

Ribosomal Mutations Associated with Ketolide Resistance in *Haemophilus Influenzae* Found in the SENTRY Antimicrobial Surveillance Program

Abstract 1452

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Objectives: To determine the mechanisms of ketolide resistance in *H. influenzae*. Ketolide resistance is very rare in *H. influenzae* and is usually associated with a variety of ribosomal mutations. We report on the ribosomal mutations detected in 9 telithromycin (TELI) -resistant *H. influenzae* found in the SENTRY Program (2009) and assess the activity of solithromycin (SOLI, formerly CEM-101), a new fluoroketolide in clinical development.

Methods: 1,198 *H. influenzae* isolates obtained from patients with community-acquired bacterial pneumonia in 24 countries were tested for susceptibility to TELI by CLSI methods (M07-A8 and M100-S20-U) as part of the SENTRY Program during 2009. Only nine (0.8%) isolates were found to be TELI-resistant (MIC, ≥ 16 mg/L). Extended MICs were performed by Etest and strains were screened for mutations in the 23S rRNA, L22 and L4 proteins by PCR and DNA sequencing.

Results: Seven different mutation patterns were observed in 8 of the 9 strains. No mutations were detected in the genes sequenced for one strain (Isolate 3042). The highest TELI MIC values (>256 mg/L) were found in two geographically diverse (Sweden and USA) strains with a 23S rRNA A2059G mutation. *H. influenzae* with L4 and L22 riboprotein mutations showed TELI MIC values from 32 to 256 mg/L. TELI was 1.5- to at least 4- fold more active than azithromycin (AZI); and SOLI was 2- to at least 4-fold more active than TELI. Against all 1,198 *H. influenzae* isolates, the MIC_{50/90} for TELI and SOLI were 1/4 and 1/2 mg/L, respectively.

Conclusions: Ketolide resistance in *H. influenzae* continues to be rare (<1%) globally. Resistance was found to be associated with a variety of ribosomal mutations and was widely distributed geographically thus suggesting a lack of both local and global spread. Although solithromycin MIC results were 2- to at least 4-fold lower than telithromycin against these strains, cross-resistance to solithromycin was confirmed. The mechanism of ketolide resistance in one UK strain is under further investigation.

Isolate	Country	Mutation	MIC in mg/L		
			TELI	SOLI	AZI
279	Sweden	23S_A2059G	>256	64	>256
1540	USA	23S_A2059G	>256	128	>256
3904	Hong Kong	L22_87insRVMPRVMP88	256	128	>256
822	USA	L22_del95RIL	32	16	128
3302	USA	L22_G91D	32	16	48
684	Chile	L22_R88P, L22_R99L	128	64	>256
995	USA	L4_63insKG64	32	8	48
3432	Australia	L4_T64K	64	16	>256
3042	UK	None found	256	128	>256