KPI-10 In Vitro Activity Tested Against Pathogens Commonly Associated with Community-Acquired Bacterial Pneumonia (CABP) Infections

R.K. FLAMM, D.J. BIEDENBACH, H.S. SADER, M.L. KONRARDY, R.N. JONES
JMI Laboratories, North Liberty, Iowa, USA

F-2051

Robert K. Flamm, PhD
JMI Laboratories
345 Beaver Kreek Ctr, Ste A
North Liberty, Iowa, 52317, USA
Phone: 319-665-3370
Email: robert-flamm@jmilabs.com

Abstract

Background: KPI-10, formerly WQ-3813, is a new FQ with broad-spectrum potencies against Gram-positive (GP) and -negative (GN) bacteria including FQ-resistant (FQR) strains of *S. pneumoniae* and other CABP pathogens. In this study, KPI-10 and comparator FQs were evaluated against contemporary bacterial isolates commonly associated with CABP.

Methods: Isolates were collected from medical centers in North America, Europe , Latin America , and Asia-Pacific (APAC) during 2008-2010. MIC values for KPI-10 and comparator agents including ciprofloxacin, levofloxacin, and moxifloxacin were determined using CLSI reference broth microdilution methods. QC organisms and interpretive criteria for comparator compounds were those recommended by CLSI.

Results: 203 *S. pneumoniae* (SPN), 90 *H. influenzae* (HI), 88 *M. catarrhalis* (MC), and 259 community-acquired MRSA (CA-MRSA) were tested. KPI-10 was the most potent agent against SPN with a MIC_{90} of 0.06 µg/ml overall for all isolates and for each of the four regions. For HI, KPI-10 was the most potent agent, exhibiting regional and overall MIC_{90} values of 0.008 µg/ml. It was the only FQ which did not have an increased MIC_{90} in APAC. For MC, KPI-10 was the most potent agent with a MIC_{90} value for all isolates at 0.015 µg/ml. There were no differences noted in the activity of KPI-10 for beta-lactamase-positive or -negative isolates of HI and MC. For CA-MRSA, KPI-10 was the most potent FQ with overall $MIC_{50/90}$ values of 0.25/1 µg/ml. This was eight-fold or greater activity when compared to other FQs which had MIC_{90} values of ≥8 µg/ml. KPI-10 retained potent activity against the FQR subset of CA-MRSA with 85.7% of the KPI-10 MIC values at ≤1 µg/ml.

Conclusions: KPI-10 was the most active FQ against GP organisms and among the most active for GN associated with CABP. Its overall potent activity, including coverage of selected groups of FQR organisms, suggests that it warrants further evaluation for its potential role in the treatment of CABP.

Introduction

Respiratory tract infections are common in community and healthcare facilities, and may be associated with significant morbidity and mortality. Inadequate, inappropriate, or delayed therapy may increase the length of hospital stay and costs and increase mortality associated with these infections. Among the major pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*. The emergence of multidrug-resistant (MDR) organisms among these pathogens such as MDR *S. pneumoniae* and methicillin-resistant *S. aureus* (MRSA) are limiting the use of currently available agents. For example, Jones et. al published in 2010 an analysis of the SENTRY Antimicrobial Surveillance Program (1998-2009), which indicated striking declines in susceptibility rates for β-lactams and other antimicrobials in *S. pneumoniae*. For the fluoroquinolones, the overall decrease in susceptibility for levofloxacin was only 0.6% and the proportion of isolates with possible single-step mutational resistance (ciprofloxacin MIC of at least 4 µg/ml) was relatively stable (range 1.5-4.9%). Doern et. al demonstrated that fluoroquinolone-resistant *S. pneumoniae* have become more prevalent over the past decade, even though the rates of *S. pneumoniae* resistance to β-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole have plateaued or decreased. In an in vitro susceptibility survey of 1,817 *S. pneumoniae* isolates obtained from patients with community-acquired respiratory tract infections in 44 US medical centers, 22.2% of isolates were multidrug resistant, and 2.3% of isolates had a ciprofloxacin MIC of at least 4 µg/ml.

