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## Abstract

**Background:** CEM-101 is a new fluoroketolide with potent activity against Gram-positive pathogens and key respiratory tract Gram-negative species (*H. influenzae* and *M. catarrhalis*). We report CEM-101 potencies tested against *S. pneumoniae* (SPN) isolates focusing on various multidrug-resistant (MDR) subsets.

**Methods:** 1,737 SPN strains were collected in 2008 from medical centers in the USA, Europe, and Latin America. A central monitoring laboratory susceptibility (S) tested each isolate against > 25 antimicrobials by CLSI (M07-A8, M100-S19) methods. MDR patterns were defined by resistance (R) to penicillin (PEN), erythromycin (ERY), clindamycin (CLI), tetracycline (TET), and TMP/SMX (T/S). A ketolide, telithromycin (TEL), and levofloxacin (LEV) were also tested.

**Results:** The CEM-101 inhibition at  $\leq 1$   $\mu\text{g/ml}$  was compared in a SPN population with the following R-rates (%): PEN (21.4), ERY (36.3), CLI (20.0), TET (25.8), T/S (21.7) and LEV (1.1). CEM-101 (MIC<sub>50/90</sub>, 0.015/0.25  $\mu\text{g/ml}$ ) showed increased MIC<sub>50</sub> and MIC<sub>90</sub> results for MDR patterns that included ERY and CLI (0.25/0.5  $\mu\text{g/ml}$ , respectively). TEL (S rate, 99.9%) MIC results were slightly higher than CEM-101 (100.0%S). Amoxicillin/clavulanate non-S rate was 12.8%, but 86.9% among isolates R to all 5 listed drugs (Table). Ceftriaxone non-S rate was an alarming 8.6% (8.2% for cefepime). CEM-101 was effective (MIC,  $\leq 1$   $\mu\text{g/ml}$ ) versus all LEV-R isolates and those strains with ciprofloxacin MIC values at  $\geq 4$   $\mu\text{g/ml}$  (QRDR mutants).

R patterns						MIC ( $\mu\text{g/ml}$ )			
PEN	ERY	CLI	TET	T/S	LEV	No. tested	50%	90%	% $\leq 1$ $\mu\text{g/ml}$
X						371	0.06	0.25	100.0
X	X					307	0.06	0.5	100.0
X	X	X				184	0.25	0.5	100.0
X	X	X	X			165	0.25	0.5	100.0
X	X	X	X	X		145	0.06	0.25	100.0
					X	21	0.015	0.12	100.0
All strains						1737	0.015	0.25	100.0

**Conclusions:** CEM-101 was the most active agent against all SPN at  $\leq 1$   $\mu\text{g/ml}$ , like glycopeptides and linezolid. MDR isolates with ERY-CLI R showed elevated, yet S-level, CEM-101 MIC values. CEM-101 potency against current SPN indicates potential use against community-acquired bacterial pneumonia.

## Introduction

CEM-101 is a novel fluoroketolide selected as a candidate for parenteral and oral therapy of community-acquired respiratory tract infections (CA-RTI). Initial in vitro studies indicated activity comparable or superior to telithromycin, cethromycin, erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive isolates having documented resistance to macrolides or lincosamides (MLS<sub>B</sub> agents). CEM-101 activity is directed against Gram-positive pathogens, but the drug also possesses measurable potencies against fastidious Gram-negative species (*Haemophilus*, *Moraxella*), some *Enterobacteriaceae* (*Salmonella*, *Shigella*), atypical respiratory tract species, *Helicobacter pylori*, telithromycin-resistant  $\beta$ -haemolytic streptococci, and pathogens causing various sexually transmitted diseases (STD).

In this presentation, we report CEM-101 activity measured by reference Clinical and Laboratory Standards Institute (CLSI) methods when testing *Streptococcus pneumoniae* isolates from CA-RTI. Emerging resistant subsets and various patterns of MLS<sub>B</sub>-ketolide resistance found among these tested organisms collected from an international surveillance program in 2008 are analyzed for comparative ketolide activity.

