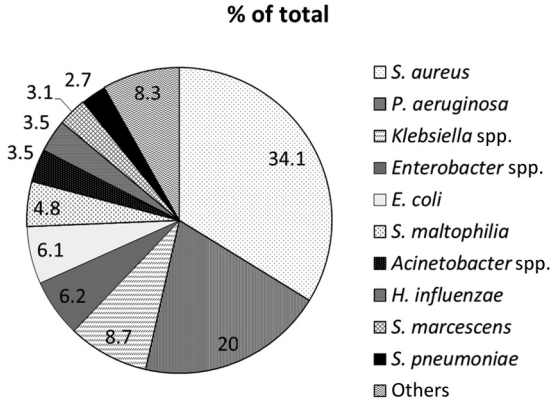

FIG 1 Frequency of occurrence of organisms from hospitalized patients with pneumonia (excluding ventilator-associated pneumonia) in U.S. hospitals (n = 1,864; SENTRY Program, 2012).

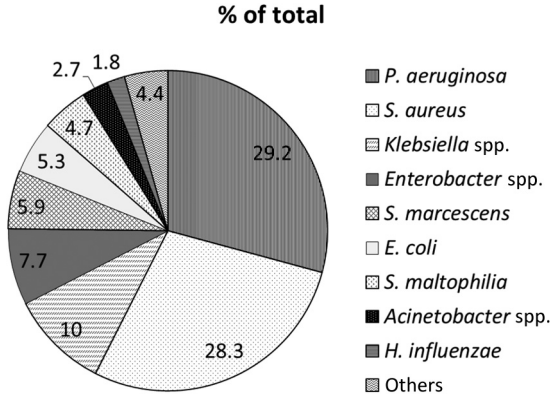

FIG 2 Frequency of occurrence of organisms from patients with ventilator-associated pneumonia (VAP) in U.S. hospitals (n = 339; SENTRY Program, 2012).

[40 isolates]-, CTX-M [16 isolates]-, and SHV [22 isolates]-producing strains), ceftazidime-resistant (AmpC-derepressed) *Enterobacter cloacae* (21 isolates) and *Citrobacter freundii* (20 isolates), imipenem-resistant *P. aeruginosa* (31 isolates), imipenem-resistant *Acinetobacter baumannii* (50 isolates), and MRSA (70 isolates, including heteroresistant vancomycin-intermediate *S. aureus* [hVISA] [20 isolates], community-acquired [CA-MRSA] [30 isolates], and gentamicin-resistant [22 isolates] strains, among others). Isolates were tested for β-lactamase-encoding genes using the microarray-based assay Check-MDR CT101 kit (Check-points, Wageningen, Netherlands). The assay was performed according to the manufacturer's instructions. This kit has the capability to detect CTX-M groups 1, 2, 8 + 25, and 9, wild-type (WT) and ESBL TEM, WT and ESBL SHV, ACC, ACT/MIR, CMYII, DHA, FOX, KPC, and NDM-1 (12).

Susceptibility testing. Reference broth microdilution tests were conducted according to the Clinical and Laboratory Standards Institute (CLSI M07-A9) (13) methods. *S. aureus* and Gram-negative bacilli were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), *Streptococcus pneumoniae* isolates were tested in CA-MHB supplemented with 2.5 to 5% lysed horse blood, and *Haemophilus influenzae* strains were tested in *Haemophilus* test medium (HTM). CLSI interpretative criteria (M100-S24) (14, 15) were applied for the comparator agents. Concurrent testing of quality control (QC) strains per M07-A9 (13) and M100-S24 (14) documents ensured proper test conditions. The QC strains tested were *S. aureus* ATCC 29213, *E. coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 and 49766.

RESULTS

Frequency of occurrence of bacterial organisms from PHP. The most frequently isolated organisms from patients with non-VAP and VAP are shown in Fig. 1 and 2, respectively. The main differences in the frequency and rank order of organisms between non-VAP and VAP patients were as follows: (i) *S. aureus* ranked first in non-VAP patients (34.1% of total) and second in VAP patients (28.3%), whereas *P. aeruginosa* ranked second in non-VAP patients (20.0%) and first in VAP patients (29.2%), and (ii) *Serratia marcescens* was more frequently isolated from VAP patients (5.9%; fifth most common) than non-VAP patients (3.1%; ninth most common). Of note, *Stenotrophomonas maltophilia* and *Acinetobacter* spp. exhibited similar frequencies among non-VAP patients (4.8 and 3.5%, respectively) compared to VAP patients (4.7 and 2.7%, respectively).

Antimicrobial activity of arbekacin and comparators tested against organisms from PHP. When arbekacin was tested against *S. aureus* (43.0% MRSA), its potency (MIC_{50}, 0.25 μg/ml, and MIC_{90}, 0.5 μg/ml; highest MIC, 4 μg/ml) was very similar to that of gentamicin (MIC_{50}, 0.25 μg/ml, and MIC_{90}, 0.5 μg/ml) and greater than those of tobramycin (MIC_{50}, 0.5 μg/ml, and MIC_{90}, >128 μg/ml) and amikacin (MIC_{50}, 4 μg/ml, and MIC_{90}, 16 μg/ml). Susceptibility rates (CLSI) for gentamicin, tobramycin, and amikacin were 95.0, 76.0, and 96.0%, respectively. Moreover, MICs of ≥32 μg/ml were observed for all three comparative aminoglycosides (Tables 1 and 2). All *S. aureus* isolates were susceptible to vancomycin (MIC_{50} and MIC_{90}, 1 μg/ml), linezolid (MIC_{50}, 1 μg/ml and MIC_{90}, 2 μg/ml), and daptomycin (MIC_{50}, 0.25 μg/ml and MIC_{90}, 0.5 μg/ml) (Table 2).

