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Activities of Faropenem, an Oral β-Lactam, against Recent U.S. Isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*

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The in vitro activities of faropenem and other antimicrobial agents were determined against 4,725 *Streptococcus pneumoniae* isolates, 2,614 *Haemophilus influenzae* isolates, and 1,193 *Moraxella catarrhalis* isolates collected from 273 U.S. laboratories during 1999. Faropenem MICs at which 90% of isolates are inhibited were 0.008, 0.25, and 1 μg/ml for penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae* strains, respectively; 0.5 and 1 μg/ml for β-lactamase-positive and -negative *H. influenzae* strains, respectively; and 0.12 and 0.5 μg/ml for β-lactamase-negative and -positive *M. catarrhalis* strains, respectively. Faropenem holds promise as an oral therapy for community-acquired respiratory tract infections.

The increasing levels of antimicrobial resistance among community-acquired respiratory tract pathogens limit the options for empirical therapy (2). Penicillin resistance among *Streptococcus pneumoniae* strains is now widely accepted as a global problem (1, 7, 10), and the widespread dissemination of plasmid-encoded β-lactamases in *Haemophilus influenzae* and *Moraxella catarrhalis* has eliminated amoxicillin as a treatment option for infections caused by β-lactamase-producing isolates (6). Although penem antimicrobials have broad-spectrum activities, remarkable potencies, and stabilities against β-lactamases, none are available, to date, for oral administration. The parenteral carbapenems imipenem (14) and meropenem (5) are prescribed in the United States, and a number of new oral carbapenems are now in development, including L-084 (11) and DU-6681a (16).

Faropenem is a novel β-lactam antimicrobial with a penem (furanem) structure that is being developed for use as an oral therapy for community-acquired respiratory tract infections. Although recent studies have highlighted the broad-spectrum antibacterial activity of faropenem (previously known as SUN/SY 5555, ALP-201, or WY-49605) (8, 9, 15, 17–19), new attention has focused on its activity against the respiratory pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (3). The aim of the present study was to benchmark the activity of faropenem against recent bacterial pathogens isolated from patients with respiratory tract infections.

Respiratory tract isolates were collected from 273 hospital laboratories distributed throughout the United States during 1999 as part of the LIBRA surveillance program. Isolates were limited to one per patient and were collected from clinical samples derived from various upper and lower respiratory tract sites, blood, ears, and eyes. All isolates were shipped to the central laboratory of Focus Technologies, Inc. (Herndon, Va.), where each isolate was subcultured and reidentified by standard methods (12).

A total of 4,725 isolates of *S. pneumoniae* were available for antimicrobial susceptibility testing; 58.9% (2,783 isolates) originated from respiratory specimens, 32.1% (1,517 isolates) originated from blood or cerebrospinal fluid, 4.7% (220 isolates) originated from eye specimens, and 4.3% (205 isolates) originated from other or unknown specimen sources. A total of 2,614 isolates of *H. influenzae* were tested for their susceptibilities to faropenem and imipenem; 2,483 of the 2,614 isolates were tested for their susceptibilities to all other agents. Of the 2,614 isolates, 83.3% (2,177 isolates) originated from respiratory specimens, 10.1% (264 isolates) originated from eye specimens, 3.2% (83 isolates) originated from blood or cerebrospinal fluid, and 3.4% (90 isolates) originated from other or unknown specimen sources. A total of 1,193 isolates *M. catarrhalis* were available: 91.0% (1,086 isolates) originated from respiratory sources, 4.9% (58 isolates) originated from eye specimens, 1.4% (17 isolates) originated from blood, and 2.7% (32 isolates) originated from other or unknown specimen sources.