KPI-10 (formerly WQ-3813, the maelic acid salt of WQ-3810) is a novel fluoroquinolone containing a 6-amino-3,5-difluoropyridine at the 1-position and 3-isopropylaminoazetidine at the 7-position, which has potent activity against common respiratory pathogens, including activity against strains that are resistant to the currently-available fluoroquinolones. In this study, KPI-10 and comparator agents including fluoroquinolones were evaluated against contemporary bacterial isolates commonly associated with community-acquired bacterial pneumonia (CABP).

Materials & Methods

Fastidious respiratory tract pathogens (381 isolates) and CA-MRSA (259) were randomly selected from a collection of pathogens from North America (NA; 27 sites), Latin America (LA; 9 sites), Europe (EU; 23 sites) and the Asia-Pacific (APAC; 30 sites) and included the following species (number of strains in each region): a) *S. pneumoniae* (203); NA (51), LA (50), EU (51), APAC (51) b) *H. influenzae* (90); NA (23), LA (22), EU (22), APAC (23) c) *M. catarrhalis* (88); NA (23), LA (21), EU (21), APAC (23) and d) community-acquired MRSA (CA-MRSA [MRSA isolated from patients less than 48 hours post-admission]; 259); NA (101), LA (53), EU (51) and APAC (54).

KPI-10 antimicrobial powder was provided by Kalidex. The antimicrobial powder was dissolved in distilled water to make a stock solution for testing of 1280 µg/ml. Comparator agent powder lots were provided by JMI Laboratories through Sigma-Aldrich or respective manufacturers. Antimicrobials tested for Gram-positive bacteria were KPI-10, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, erythromycin, clindamycin, cefepime, meropenem, linezolid, and vancomycin. For Gram-negative bacteria, KPI-10, ciprofloxacin, levofloxacin, moxifloxacin, azithromycin, ceftazidime, cefepime, meropenem, piperacillin/tazobactam, and tetracycline were tested. MIC values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method as described in M07-A9 [2012] or broth microdilution for *M. catarrhalis* as described in M45-A2 [2010]. Reference frozen-form assay panels were produced by JMI Laboratories (North Liberty, Iowa USA) and consisted of three media types; cation-adjusted Mueller-Hinton broth (MHB), Haemophilus test medium (HTM), and MHB plus 2.5-5% lysed horse blood. Quality control (QC) ranges and interpretive criteria for comparator compounds were as published in CLSI M100-S22 [2012]; tested QC strains *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. All QC results were within CLSI established ranges.

Results

- The MIC distributions for KPI-10 and comparator fluroquinolones for the fastidious respiratory pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are presented in Table 1 and for CA-MRSA in Table 2.

- *S. pneumoniae*
  - KPI-10 was the most potent agent tested against *S. pneumoniae* with a MIC_{90} of 0.06 µg/ml overall for all isolates and for each of the four regions individually (NA, LA, EU, and APAC). The next most potent agent was moxifloxacin with a four-fold higher MIC_{90} value of 0.25 µg/ml. Gatifloxacin, meropenem, and vancomycin exhibited overall MIC_{90} values of 0.5 µg/ml followed by levofloxacin, cefepime, and linezolid at 1 µg/ml (Table 3). In the collection of 203 isolates, the highest KPI-10 MIC value was at 0.25 µg/ml (2 isolates). There were six isolates that were levofloxacin-resistant (MIC ≥8 µg/ml) and 15 isolates with ciprofloxacin MIC values at ≥4 µg/ml).

- *H. influenzae*
  - KPI-10 was the most potent agent tested against *H. influenzae* with a MIC_{90} value of 0.008 µg/ml for each of the four regions individually (NA, LA, EU, and APAC) and overall (Table 3). It was the only fluoroquinolone which did not have an increased MIC_{90} in the Asia-W. Pacific Region. Ciprofloxacin was the next most potent agent followed by levofloxacin and moxifloxacin with MIC_{90} values at 0.015, 0.03, and 0.06 µg/ml, respectively. Ceftazidime, cefepime, meropenem, and piperacillin-tazobactam all had MIC_{90} values ≤0.5 µg/ml. The highest MIC_{90} values for the fluoroquinolones other than KPI-10 were in the APAC Region where the MIC_{90} values were 0.06, 0.06, and 0.12 µg/ml, respectively for ciprofloxacin, levofloxacin, and moxifloxacin. There were no differences noted in MIC_{90} values for KPI-10, ciprofloxacin, and moxifloxacin for β-lactamase-positive or β-lactamase-negative isolates of *H. influenzae*; the levofloxacin MIC_{90} value was two-fold higher for the β-lactamase-negative isolates.