## Materials and Methods

**Organisms tested.** All organisms tested in this 2008 CEM-101 surveillance program were collected from patients in the United States (USA), Europe and Latin America (LA). These pathogenic strains were isolated from CA-RTI e.g. the most common species (*Streptococcus pneumoniae*, *H. influenzae* and *S. aureus*). The distribution of pneumococci only and the geographic contributions were:

- S. pneumoniae* (1,737)
  - geography: USA (766), Europe (828), and LA (145)
  - penicillin-susceptible,  $\leq 0.06$   $\mu\text{g/ml}$  (1,115)
  - penicillin-intermediate, 0.12-1  $\mu\text{g/ml}$  (251)
  - penicillin-resistant,  $\geq 2$   $\mu\text{g/ml}$  (371)

**Susceptibility testing.** All susceptibility tests were performed by CLSI broth microdilution methods (M07-A8, 2009) by a central monitoring CLIA/GLP-compliant laboratory (JMI Laboratories, North Liberty, Iowa, USA). Testing used cation-adjusted Mueller-Hinton broth (CA-MHB) with 2.5-5% lysed horse blood. CLSI M100-S19 was utilized to interpret MIC results by categories and for quality control (QC) ranges where criteria were available. Tested QC strains included: *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. All QC results were within published limits.

A wide variety of comparison agents were utilized including: amoxicillin/clavulanate, ceftriaxone, cefuroxime, penicillin, tetracycline, vancomycin, azithromycin, cefepime, clarithromycin, clindamycin, erythromycin, ciprofloxacin (screen for possible initial gyrase target mutations, MIC at  $\geq 4$   $\mu\text{g/ml}$ ), levofloxacin, moxifloxacin, linezolid, imipenem, telithromycin and trimethoprim/sulfamethoxazole (TMP/SMX), all assessed by the broth microdilution method only (Table 1).

**Analysis.** Resistance profiles using six antimicrobial classes (penicillins, macrolides, clindamycin, tetracycline, TMP/SMX and fluoroquinolones) were assessed, and the influence on CEM-101 and telithromycin MIC/potency is tabulated in Table 2.

## Results

- CEM-101 exhibited slightly greater activity against *S. pneumoniae* isolates when directly compared to another ketolide (telithromycin), with all CEM-101 MIC values at  $\leq 1$   $\mu\text{g/ml}$ . Telithromycin non-susceptible strains (MIC,  $\geq 2$   $\mu\text{g/ml}$ ) were detected (0.1%; see Figure 1 and Table 1).

- CEM-101 was quite potent (MIC<sub>50/90</sub>, 0.015/0.25  $\mu\text{g/ml}$ ) and showed a wider spectrum (100.0% at  $\leq 1$   $\mu\text{g/ml}$ ) compared to macrolides (63.3-63.6% susceptible), clindamycin (79.6% susceptible), oral or parenteral cephalosporins (74.6-91.8% susceptible), penicillins (64.2-87.2% susceptible), tetracycline (73.2% susceptible), and TMP/SMX (only 66.8% susceptible). As with CEM-101, all tested *S. pneumoniae* strains were inhibited at CLSI susceptible breakpoints for linezolid and vancomycin.

- Lowest CEM-101 MIC results among various MDR patterns (Table 2) were noted for pneumococci having isolated resistance to penicillins (MIC<sub>90</sub>, 0.25  $\mu\text{g/ml}$ ), resistance to all five drug classes (MIC<sub>90</sub>, 0.25  $\mu\text{g/ml}$ ), resistance to levofloxacin and other fluoroquinolones (MIC<sub>90</sub>, 0.12  $\mu\text{g/ml}$ ), and with resistance to macrolides only (MIC<sub>90</sub>, 0.25  $\mu\text{g/ml}$ ). Telithromycin non-susceptible isolates were noted (95.2-99.8% susceptible) for *S. pneumoniae* among six of the eight analyzed resistance patterns (Table 2).

Table 1. Comparative activity of CEM-101 and 19 other antimicrobials tested against 1,737 *S. pneumoniae* isolates from a pre-marketing surveillance program in Europe and the Americas.

