Antimicrobial Activity of a New Fluoroketolide (CEM-101) Tested Against *Streptococcus pneumoniae* Tested by the SENTRY Surveillance Program (2008-2009)

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Abstract

Background: Ketolides are semisynthetic antimicrobials designed to overcome macrolide-resistant (R) *S. pneumoniae* (SPN). CEM-101 (solithromycin) is a fluoroketolide for oral and/or parenteral therapy of community-acquired bacterial pneumonia (CABP) with superior activity compared to other MLS_B agents.

Methods: A total of 1,737 (USA, Latin America [LA] and Europe [EU]) and 1,363 (USA and EU) SPN strains were collected in 2008 and 2009, respectively. Solithromycin and comparator agents were susceptibility (S) tested in Mueller-Hinton supplemented with lysed horse blood using CLSI broth microdilution methods (M07-A8).

Results: In 2008 and 2009, ≥99.8% of the strains displayed solithromycin MIC values ≤0.5 µg/mL, and 100.0% were inhibited at 1 µg/mL (CLSI breakpoint for telithromycin [TELI]). Six strains showed solithromycin MIC results at 1 µg/mL (3 EU countries and Israel). Solithromycin was among the most active agents tested against SPN (MIC_{90}, 0.12 or 0.25 µg/mL) each year with some observed regional variation. Erythromycin/clindamycin-R was 36.3/20.0% in 2008 and 34.0/18.1% in 2009. Linezolid and vancomycin provided complete coverage (100.0% S). Solithromycin exhibited reduced activity against penicillin (PEN)-R SPN (MIC_{90} 0.25 µg/mL) compared to PEN-S strains (MIC_{90} ≤0.03 µg/mL). Non-β-lactam compounds, such as tetracycline, trimethoprim/sulfamethoxazole and macrolides were also compromised in the PEN-R population.

Conclusion: Solithromycin was observed to be among the most active antimicrobials tested against SPN. solithromycin had greater potency than TELI (two-fold) and was active against all TELI-R SPN. These study results suggest that solithromycin is a promising agent for CABP treatment including strains R to currently used MLS_B ketolide agents.

Year/Continent (no. tested)	Cumulative % inhibited at solithromycin MIC (µg/mL) of:							
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1
2008 (1,737)	30.7	70.5	80.4	87.3	89.6	97.4	99.8	100.0
North America (765)	26.4	64.2	71.9	79.1	82.1	96.6	100.0	
Latin America (145)	47.6	82.1	85.5	95.9	98.6	99.3	100.0	
Europe (827)	31.7	74.2	87.3	93.2	95.0	97.8	99.5	100.0
2009 (1,363)	-[a]	-	79.5	86.1	90.8	98.8	99.9	100.0
USA (796)	-	-	70.6	79.8	86.8	98.5	100.0	
Europe (567)	-	-	92.1	95.1	96.5	99.1	99.6	100.0

a. - = MIC not tested

Introduction

Bacterial pneumonia is a significant burden on the healthcare system with regards to the associated cost for treatment of this disease process. Antimicrobial agents that are currently available for empiric treatment impact both patient outcome and fiscal concerns. The diversity of species that cause respiratory tract infections is well known and includes fastidious and atypical bacterial pathogens as the primary species associated with community-acquired bacterial pneumonia (CABP). *Streptococcus pneumoniae* is the most commonly isolated species that causes CABP. Although immunization has been effective in reducing invasive pneumococcal infections; but using the current formulations of capsular vaccines, resistance to commonly prescribed antimicrobial agents persists. Thus, it can be expected that regardless of vaccination attempts, the evolution of resistant bacteria will continue and that new or more effective treatment options should be developed and moved forward as potential clinical candidates.

Ketolides have been developed to overcome commonly occurring macrolide resistance that is increasing among various Gram-positive pathogens, including *S. pneumoniae*. Macrolide-resistant *S. pneumoniae* phenotypes include high-level resistance to all macrolide, lincosamide and streptogramin$_B$ (MLS_B) agents due to ribosomal dimethylation, 23S rRNA mutations and other ribosomal mutations or low-level resistance due to drug efflux.

Solithromycin is a novel fluoroketolide for oral and/or parenteral therapy as treatment of CABP and other indications. Solithromycin has superior activity compared to other MLS_B agents, which have been globally monitored against *S. pneumoniae* during all years (1997-current) of the SENTRY Antimicrobial Surveillance Program. The objective of this study was to examine the activity of solithromycin and comparison agents when tested against contemporary clinical isolates of *S. pneumoniae* collected in United States (USA), Latin American and European medical centers. The presentation of this data is focused on the most recently validated collection of isolates selected from the 2008-2009 global surveillance.

