Emergence of telithromycin resistance in *Haemophilus influenzae* in Japan

An isolate of *Haemophilus influenzae* type d from a Japanese patient with pneumonia was found to have a MIC of 64 μg telithromycin ml⁻¹. Emergence of telithromycin resistance in *H. influenzae* is an important clinical problem, although reports concerning resistance to telithromycin in clinical isolates of *H. influenzae* are few (Bogdanovich et al., 2006).

A 76-year-old man with a history of asthma and smoking was admitted to a hospital because of fever, cough and coxalgia in November 2004. No antimicrobial agent had been administered before admission. Laboratory results showed a count of 14,000 white blood cells mm⁻³, a count of 14,000 white blood cells mm⁻³ with 86.5% neutrophils, a concentration of 140.0 mg C-reactive protein l⁻¹ and a concentration of 140.0 mg C-reactive protein l⁻¹. The man was diagnosed with pneumonia and treated with intravenous sulbactam/ampicillin (3 g, twice a day). *H. influenzae* type d and penicillin-susceptible *Streptococcus pneumoniae* were recovered from sputum. Both isolates, including the telithromycin-resistant *H. influenzae*, showed susceptibility to β-lactams. On hospital day 7, the patient had no fever or cough, and abnormal breath sounds had resolved. Antimicrobial treatment was stopped on day 11.

In the present case pneumonia was caused by *H. influenzae* and penicillin-susceptible *S. pneumoniae*, both susceptible to β-lactams. MICs for the *H. influenzae* isolate determined by a microbroth dilution method, as described by the Clinical and Laboratory Standards Institute (CLSI, 2006), were 64 μg telithromycin ml⁻¹, >64 μg clarithromycin ml⁻¹, >64 μg azithromycin ml⁻¹ and 16 μg clindamycin ml⁻¹. Nucleotide sequences of the 23S rDNA in our isolate were 98.6% identical to those of *H. influenzae* ATCC49766. Domain II showed a mutation of A654G and domain V a mutation of C2164G. Wild-type nucleotides were preserved at A752, A2058, A2059, A2062, G2160, C2610 and C2611 (Hansen et al., 1999; Bozdogan & Appelbaum, 2004). Three insertions of one nucleotide were identified in domain I of 23S rDNA, to which ribosomal proteins L4 and L22 bind (Bozdogan & Appelbaum, 2004). The isolate also had 36 point mutations in other domains, as well as an amino acid mutation of G65A in L4. However, no mutation was found in L22. In the present isolate the effect of efflux on telithromycin resistance remains unclear.

In Japan, telithromycin has been approved since December 2003 for the treatment of respiratory tract infections, such as pneumonia, bronchitis, pharyngitis, tonsillitis and sinusitis. In 2004, however, telithromycin resistance emerged rapidly in *H. influenzae* in Japan. To the best of our knowledge, this report is the first detailed account of telithromycin-resistant *H. influenzae* in Japan. In this report the mechanisms conferring telithromycin resistance have been partially characterized. Multiple mutations in 23S rDNA from domains I to VI were identified, as well as an amino acid mutation in the L4 ribosomal protein. To determine genetic traits associated with the emergence of telithromycin resistance, however, relationships between alterations in 23S rDNA and/or ribosomal proteins and telithromycin resistance require more definitive characterization.

In recent studies (Bogdanovich et al., 2006), *H. influenzae* isolates showing MICs ≥0.5 μg telithromycin ml⁻¹, which include those ‘susceptible’ according to CLSI (2006) categories, had telithromycin efflux mechanisms. High-level telithromycin resistance in *H. influenzae* is rare, but has been characterized by alterations of ribosomal proteins and/or 23S rDNA, as well as efflux mechanisms (Bogdanovich et al., 2006). Although continuing studies are required, multiple mutations in 23S rDNA from domains I to VI may play some role in conferring high-level telithromycin resistance, in addition to ribosomal protein alterations and telithromycin efflux. These mechanisms differ from those conferring high-level macrolide resistance, that is ribosomal protein alterations combined with macrolide efflux, and/or specific mutations in domain II and V of 23S rDNA (Peric et al., 2003, 2004). Control and prevention of telithromycin resistance will require further epidemiological investigation and characterization of the underlying mechanisms.

**References**


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DOI 10.1099/jmm.0.47259-0 © 2007 SGM