- *M. catarrhalis*
  - KPI-10 was the most potent agent tested against *M. catarrhalis* with a MIC_{90} value for all isolates at 0.015 µg/ml (Table 3). NA, EU, and the APAC MIC_{90} values were 0.015 µg/ml; the MIC_{90} for LA was two-fold lower at 0.008 µg/ml. Ciprofloxacin, was the next most potent agent overall with a MIC_{90} value of 0.03 µg/ml followed by levofloxacin, moxifloxacin, gatifloxacin, and meropenem at ≤0.06 µg/ml. There were no differences noted in MIC_{50} values for KPI-10, ciprofloxacin, and levofloxacin for β-lactamase-positive or β-lactamase-negative isolates; the moxifloxacin MIC value was two-fold lower for the β-lactamase isolates positive isolates.

- CA-MRSA
  - KPI-10 was the most potent fluoroquinolone agent overall for CA-MRSA with a $MIC_{50/90}$ value of 0.25/1 µg/ml (Table 3). This was eight-fold or greater activity than other fluoroquinolones which had MIC_{90} values of 8 to >8 µg/ml. KPI-10 was also the most potent fluoroquinolone against the fluoroquinolone-susceptible and fluoroquinolone-resistant subsets of CA-MRSA with MIC_{90} values of 0.015 and 2 µg/ml, respectively. For the fluoroquinolone-resistant subset, 85.7% of the KPI-10 MIC values were at ≤1 µg/ml. KPI-10 and vancomycin were the most potent agents tested with MIC_{90} values of 1 µg/ml. The next most potent agent was linezolid with a MIC_{90} value of 2 µg/ml. The MIC_{90} value for KPI-10 was 2 µg/ml in the NA subset and 1 µg/ml in EU, LA, and APAC. The vancomycin MIC_{90} did not vary between regions.

Figure 1. Chemical structure of KPI-10 (WQ-3810)

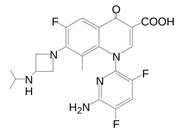

Table 1. MIC frequency distributions and cumulative percent inhibited for KPI-10 and comparator fluoroquinolone antimicrobial agents for pathogens associated with community-acquired respiratory tract infections.

Organism/antimicrobial agent (no. tested)	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml):														MIC_{50}	MIC_{90}
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
S. pneumoniae (203)																
KPI-10	NT[a]	-[b]	-	34 (16.8)	139 (85.2)	25 (97.5)	3 (99.0)	2 (100.0)	-	-	-	-	-	-	0.03	0.06
Ciprofloxacin	NT	-	-	-	-	-	-	1 (0.5)	66 (33.0)	100 (82.3)	21 (92.6)	7 (96.1)	2 (97.0)	6 (100.0)	1	2
Levofloxacin	NT	-	-	-	-	-	-	1 (0.5)	66 (33.0)	122 (93.1)	8 (97.0)	0 (97.0)	0 (97.0)	6 (100.0)	1	1
Moxifloxacin	NT	-	-	-	-	24 (11.8)	133 (77.3)	39 (96.6)	1 (97.0)	0 (97.0)	3 (98.5)	3 (100.0)	-	-	0.12	0.25
Gatifloxacin	NT	-	-	-	-	-	16 (7.9)	141 (77.3)	39 (96.6)	1 (97.0)	0 (97.0)	4 (99.0)	2 (100.0)	-	0.25	0.5
H. influenzae (90)																
KPI-10	10 (11.1)	48 (64.4)	28 (95.6)	3 (98.9)	1 (100.0)	-	-	-	-	-	-	-	-	-	0.004	0.008
Ciprofloxacin	1 (1.1)	0 (1.1)	51 (57.8)	31 (92.2)	1 (93.3)	2 (95.6)	4 (100.0)	-	-	-	-	-	-	-	0.008	0.015
Levofloxacin	-	-	2 (2.2)	76 (86.7)	5 (92.2)	4 (96.7)	3 (100.0)	-	-	-	-	-	-	-	0.015	0.03
Moxifloxacin	-	-	-	38 (42.2)	37 (83.3)	9 (93.3)	4 (97.8)	2 (100.0)	-	-	-	-	-	-	0.03	0.06
M. catarrhalis (88)																
KPI-10	NT	11 (12.5)[c]	57 (77.3)	17 (96.6)	2 (98.9)	1 (100.0)	-	-	-	-	-	-	-	-	0.008	0.015
Ciprofloxacin	NT	-	3 (3.4)	45 (54.6)	34 (93.2)	5 (98.9)	1 (100.0)	-	-	-	-	-	-	-	0.015	0.03
Levofloxacin	NT	-	2 (2.3)	7 (10.2)	67 (86.4)	10 (97.7)	0 (97.7)	0 (97.7)	1 (98.9)	1 (100.0)	-	-	-	-	0.03	0.06
Moxifloxacin	NT	2 (2.3)[c]	1 (3.4)	3 (6.8)	42 (54.6)	37 (96.6)	1 (97.7)	2 (100.0)	-	-	-	-	-	-	0.03	0.06
Gatifloxacin	NT	NT	NT	NT	NT	86 (97.7)[d]	0 (97.7)	2 (100.0)	-	-	-	-	-	-	≤0.06	≤0.06