Tobramycin (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 4 μg/ml; 90.0% susceptible) and arbekacin (MIC_{50}, 1 μg/ml, and MIC_{90}, 4 μg/ml; 96.0% inhibited at ≤4 μg/ml) were the most potent (i.e., they had the lowest MIC_{50} and MIC_{90} values) aminoglycosides tested against *P. aeruginosa*, followed by gentamicin (MIC_{50}, 2 μg/ml, and MIC_{90}, 16 μg/ml; 88.0% susceptible) and amikacin (MIC_{50}, 4 μg/ml, and MIC_{90}, 8 μg/ml; 98.0% susceptible) (Table 1). *P. aeruginosa* susceptibility (CLSI and EUCAST criteria) to β-lactams was highest for ceftazidime (86.0%), followed by piperacillin-tazobactam (78.0%), cefepime (77.0%), and meropenem (75.0%) (Table 2). All isolates were susceptible to colistin (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 1 μg/ml) (Table 2).

Arbekacin (MIC_{50}, 2 μg/ml, and MIC_{90}, >128 μg/ml; 65.0% inhibited at ≤4 μg/ml) and tobramycin (MIC_{50}, 4 μg/ml, and MIC_{90}, >128 μg/ml; 51.0% susceptible at ≤4 μg/ml [CLSI]) were also the most potent aminoglycosides tested against *A. baumannii* (Table 1), whereas against *Enterobacteriaceae* species, arbekacin and gentamicin (MIC_{50}, 0.25 to 1 μg/ml, and MIC_{90}, 1 to 8 μg/ml for both compounds) were generally more potent than tobramycin (MIC_{50}, 0.25 to 2 μg/ml, and MIC_{90}, 1 to 32 μg/ml) and amikacin (MIC_{50}, 1 to 2 μg/ml, and MIC_{90}, 2 to 32 μg/ml) (Table 1). Among the β-lactam compounds, ceftazidime was active against 77.5% of *K. pneumoniae* (MIC_{50}, 0.25 μg/ml, and MIC_{90}, >128 μg/ml) and 72.0% of *Enterobacter* (MIC_{50}, 0.25 μg/ml, and MIC_{90}, 64 μg/ml) strains, whereas meropenem inhibited 91.2% of *K. pneumoniae* (MIC_{50}, ≤0.06 μg/ml, and MIC_{90}, 0.12 μg/ml) and 100.0% of *Enterobacter* (MIC_{50} and MIC_{90}, ≤0.06 μg/ml) strains when the CLSI breakpoint criteria were applied (Table 2).

Gentamicin was the most potent aminoglycoside tested against

TABLE 1 Frequency of occurrence of arbekacin and three comparator aminoglycoside MICs for the organisms tested