Antimicrobial agent	MIC ( $\mu\text{g/ml}$ )				% by category <sup>a</sup> Susceptible/resistant
	Mode	50%	90%	Range	
CEM-101	0.015	0.015	0.25	$\leq 0.008$ -1	100.0/0.0
Telithromycin	$\leq 0.06$	$\leq 0.06$	0.25	$\leq 0.06$ -2	99.9/0.0
Azithromycin	$\leq 0.5$	$\leq 0.5$	>4	$\leq 0.5$ ->4	63.3/36.2
Clarithromycin	$\leq 0.25$	$\leq 0.25$	>32	$\leq 0.25$ ->32	63.6/35.6
Erythromycin	$\leq 0.06$	$\leq 0.06$	>8	$\leq 0.06$ ->8	63.4/36.3
Clindamycin	$\leq 0.25$	$\leq 0.25$	>2	$\leq 0.25$ ->2	79.6/20.0
Penicillin	$\leq 0.03$	$\leq 0.03$	4	$\leq 0.03$ ->4	64.2/21.4
Amox/clav <sup>b</sup>	$\leq 1$	$\leq 1$	4	$\leq 1$ -16	87.2/8.6
Ceftriaxone	$\leq 0.25$	$\leq 0.25$	1	$\leq 0.25$ -8	91.4/1.4
Cefepime	$\leq 0.12$	$\leq 0.12$	1	$\leq 0.12$ -4	91.8/0.6
Cefuroxime	$\leq 1$	$\leq 1$	8	$\leq 1$ -8	74.6/25.4
Imipenem	$\leq 0.12$	$\leq 0.12$	0.5	$\leq 0.12$ -2	77.5/6.8
Ciprofloxacin <sup>c</sup>	2	2	2	$\leq 0.03$ ->4	-(7.0) <sup>b</sup>
Levofloxacin	1	1	2	$\leq 0.5$ ->4	98.8/1.1
Moxifloxacin	$\leq 0.5$	$\leq 0.5$	$\leq 0.5$	$\leq 0.5$ -4	98.9/0.6
Tetracycline	$\leq 2$	$\leq 2$	>8	$\leq 2$ ->8	73.2/25.8
Tigecycline <sup>d</sup>	$\leq 0.03$	$\leq 0.03$	0.12	$\leq 0.03$ -0.25	89.5/-
TMP/SMX <sup>e</sup>	$\leq 0.5$	$\leq 0.5$	>2	$\leq 0.5$ ->2	66.8/21.7
Linezolid	1	1	1	$\leq 0.12$ -2	100.0/-
Vancomycin	$\leq 1$	$\leq 1$	$\leq 1$	$\leq 1$	100.0/-

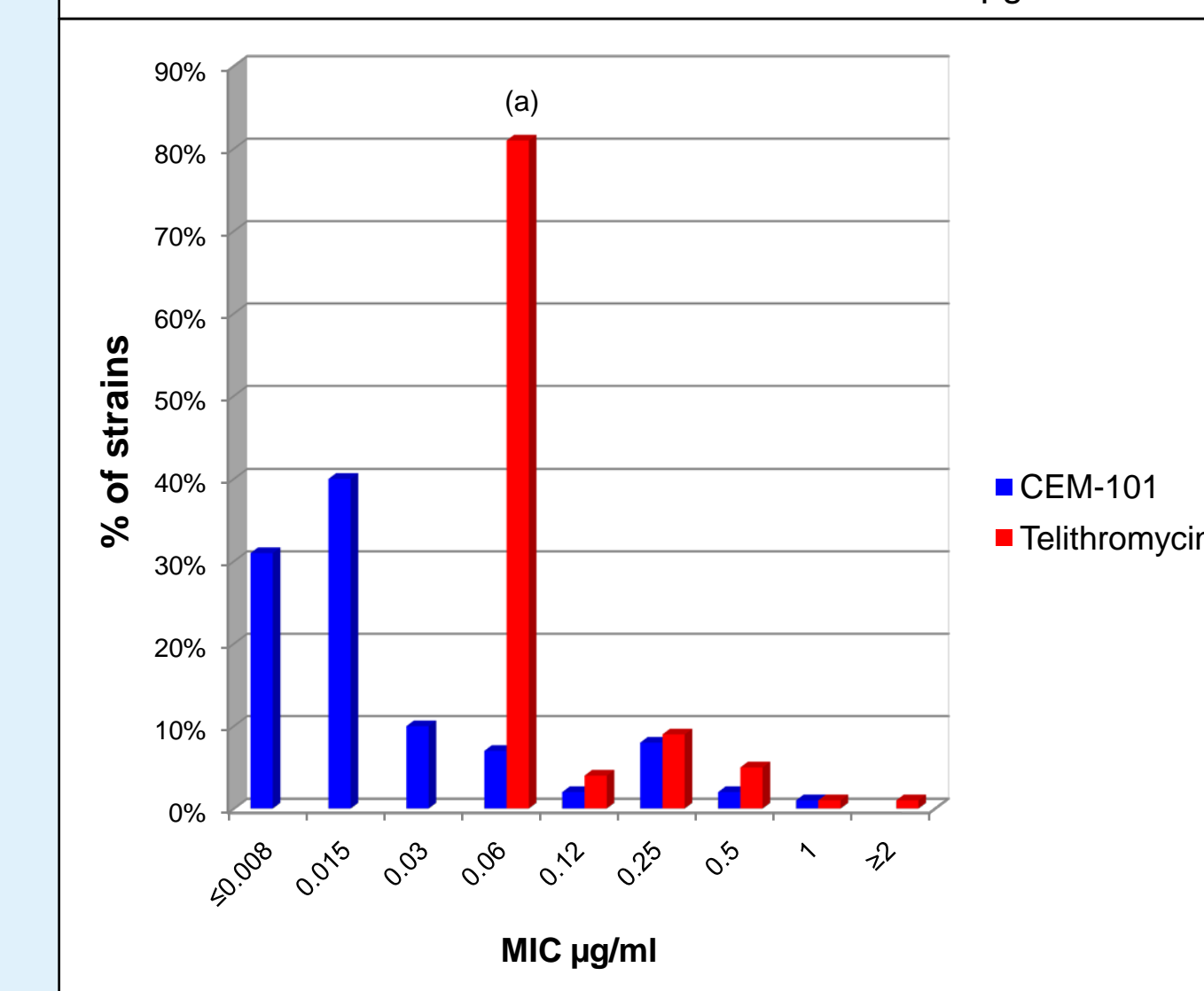
- Interpretive criteria of the CLSI (M100-S19, 2009).
- Amox/clav = amoxicillin/clavulanate.
- Percentage of values at  $\geq 4$   $\mu\text{g/ml}$ , indicating proportion of possible single-step target mutations.
- Interpretive criteria from the USA-FDA product labeling.
- TMP/SMX = trimethoprim/sulfamethoxazole.