a. NT = dilution was not tested.
b. A dash indicates that no values were observed at that MIC value.
c. All isolates had MIC values of ≤0.004 µg/ml.
d. All isolates had MIC values of ≤0.06 µg/ml.

Table 2. MIC frequency distributions and cumulative percent inhibited for KPI-10 and comparator fluoroquinolone antimicrobial agents tested against CA-MRSA.

Organism/antimicrobial agent (no. tested)	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml):												MIC_{50}	MIC_{90}
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
CA-MRSA (259)															
KPI-10	-[a]	8 (3.1)	70 (30.1)	6 (32.4)	1 (32.8)	3 (34.0)	47 (52.1)	34 (65.3)	65 (90.4)	16 (96.5)	9 (100.0)	-	-	0.25	1
Ciprofloxacin	-	-	-	-	-	2 (0.8)	58 (23.2)	20 (30.9)	2 (31.7)	1 (32.1)	3 (33.2)	28 (44.0)	145 (100.0)	>8	>8
Levofloxacin	-	-	-	-	-	34 (13.1)	46 (30.9)	4 (32.4)	0 (32.4)	1 (32.8)	44 (49.8)	26 (59.9)	104 (100.0)	8	>8
Moxifloxacin	-	-	1 (0.4)	47 (18.5)	32 (30.9)	4 (32.4)	0 (32.4)	0 (32.4)	23 (41.3)	45 (58.7)	41 (74.5)	50 (93.8)	16 (100.0)	2	8
Gatifloxacin	NT[b]	NT	NT	NT	38 (14.7)	42 (30.9)	4 (32.4)	0 (32.4)	0 (32.4)	47 (50.6)	37 (64.9)	66 (90.4)	25 (100.0)	2	8
Levofloxacin-susceptible CA-MRSA (84)															
KPI-10	-	8 (9.5)	70 (92.9)	6 (100.0)	-	-	-	-	-	-	-	-	-	0.015	0.015
Ciprofloxacin	-	-	-	-	-	2 (2.4)	58 (71.4)	20 (95.2)	2 (97.6)	1 (98.8)	1 (100.0)	-	-	0.25	0.5
Levofloxacin	-	-	-	-	-	34 (40.5)	46 (95.2)	4 (100.0)	-	-	-	-	-	0.25	0.25
Moxifloxacin	-	-	1 (1.2)	47 (57.1)	32 (95.2)	4 (100.0)	-	-	-	-	-	-	-	0.03	0.06
Gatifloxacin	NT	NT	NT	NT	38 (45.2)	42 (95.2)	4 (100.0)	-	-	-	-	-	-	0.12	0.12
Levofloxacin non-susceptible CA-MRSA (175)															
KPI-10	-	-	-	-	1 (0.6)	3 (2.3)	47 (29.1)	34 (48.6)	65 (85.7)	16 (94.9)	9 (100.0)	-	-	1	2
Ciprofloxacin	-	-	-	-	-	-	-	-	-	-	2 (1.1)	28 (17.1)	145 (100.0)	>8	>8
Levofloxacin	-	-	-	-	-	-	-	-	-	1 (0.6)	44 (25.7)	26 (40.6)	104 (100.0)	>8	>8
Moxifloxacin	-	-	-	-	-	-	-	-	23 (13.1)	45 (38.9)	41 (62.3)	50 (90.9)	16 (100.0)	4	8
Gatifloxacin	NT	NT	NT	NT	-	-	-	-	-	47 (26.9)	37 (48.0)	66 (85.7)	25 (100.0)	8	>8

a. A dash indicates that no values were observed at that MIC value.
b. NT = dilution not tested.