Materials and Methods

Bacterial Strain Collection. A total of 1,737 (USA, Latin America and Europe) and 1,363 (USA and Europe) *S. pneumoniae* isolates were tested during 2008 and 2009, respectively. Only consecutively collected isolates from individual patients with respiratory tract infections or blood stream infections were included. Strains were identified by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute (CLSI) recommendations (M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). Isolates were tested in Mueller-Hinton broth supplemented with 3-5% lysed horse blood. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control *S. pneumoniae* strain ATCC 49619. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) and EUCAST criteria, when available.

Results

- During 2008 and 2009, 99.7% and 99.9% of the *S. pneumoniae* strains displayed solithromycin MIC values at ≤0.5 µg/mL, respectively (Table 1). Over these two years of surveillance, 100.0% of isolates were inhibited at a solithromycin MIC value of ≤1 µg/mL (Table 1), which is the current CLSI susceptible breakpoint for telithromycin.
- Only six strains (0.19%) collected during 2008-2009 showed solithromycin MIC results at 1 µg/mL (Table 1). These strains were collected from three European countries (Belgium, France, and Ireland) and Israel, and each demonstrated telithromycin MIC results at only 1 or 2 µg/mL. These strains were non-susceptible to other macrolides and clindamycin.
- During 2009, telithromycin susceptibility rates were >99.0% in all regions applying current CLSI breakpoints; however these susceptibility rates were lower when using the EUCAST breakpoint criteria at 56.0 - 96.8%, which was influenced by susceptibility to penicillin and associated co-resistance to MLS_B agents (Table 2).
- Strains collected in 2009 that were non-susceptible to erythromycin and susceptible to clindamycin had a solithromycin MIC_{90} value (0.12 µg/mL) that was four-fold lower compared to telithromycin (0.5 µg/mL) as shown in Table 3.
- The collection of 2009 isolates that were non-susceptible to erythromycin and clindamycin had a slightly higher solithromycin MIC_{90} value (0.25 µg/mL), compared to strains that were susceptible to clindamycin, which was two-fold lower compared to telithromycin (0.5 µg/mL), see Table 4.

Table 1. Frequency distributions of solithromycin and telithromycin tested against *S. pneumoniae* strains collected in 2008-2009.

Year/ antimicrobial agent (no. tested)	Number of strains inhibited at MIC in µg/mL (cumulative percentage inhibited):								
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
2008 (1,737)									
Solithromycin	533 (30.7%)	691 (70.5%)	172 (80.4%)	120 (87.3%)	41 (89.6%)	135 (97.4%)	41 (99.7%)	4 (100.0%)	
Telithromycin	-[a]	-	-	1404 (80.8%)	73 (85.0%)	162 (94.3%)	81 (99.0%)	16 (99.9%)	1 (100.0%)
2009 (1,363)									
Solithromycin	-	-	1084 (79.5%)	90 (86.1%)	64 (90.8%)	108 (98.8%)	15 (99.9%)	2 (100.0%)	
Telithromycin	-	-	-	-	-	1,214 (89.1%)	135 (99.0%)	12 (99.9%)	2 (100.0%)

a. - = untested concentration

Table 2. Antimicrobial activity of solithromycin and comparator antimicrobial agents when tested against 1,363 strains of *Streptococcus pneumoniae* (2009, all regions).

Antimicrobial agent/ category (no.tested)	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Penicillin-susceptible (870)					
Solithromycin	≤0.03	≤0.03	≤0.03 – 0.25	- / -	- / -
Telithromycin	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0	96.8 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0	- / -
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	99.9 / 0.0
Cefuroxime	≤1	≤1	≤1 – 4	99.2 / 0.3	99.2[b] / 0.8
Tetracycline	≤2	≤2	≤2 – >8	93.6 / 5.6	93.6 / 6.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	90.8 / 4.0	94.4 / 4.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.3 / 3.2	96.8 / 3.2
Erythromycin	≤0.25	2	≤0.25 – >2	88.6 / 10.6	88.6 / 10.6
Levofloxacin	1	1	≤0.5 – >4	99.7 / 0.2	99.7 / 0.3

Table 2 – Continued.