Organism (no. of isolates tested) and drug	No. (cumulative %) of isolates inhibited at MIC (μg/ml)[a]											
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
S. aureus (100)												
Arbekacin	1 (1.0)	54 (55.0)	38 (93.0)	6 (99.0)	0 (99.0)	1 (100.0)						
Gentamicin	4 (4.0)	64 (68.0)	25 (93.0)	1 (94.0)	1 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	1 (96.0)	2 (98.0)	1 (99.0)	1 (100.0)
Tobramycin	3 (3.0)	42 (45.0)	27 (72.0)	4 (76.0)	0 (76.0)	0 (76.0)	0 (76.0)	1 (77.0)	1 (78.0)	2 (80.0)	1 (81.0)	19(100.0)
Amikacin			2 (2.0)	6 (8.0)	40 (48.0)	25 (73.0)	12 (85.0)	11 (96.0)	3 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)
P. aeruginosa (100)												
Arbekacin	2 (2.0)	3 (5.0)	16 (21.0)	31 (52.0)	26 (78.0)	18 (96.0)	1 (97.0)	2 (99.0)	0 (99.0)	1 (100.0)		
Gentamicin	2 (2.0)	3 (5.0)	10 (15.0)	34 (49.0)	30 (79.0)	9 (88.0)	1 (89.0)	2 (91.0)	4 (95.0)	2 (97.0)	0 (97.0)	3 (100.0)
Tobramycin	3 (3.0)	21 (24.0)	46 (70.0)	16 (86.0)	3 (89.0)	1 (90.0)	1 (91.0)	4 (95.0)	3 (98.0)	1 (99.0)	0 (99.0)	1 (100.0)
Amikacin		2 (2.0)	1 (3.0)	9 (12.0)	28 (40.0)	37 (77.0)	19 (96.0)	2 (98.0)	1 (99.0)	0 (99.0)	1 (100.0)	
A. baumannii (100)												
Arbekacin	2 (2.0)	6 (8.0)	21 (29.0)	15 (44.0)	14 (58.0)	7 (65.0)	6 (71.0)	5 (76.0)	2 (78.0)	4 (82.0)	1 (83.0)	17 (100.0)
Gentamicin	2 (2.0)	4 (6.0)	16 (22.0)	8 (30.0)	5 (35.0)	2 (37.0)	6 (43.0)	5 (48.0)	1 (49.0)	7 (56.0)	9 (65.0)	35 (100.0)
Tobramycin	1 (1.0)	5 (6.0)	21 (27.0)	14 (41.0)	6 (47.0)	4 (51.0)	6 (57.0)	5 (62.0)	1 (63.0)	7 (70.0)	7 (77.0)	23 (100.0)
Amikacin		1 (1.0)	1 (2.0)	16 (18.0)	19 (37.0)	11 (48.0)	7 (55.0)	3 (58.0)	6 (64.0)	12 (76.0)	6 (82.0)	18 (100.0)
K. pneumoniae (102)												
Arbekacin	1 (1.0)	54 (53.9)	28 (81.4)	3 (84.3)	0 (84.3)	2 (86.3)	7 (93.1)	4 (97.1)	0 (97.1)	1 (98.0)	1 (99.0)	1 (100.0)
Gentamicin	2 (2.0)	51 (52.0)	28 (79.4)	3 (82.4)	2 (84.3)	5 (89.2)	2 (91.2)	0 (91.2)	1 (92.2)	2 (94.1)	2 (96.1)	4 (100.0)
Tobramycin	3 (2.9)	55 (56.9)	20 (76.5)	1 (77.5)	0 (77.5)	5 (82.4)	3 (85.3)	3 (88.2)	5 (93.1)	3 (96.8)	0 (96.8)	4 (100.0)
Amikacin			9 (8.8)	70 (77.5)	7 (84.3)	1 (85.3)	1 (86.3)	2 (88.2)	10 (98.0)	0 (98.0)	0 (98.0)	2 (100.0)
Enterobacter spp.(100)												
Arbekacin		21 (21.0)	67 (88.0)	8 (96.0)	2 (98.0)	2 (100.0)						
Gentamicin	1 (1.0)	25 (26.0)	62 (88.0)	8 (96.0)	1 (97.0)	0 (97.0)	1 (98.0)	0 (98.0)	0 (98.0)	1 (99.0)	1 (100.0)	
Tobramycin	1 (1.0)	17 (18.0)	65 (83.0)	11 (94.0)	0 (94.0)	2 (96.0)	1 (97.0)	2 (99.0)	0 (99.0)	1 (100.0)		
Amikacin			1 (1.0)	55 (56.0)	37 (93.0)	5 (98.0)	2 (100.0)					
E. coli (102)												
Arbekacin	1 (1.0)	1 (2.0)	28 (29.4)	59 (87.3)	8 (95.1)	2 (97.1)	2 (99.0)	1 (100.0)				
Gentamicin	1 (1.0)	3 (3.9)	46 (49.0)	34 (82.4)	6 (88.2)	0 (88.2)	2 (90.2)	0 (90.2)	1 (91.2)	5 (96.1)	4 (100.0)	
Tobramycin	1 (1.0)	2 (2.9)	36 (38.2)	42 (79.4)	5 (84.3)	2 (86.3)	4 (90.2)	5 (95.1)	2 (97.1)	3 (100.0)		
Amikacin				15 (14.7)	57 (70.6)	24 (94.1)	4 (98.0)	1 (99.0)	1 (100.0)			
S. marcescens (100)												
Arbekacin			5 (5.0)	48 (53.0)	42 (95.0)	2 (97.0)	1 (98.0)	1 (99.0)	1 (100.0)			
Gentamicin		3 (3.0)	60 (63.0)	28 (91.0)	5 (96.0)	1 (97.0)	2 (99.0)	1 (100.0)				
Tobramycin			4 (4.0)	35 (39.0)	46 (85.0)	9 (94.0)	3 (97.0)	1 (98.0)	1 (99.0)	1 (100.0)		
Amikacin				15 (15.0)	70 (85.0)	12 (97.0)	2 (99.0)	1 (100.0)				
H. influenzae (100)												
Arbekacin				2 (2.0)	23 (25.0)	65 (90.0)	10 (100.0)					
Gentamicin			2 (2.0)	16 (18.0)	72 (90.0)	10 (100.0)						
Amikacin					4 (4.0)	32 (36.0)	53 (89.0)	11 (100.0)				
S. pneumoniae (100)												
Arbekacin							2 (2.0)	12 (14.0)	38 (52.0)	46 (98.0)	2 (100.0)	
Gentamicin						3 (3.0)	35 (38.0)	60 (98.0)	2 (100.0)			
Amikacin								2 (2.0)	12 (14.0)	75 (89.0)	11 (100.0)	

[a] Underlined values correspond to MIC_{50} and MIC_{90}, and boldface indicates the percentage susceptible by CLSI criteria (14).

