

## Telithromycin-resistant *Streptococcus pneumoniae*

**To the Editor:** In recent years, antimicrobial drug resistance in *Streptococcus pneumoniae* has increased worldwide and is a major health concern. Resistance to  $\beta$ -lactams and macrolides, considered to be first-line therapeutic agents, is particularly high in France and many Asian countries (1–3). Resistance to new fluoroquinolones is reported with increasing frequency, which emphasizes the need for new effective drugs.

Telithromycin, the first member of a new macrolide family, the ketolides, has been developed to overcome macrolide resistance. In vitro data have shown that telithromycin remains active against 98% to 100% of erythromycin-resistant strains (2,3). However, resistant mutants have been isolated in vitro, and a few poorly documented clinical failures have been reported in the treatment of pneumococcal infections. We report the first isolation of telithromycin-resistant *S. pneumoniae* from a blood culture after therapy.

An 87-year-old woman was admitted on March 28, 2004, to St Joseph Hospital in Paris with typical upper left lobar pneumonia, as inferred from auscultatory results, radiologic findings, and laboratory data: leukocytes 37,300 cells/ $\mu$ L, C-reactive protein 455 mg/L, and positive urinary pneumococcal antigen (BinaxNOW, Binax, Inc., Portland, ME, USA). She was not febrile. She had been followed for many years for chronic obstructive pulmonary disease (COPD), with acute exacerbation only in 2001. At that time, she was treated with the macrolide roxithromycin, without bacteriologic documentation, in addition to acetylcysteine (3  $\times$  200 mg/d) and aerosolized terbutaline. On March 13,

her COPD was exacerbated. On March 20, she visited her general practitioner and received 800 mg/day telithromycin for 5 days without improvement. Because of a cutaneous rash attributed to telithromycin, she received 20 mg prednisolone. After 48 hours, she was admitted to St Joseph Hospital because her respiratory syndrome was aggravated. A blood culture drawn on admission yielded a *S. pneumoniae* serotype 14 with decreased  $\beta$ -lactam susceptibility (MICs: penicillin G: 1  $\mu$ g/mL; amoxicillin: 0.75  $\mu$ g/mL; cefotaxime: 0.5  $\mu$ g/mL, as determined by Etest). The strain was resistant to tetracyclines, cotrimoxazole, macrolides, and lincosamides (erythromycin and clindamycin MIC  $>32$   $\mu$ g/mL). The MIC of telithromycin, performed on Mueller-Hinton agar + 5% horse blood by serial 2-fold dilution, was equal to 2  $\mu$ g/mL in air and 8  $\mu$ g/mL under CO<sub>2</sub> (0.01–0.03  $\mu$ g/mL for control strains ATCC 49619 and 10 clinical isolates, including 5 that were MLSB [macrolide-lincosamide-streptogramin B]-resistant). The patient was treated with 100 mg/kg/day intravenous amoxicillin and improved within 48 hours. She was discharged from the hospital 1 week later in good condition but remained a healthy carrier of resistant *S. pneumoniae*.

Resistance to macrolides has been documented in France since our first report in 1978 (4). In the last 10 years, resistance has increased to  $\approx$ 50% of the strains in adults and  $\geq$ 70% in children, the highest in the Western world. More than 98% of the strains are of the MLSB phenotype, conferring high-level resistance to macrolides, lincosamides, and streptogramin B, in contrast to the situation in the United States, where most strains are of the *mefE* type (efflux), which confers low-level resistance to 14- and 15-membered macrolides only. However,  $<2\%$  of the macrolide-resistant strains have a decreased susceptibility to telithro-

mycin (2,3). Resistance to  $\beta$ -lactams is also very frequent ( $\approx$ 50%), particularly in erythromycin-resistant strains ( $<90\%$ ); these figures explain why macrolides may more likely select a penicillin-resistant strain than most  $\beta$ -lactams (5).

Since resistance to telithromycin was documented before ketolides were introduced in clinical practice, we cannot exclude the possibility that the telithromycin-resistant strain was selected in 2001, while our patient was treated with roxithromycin.

The clinical impact of macrolide resistance has been occasionally questioned since these antimicrobial agents achieve high tissue and intracellular levels. However, *S. pneumoniae* is an extracellular bacterial pathogen; well-designed clinical studies have documented the failure of macrolides in treating high-level resistant strains with an MLSB phenotype (6). After an 800-mg oral dose, telithromycin achieves serum and epithelial lining fluid concentrations of 2.2 and 15  $\mu$ g/mL, respectively, yielding a free drug concentration of 0.7  $\mu$ g/mL in the serum and 15  $\mu$ g/mL in the epithelial lining fluid. In an excellent in vitro model, telithromycin eradicated *S. pneumoniae* of the *mefE* phenotype with MICs  $\geq$ 0.25 and 1  $\mu$ g/mL (7). The drug was not effective against strains with MICs 2–8  $\mu$ g/mL, as was seen in our patient. When incubated under CO<sub>2</sub>, MICs of macrolides increase by 1 dilution compared to the MIC in air, against both susceptible and resistant strains. With telithromycin, the MIC increase is 2–6 dilutions but only for macrolide-resistant strains (8). The clinical impact of this finding is still to be determined. This report emphasizes the need for routine testing of *S. pneumoniae* isolates for resistance to telithromycin.