The isolates were tested for their susceptibilities to faropenem, ampicillin (*H. influenzae* and *M. catarrhalis* only), amoxicillin-clavulanate, ceftriaxone, cefuroxime, imipenem, levofloxacin, penicillin (*S. pneumoniae* only), and trimethoprim-sulfamethoxazole (SXT) by using antimicrobial concentrations that extended at least 1 twofold concentration above and 1 twofold concentration below the NCCLS breakpoints (where available). Antimicrobial susceptibility testing was conducted by the broth microdilution method with frozen panels prepared by PML Biologicals (Wilsonville, Oreg.) in accordance with NCCLS guidelines. For *S. pneumoniae* and *H. influenzae*, breakpoint interpretations were conducted according to the recommendations of NCCLS (13) with the exception of those for faropenem, for which no NCCLS breakpoints are available. In the case of *M. catarrhalis*, no NCCLS breakpoints were available. *H. influenzae* and *M. catarrhalis* isolates were

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TABLE 1. Susceptibilities of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* to faropenem and comparator antimicrobials

Organism, antimicrobial, and phenotype	MIC (μg/ml)				% of isolates that were[a]:		
	Range	Mode	50%	90%	S	I	R
S. pneumoniae[b]							
Faropenem							
All	≤0.004–2	≤0.004	0.008	0.25			
Penicillin susceptible	≤0.004–0.12	≤0.004	≤0.004	0.008			
Penicillin intermediate	≤0.004–1	0.25	0.12	0.25			
Penicillin resistant	≤0.004–2	0.25	0.5	1			
Amoxicillin-clavulanate							
All	≤0.015–16	≤0.015	≤0.015	1	95.1	3.9	1.0
Penicillin susceptible	≤0.015–1	≤0.015	≤0.015	0.03	100	0	0
Penicillin intermediate	≤0.015–4	1	0.5	1	98.3	1.7	0
Penicillin resistant	0.5–16	4	2	4	57.0	33.3	9.7
Cefuroxime[c]							
All	≤0.12–>32	≤0.12	≤0.12	4	73.5	4.8	21.7
Penicillin susceptible	≤0.12–1	≤0.12	≤0.12	≤0.12	100	0	0
Penicillin intermediate	≤0.12–32	4	2	4	34.1	19.1	46.8
Penicillin resistant	2–>32	4	8	16	0	1.2	98.8
Imipenem							
All	≤0.015–1	≤0.015	≤0.015	0.25	85.3	14.5	0.2
Penicillin susceptible	≤0.015–0.25	≤0.015	≤0.015	≤0.015	99.9	0.1	0
Penicillin intermediate	≤0.015–0.5	0.12	0.12	0.25	78.6	21.4	0
Penicillin resistant	0.06–1	0.25	0.25	0.5	9.3	88.4	2.2
Ceftriaxone							
All	≤0.015–8	≤0.015	≤0.015	0.5	90.9	6.2	2.9
Penicillin susceptible	≤0.015–0.5	≤0.015	≤0.015	0.03	100	0	0
Penicillin intermediate	≤0.015–4	0.5	0.25	0.5	92.7	6.2	1.0
Penicillin resistant	0.25–8	1	1	4	29.6	45.2	25.2
Levofloxacin							
All	≤0.004–>8	1	1	1	99.2	0.1	0.7
Penicillin susceptible	≤0.004–>8	1	1	1	99.3	0.1	0.6
Penicillin intermediate	0.25–>8	1	1	1	99.0	0.3	0.8
Penicillin resistant	0.25–>8	1	1	1	99.4	0.0	0.6
Penicillin							
All	≤0.03–>4	≤0.03	≤0.03	2	65.1	24.4	10.4
Penicillin susceptible	≤0.03–0.06	≤0.03	≤0.03	≤0.03	100	0	0
Penicillin intermediate	0.12–1	1	0.5	1	0	100	0
Penicillin resistant	2–>4	2	2	4	0	0	100
SXT							
All	≤0.015–>4	0.25	0.25	>4	60.8	7.8	31.3
Penicillin susceptible	≤0.015–>4	0.25	0.25	2	84.6	7.0	8.5
Penicillin intermediate	0.06–>4	>4	4	>4	22.3	11.5	66.2
Penicillin resistant	0.25–>4	>4	>4	>4	3.0	4.5	92.5
H. influenzae[d]							
Faropenem							
All	≤0.004–4	0.25	0.25	1			
β-lactamase positive	≤0.004–4	0.25	0.25	0.5			
β-lactamase negative	≤0.004–4	0.25	0.25	1			
Amoxicillin-clavulanate							
All	≤0.015–8	0.5	0.5	2	>99.9		<0.1
β-Lactamase positive	0.03–8	1	1	2	99.9		0.1
β-Lactamase negative	≤0.015–4	0.5	0.5	1	100		0
Cefuroxime[c]							
All	≤0.12–16	0.5	0.5	2	99.9	0.1	<0.1
β-Lactamase positive	≤0.12–8	0.5	0.5	2	99.9	0.1	0
β-Lactamase negative	≤0.12–16	0.5	0.5	2	99.9	0.1	0.1
Imipenem							
All	≤0.015–4	0.25	0.5	1	100		
β-Lactamase positive	≤0.015–4	0.25	0.5	1	100		
β-Lactamase negative	≤0.015–4	0.5	0.5	1	100		