S. pneumoniae (MIC_{50} and MIC_{90}, 16 μg/ml) (Tables 1 and 2) and *H. influenzae* (MIC_{50} and MIC_{90}, 2 μg/ml), followed by arbekacin (MIC_{50}, 32 μg/ml, and MIC_{90}, 64 μg/ml for *S. pneumoniae*; MIC_{50} and MIC_{90}, 4 μg/ml for *H. influenzae*) and amikacin (MIC_{50}, 64 μg/ml, and MIC_{90}, 128 μg/ml for *S. pneumoniae*; MIC_{50}, 8 μg/ml, and MIC_{90}, 16 μg/ml for *H. influenzae*) (Table 1).

Antimicrobial activity of arbekacin and comparators tested against antimicrobial-resistant organism subsets. MIC_{90} values of aminoglycosides were generally elevated for ESBL-producing *E. coli* and ESBL- and KPC-producing *K. pneumoniae* (Tables 3 and 4). Based on MIC_{50} results, arbekacin (MIC_{50}, 2 μg/ml, and MIC_{90}, 16 μg/ml) was 2-, 4-, and 16-fold more potent than ami-

TABLE 2 Activity of arbekacin and comparator antimicrobial agents when tested against organisms isolated from pneumonia in hospitalized patients (United States, 2012)

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% S/% I/% R[a]	
	50%	90%	Range	CLSI	EUCAST
S. aureus (100)					
Arbekacin	0.25	0.5	0.12–4	—/—/—	—/—/—
Amikacin	4	16	0.5–>128	96.0/3.0/1.0	85.0/11.0/4.0
Gentamicin	0.25	0.5	≤0.06–>128	95.0/0.0/5.0	94.0/0.0/6.0
Tobramycin	0.5	>128	0.12–>128	76.0/0.0/24.0	76.0/0.0/24.0
Vancomycin	1	1	0.5–2	100.0/0.0/0.0	100.0/0.0/0.0
Linezolid	1	2	0.5–2	100.0/0.0/0.0	100.0/0.0/0.0
Daptomycin	0.25	0.5	0.12–0.5	100.0/—/—	100.0/0.0/0.0
Clindamycin	0.12	>128	≤0.06–>128	77.0/1.0/22.0	77.0/0.0/23.0
Oxacillin	1	>32	0.12–>32	57.0/0.0/43.0	57.0/0.0/43.0
P. aeruginosa (100)					
Arbekacin	1	4	0.12–64	—/—/—	—/—/—
Amikacin	4	8	0.25–128	98.0/1.0/1.0	96.0/2.0/2.0
Gentamicin	2	16	≤0.06–>128	88.0/1.0/11.0	88.0/0.0/12.0
Tobramycin	0.5	4	≤0.06–>128	90.0/1.0/9.0	90.0/0.0/10.0
Aztreonam	8	32	0.25–128	69.0/11.0/20.0	11.0/69.0/20.0
Piperacillin-tazobactam	4	64	≤0.12–>128	78.0/12.0/10.0	78.0/0.0/22.0
Cefepime	4	16	0.25–32	77.0/13.0/10.0	77.0/0.0/23.0
Ceftazidime	2	32	0.25–128	86.0/3.0/11.0	86.0/0.0/14.0
Imipenem	1	16	≤0.06–32	74.0/4.0/22.0	78.0/8.0/14.0
Meropenem	0.5	16	≤0.06–32	75.0/4.0/21.0	75.0/14.0/11.0
Levofloxacin	0.5	32	≤0.015–>32	76.0/3.0/21.0	64.0/12.0/24.0
Colistin	0.5	1	0.12–2	100.0/0.0/0.0	100.0/0.0/0.0
K. pneumoniae (102)					
Arbekacin	0.25	8	0.12–>128	—/—/—	—/—/—
Amikacin	1	32	0.5–>128	88.2/9.8/2.0	86.3/1.9/11.8
Gentamicin	0.25	8	0.12–>128	89.2/2.0/8.8	84.3/4.9/10.8
Tobramycin	0.25	32	0.12–>128	82.4/2.9/14.7	77.5/4.9/17.6
Aztreonam	≤0.06	>128	≤0.06–>128	77.5/0.0/22.5	77.5/0.0/22.5
Piperacillin-tazobactam	2	>128	1–>128	86.3/0.0/13.7	80.4/5.9/13.7
Cefepime	≤0.06	32	≤0.06–>128	83.3/1.0/15.7	80.4/2.0/17.6
Ceftazidime	0.25	>128	≤0.06–>128	77.5/0.9/21.6	76.5/1.0/22.5
Imipenem	0.12	1	≤0.06–>128	93.1/0.0/6.9	93.1/1.0/5.9
Meropenem	≤0.06	0.12	≤0.06–>128	91.2/1.0/7.8	92.2/2.9/4.9
Levofloxacin	0.06	32	≤0.015–>32	80.4/0.0/19.6	79.4/1.0/19.6
Colistin	0.25	0.25	0.12–>32	—/—/—	95.1/0.0/4.9
Enterobacter spp.[b] (100)					
Arbekacin	0.5	1	0.25–4	—/—/—	—/—/—
Amikacin	1	2	0.5–8	100.0/0.0/0.0	100.0/0.0/0.0
Gentamicin	0.5	1	0.12–128	97.0/1.0/2.0	97.0/0.0/3.0
Tobramycin	0.5	1	0.12–64	96.0/1.0/3.0	94.0/2.0/4.0
Aztreonam	0.12	32	≤0.06–>128	73.0/4.0/23.0	72.0/1.0/27.0
Piperacillin-tazobactam	2	64	0.5–>128	78.0/14.0/8.0	71.0/7.0/22.0
Cefepime	≤0.06	2	≤0.06–>128	96.0/0.0/4.0	87.0/8.0/5.0
Ceftazidime	0.25	64	≤0.06–>128	72.0/1.0/27.0	70.0/2.0/28.0
Imipenem	0.5	1	≤0.06–2	97.0/3.0/0.0	100.0/0.0/0.0
Meropenem	≤0.06	≤0.06	≤0.06–1	100.0/0.0/0.0	100.0/0.0/0.0
Levofloxacin	0.03	0.5	≤0.015–>32	97.0/1.0/2.0	96.0/1.0/3.0
Colistin	0.25	16	0.12–>32	—/—/—	88.0/0.0/12.0