Antimicrobial agent/ category (no.tested)	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Penicillin-intermediate (252)					
Solithromycin	≤0.03	0.06	≤0.03 – 0.5	- / -	- / -
Telithromycin	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	94.0 / 0.4
Amoxicillin/clavulanate	≤1	≤1	≤1 – 4	99.6 / 0.0	- / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 4	98.0 / 0.4	90.9 / 0.4
Cefuroxime	≤1	4	≤1 – >8	71.3 / 17.7	71.3[b] / 28.7
Tetracycline	≤2	>8	≤2 – >8	61.5 / 38.5	61.5 / 38.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	50.8 / 31.0	59.5 / 31.0
Clindamycin	≤0.25	>2	≤0.25 – >2	68.3 / 31.7	68.3 / 31.7
Erythromycin	>2	>2	≤0.25 – >2	32.5 / 66.3	32.5 / 66.3
Levofloxacin	1	1	≤0.5 – >4	98.0 / 2.0	98.0 / 2.0
Penicillin-resistant (241)					
Solithromycin	0.12	0.25	≤0.03 – 1	- / -	- / -
Telithromycin	≤0.25	0.5	≤0.25 – 2	99.2 / 0.0	56.0 / 5.4
Penicillin[c]	4	4	2 – >4	44.8 / 6.6	- / -
Penicillin[d]	4	4	2 – >4	0.0 / 100.0	0.0 / 55.2
Amoxicillin/clavulanate	4	8	≤1 – 16	36.1 / 49.4	- / -
Ceftriaxone	2	2	≤0.25 – 8	47.7 / 6.6	1.7 / 6.6
Cefuroxime	8	>8	≤1 – >8	0.5 / 98.5	0.5[b] / 99.5
Tetracycline	>8	>8	≤2 – >8	30.3 / 69.7	30.3 / 69.7
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	15.8 / 74.7	22.8 / 74.7
Clindamycin	>2	>2	≤0.25 – >2	36.9 / 61.4	38.6 / 61.4
Erythromycin	>2	>2	≤0.25 – >2	14.9 / 85.1	14.9 / 85.1
Levofloxacin	1	1	≤0.5 – >4	97.5 / 1.7	97.5 / 2.5

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. Includes susceptible and intermediate.
c. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Table 3. Antimicrobial activity of solithromycin and comparator antimicrobial agents when tested against 281 strains of erythromycin-non-susceptible and clindamycin-susceptible *Streptococcus pneumoniae* (2009, all regions).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Solithromycin	0.06	0.12	≤0.03 – 0.25	- / -	- / -
Telithromycin	≤0.25	0.5	≤0.25 – 1	100.0 / 0.0	81.5 / 0.5
Penicillin[b]	0.25	2	≤0.03 – >4	94.0 / 0.9	- / -
Penicillin[c]	0.25	2	≤0.03 – >4	33.3 / 24.5	33.3 / 6.0
Amoxicillin/clavulanate	≤1	2	≤1 – 16	90.7 / 5.6	- / -
Ceftriaxone	≤0.25	1	≤0.25 – 8	91.2 / 1.9	71.3 / 1.9
Tetracycline	≤2	>8	≤2 – >8	74.1 / 25.9	74.1 / 25.9
Trimethoprim/sulfamethoxazole	1	>2	≤0.5 – >2	43.1 / 39.8	50.9 / 39.8
Clindamycin	≤0.25	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	0.5 – >2	0.0 / 96.8	0.0 / 96.8
Levofloxacin	1	2	≤0.5 – >4	97.7 / 1.9	97.7 / 2.3

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
c. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Table 4. Antimicrobial activity of solithromycin and comparator antimicrobial agents when tested against 258 strains of erythromycin- and clindamycin-non-susceptible *Streptococcus pneumoniae* (2009, all regions).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Solithromycin	0.06	0.25	≤0.03 – 1	- / -	- / -
Telithromycin	≤0.25	0.5	≤0.25 – 2	99.2 / 0.0	58.1 / 5.0
Penicillin[b]	2	4	≤0.03 – >4	57.0 / 5.4	- / -
Penicillin[c]	2	4	≤0.03 – >4	10.5 / 58.9	10.5 / 43.0
Amoxicillin/clavulanate	2	8	≤1 – 16	54.3 / 39.5	- / -
Ceftriaxone	1	2	≤0.25 – 8	62.4 / 3.5	38.0 / 3.5
Cefuroxime	4	>8	≤1 – >8	30.4 / 66.7	30.4[d] / 69.6
Tetracycline	>8	>8	≤2 – >8	9.7 / 89.9	9.7 / 90.3
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	31.4 / 58.9	37.6 / 58.9
Clindamycin	>2	>2	0.5 – >2	0.0 / 98.1	1.9 / 98.1
Erythromycin	>2	>2	0.5 – >2	0.0 / 98.8	0.0 / 98.8
Levofloxacin	1	1	≤0.5 – >4	97.3 / 1.9	97.3 / 2.7

a. Criteria as published by the CLSI [2010] and EUCAST [2010].
b. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
c. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.
d. Includes susceptible and intermediate.

Conclusions

- Solithromycin was the most active antimicrobial agent tested against penicillin- and multidrug-resistant *S. pneumoniae*, with the highest MIC_{90} for these resistant strains at 0.25 µg/mL.
- Solithromycin demonstrated wide coverage for *S. pneumoniae* isolated from the USA, Europe and Latin America. Solithromycin potency was comparable or superior to telithromycin and currently marketed macrolides.
- Solithromycin activity against erythromycin-resistant *S. pneumoniae* was slightly lower, but was more potent than telithromycin.
- Although solithromycin exhibited slightly reduced activity against penicillin-resistant *S. pneumoniae* compared to penicillin-susceptible strains, this observation is in accord with a trend reported in the literature that penicillin-resistant *S. pneumoniae* also exhibit resistance to other non-β-lactam compounds especially MLS_B agents.

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