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TABLE 1—*Continued*

Organism, antimicrobial, and phenotype	MIC (μg/ml)				% of isolates that were[a]:		
	Range	Mode	50%	90%	S	I	R
Ceftriaxone							
All	≤0.015–0.25	≤0.015	≤0.015	≤0.015	100		
β-Lactamase positive	≤0.015–0.25	≤0.015	≤0.015	≤0.015	100		
β-Lactamase negative	≤0.015–0.25	≤0.015	≤0.015	≤0.015	100		
Ampicillin							
All	≤0.06–>8	0.5	0.5	>8	66.3	0.2	33.5
β-Lactamase positive	0.5–>8	>8	>8	>8	0.1	0.5	99.4
β-Lactamase negative	≤0.06–4	0.5	0.5	1	99.8	0.1	0.1
Levofloxacin							
All	≤0.004–0.06	0.015	0.015	0.015	100		
β-Lactamase positive	≤0.004–0.06	0.015	0.015	0.015	100		
β-Lactamase negative	≤0.004–0.06	0.015	0.015	0.015	100		
SXT							
All	≤0.015–>4	0.12	0.12	4	86.5	2.7	10.8
β-Lactamase positive	≤0.015–>4	0.06	0.12	>4	82.0	3.1	14.9
β-Lactamase negative	≤0.015–>4	0.12	0.12	2	88.8	2.4	8.8
M. catarrhalis[e]							
Faropenem							
All	0.008–2	0.5	0.25	0.5			
β-Lactamase positive	0.008–2	0.5	0.25	0.5			
β-Lactamase negative	0.015–1	0.03	0.03	0.12			
Amoxicillin-clavulanate							
All	≤0.015–1	0.25	0.25	0.5			
β-Lactamase positive	≤0.015–1	0.25	0.25	0.5			
β-Lactamase negative	≤0.015–0.5	≤0.015	≤0.015	0.03			
Cefuroxime							
All	≤0.12–8	2	1	2			
β-Lactamase positive	≤0.12–8	2	1	2			
β-Lactamase negative	≤0.12–1	0.25	0.5	0.5			
Imipenem							
All	≤0.015–0.5	0.12	0.06	0.12			
β-Lactamase positive	≤0.015–0.5	0.12	0.06	0.12			
β-Lactamase negative	≤0.015–0.25	≤0.015	≤0.015	0.03			
Ceftriaxone							
All	≤0.015–4	0.5	0.5	1			
β-Lactamase positive	≤0.015–4	0.5	0.5	1			
β-Lactamase negative	≤0.015–0.12	≤0.015	≤0.015	≤0.015			
Ampicillin							
All	≤0.06–>8	4	4	8			
β-Lactamase positive	≤0.06–>8	4	4	8			
β-Lactamase negative	≤0.06–0.25	≤0.06	≤0.06	≤0.06			
Levofloxacin							
All	0.015–1	0.03	0.03	0.06			
β-Lactamase positive	0.015–1	0.03	0.03	0.06			
β-Lactamase negative	0.03–0.25	0.03	0.03	0.06			
SXT							
All	0.06–>4	0.25	0.25	0.5			
β-Lactamase positive	0.06–>4	0.25	0.25	0.5			
β-Lactamase negative	0.06–0.5	0.12	0.25	0.25			