[a] Criteria as published by the CLSI (14) and EUCAST (15). —, no criteria available.
[b] Includes *Enterobacter aerogenes* (37 strains), *E. asburiae* (two strains), and *E. cloacae* (61 strains).

kacin (MIC_{50}, 4 μg/ml, and MIC_{90}, 32 μg/ml), gentamicin (MIC_{50}, 8 μg/ml, and MIC_{90}, >128 μg/ml), and tobramycin (MIC_{50}, 32 μg/ml, and MIC_{90}, 512 μg/ml) against ESBL-producing *E. coli*, respectively (Table 4), and inhibited 66.7% of gentamicin-resistant strains at a MIC of ≤8 μg/ml (Table 3).

Arbekacin (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 16 μg/ml) and amikacin (MIC_{50}, 2 μg/ml, and MIC_{90}, >512 μg/ml; 84.2% susceptible) were the most potent aminoglycosides tested against ESBL-producing *K. pneumoniae*, and arbekacin (MIC_{50}, 8 μg/ml, and MIC_{90}, 16 μg/ml) and gentamicin (MIC_{50}, 2 μg/ml, and MIC_{90},

TABLE 3 Arbekacin MIC distributions when tested against antimicrobial resistant organism subsets

Organism or phenotype (no. of isolates tested)[a]	No. of isolates (cumulative %) inhibited at an arbekacin MIC (μg/ml) of:									
	≤0.25	0.5	1	2	4	8	16	32	64	≥128
ESBL *E. coli* (33)[b]	2 (6.1)	5 (21.2)	8 (45.5)	4 (57.6)	4 (69.7)	3 (78.8)	2 (84.8)	3 (93.9)	1 (97.0)	1 (100.0)
Gentamicin resistant[c] (15)	1 (6.7)	2 (20.0)	2 (33.3)	3 (53.3)	1 (60.0)	1 (66.7)	1 (73.3)	2 (86.7)	1 (93.3)	1 (100.0)
ESBL/KPC *K. pneumoniae* (78)	8 (10.3)	18 (33.3)	1 (34.6)	4 (39.7)	4 (44.9)	13 (61.5)	26 (94.9)	0 (94.9)	0 (94.9)	4 (100.0)
ESBL producing (38)[d]	6 (15.8)	14 (52.4)	1 (55.3)	2 (60.5)	1 (63.2)	3 (71.1)	8 (92.1)	0 (92.1)	0 (92.1)	3 (100.0)
KPC-2/3 producing (40)	2 (5.0)	4 (15.0)	0 (15.0)	2 (20.0)	3 (27.5)	10 (52.5)	18 (97.5)	0 (97.5)	0 (97.5)	1 (100.0)
Gentamicin resistant[c] (37)	2 (5.4)	8 (27.0)	0 (27.0)	0 (27.0)	3 (35.1)	9 (59.5)	11 (89.2)	0 (89.2)	0 (89.2)	4 (100.0)
CAZ-R *E. cloacae* (21)	2 (9.5)	13 (71.4)	6 (100.0)							
CAZ-R *C. freundii* (20)		14 (70.0)	4 (90.0)	0 (90.0)	0 (90.0)	1 (95.0)	1 (100.0)			
IMI-R *P. aeruginosa* (31)		1 (3.2)	5 (19.4)	6 (38.7)	6 (58.1)	2 (64.5)	4 (77.4)	2 (83.9)	3 (93.5)	2 (100.0)
MBL producing[e] (13)			1 (7.7)	2 (23.1)	3 (46.2)	3 (69.2)	1 (76.9)	1 (84.6)	2 (100.0)	
Gentamicin resistant (19)		1 (5.3)	3 (21.1)	4 (42.1)	3 (57.9)	1 (63.2)	2 (73.7)	2 (84.2)	2 (94.7)	1 (100.0)
Tobramycin resistant (17)		1 (5.9)	2 (17.6)	4 (41.2)	3 (58.8)	1 (64.7)	2 (76.5)	2 (88.2)	2 (100.0)	
AMK, GEN and TOB-NS[f] (9)		1 (11.1)	2 (33.3)	3 (66.7)	1 (77.8)	1 (88.9)	1 (100.0)			
IMI-R *A. baumannii* (50)		1 (2.0)	5 (12.0)	6 (24.0)	8 (40.0)	9 (58.0)	10 (78.0)	8 (94.0)	1 (96.0)	2 (100.0)
Gentamicin resistant (42)			5 (11.9)	4 (21.4)	4 (31.0)	8 (50.0)	10 (73.8)	8 (92.2)	1 (95.2)	2 (100.0)
MRSA (70)	5 (7.1)	27 (45.7)	34 (94.3)	3 (98.6)	1 (100.0)					
hVISA (20)	4 (20.0)	6 (50.0)	9 (95.0)	0 (95.0)	1 (100.0)					
CA-MRSA (30)	1 (3.3)	14 (50.0)	15 (100.0)							
Gentamicin-resistant (22)		7 (31.8)	11 (81.8)	3 (95.5)	1 (100.0)					