Table 2. Activity of CEM-101 and telithromycin tested against *S. pneumoniae* isolates having various antimicrobial resistance patterns.

PEN	Resistance patterns <sup>a</sup>					No. tested	CEM-101			Telithromycin		
	ERY	CLI	TET	T/S	LEV		MIC ( $\mu\text{g/ml}$ )			MIC ( $\mu\text{g/ml}$ )		
							50%	90%	% $\leq 1$ $\mu\text{g/ml}$	50%	90%	% $\leq 1$ $\mu\text{g/ml}$
X <sup>b</sup>						371	0.06	0.25	100.0	0.12	0.5	99.7
X <sup>c</sup>						13	0.12	0.25	100.0	0.25	0.5	100.0
X	X					307	0.06	0.5	100.0	0.25	0.5	99.7
X	X	X				184	0.25	0.5	100.0	0.25	0.5	99.5
X	X	X	X			165	0.25	0.5	100.0	0.25	0.5	100.0
X	X	X	X	X		145	0.06	0.25	100.0	0.25	0.5	100.0
					X	21	0.015	0.12	100.0	$\leq 0.06$	0.25	95.2
	X	X				347	0.03	0.5	100.0	$\leq 0.06$	0.5	99.7
	X					631	0.06	0.25	100.0	0.12	0.5	99.8

- PEN = penicillin (MIC,  $\geq 2$   $\mu\text{g/ml}$  or >4  $\mu\text{g/ml}$ ; see footnotes b and c), ERY=erythromycin (MIC,  $\geq 1$   $\mu\text{g/ml}$ ), CLI = clindamycin (MIC,  $\geq 1$   $\mu\text{g/ml}$ ), TET = tetracycline (MIC,  $\geq 8$   $\mu\text{g/ml}$ ), T/S or TMP/SMX = trimethoprim/sulfamethoxazole, and LEV = levofloxacin (MIC,  $\geq 4$   $\mu\text{g/ml}$ ).
- MIC at  $\geq 2$   $\mu\text{g/ml}$  per penicillin V interpretive criteria (CLSI, 2009).
- MIC at > 4  $\mu\text{g/ml}$  per high-dose parenteral regimens (CLSI, 2009).

Figure 1. MIC distribution for CEM-101 and telithromycin tested against over 1,700 *S. pneumoniae* isolates from an international surveillance program (2008). Telithromycin was not tested at concentrations below 0.06  $\mu\text{g/ml}$ .<sup>a</sup>



## Conclusions

- CEM-101, a novel fluoroketolide, provides complete coverage (100.0% inhibition at  $\leq 1$   $\mu\text{g/ml}$ ; telithromycin breakpoint) against contemporary (2008) isolates of *S. pneumoniae* from patients on three continents.
- CEM-101 potency and overall spectrum was slightly superior to telithromycin and was at least four-fold more active than linezolid or vancomycin.
- CEM-101 appears to be a viable candidate for the therapy of CA-RTI (CABP) caused by *S. pneumoniae* that may be resistant to other antimicrobial classes such as macrolides, lincosamides,  $\beta$ -lactams (penicillin, cephalosporins, carbapenems) and even so-called "respiratory fluoroquinolones" (levofloxacin and moxifloxacin). Further clinical development seems warranted via parenteral and/or oral delivery.

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