Abstract 251

David J. Farrell, Ph.D., Lalitagaurie M. Deshpande, Ph.D., Rodrigo E. Mendes, Ph.D., Ronald N. Jones, M.D.
JMI Labs, North Liberty, IA, USA

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 \textit{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 \textit{erm}(B) and \textit{mef}(A/E) resistance genes by PCR, and mutations in the 23S rRNA, L22 and L4 proteins, and the \textit{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 \textit{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 \textit{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 \textit{erm}(B) and appear to result in increased production of \textit{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.