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SUSCEPTIBILITY TO FAROPENEM AMONG RECENT *HAEMOPHILUS INFLUENZA*

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ABSTRACT

Background: Currently in the U.S., 35% of clinical pneumococcal isolates are penicillin (PEN)-intermediate or PEN-resistant (R), and 30% of *H. influenzae* (*HI*) and 95% of *M. catarrhalis* (*MC*) produce β-lactamase (BL). Among the agents being developed as therapy for respiratory pathogens, faropenem (FAR), an oral antimicrobial, has demonstrated *in vitro* activity against PEN-R *S. pneumoniae* (*SP*) and BL-positive (P) *HI* and *MC* in preliminary studies. As new antimicrobials are developed, comprehensive baseline studies are needed to determine initial efficacy and serve as a reference for future surveillance studies.

Methods: 4,725 *SP*, 2,614 *HI*, and 1,193 *MC* from 273 geographically representative U.S. hospitals in 1999 were centrally tested by NCCLS broth microdilution against FAR, PEN (*SP* only), ampicillin (*HI* and *MC* only), amoxicillin-clavulanate (AMC), cefuroxime (CFX), ceftriaxone (CRO), imipenem (IMI), and relevant non-β-lactam comparators.

Results: By MIC_{90} (μg/mL), the hierarchy of β-lactam activity for all *SP* was FAR (0.25) = IMI (0.25) > CRO (0.5) > AMC (1) > PEN (2) > CFX (4). Against PEN-R isolates (n = 493), IMI (MIC_{90}, 0.5 μg/mL) was most potent, followed by FAR (MIC_{90}, 1 μg/mL). All *SP* were inhibited by ≤2 μg/mL FAR and ≤1 μg/mL IMI. FAR and IMI MIC_{90}s were both 1 μg/mL for all *HI*. Against BL-P *HI* (n = 847), FAR and IMI MIC_{90}s were 0.5 and 1 μg/mL, respectively. ≤4 μg/mL FAR and IMI inhibited all isolates of *HI*. Against *MC*, the 3 most potent β-lactams by MIC_{90} (μg/mL) were IMI (0.12), FAR (0.5), and AMC (0.5).

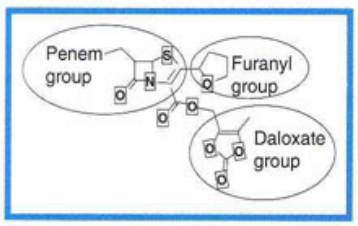
Conclusions: FAR demonstrated activity comparable to IMI and was more active than other oral β-lactams against isolates of *SP*, *HI*, and *MC* in a recent U.S. surveillance study. This study suggests that FAR may have utility in the treatment of outpatient respiratory infections, including those resistant to other antimicrobials.

INTRODUCTION

β-lactam resistance in *Streptococcus pneumoniae* has arisen because of alterations in penicillin-binding proteins. In *Haemophilus influenzae* and *Moraxella catarrhalis*, the production of β-lactamase commonly results in reduced β-lactam susceptibility. Oral β-lactams are becoming less commonly prescribed for respiratory tract infections because of reported *in vitro* resistance to these agents.

Faropenem is a novel oral β-lactam with a penem structure unique from the carbapenems (Figure 1). Faropenem has shown good *in vitro* activity against common bacterial respiratory pathogens. This study, part of the LIBRA Surveillance initiative, provides a baseline for the *in vitro* activity of faropenem against recent clinical isolates of common bacterial respiratory pathogens in the United States and a benchmark against the other currently available β-lactam classes.

Figure 1: Chemical structure of faropenem daloxate



METHODS

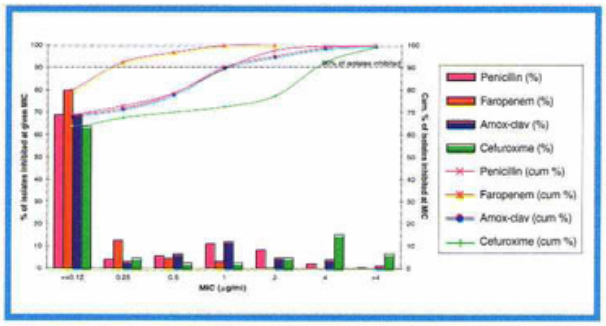
During 1999, 4,725 *S. pneumoniae*, 2,614 *H. influenzae*, and 1,193 *M. catarrhalis* isolates from non-repeat patient specimens were collected from 273 geographically representative U.S. hospitals and sent to our centralized laboratory. Broth microdilution testing was performed using NCCLS guidelines and interpretive criteria[1] for faropenem and the following β-lactam class representatives:

- Penams
  - penicillin (*S. pneumoniae* only)
  - ampicillin (*H. influenzae* and *M. catarrhalis* only)
  - amoxicillin-clavulanate
- Cephalosporins
  - cefuroxime axetil
  - ceftriaxone
- Carbapenems
  - imipenem
- Relevant non-β-lactam comparators
  - levofloxacin
  - trimethoprim-sulfamethoxazole