[a] ESBL, extended-spectrum β-lactamase producing; KPC, *Klebsiella pneumoniae* carbapenemase; CAZ-R, ceftazidime-resistant (MIC, ≥16 μg/ml); IMI-R, imipenem-resistant (MIC, ≥8 μg/ml); hVISA, heterogeneous vancomycin-intermediate *S. aureus*; CA-MRSA, community-acquired MRSA.
[b] Includes CTX-M-type (19 isolates), SHV-type (8 isolates), and TEM-type (5 isolates) ESBLs, as well as one strain with OXA-1.
[c] Gentamicin MIC ≥16 μg/ml (CLSI 2014 [14]).
[d] Includes CTX-M-type (16 isolates) and SHV-type (22 isolates) ESBLs.
[e] Include VIM-type (6 isolates), IMP-type (5 isolates), GIM-1 (1 isolate), and SPM-1 (1 isolate).
[f] Isolates that were nonsusceptible to amikacin (MIC, ≥32 μg/ml), gentamicin (MIC, ≥8 μg/ml), and tobramycin (MIC, ≥8 μg/ml) (14).

128 μg/ml; 50.0% susceptible) were the most potent aminoglycosides tested against KPC-producing *K. pneumonia* (Table 4). Moreover, arbekacin was active against 61.5% of gentamicin-resistant strains at ≤8 μg/ml (Table 3).

All aminoglycosides exhibited good activity against ceftazidime-resistant *E. cloacae* (MIC_{50}, 0.5 to 2 μg/ml, and MIC_{90}, 1 to 2 μg/ml), whereas arbekacin (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 1 μg/ml) and amikacin (MIC_{50}, 2 μg/ml, and MIC_{90}, 4 μg/ml) were the most potent (i.e., they had the lowest MIC_{50} and MIC_{90} values) aminoglycosides tested against ceftazidime-resistant *C. freundii* (Tables 3 and 4). All ceftazidime-resistant strains of *E. cloacae* and *C. freundii* (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 1 μg/ml for both) were susceptible to imipenem (Table 4).

When tested against imipenem-resistant *P. aeruginosa*, arbekacin (MIC_{50}, 4 μg/ml, and MIC_{90}, 64 μg/ml) inhibited 64.5% of strains at ≤8 μg/ml, and it was the most potent aminoglycoside tested against these organisms (Tables 3 and 4). Moreover, arbekacin inhibited 69.2% of MBL-producing strains and 88.9% of strains nonsusceptible to amikacin, gentamicin, and tobramycin at a MIC of ≤8 μg/ml (Table 3). Tobramycin (MIC_{50}, 32 μg/ml, and MIC_{90}, >128 μg/ml) inhibited only 41.9% of imipenem-resistant *P. aeruginosa* strains at the CLSI susceptible breakpoint of ≤4 μg/ml (Table 4). Arbekacin was also the most potent aminoglycoside tested against imipenem-resistant *A. baumannii* (MIC_{50}, 8 μg/ml, and MIC_{90}, 32 μg/ml) (Table 4) and inhibited 58.0% of strains at ≤8 μg/ml (Table 3).

Arbekacin was very active against MRSA (highest MIC, 4 μg/ml; one strain), including *S. aureus* with heterogeneous resistance to vancomycin (hVISA), community-acquired MRSA (CA-MRSA) (MIC_{50}, 0.5 μg/ml, and MIC_{90}, 1 μg/ml for both groups) and gentamicin-resistant strains (MIC_{50}, 1 μg/ml, and MIC_{90}, 2 μg/ml) (Table 3). Gentamicin and amikacin were active against 68.6 and 90.0% of MRSA strains at the respective CLSI susceptible breakpoints (Table 4).

DISCUSSION

The initial antimicrobial management of patients with pneumonia is driven mainly by the understanding of causative pathogens (16). The frequency of occurrence of organisms observed in the current study is very similar to that reported by other investigators. The main reported causes of health care-associated pneumonia are *S. aureus*, *P. aeruginosa*, and the *Enterobacteriaceae Klebsiella* spp., *Enterobacter* spp., *E. coli*, and *Serratia* spp. (11, 17, 18). In the present study, *S. aureus* and *P. aeruginosa* were the most common causes of PHP (non-VAP and VAP), followed by *Klebsiella* spp. and *Enterobacter* spp. Although in the current study we could not separate community-acquired pneumonia that requires hospitalization from hospital-acquired pneumonia (HAP), the fact that *S. pneumoniae* and *H. influenzae* combined were responsible for only 5.5% of cases indicates that the vast majority of cases included in the study were HAP.