Table 3. Activity of KPI-10 and comparator antimicrobial agents when tested against pathogens associated with community-tract infections.

Organism/antimicrobial agent (no. isolates tested)	MIC (µg/ml)			CLSI[a] %S / %R	EUCAST[a] %S / %R
	MIC_{50}	MIC_{90}	Range		
Streptococcus pneumoniae (**All regions**, 203)					
KPI-10	0.03	0.06	0.015 – 0.25	- / -	- / -
Ciprofloxacin	1	2	0.25 – >8	- / -	0.0 / 7.4
Levofloxacin	1	1	0.25 – >8	97.0 / 3.0	97.0 / 3.0
Moxifloxacin	0.12	0.25	0.06 – 4	97.0 / 1.5	97.0 / 3.0
Gatifloxacin	0.25	0.5	0.12 – 8	97.0 / 3.0	- / -
Erythromycin	≤0.06	>8	≤0.06 – >8	57.6 / 41.9	57.6 / 41.9
Clindamycin	≤0.25	>1	≤0.25 – >1	74.9 / 25.1	74.9 / 25.1
Cefepime	≤0.12	1	≤0.12 – 16	90.1 / 1.5	90.1 / 1.5
Meropenem	≤0.06	0.5	≤0.06 – 2	75.9 / 9.4	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
S. pneumoniae (**North America**, 51)					
KPI-10	0.03	0.06	0.015 – 0.25	- / -	- / -
Ciprofloxacin	1	2	0.5 – >8	- / -	0.0 / 9.8
Levofloxacin	1	1	0.5 – >8	94.1 / 5.9	94.1 / 5.9
Moxifloxacin	0.12	0.25	0.06 – 4	94.1 / 3.9	94.1 / 5.9
Gatifloxacin	0.25	0.5	0.12 – 8	94.1 / 5.9	- / -
Erythromycin	≤0.06	>8	≤0.06 – >8	60.8 / 39.2	60.8 / 39.2
Clindamycin	≤0.25	>1	≤0.25 – >1	84.3 / 15.7	84.3 / 15.7
Cefepime	≤0.12	1	≤0.12 – 2	90.2 / 0.0	90.2 / 0.0
Meropenem	≤0.06	1	≤0.06 – 2	78.4 / 11.8	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
S. pneumoniae (**Europe**, 51)					
KPI-10	0.03	0.06	0.015 – 0.06	- / -	- / -
Ciprofloxacin	1	2	0.25 – >8	- / -	0.0 / 7.8
Levofloxacin	1	1	0.25 – >8	98.0 / 2.0	98.0 / 2.0
Moxifloxacin	0.12	0.25	0.06 – 2	98.0 / 0.0	98.0 / 2.0
Gatifloxacin	0.25	0.5	0.12 – 4	98.0 / 2.0	- / -
Erythromycin	≤0.06	>8	≤0.06 – >8	66.7 / 33.3	66.7 / 33.3
Clindamycin	≤0.25	>1	≤0.25 – >1	80.4 / 19.6	80.4 / 19.6
Cefepime	≤0.12	1	≤0.12 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.06	0.5	≤0.06 – 0.5	86.3 / 0.0	100.0 / 0.0
Linezolid	1	1	0.25 – 1	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
S. pneumoniae (**Latin America**, 50)					
KPI-10	0.03	0.06	0.015 – 0.06	- / -	- / -
Ciprofloxacin	1	2	0.5 – 4	- / -	0.0 / 2.0
Levofloxacin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.12	0.25	0.06 – 0.25	100.0 / 0.0	100.0 / 0.0
Gatifloxacin	0.25	0.5	0.12 – 0.5	100.0 / 0.0	- / -
Erythromycin	≤0.06	>8	≤0.06 – >8	68.0 / 30.0	68.0 / 30.0
Clindamycin	≤0.25	>1	≤0.25 – >1	86.0 / 14.0	86.0 / 14.0