[a] Percentages of isolates that were susceptible (S), intermediate (I), and resistant (R) according to NCCLS breakpoints. Breakpoints are not available for faropenem.
[b] Of the 4,725 isolates of *S. pneumoniae*, 3,078 were penicillin susceptible, 1,154 were penicillin intermediate, and 493 were penicillin resistant.
[c] NCCLS breakpoints for cefuroxime axetil were used to interpret cefuroxime MICs.
[d] A total of 2,614 isolates of *H. influenzae* were tested against faropenem and imipenem; 847 were β-lactamase-positive isolates and 1,767 were β-lactamase-negative isolates. Of the 2,614 isolates, 2,483 were tested against amoxicillin-clavulanate, cefuroxime, ceftriaxone, ampicillin, levofloxacin, and SXT; 834 were β-lactamase-positive isolates and 1,649 were β-lactamase-negative isolates.
[e] A total of 1,193 isolates of *M. catarrhalis* were tested; 1,121 were β-lactamase-positive isolates and 72 were β-lactamase-negative isolates. NCCLS breakpoints are not available for *M. catarrhalis*.

TABLE 2. Antimicrobial susceptibilities and MIC distributions for 4,725 *S. pneumoniae* isolates by penicillin susceptibility status[a]

Antimicrobial and phenotype	No. of isolates for which the MIC (μg/ml) was as follows:														
	≤0.004	0.008	≤0.015	0.03	0.06	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Faropenem[b]															
All	1,655	1,247	172	173	168	358	**592**	209	148	3					
Penicillin susceptible	1,646	**1,234**	138	42	12	6									
Penicillin intermediate	8	13	34	131	155	333	**408**	63	9						
Penicillin resistant	1	0	0	0	1	19	184	146	**139**	3					
Amoxicillin-clavulanate															
All			2,503	445	171	125	148	305	**572**	224[d]	184[e]	46[f]	2		
Penicillin susceptible			2,490	**427**	113	36	7	4	1						
Penicillin intermediate			13	18	58	89	141	299	**423**	93	20				
Penicillin resistant								2	148	131	**164**	46	2		
Cefuroxime															
All						3,017	217	116	122[d]	226[e]	**716**[f]	217	68	25	1
Penicillin susceptible						**2,942**	100	29	7						
Penicillin intermediate						75	117	87	115	220	**486**	50	3	1	
Penicillin resistant										6	230	167	**65**	24	1
Imipenem															
All			3,129	204	201	495[d]	**454**[e]	231[e]	11[f]						
Penicillin susceptible			**3,026**	44	6	0	2								
Penicillin intermediate			103	160	194	450	**219**	28							
Penicillin resistant					1	45	233	**20**	11						
Ceftriaxone															
All			2,688	323	200	221	344	**518**[d]	295[e]	76[f]	53	7			
Penicillin susceptible			2,662	264	96	49	6	1							
Penicillin intermediate			26	59	104	172	332	**377**	72	8	4				
Penicillin resistant							6	140	223	68	**49**	7			

[a] Of the 4,725 isolates of *S. pneumoniae*, 3,078 were penicillin susceptible, 1,154 were penicillin intermediate, and 493 were penicillin resistant.
[b] NCCLS breakpoints are not available for faropenem.
[c] Boldface numbers represent the points at which the MIC_{90} was achieved.
[d] NCCLS MIC interpretive breakpoint for susceptibility.
[e] NCCLS MIC interpretive breakpoint for intermediate.
[f] NCCLS MIC interpretive breakpoint for resistance.

tested for the production of β-lactamase by the DrySlide nitrocefin test (Difco Laboratories, Detroit, Mich.).