Inhaled antimicrobials have a long history of use in the treat-

TABLE 4 Antimicrobial activity of arbekacin and comparator agents when tested against multidrug-resistant organisms

Organism (no. of isolates tested) and antimicrobial agent[a]	MIC (μg/ml)			% S/% I/% R[b]	
	50%	90%	Range	CLSI	EUCAST
ESBL-producing *E. coli* (33)					
Arbekacin	2	16	0.25–>512	—/—/—	—/—/—
Amikacin	4	32	1–>512	81.8/9.1/9.1	69.7/12.1/18.2
Gentamicin	8	>128	0.12–>128	48.5/6.0/45.5	45.5/3.0/51.5
Tobramycin	32	512	0.25–>512	27.3/12.1/60.6	24.2/3.0/72.8
Ceftazidime	16	512	0.25–>512	42.4/0.0/57.6	15.2/27.2/57.6
Imipenem	0.25	0.5	0.12–0.5	100.0/0.0/0.0	100.0/0.0/0.0
ESBL -producing *K. pneumoniae* (38)					
Arbekacin	0.5	16	0.25–16	—/—/—	—/—/—
Amikacin	2	>512	0.5–>512	84.2/5.3/10.5	68.4/15.8/15.8
Gentamicin	4	128	0.25–256	50.0/21.1/28.9	44.7/5.3/50.0
Tobramycin	8	128	0.25–>512	26.3/23.7/50.0	21.1/6.2/73.7
Ceftazidime	64	>512	1–>512	21.1/2.6/76.3	15.8/2.6/81.6
Imipenem	0.12	0.5	≤0.06–0.5	100.0/0.0/0.0	100.0/0.0/0.0
KPC-producing *K. pneumoniae* (40)					
Arbekacin	8	16	0.25–>512	—/—/—	—/—/—
Amikacin	16	64	0.5–>512	42.5/32.5/25.0	30.0/12.5/57.5
Gentamicin	4	128	0.25–>128	50.0/5.0/45.0	42.5/7.5/50.0
Tobramycin	32	64	0.25–>512	25.0/0.0/75.0	25.0/0.0/75.0
Ceftazidime	265	512	1–>512	7.5/10.0/82.5	0.0/12.8/79.5
Imipenem	2	64	≤0.06–256	0.0/5.0/95.0	5.0/27.5/67.5
CAZ-R *E. cloacae* (21)					
Arbekacin	0.5	1	0.25–1	—/—/—	—/—/—
Amikacin	2	2	0.5–4	100.0/0.0/0.0	100.0/0.0/0.0
Gentamicin	0.5	1	0.25–128	90.5/0.0/9.5	90.5/0.0/9.5
Tobramycin	1	1	0.25–32	90.5/4.8/4.8	90.5/0.0/9.5
Ceftazidime	64	128	32–256	0.0/0.0/100.0	0.0/0.0/100.0
Imipenem	0.5	1	0.12–1	100.0/0.0/0.0	100.0/0.0/0.0
CAZ-R *C. freundii* (20)					
Arbekacin	0.5	1	0.5–16	—/—/—	—/—/—
Amikacin	2	4	1–64	95.0/0.0/5.0	95.0/0.0/5.0
Gentamicin	1	32	0.5–>128	80.0/0.0/20.0	80.0/0.0/20.0
Tobramycin	1	32	0.5–256	75.0/0.0/25.0	75.0/0.0/25.0
Ceftazidime	128	128	16–256	0.0/0.0/100.0	0.0/0.0/100.0
Imipenem	0.5	1	0.25–1	100.0/0.0/0.0	100.0/0.0/0.0
IMI-R *P. aeruginosa* (31)					
Arbekacin	4	64	0.5–>512	—/—/—	—/—/—
Amikacin	8	256	1–>512	64.5/9.7/25.8	54.8/9.7/35.5
Gentamicin	16	>128	0.5–>128	38.7/6.5/54.8	38.7/0.0/61.3
Tobramycin	32	>128	0.25–512	41.9/3.3/54.8	41.9/0.0/58.9
Ceftazidime	64	>512	2–128	32.3/6.4/61.3	32.3/6.4/61.3
Imipenem	16	256	8–>512	0.0/0.0/100.0	0.0/0.0/100.0
IMI-R *A. baumannii* (50)					
Arbekacin	8	32	0.5–>512	—/—/—	—/—/—
Amikacin	128	>512	1–>512	28.0/10.0/62.0	20.0/8.0/72.0
Gentamicin	128	>128	0.25–>128	14.0/2.0/84.0	14.0/0.0/86.0
Tobramycin	32	64	0.5–>512	24.0/12.0/64.0	24.0/0.0/76.0
Ceftazidime	128	>512	0.25–>512	10.0/2.0/88.0	—/—/—
Imipenem	64	128	8–256	0.0/0.0/100.0	0.0/0.0/100.0
MRSA (70)					
Arbekacin	1	1	0.12–4	—/—/—	—/—/—
Amikacin	8	16	1–256	90.0/7.1/2.9	68.6/21.4/10.0
Gentamicin	1	64	0.12–>128	68.6/0.0/31.4	68.9/0.0/31.4
Tobramycin	2	256	0.5–>512	51.4/0.0/48.6	44.3/7.1/18.6

