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In vitro activity of ME1036 versus other β-lactams against penicillin-resistant *Streptococcus pneumoniae* serotypes exhibiting higher amoxicillin than penicillin MIC

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Sir,

It has been postulated that pneumococcal infections should be considered among the severe nosocomial diseases,[1] and that *Streptococcus pneumoniae* should be covered by empirical therapy of hospital-acquired pneumonia together with methicillin-resistant *Staphylococcus aureus* (MRSA), the other principal Gram-positive, nosocomial respiratory pathogen. In a retrospective study carried out in Spain over the period 1995–2002, serotypes 14, 23F and 19 were those most frequently isolated in nosocomial *S. pneumoniae* bloodstream infections.[1] These serotypes, together with 6B and 9V, have been reported as some of the most troublesome with regard to antimicrobial resistance.[2] An additional problem is the reported spread of clones with higher amoxicillin than penicillin MIC.[2] The emergence of resistance to amoxicillin within existing penicillin-resistant clones is also related to macrolide and ciprofloxacin resistance,[2] with levofloxacin non-susceptibility rates of 34% among the serotype 14 Spanish multi-resistant clone.[2] The genetic relatedness of these multidrug-resistant isolates, which suggests possible clonal expansion, raises the concern that it may be increasingly difficult to find adequate therapies for *S. pneumoniae* infections.

ME1036 is a novel parenteral carbapenem active against MRSA, β-lactamase-producing *Haemophilus influenzae* and ESBL-producing Enterobacteriaceae.[3–5] The aim of this study was to explore the *in vitro* activity of ME1036 against recent penicillin-resistant isolates of *S. pneumoniae* showing higher amoxicillin versus penicillin MIC.

From the *S. pneumoniae* isolates received in the Spanish Pneumococcal Reference Laboratory (Instituto de Salud Carlos III) in the period January 2005 to September 2007, 220 penicillin-resistant isolates showing higher amoxicillin versus penicillin MIC were tested. Antimicrobial susceptibility was determined by the agar dilution method[6] using Mueller–Hinton agar (Difco Laboratories, Detroit, MI, USA) as culture media supplemented with 5% sheep blood (Biomedics, Madrid, Spain), with final inocula of 10^5 cfu/mL, and incubating under 5% CO_2 atmosphere. *S. pneumoniae* ATCC 6303, *S. pneumoniae* ATCC 49619 and five clinical isolates were used as quality control strains as in all determinations carried out in the Spanish Reference Laboratory for Pneumococci. Minimum concentrations (mg/L) tested in the plates were 0.001 for ME1036, 0.007 for imipenem and meropenem, 0.015 for penicillin, ampicillin, cefotaxime, ceftriaxone and cefepime, 0.03 for cefuroxime, 0.06 for amoxicillin, 0.12 for erythromycin and 1 for levofloxacin. For all compounds, the maximum concentration tested in the plates was 32 mg/L, except for ampicillin (16 mg/L). Susceptibility breakpoints (mg/L) defined by CLSI were penicillin ≤0.06, amoxicillin ≤2, cefuroxime sodium ≤0.5, cefotaxime, ceftriaxone and cefepime ≤1, imipenem ≤0.12, meropenem ≤0.25, erythromycin ≤0.25 and levofloxacin ≤2. CLSI breakpoints are not defined for ampicillin and ME1036. Serotyping was performed by the Quellung reaction and/or dot blot assay.