Table 1 shows the antimicrobial activities of faropenem and the comparator agents against *S. pneumoniae* by penicillin susceptibility status. In all, 493 (10.4%) isolates were penicillin resistant and 1,154 (24.4%) were penicillin intermediate. The MICs at which 90% of isolates are inhibited (MIC_{90}s) were lower for faropenem and imipenem than for the other agents tested for all isolates (0.25 μg/ml). As demonstrated by other β-lactams, the activity of faropenem was affected by the penicillin susceptibility status of the isolates, with the faropenem MIC_{90} increasing from 0.008 μg/ml for penicillin-susceptible isolates to 1 μg/ml for penicillin-resistant isolates. Imipenem and faropenem were more active (MIC_{90}s, 0.5 and 1 μg/ml, respectively) than amoxicillin-clavulanate, ceftriaxone, and cefuroxime (MIC_{90}s, 4, 4, and 16 μg/ml, respectively) against penicillin-resistant isolates. For penicillin-resistant isolates, the MIC_{90}s of levofloxacin and SXT were 1 and >4 μg/ml, respectively. The distributions of the faropenem MICs for penicillin-susceptible, -intermediate, and -resistant isolates are compared in Table 2 with the distributions of the MICs of the other β-lactams tested. The distributions of the faropenem MICs for isolates resistant to comparator agents are provided in Table 3. For all 11 imipenem-resistant isolates, faropenem MICs were

TABLE 3. Distribution of faropenem MICs for *S. pneumoniae* isolates resistant to comparator antimicrobials

Drug to which isolates were resistant	No. of isolates for which the faropenem MIC (μg/ml) was as follows:													
	Total	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
Amoxicillin-clavulanate	48							1	8	**39**[a]				
Cefuroxime	1,027	3				12	188	476	197	**148**	3			
Imipenem	11									11				
Ceftriaxone	136	1				3	2	30	47	**51**	2			
Levofloxacin	31	17	1	1		1	2	**8**	1					
Penicillin	493	1				1	19	184	146	**139**	3			
SXT	1,481	115	93	56	66	70	276	478	**182**	142	3			

[a] Boldface numbers represent the point at which the MIC_{90} was achieved for groups of antimicrobial-resistant isolates when 30 or more isolates were tested.

elevated (1 μg/ml). For 48 amoxicillin-clavulanate-resistant isolates, faropenem MICs ranged from 0.25 to 1 μg/ml. The ranges of MICs of faropenem were wide for 31 levofloxacin-resistant isolates (≤0.004 to 0.5 μg/ml) and for ceftriaxone-resistant, cefuroxime-resistant, penicillin-resistant, and SXT-resistant isolates (≤0.004 to 2 μg/ml).

All 2,614 isolates of *H. influenzae* were tested for their abilities to produce β-lactamase; 847 isolates (32.4%) were β-lactamase positive and 1,767 (67.6%) were β-lactamase negative (Table 1). Faropenem and imipenem displayed equivalent activities against all isolates tested (MIC_{90}s, 1 μg/ml). The activity of faropenem was not compromised by the production of β-lactamase; in fact, the agent was more active against β-lactamase-positive isolates than β-lactamase-negative isolates (MIC_{90}s, 0.5 and 1 μg/ml, respectively). Ceftriaxone was the most potent agent against the *H. influenzae* isolates tested (n = 2,483; MIC_{90}s, ≤0.015 μg/ml), and its activity was unaffected by β-lactamase production. There were two β-lactamase-negative, ampicillin-resistant (BLNAR) isolates in the collection of isolates tested (confirmed by repeat testing); the faropenem MICs for these two isolates were 1 and 2 μg/ml, respectively.

