

Mutations Associated with Ketolide Resistance in *S. pneumoniae* Collected in the 2009 SENTRY Antimicrobial Surveillance Program

Abstract 251

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Background:

Ketolide resistance (R) is very rare in *S. pneumoniae* (SPN) and is usually associated with a variety of ribosomal mutations and/or mutations in the region upstream of the *erm* (B) gene that control expression. We investigated the mechanisms of resistance in 5 telithromycin (TELI) -R SPN found in the SENTRY Program (2009) and assessed the activity of solithromycin (CEM-101), a new fluoroketolide in clinical development.

Methods:

2,123 SPN isolates obtained from patients with community-acquired bacterial pneumonia in 23 countries were tested for susceptibility to TELI by CLSI methods (M07-A8 and M100-S20-U). Only 5 (0.2%) isolates were observed to be TELI-R. Strains were screened for *erm*(B) and *mef*(A/E) resistance genes by PCR, and mutations in the 23S rRNA, L22 and L4 proteins, and the *erm*(B) promoter region by PCR and DNA sequencing.

Results:

All TELI-R strains were from the Peoples Republic of China and had TELI MIC values of 8 µg/ml, however the CEM-101 MICs were only 0.06-0.25 µg/ml. Significant 23S rRNA, L4 and L22 mutations were not present in any strains. Novel amino acid substitutions in the *erm*(B) leader peptide were detected in 4/5 strains and an identical pattern of mutations were found in all 5 strains in the region between the *erm*(B) and leader peptide genes.

Conclusion:

Ketolide-R in SPN continues to be rare (<1%) globally. R was found to be associated with a variety of mutations upstream of *erm*(B) and appear to result in increased production of *erm*B with subsequent increases in the rate of dimethylation of A2058 in domain V of the 23S rRNA. CEM-101 remained very active against these strains and hence appeared refractory to the effect of these resistance mechanisms and a good clinical candidate.