Cefepime	≤0.12	1	≤0.12 – 2	94.0 / 0.0	94.0 / 0.0
Meropenem	≤0.06	0.5	≤0.06 – 1	76.0 / 8.0	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
S. pneumoniae (**Asia-Pacific**, 51)					
KPI-10	0.03	0.06	0.015 – 0.25	- / -	- / -
Ciprofloxacin	1	2	0.5 – >8	- / -	0.0 / 9.8
Levofloxacin	1	1	0.5 – >8	96.1 / 3.9	96.1 / 3.9
Moxifloxacin	0.12	0.25	0.06 – 4	96.1 / 2.0	96.1 / 3.9
Gatifloxacin	0.25	0.5	0.12 – 8	96.1 / 3.9	- / -
Erythromycin	>8	>8	≤0.06 – >8	35.3 / 64.7	35.3 / 64.7
Clindamycin	>1	>1	≤0.25 – >1	49.0 / 51.0	49.0 / 51.0
Cefepime	0.5	2	≤0.12 – 16	76.5 / 5.9	76.5 / 5.9
Meropenem	0.12	1	≤0.06 – 2	62.7 / 17.6	100.0 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Community-acquired *Staphylococcus aureus* (**All regions**, 259)					
KPI-10	0.25	1	0.008 – 4	- / -	- / -
Ciprofloxacin	>8	>8	0.12 – >8	31.7 / 68.0	31.7 / 68.3
Levofloxacin	8	>8	0.12 – >8	32.4 / 67.2	32.4 / 67.2
Moxifloxacin	2	8	0.015 – >8	32.4 / 58.7	32.4 / 58.7
Gatifloxacin	2	8	≤0.06 – >8	32.4 / 67.6	- / -
Erythromycin	>4	>4	≤0.25 – >4	23.6 / 76.1	23.6 / 76.4
Clindamycin	≤0.25	>2	≤0.25 – >2	55.2 / 44.4	54.8 / 44.8
Amikacin	8	64	1 – >64	81.9 / 14.3	62.5 / 18.1
Linezolid	1	2	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
H. influenzae (**All regions**, 90)					
KPI-10	0.004	0.008	0.002 – 0.03	- / -	- / -
Ciprofloxacin	0.008	0.015	0.002 – 0.12	100.0 / -	100.0 / 0.0
Levofloxacin	0.015	0.03	0.008 – 0.12	100.0 / -	100.0 / 0.0
Moxifloxacin	0.03	0.06	0.015 – 0.25	100.0 / -	100.0 / 0.0
Azithromycin	2	4	≤0.5 – >64	95.6 / -	3.3 / 4.4
Ceftazidime	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	- / -
Cefepime	≤0.12	≤0.12	≤0.12 – 0.5	100.0 / -	97.8 / 2.2
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	100.0 / -	- / -
Tetracycline	0.5	1	≤0.12 – 2	100.0 / 0.0	97.8 / 0.0
Moraxella catarrhalis (**All regions**, 88)					
KPI-10	0.008	0.015	≤0.004 – 0.06	- / -	- / -
Ciprofloxacin	0.015	0.03	0.008 – 0.25	100.0 / 0.0	100.0 / 0.0
Levofloxacin	0.03	0.06	0.008 – 1	100.0 / -	100.0 / 0.0
Moxifloxacin	0.03	0.06	≤0.004 – 0.25	- / -	100.0 / 0.0
Gatifloxacin	≤0.06	≤0.06	≤0.06 – 0.25	- / -	- / -
Azithromycin	≤0.25	≤0.25	≤0.25 – >8	96.6 / -	97.7 / 2.3
Ceftazidime	≤0.25	≤0.25	≤0.25	100.0 / -	- / -
Cefepime	0.25	1	≤0.12 – 2	- / -	56.8 / 43.2
Meropenem	≤0.06	≤0.06	≤0.06 – 0.25	- / -	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2012] and EUCAST [2012].