Of the 1,193 isolates of *M. catarrhalis* tested, 1,121 (94.0%) were β-lactamase positive and 72 (6.0%) were β-lactamase negative (Table 3). Imipenem was the most active β-lactam (MIC_{90}, 0.12 μg/ml) against *M. catarrhalis*, followed by faropenem and amoxicillin-clavulanate (MIC_{90}s, 0.5 μg/ml). The antimicrobial activity of faropenem was marginally compromised by the production of β-lactamase, with an MIC_{90} of 0.12 μg/ml for β-lactamase-negative isolates and an MIC_{90} of 0.5 μg/ml for β-lactamase-positive isolates.

Increasing resistance to some first-line antimicrobials has created a need for new empirical therapies for community-acquired respiratory tract infections (4, 20). Because faropenem is orally bioavailable and has been demonstrated to have in vitro activity against collections of respiratory tract pathogens of limited sizes (9, 17), it is believed to hold therapeutic promise. The present study provides faropenem susceptibility information for a far larger collection of present U.S. respiratory tract isolates and may serve as a benchmark for future studies.

Among the 4,725 *S. pneumoniae* isolates tested, faropenem displayed activity similar to that of imipenem, although both agents were less active against penicillin-intermediate and -resistant isolates than isolates susceptible to penicillin. The activity of faropenem against penicillin-resistant isolates of *S. pneumoniae* (MIC_{90}, 1 μg/ml) was in agreement with results reported previously by Spangler et al. (19), who studied 47 penicillin-resistant *S. pneumoniae* isolates collected prior to and during 1994. Although the data set of Spangler et al. was small, comparison with our results suggests that there was no major change in the faropenem susceptibilities of penicillin-resistant pneumococci between 1994 and 1999. A more recent study by Black et al. also reported that faropenem had an MIC_{90} of 1 μg/ml for 49 penicillin-resistant pneumococcal isolates (J. A. Black et al., Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 365, 2000).

To succeed clinically, faropenem must also be effective against β-lactamase-producing *H. influenzae* and *M. catarrhalis* strains. Sewell et al. (17) reported faropenem MIC_{90}s of 2 μg/ml for 30 β-lactamase-positive *H. influenzae* isolates and 1 μg/ml for 70 β-lactamase-negative *H. influenzae* isolates. In contrast, we found that faropenem was more active against the 847 β-lactamase-positive isolates than the 1,767 β-lactamase-negative isolates, for which faropenem MIC_{90}s were 0.5 and 1 μg/ml, respectively. The activity of faropenem against BLNAR isolates of *H. influenzae* in our study (2 isolates; MICs, 1 and 2 μg/ml) was similar to the activity reported by Felmingham et al. (12 isolates; MICs, 2 or 4 μg/ml) (D. Felmingham et al., Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 361, 2000).

In the case of *M. catarrhalis*, several investigators have shown that the activity of faropenem was affected by the production of β-lactamase (17; Felmingham et al., 40th ICAAC). They found that there was at least a twofold difference between the MIC_{90}s for β-lactamase-positive and β-lactamase-negative organisms. Comparison of the results of the present study with those of in vitro studies conducted in the mid-1990s suggests that there has been no major shift in the MIC_{90} of faropenem for *M. catarrhalis* during the last 5 years (8).

In conclusion, the present study has demonstrated that faropenem is highly active against an extensive collection of recent bacterial respiratory isolates from the United States. Faropenem had activity similar to or greater than those of the comparator agents tested and appears to hold promise for use in the therapy of community-acquired respiratory tract infections, given its oral bioavailability. However, therapeutic success will depend on its pharmacokinetic and pharmacodynamic profiles following oral administration in humans. The results of this LIBRA surveillance study may serve as a benchmark for future initiatives describing the activity of faropenem against respiratory tract pathogens in the United States.

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