RESULTS

- Faropenem (modal MIC, ≤0.004 μg/mL; MIC_{90}, 0.25 μg/mL) showed higher intrinsic activity among all isolates of *S. pneumoniae* than all other oral β-lactam comparators and ceftriaxone (Table 1).
- All *S. pneumoniae* isolates tested against faropenem had an MIC of ≤2 μg/mL. Faropenem was 4 to 16 times more active based on MIC_{90} than penicillin, amoxicillin-clavulanate, and cefuroxime axetil (Table 1, Figure 2).
- 32.4% of all *H. influenzae* isolates tested produced β-lactamase. Against all isolates of *H. influenzae*, faropenem had a lower MIC_{90} (1 μg/mL) than the other oral β-lactams. Also, among β-lactamase-positive isolates, based on MIC_{90} (μg/mL), faropenem (0.5) activity was greater than that of amoxicillin-clavulanate (2), cefuroxime (2), and ampicillin (>8) (Table 2).
- β-lactamase production was detected in 94.0% of *M. catarrhalis* isolates tested. Against all isolates of *M. catarrhalis*, based on MIC_{90} (μg/mL), faropenem (0.5) demonstrated comparable activity to amoxicillin-clavulanate (0.5). The faropenem MIC_{90} was 2-fold to 4-fold lower than ceftriaxone (1) and cefuroxime (2) (Table 3).

Figure 2: MIC distributions of faropenem and other oral β-lactam agents against *S. pneumoniae*



RESULTS (continued)

Table 1: Susceptibility of *S. pneumoniae* to faropenem and com

	Penicillin status[a]	n	MIC (μg/mL) Range	Mode	50%	90%
Faropenem	All	4,725	≤0.004-2	≤0.004	0.008	0.25
	Pen-S	3,078	≤0.004-0.12	≤0.004	≤0.004	0.008
	Pen-I	1,154	≤0.004-1	0.25	0.12	0.25
	Pen-R	493	≤0.004-2	0.25	0.5	1
Penicillin	All	4,725	≤0.03->4	≤0.03	≤0.03	2
	Pen-S	3,078	≤0.03-0.06	≤0.03	≤0.03	≤0.03
	Pen-I	1,154	0.12-1	1	0.5	1
	Pen-R	493	2->4	2	2	4
Amox-clav[c]	All	4,725	≤0.015-16	≤0.015	≤0.015	1
	Pen-S	3,078	≤0.015-1	≤0.015	≤0.015	0.03
	Pen-I	1,154	≤0.015-4	1	0.5	1
	Pen-R	493	0.5-16	4	2	4
Cefuroxime-axetil	All	4,725	≤0.12->32	≤0.12	≤0.12	4
	Pen-S	3,078	≤0.12-1	≤0.12	≤0.12	≤0.12
	Pen-I	1,154	≤0.12-32	4	2	4
	Pen-R	493	2->32	4	8	16
Ceftriaxone	All	4,725	≤0.015-8	≤0.015	≤0.015	0.5
	Pen-S	3,078	≤0.015-0.5	≤0.015	≤0.015	0.03
	Pen-I	1,154	≤0.015-4	0.5	0.25	0.5
	Pen-R	493	0.25-8	1	1	4
Imipenem	All	4,725	≤0.015-1	≤0.015	≤0.015	0.25
	Pen-S	3,078	≤0.015-0.25	≤0.015	≤0.015	≤0.015
	Pen-I	1,154	≤0.015-0.5	0.12	0.12	0.25
	Pen-R	493	0.06-1	0.25	0.25	0.5
Levofloxacin	All	4,725	≤0.004->8	1	1	1
	Pen-S	3,078	≤0.004->8	1	1	1
	Pen-I	1,154	0.25->8	1	1	1
	Pen-R	493	0.25->8	1	1	1
SXT[c]	All	4,725	≤0.015->4	0.25	0.25	>4
	Pen-S	3,078	≤0.015->4	0.25	0.25	2
	Pen-I	1,154	0.06->4	>4	4	>4
	Pen-R	493	0.25->4	>4	>4	>4

[a]Analysis for all isolates, penicillin-susceptible (Pen-S) isolates, penicillin-intermediate
[b]NCCLS breakpoints to interpret as susceptible (S), intermediate (I), or resistant (R) are
[c]Amox-clav=amoxicillin-clavulanate; SXT=trimethoprim-sulfamethoxazole

Table 3: Susceptibility of *M. catarrhalis*[a] to faropenem ar

	β-lactamase status[b]	n	MIC (μg/mL) Range	Mode	50%	90%
Faropenem	All	1,193	0.008-2	0.5	0.25	0.5
	β-lac +	1,121	0.008-2	0.5	0.25	0.5
	β-lac -	72	0.015-1	0.03	0.03	0.12
Ampicillin	All	1,193	≤0.06->8	4	4	8
	β-lac +	1,121	≤0.06->8	4	4	8
	β-lac -	72	≤0.06-0.25	≤0.06	≤0.06	≤0.06
Amox-clav[c]	All	1,193	≤0.015-1	0.25	0.25	0.5
	β-lac +	1,121	≤0.015-1	0.25	0.25	0.5
	β-lac -	72	≤0.015-0.5	≤0.015	≤0.015	0.03
Cefuroxime-axetil	All	1,193	≤0.12-8	2	1	2
	β-lac +	1,121	≤0.12-8	2	1	2
	β-lac -	72	≤0.12-1	0.25	0.5	0.5
Ceftriaxone	All	1,193	≤0.015-4	0.5	0.5	1
	β-lac +	1,121	≤0.015-4	0.5	0.5	1
	β-lac -	72	≤0.015-0.12	≤0.015	≤0.015	≤0.015

Imipenem
Levofloxacin
SXT[c]

[a]NCCLS breakp currently publi
[b]Analysis for al
[c]Amox-clav=am