

# Activity of Solithromycin Against Azithromycin-resistant *Streptococcus pneumoniae* with Characterized Resistance Mechanisms

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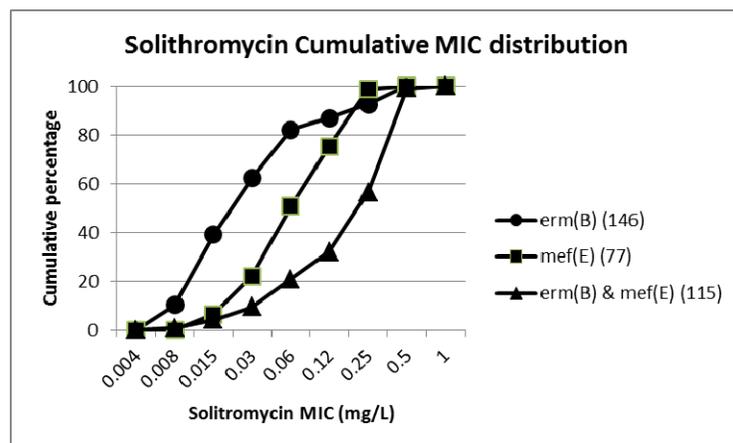
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**Objectives:** Solithromycin is a fourth generation macrolide, the first fluoroketolide being developed in oral capsules, intravenous and pediatric suspension, that is currently undergoing Phase III clinical development for the treatment of community-acquired bacterial pneumonia. This study evaluated the *in vitro* activity of solithromycin against *S. pneumoniae* resistant to azithromycin and characterized the associated macrolide resistance mechanisms.

**Methods:** A total of 927 *S. pneumoniae* were collected from Europe, Asia-Pacific, North America and the rest of the world. Isolates were tested in a central laboratory with MIC and susceptibility for solithromycin and comparators determined according to CLSI broth microdilution methodology and breakpoints. Those isolates found to be resistant to azithromycin were evaluated for the presence of *erm(A)*, *erm(B)*, *erm(C)*, *MsrA/B*, *ereA*, *ereB*, *mphA*, *mef(A)* and *mef(E)* genes by PCR.

**Results:** A total of 395 *S. pneumoniae* were found to be azithromycin-resistant (MIC  $\geq 2$  mg/L) and 394 were available for molecular evaluation. Overall, the main genotypes were *erm(B)* (146, 37.1%), *erm(B)* & *mef(E)* (115, 29.2%) and *mef(E)* (77, 19.5%). Eight isolates (2.0%) were negative for all genes and 33 (8.4%) gave inconclusive results. The dominant genotype was *erm(B)* in Europe (47.9%) and Asia-pacific (53.8%), but *mef(E)* in North America (44.4%). Other mechanisms were found in fewer than 6 isolates each (data not shown). Solithromycin was more active against *erm(B)* isolates than *mef(E)* and least active against isolates with both mechanisms (see Figure). Nevertheless, solithromycin MICs were no greater than 1 mg/L against all azithromycin-resistant isolates.



**Conclusions:** Solithromycin showed excellent activity against pneumococci resistant to azithromycin, particularly against strains with *erm(B)*, which is the most common resistance mechanism world-wide. This strong potency was present even against isolates with multiple macrolide resistance mechanisms. These data support the continued development of solithromycin for the treatment of respiratory infections caused by pneumococci, even for those isolates resistant to macrolides.