[a] ESBL, extended spectrum β-lactamase, CAZ-R, ceftazidime-resistant (MIC, ≥16 μg/ml); IMI-R, imipenem-resistant (MIC, ≥8 μg/ml); MRSA, methicillin-resistant *S. aureus* (14).
[b] Criteria as published by the CLSI (2014) (14). —, no criteria available.

ment of lower respiratory tract infections. These therapies have clearly transformed the management of cystic fibrosis patients, and there has been growing interest in the use of inhaled antimicrobials in other clinical settings, such as in cases of HAP and VAP (19). Aerosolized tobramycin was the first antimicrobial agent approved by the U.S. FDA for inhaled therapy, and the aminoglycoside agents have been a mainstay of inhaled antimicrobial therapy for many years, mainly due to their spectrum of antimicrobial activity (19–21). In the present study, we evaluated the *in vitro* activity of arbekacin against 904 contemporary (2012) isolates from PHP collected in 62 U.S. medical centers. The collection included at least 100 isolates from nine of the 10 most frequently isolated bacterial species from HAP (only *S. maltophilia* was not tested), and arbekacin demonstrated potent activity and good coverage against these organisms, with 87.3 and 91.8% of all strains being inhibited at ≤16 and ≤32 μg/ml, respectively. Arbekacin was the most potent aminoglycoside tested against *S. aureus* and *P. aeruginosa*, and these two organisms together comprised more than one-half of the organisms isolated from PHP in U.S. medical centers. Furthermore, arbekacin potency was similar or superior to the most potent comparators in its antimicrobial class (namely, amikacin, gentamicin, and tobramycin) when tested against *Acinetobacter* spp. and the *Enterobacteriaceae* species commonly isolated from PHP.

MDR Gram-negative organisms, especially ESBL- and KPC-producing *Enterobacteriaceae* and carbapenem-resistant *P. aeruginosa* and *Acinetobacter* spp., represent important therapeutic challenges, especially when causing serious infections such as pneumonia (11, 16, 17). The results of this investigation also showed that arbekacin retained activity against many of these MDR organisms. Arbekacin was the most potent aminoglycoside tested against ESBL-producing *E. coli* and inhibited 66.7% of gentamicin-resistant strains at a MIC of ≤8 μg/ml. When tested against *K. pneumoniae*-producing ESBL and/or KPC, arbekacin was slightly more active (2- to 16-fold lower MIC_{50}) than amikacin or tobramycin, and although arbekacin was slightly (2-fold) less active than gentamicin when tested against KPC-producing *K. pneumoniae*, it inhibited 59.5% of gentamicin-resistant strains at a MIC of ≤8 μg/ml.

The multiple resistance mechanisms present in *P. aeruginosa* and *A. baumannii* isolates make these organisms major clinical concerns. The combination of various mechanisms or even the expression of a single broad-spectrum resistance mechanism turns these bacteria resistant to multiple commercially available antimicrobials and, consequently, makes the therapy of these infections extremely difficult (22, 23). Furthermore, it has been suggested that patients with VAP attributed to *P. aeruginosa* and *Acinetobacter* spp. may benefit from adjunctive aerosolized therapy (24). In the present study, arbekacin demonstrated greater activity against *P. aeruginosa* and *Acinetobacter* spp., including MDR strains, than other agents in its class and retained activity against a considerable proportion of strains that are resistant to aminoglycosides commonly used in clinical practice when applying clinical susceptible breakpoints (4, 14, 15).

In summary, arbekacin was notably active against a large collection of contemporary (2012) organisms isolated from hospitalized patients with pneumonia in U.S. medical centers, as well as against a collection of well-characterized MDR organisms selected from species commonly isolated from patients with pneumonia. The results of this study indicate that arbekacin could represent a valuable addition to the limited group of antimicrobials currently available for the inhalation treatment of PHP caused by MDR organisms.

ACKNOWLEDGMENTS

This study was supported by Meiji Seika Pharma Co., Ltd.

JMI Laboratories, Inc., received research and educational grants in 2012-2014 from Achaogen, Actavis, Actelion, Affinium, American Proficiency Institute (API), AmpliPhi Bio, Anacor, Astellas, AstraZeneca, Basilea, BioVersys, Cardeas, Cempra, Cerexa, Cubist, Daiichi, Dipexium, Durata, Fedora, Forest, Furiex, Genentech, GlaxoSmithKline, Janssen, Johnson & Johnson, Medpace, Meiji Seika Pharma, Melinta, Merck, Methylgene, Nabriva, Nanosphere, Novartis, Pfizer, Polyphor, Rempex, Roche, Seachaid, Shionogi, Synthes, The Medicines Co., Theravance, ThermoFisher, Venatorx, Vertex, Wockhardt and Waterloo. Some JMI employees are advisors/consultants for Astellas, Cubist, Pfizer, Cempra, Cerexa-Forest, and Theravance. In regards to speakers' bureaus and stock options, we have none to declare.

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