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**Fred Goldstein,\* Barbara Vidal,\*  
and Marie D. Kitzis\***

\*Hospital St Joseph, Paris, France

#### References

1. Song JH, Chang HH, Suh JY, Ko KS, Jung SI, Oh WS, et al. Macrolide resistance and genotypic characterization of *Streptococcus pneumoniae* in Asian countries: a study of the Asian network for surveillance of resistant pathogens (ANSORP). *J Antimicrob Chemother.* 2004;53:457–63.
2. Leclercq R. Overcoming antimicrobial resistance: profile of a new ketolide antibacterial, telithromycin. *J Antimicrob Chemother.* 2001;48:9–23.
3. Farrell J, Felmingham D. Activities of telithromycin against 13,874 *Streptococcus pneumoniae* isolates collected between 1999 and 2003. *Antimicrob Agents Chemother.* 2004;48:1882–4.
4. Goldstein FW, Dang Van A, Bouanchaud DH, Acar JF. Increased resistance of *Streptococcus pneumoniae* to antibiotic and prevalence of their capsular serotypes. *Pathol Biol.* 1978;26:173–80.
5. Goldstein FW. Penicillin-resistant *Streptococcus pneumoniae*: section by beta-lactam and non-beta-lactam antibiotics. *J Antimicrob Chemother.* 1999;44:141–4.
6. Lonks JR. What is the clinical impact of macrolide resistance? *Current Infect Dis Rep.* 2004;6:7–12.
7. Zhanel G, Johanson C, Laing N, Hisanaga T, Wierzbowski A, Hoban DJ. Pharmacodynamic activity of telithromycin at simulated clinically achievable free-drug concentrations in serum and epithelial lining fluid against efflux (*mefE*)-producing macrolide-resistant *Streptococcus pneumoniae* for which telithromycin MICs vary. *Antimicrob Agents Chemother.* 2005;49:1943–8.
8. Batard E, Juvin ME, Jacqueline C, Bugnon D, Caillon J, Potel G, et al. Influence of carbon dioxide on the MIC of telithromycin for *Streptococcus pneumoniae*: an in vitro–in vivo study. *Antimicrob Agents Chemother.* 2005;49:464–6.

Address for correspondence: Fred W. Goldstein, Hospital St Joseph, 185 Rue Raymond Losserand, Paris, France, 75014; fax: 33-1-44-123685; email: fgoldstein@hopital-saint-joseph.org

## Integrated Human-Animal Disease Surveillance

**To the Editor:** Early identification of zoonotic disease occurrence through simultaneous monitoring of human and animal disease surveillance systems is critical to protect health in both populations. We assessed the surveillance and reporting needs of a small but diverse group of Michigan veterinarians by examining their perspective of the current animal disease reporting system, the system enhancements desired, and their computer and Internet accessibility.

Developing systems that link human and animal disease reporting systems can help identify and facilitate a response to known and emerging zoonotic diseases. A system that allows simultaneous electronic capture and assessment of human and animal disease reports is being implemented in Michigan. The system will be based on the Michigan Disease Surveillance System platform, a Web-based human disease reporting system implemented by the Michigan Department of Community Health (1,2).

To ensure an integrated system that meets both human and veterinary public health needs, we developed a questionnaire for veterinarians to collect information on the current animal disease reporting system, system enhancements that are desired, and computer and Internet access capabilities (University Human Research Committee approved). In July 2003, a total of 112 questionnaires was sent to a convenience sample of Michigan veterinarians who represent a variety of practice types and sizes, participate in organized veterinary medicine and academia, and would be motivated to participate in system development. Of the 112 questionnaires, 84 (75%) were completed. Of 79 practices represent-

ed, 19 (24%) treated companion animals, 15 (19%) treated equids, 4 (5%) treated food animals (dairy, beef, small ruminant, poultry, or swine), 32 (41%) treated a variety of animals (no patient type >75%), 4 (5%) treated zoo animals, and 5 (6%) veterinarians were not in clinical practice.

Of 81 respondents, 75 (93%) indicated that they were aware of the Michigan reportable animal disease list. Yet, 37 (47%) of 79 respondents have reported no cases and 32 (41%) of 79 have reported 1 to 5 cases annually. Furthermore, only 19 (25%) of 76 respondents reported that their clients might have confidentiality issues that could impede disease reporting. Therefore, it will be important to continue educating veterinarians to ensure that suspected disease cases are reported as well as confirmed cases, which may have been reported by the laboratory also.

Positive feedback was received regarding the current animal disease reporting system. Respondents evaluated the availability of a published list of reportable diseases (68 [89%] of 76) and the availability and quality of laboratory testing and disease confirmation (57 [75%] of 76) as Strongly Like/Like (Scale = Strongly Dislike, Dislike, No Opinion, Like, Strongly Like). However, case submission feedback may need to be assessed as only 34 (45%) of 76 respondents evaluated this service as Strongly Like/Like and 13 (17%) of 76 evaluated it as Strongly Dislike/Dislike.

Of 73 respondents, 68 (93%) reported that routinely published animal disease surveillance data would be beneficial for themselves or their clients. Of 55 respondents, 24 (44%) indicated that these data would be used to increase disease awareness and 23 (42%) indicated the data would be used for risk assessment and prevention planning. Outbreak alert information, easy access to regulatory requirements, and animal disease information were also desired.