Tetracycline and Erythromycin Resistance among Clinical Isolates of Branhamella catarrhalis

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We reviewed tetracycline and erythromycin disk diffusion susceptibility of 457 isolates of Branhamella catarrhalis. Four isolates were resistant to tetracycline, with MICs for two available isolates of 16 μg/ml. Sixteen isolates were in the moderately susceptible range for erythromycin, with an MIC for one available isolate being >8 μg/ml. These are the first tetracycline- and (by MIC) erythromycin-resistant B. catarrhalis isolates reported from the United States.

Our laboratory in Texas has performed disk diffusion susceptibility testing on respiratory isolates of Branhamella catarrhalis since 1982. The recovery in November and December of 1988 of three isolates of B. catarrhalis with small zones of inhibition to tetracycline by disk diffusion prompted us to review our susceptibility results with this drug, as well as with erythromycin. Identified within this study were the first isolates of B. catarrhalis resistant to tetracycline and erythromycin reported from the United States.


B. catarrhalis isolates recovered from respiratory samples submitted to the clinical laboratory of the University of Texas Health Center were used for study. They were identified by standard methods (12). β-Lactamase testing was performed with nitrocefin disks (Cefinase; BBL Microbiology Systems, Cockeysville, Md.). Disk diffusion susceptibility testing was done at the time of isolation by using Mueller-Hinton agar and National Committee for Clinical Laboratory Standards guidelines (16). Broth microdilution susceptibility testing was performed by using cation-supplemented Mueller-Hinton broth or Mueller-Hinton broth supplemented with 1% supplement B (Difco Laboratories, Detroit, Mich.). Repeat MICs were determined with selected strains at the Centers for Disease Control (Atlanta, Ga.). Charts of the patients with resistant isolates were screened for their clinical history.

From 27 December 1982 to 29 December 1989, 457 isolates of B. catarrhalis were identified. β-Lactamase production (12, 17) and the range and median values of disk zone sizes for erythromycin and tetracycline for 231 of the isolates (12) have previously been reported.

The recently revised National Committee for Clinical Laboratory Standards disk breakpoints for erythromycin use zone sizes of >23 mm for susceptible, 14 to 22 mm for moderately susceptible, and ≤13 mm for resistant. Of the 457 isolates of B. catarrhalis, none fell in the resistant category and 16 (3.5%) had zones in the moderately susceptible category, of which 11 were recovered in 1987 and 1988. Two of these isolates were available for MIC determinations. For one the MIC was 0.25 μg/ml, and for the other the zone was 19 mm and MICs were 4 and 8 μg/ml when tested on two occasions in the Texas laboratory and >8 μg/ml when tested at the Centers for Disease Control. MICs for 106 random isolates with susceptible zones were all ≤0.5 μg/ml (Table 1).

Of the 457 isolates tested with tetracycline, four isolates seen in 1987 and 1988 had zone sizes (11 to 12 mm) in the resistant category for tetracycline (≤14 mm) (16). The MICs for the two isolates available for MIC determinations were 16 μg/ml. The remaining 453 isolates all had zone sizes within the susceptible range (≥19 mm) (16), and MICs for 108 random isolates were all ≤0.5 μg/ml (Table 1). MICs of multiple drugs for the three isolates resistant by MIC determinations are shown in Table 2.

Of the five patients with isolates within the resistant category for tetracycline or erythromycin, all were adults with chronic lung disease. Two patients were taking the drug to which their isolate of B. catarrhalis was resistant at the time it was recovered (one erythromycin and one tetracycline), and both presented to the hospital with worsening symptoms of cough and sputum production despite the use of their antibiotic, demonstrating that the isolates were also clinically resistant.

Erythromycin resistance among isolates of B. catarrhalis was seen as early as 1983 (8, 9). In that year, Kallings reported seven strains from Sweden for which MICs were 4 to >8 μg/ml, a resistance rate of 3%. In 1986 Maesen and Davies reported that 6% of isolates from The Netherlands were resistant to erythromycin by a disk diffusion method. Breakpoints used to define this resistance were not given (13). In that same year Thornley et al. noted that 3 of 96 (3%) of B. catarrhalis isolates from New Zealand were also erythromycin resistant (20). Numerous other studies from Japan, England, Europe, and the United States have failed to detect erythromycin resistance (1, 2, 6, 7, 10, 19).

The two tetracycline-resistant isolates of B. catarrhalis available for MIC determinations were resistant to tetracycline, were moderately susceptible to doxycycline, and were highly susceptible to minocycline. One study as early as 1983 in Sweden described isolates with this level of doxycycline MICs, but tetracycline was not studied (8, 9). Numerous studies since that time from the United States, Europe, and New Zealand have failed to demonstrate tetracycline resistance. Although a number of studies evaluated minocycline and doxycycline rather than the parent tetracycline compound (1, 2, 6, 7, 13, 19). In 1988, however, two reports of...
Erythromycin and tetracycline resistance among isolates of *B. catarrhalis* appeared. Zheng reported on 30 isolates of *B. catarrhalis* from China, of which an astounding 43% were resistant to tetracycline (21). Davies and Maesen reported that 15% of a large number of *B. catarrhalis* isolates recovered in 1987 were resistant to doxycycline by a disk diffusion method, a dramatic change from previous years (4). These studies plus the current isolates suggest that a change in tetracycline susceptibility in this species may be occurring.

The mechanisms of tetracycline and erythromycin resistance in *B. catarrhalis* are unknown but are under investigation. Plasmids appear to be common in *Moraxella subgenus Moraxella* (14) and have rarely been described in *B. catarrhalis* (3; P. Cook, D. W. Hecht, and D. R. Syndman, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1126, 1987), although no antimicrobial resistance has been associated with these plasmids. Given the recent spread of the tetM resistance determinant to related *Neisseria* species (11, 15, 18), it appears to be a logical candidate to explain tetracycline resistance in *B. catarrhalis*. However, given the previous failures to identify recognized antibiotic-resistant determinants in *B. catarrhalis* and the unique nature of their β-lactamases (BRO enzymes), it seems more likely that the resistance determinants for tetracycline and erythromycin may also be different from currently recognized genes.

In a recent review of antimicrobial susceptibility testing, Doern and Jones suggested that routine susceptibility testing of *B. catarrhalis* may not be necessary (5). The current study suggests a change in *B. catarrhalis* susceptibility to tetracycline and erythromycin, and continued surveillance of the susceptibility to these drugs is needed. The reliability of current disk diffusion breakpoints for recognition of moderately susceptible and resistant strains also requires additional study.

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**LITERATURE CITED**