Conclusions

- KPI-10 demonstrated potent activity against bacteria that are commonly the cause of community-associated respiratory tract infections.
  - KPI-10 was the most potent fluoroquinolone with a MIC_{90} value at 0.06 µg/ml against *S. pneumoniae*, including 3% of isolates that were fluoroquinolone-resistant, 26.1% that were penicillin-resistant, and 41.9% that were macrolide-resistant. KPI-10 was 4-fold and 16-fold more potent against *S. pneumoniae* than moxifloxacin and levofloxacin, respectively.
  - KPI-10 was the most potent fluoroquinolone against *H. influenzae* and *M. catarrhalis;* its activity was essentially unchanged regardless of β-lactamase production.
  - KPI-10 exhibited potent activity against CA-MRSA. It was the most potent fluoroquinolone against this pathogen with $MIC_{50/90}$ values at 0.25/1 µg/ml. This was eight-fold or greater activity than other fluoroquinolones which had MIC_{90} values of 8 to >8 µg/ml. KPI-10 retained potent activity even against the fluoroquinolone-resistant subset of CA-MRSA with 85.7% of the KPI-10 MIC values at ≤1 µg/ml.
- The broad-spectrum and potent activity exhibited by KPI-10, including coverage of selected respiratory pathogens that are resistant to currently-available fluoroquinolones, suggests that it warrants further evaluation for its potential role in the treatment of CABP.

Acknowledgments

This study at JMI Laboratories was supported by an Educational/Research grant from Kalidex, and JMI Laboratories received compensation fees for services in relation to preparing the abstract/poster, which was funded by Kalidex.

References

1. Clinical and Laboratory Standards Institute (2010). *M45-A2. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria: second edition*. Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute (2012). *M07-A9. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: ninth edition*. Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2012). *M100-S22. Performance standards for antimicrobial susceptibility testing: 22nd informational supplement*. Wayne, PA: CLSI.
4. Doern GV, Richter SS, Miller A, Miller N, Rice C, Heilmann K, Beekmann S (2005). Antimicrobial resistance among *Streptococcus pneumoniae* in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes? *Clin Infect Dis* 41: 139-148.
5. Einarsson S, Kristjansson M, Kristinsson KG, Kjartansson G, Jonsson S (1998). Pneumonia caused by penicillin-non-susceptible and penicillin-susceptible pneumococci in adults: A case-control study. *Scand J Infect Dis* 30: 253-256.
6. Feikin DR, Schuchat A, Kolczak M, Barrett NL, Harrison LH, Lefkowitz L, McGeer A, Farley MM, Vugia DJ, Lexau C, Stefonek KR, Patterson JE, Jorgensen JH (2000). Mortality from invasive *pneumococcal pneumonia* in the era of antibiotic resistance, 1995-1997. *Am J Public Health* 90: 223-229.
7. File TM, Jr. (2006). Clinical implications and treatment of multiresistant *Streptococcus pneumoniae* pneumonia. *Clin Microbiol Infect* 12 Suppl 3: 31-41.
8. Jones RN, Sader HS, Moet GJ, Farrell DJ (2010). Declining antimicrobial susceptibility of *Streptococcus pneumoniae* in the United States: Report from the SENTRY Antimicrobial Surveillance Program (1998-2009). *Diagn Microbiol Infect Dis* 68: 334-336.
9. Kazamori D, Suzuki H, Amago T, Itoh K, Yazaki A (2009). In vitro activity of WQ-3813 against nosocomial pathogens. Abstr. F1-1984. *49th ICAAC, September 12-15, 2009*, San Francisco, CA, USA.
10. Plouffe JF, Breiman RF, Facklam RR, for the Franklin County Pneumonia Study Group (1996). Bacteremia with *Streptococcus pneumoniae*. Implications for therapy and prevention. *JAMA* 275: 194-198.
11. Sherr AF (2007). Epidemiology of staphylococcal resistance. *Clin Infect Dis* 45 Suppl 3: S171-S176.
12. Suzuki H, Hayashi N, Amago T, Takenaka H, Amano H, Itoh K, Kuramoto Y, Yazaki A (2008). WQ-3810, a next generation respiratory fluoroquinolone with outstanding activity against QRSP. Abstr. F1-2051. *48th ICAAC, October 25-28, 2008*, Washington DC, USA.