Of the 220 strains, 69 belonged to serotype 9V, 65 to serotype 14, 33 to serotype 6B, 27 to serotype 19A, 7 to serotype 19F, 5 were non-typeable and the other 14 strains belonged to other serotypes with less than five isolates. Table 1 shows susceptibility to study drugs for serotypes with more than 25 isolates. Susceptibility rates for penicillin, amoxicillin and cefuroxime were 0% and that for cefepime was <28%. Susceptibility rates to cefotaxime ranged from 26.2% for serotype 14 to 82.6% for serotype 9, whereas susceptibility rates to ceftriaxone were >88% for all serotypes. Susceptibility rates for imipenem and meropenem were ≤6.2% in all cases. The MIC_{90} value for ME1036 was 0.12 mg/L for all serotypes, which was at least 4-fold lower than imipenem, meropenem and ceftriaxone. Our findings suggest that against these multidrug-resistant pneumococcal isolates, the ranking of *in vitro* activity based on MIC_{90} for the β-lactams would be ME1036 (0.12 mg/L) (most active)>imipenem (0.5 mg/L)>meropenem (1 mg/L)>ceftriaxone (1 mg/L)>cefotaxime (2 mg/L)>penicillin=cefepime (4 mg/L)>amoxicillin (8–16 mg/L)>cefuroxime (16 mg/L)>ampicillin (≥16 mg/L) (least active).

A previous study that employed agar dilution testing against a smaller number of non-selected penicillin-resistant *S. pneumoniae* isolates reported an MIC_{90} value of 0.03 mg/L for ME1036,[4] a value two dilutions lower than the MIC_{90} value determined in this study against multidrug-resistant strains belonging to troublesome serotypes exhibiting higher amoxicillin than penicillin MIC. MIC_{90} values determined for ME1036 by broth microdilution against a small number (11 strains) of penicillin-resistant *S. pneumoniae* isolates in a previous study showed values similar to those in the present study.[3]

In conclusion, ME1036 exhibited excellent intrinsic activity against penicillin-resistant *S. pneumoniae* belonging to serotypes 9V, 14, 6B and 19A, exhibiting higher amoxicillin than penicillin MIC. The spread of multidrug resistance that includes

Table 1. MIC_{50}, MIC_{90} (mg/L) and percentage of susceptibility to study drugs for penicillin-resistant strains exhibiting higher amoxicillin than penicillin MIC for serotypes with more than 25 isolates with this resistance phenotype

	Serotype 9V ($n = 69$)		Serotype 14 ($n = 65$)		Serotype 6B ($n = 33$)		Serotype 19A ($n = 27$)	
Antibiotic	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
PEN	2/4	0.0	2/4	0.0	2/2	0.0	2/4	0.0
AMP	8/≥16	—	8/≥16	—	8/≥16	—	8/8	—
AMX	8/16	0.0	8/16	0.0	8/8	0.0	8/8	0.0
CXM	8/8	0.0	8/16	0.0	8/16	0.0	8/16	0.0
CTX	1/2	82.6	2/2	26.2	1/2	66.7	2/4	33.3
CRO	0.5/1	98.6	1/1	93.8	1/1	100	1/2	88.9
FEP	2/4	18.8	2/4	15.4	2/4	27.3	2/2	18.5
IPM	0.5/0.5	1.4	0.5/1	3.1	0.5/0.5	3.0	0.5/1	0.0
MEM	1/1	0.0	1/1	6.2	0.5/1	12.1	0.5/1	3.7
ME1036	0.12/0.12	—	0.06/0.12	—	0.06/0.12	—	0.06/0.12	—
ERY	≤0.12/≥32	82.6	≤0.12/≥32	69.2	≥32/≥32	6.0	≥32/≥32	0.0
LVX	≤1/16	72.5	≤1/≤1	96.9	≤1/≤1	97.0	≤1/≤1	100.0

PEN, penicillin; AMP, ampicillin; AMX, amoxicillin; CXM, cefuroxime; CTX, cefotaxime; CRO, ceftriaxone; FEP, cefepime; IPM, imipenem; MEM, meropenem; ERY, erythromycin; LVX, levofloxacin.

β-lactams (including penicillins, second- and third-generation cephalosporins and previous carbapenems) may challenge empirical hospital treatment of lower respiratory tract infections. The high intrinsic activity of ME1036 against resistant strains of *S. pneumoniae* may represent an advantage when broad-spectrum activity is required.

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Transparency declarations

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