Assessment of the bactericidal activity of solithromycin (CEM-101) against *Streptococcus pneumoniae* with known macrolide-resistance mechanism and serotype

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Background: Solithromycin is a next-generation macrolide, an oral and intravenous fluoroketolide currently in clinical development for the treatment of community-acquired bacterial pneumonia (CABP). The current study investigated the bactericidal activity of solithromycin by determining minimum bactericidal concentration (MBC) against *Streptococcus pneumoniae* with known macrolide resistance mechanisms and serotype.

Methods: A total of 33 clinical isolates of *S. pneumoniae* (8 azithromycin-susceptible and 25 azithromycin resistant) were tested. These isolates included a diverse range of serotypes and macrolide resistance genotypes. MIC tests were performed by broth microdilution against all isolates in line with CLSI susceptibility testing standards (M07-A10). MBC was determined by sampling from the MIC plates as per CLSI guidelines (M26-A) and defined as the lowest concentration of antibacterial agent required to kill 99.9% of the test inoculum.

Results: Summary MIC and MBC data for solithromycin and azithromycin as control are shown in the Table. Most isolates had a solithromycin MBC/MIC ratio of 4 or below (22/33, 66%), although one isolate had a ratio of 256. This isolate had a very low MIC of 0.004 µg/ml, so the MBC was still relatively low at 1 µg/ml. For most macrolide-resistant isolates the azithromycin MBC was beyond the limit of detection, so MBC/MIC ratio could not be determined.

	Phenotype	MIC (µg/ml):			MBC (µg/ml):		
		50%	90%	Range	50%	90%	Range
Azithromycin	AZI-R (n=25)	>256	>256	2 to >256	>256	>256	8 to >256
	AZI-S (n=8)	0.03	0.5	0.008 - 0.5	0.06	1	0.008 - 1
Solithromycin	AZI-R (n=25)	0.03	0.5	0.002 - 0.5	0.25	1	0.002 - 4
	AZI-S (n=8)	0.002	0.015	0.002 -0.015	0.004	0.06	0.004 - 0.06

AZI-S, azithromycin-susceptible; AZI-R, azithromycin-resistant

Conclusion: Solithromycin exhibited superior MIC and MBC as compared with azithromycin. Importantly, MBC/MIC ratios for solithromycin were favourable. The ratio of MBC/MIC for solithromycin did not appear to relate to solithromycin MIC, genotype or serotype.

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