Levofloxacin Treatment Failure in a Patient with Fluoroquinolone-Resistant *Streptococcus pneumoniae* Pneumonia

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The frequency of fluoroquinolone-resistant *Streptococcus pneumoniae* has increased as fluoroquinolone administration for treatment of respiratory tract infections has increased. Levofloxacin treatment failed in a patient who had pneumococcal pneumonia and had received three previous courses of levofloxacin therapy. Susceptibility testing revealed high-level resistance to levofloxacin (minimum inhibitory concentration [MIC] > 32 µg/ml), and cross-resistance to moxifloxacin (MIC 4 µg/ml), trovafloxacin (6 µg/ml), and gatifloxacin (12 µg/ml). Sequencing of the quinolone-resistance determining region revealed a mutation of serine-81 to phenylalanine (Ser81→Phe) in the *gyrA* region of DNA gyrase and a Ser79→Phe mutation in the *parC* region of topoisomerase IV. The patient was treated successfully with intravenous ceftriaxone followed by oral cefprozil. Clinicians must be aware of local resistance patterns and the potential for fluoroquinolone treatment failures in patients with infections caused by *S. pneumoniae*.
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Streptococcus pneumoniae is a common pathogen in community-acquired respiratory tract infections, such as pneumonia, sinusitis, and acute exacerbations of chronic bronchitis. Unfortunately, strains of *S. pneumoniae* with reduced penicillin susceptibility have become increasingly common in the United States and worldwide, and many penicillin-resistant strains show cross-resistance to other antimicrobial agents.[1–6] Conversely, newer fluoroquinolones are active in vitro against *S. pneumoniae* with reduced penicillin susceptibility, and the minimum inhibitory concentration for 90% of organisms tested (MIC_{90}) is usually the same for penicillin-susceptible, -intermediate, and -resistant strains.[3, 7] As a result of their in vitro activity, pharmacokinetic characteristics, and clinical efficacy, antipneumococcal fluoroquinolones have assumed an important role in the treatment of community-acquired pneumonia, especially if penicillin-resistant pneumococci are suspected.[8, 9]

As fluoroquinolone administration has increased for treating respiratory tract infections, the frequency of fluoroquinolone-resistant pneumococci also has increased.[10–15] In Canada, the prevalence of pneumococci with reduced fluoroquinolone susceptibility (defined as ciprofloxacin MIC > 4 µg/ml) increased from 0% in 1993 to 1.7% in 1997–1998 as prescriptions for fluoroquinolones increased.[11] In addition, the rates of levofloxacin-resistant *S. pneumoniae* have increased significantly in the U.S. and Latin America.[12, 14] In North America, 0.2–0.3% of pneumococcal isolates were levofloxacin resistant

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in 1997–1998 versus 0.9% in 1999 ($p<0.05$).[12] In Indianapolis, 1.7% (5 of 307) pneumococcal isolates collected from January 1999–April 2000 were levofloxacin resistant (MIC ≥ 8 µg/ml), and all of these strains were isolated from respiratory sources (four from sputum, one from sinus).[16]

With the emergence of fluoroquinolone resistance in *S. pneumoniae*, a few case reports have described levofloxacin treatment failures in patients with pneumococcal infections.[17–20]

Case Report

A 50-year-old man was admitted to the hospital after arriving at the emergency department with progressive dyspnea, left-sided chest pain, fever, and cough. His medical history was significant for diabetes mellitus, coronary artery disease, steroid-dependent asthma, chronic obstructive pulmonary disease, chronic bronchitis, and bronchomalacia of the left main stem bronchus, which had required stent placement 2 years earlier. Two weeks before admission, he experienced increasing cough, shortness of breath, wheezing, fever, and chills. At that time his prednisone was increased to 40 mg/day, and oral levofloxacin 500 mg once/day was started. His symptoms improved until the evening before hospital admission and returned with increasing severity on the day of admission. In the emergency department, coarse rales were heard at the left base, and chest radiograph revealed an infiltrate in the left lower lobe. His heart rate was 119 beats/minute, blood pressure 154/90 mm Hg, and respiratory rate 28 breaths/minute; white blood cell count was 12.9 x $10^3/mm^3$. Sputum was collected for Gram's stain and culture, and intravenous levofloxacin 500 mg once/day was started. Gram's stain was positive for cocci in pairs and chains, and the culture was positive for *S. pneumoniae*. The organism was penicillin resistant, but levofloxacin susceptibility was not determined. The patient improved over the next 3 days and was discharged with oral levofloxacin 500 mg once/day.

Three months later, the patient came to the emergency department with intermittent chest tightness, increased sputum production, shortness of breath, and severe cough. He was admitted to the hospital, sputum cultures were collected, and chest radiograph revealed left lower lobe pneumonia. Ceftriaxone 1 g every 24 hours was begun. Three days after admission, his white blood cell count increased to 17.6 x $10^3/mm^3$; bronchoscopy revealed thick, purulent secretions in the left lower lobe and complete occlusion of the left main-stem bronchus. Respiratory cultures obtained on admission and cultures obtained during bronchoscopy indicated growth of *S. pneumoniae*. On day 4, the patient's antibiotic therapy was switched to oral levofloxacin 500 mg once/day. His symptoms improved over the next week, and he was discharged with levofloxacin to complete a 14-day course of therapy.

Three months later, the patient again returned to the emergency department with a severe cough resulting in two episodes/day of syncope and was admitted to the hospital. His cough had worsened over the past 2 weeks, with a significant increase in sputum production. On admission, he was afebrile; his heart rate was 76 beats/minute, respiratory rate 20 breaths/minute. Chest radiograph revealed a left lower lobe infiltrate consistent with pneumonia. Sputum was obtained but was inadequate for analysis (> 25 epithelial cells/low-power field). Intravenous levofloxacin 500 mg once/day was started, but his symptoms did not improve over the next 3 days. Bronchoscopy performed on day 4 of his hospital stay revealed purulent secretions in the left lower lobe and at the stent site. Cultures were positive for *S. pneumoniae*, which was resistant to penicillin (MIC 2 µg/ml) and levofloxacin (MIC > 32 µg/ml). His antibiotic therapy was switched to ticarcillin-clavulanate; he improved over the next 5 days and was discharged with amoxicillin-clavulanate 875 mg twice/day for 2 weeks.

Two weeks later, the patient was readmitted to the hospital with a 3-day history of increasing cough, myalgia, shortness of breath, and fever to 38.3°C. Sputum cultures were obtained, and levofloxacin was restarted. After 1 day, levofloxacin was discontinued because of culture and susceptibility data obtained at his previous hospital admission, and intravenous ceftriaxone 2 g every 24 hours was started. The sputum culture again indicated growth of *S. pneumoniae*, which was intermediate to ceftriaxone (MIC 0.75 µg/ml) and resistant to penicillin (2 µg/ml) and levofloxacin (> 32 µg/ml). The patient received ceftriaxone for the next 7 days; his symptoms improved, and he was discharged with oral cefprozil 500 mg 3 times/day. The infection resolved, and the patient did not have another infection in over 6 months of follow-up.

The quinolone-resistance determining region of the pneumococcal isolate was sequenced as previously described.[21] The isolate was found to

have a Ser81→Phe mutation in the *gyrA* region of DNA gyrase and a Ser79→Phe mutation in the *parC* region of topoisomerase IV. Etest MICs were determined for four additional fluoroquinolones, and cross-resistance was observed for moxifloxacin (MIC 4 µg/ml), trovafloxacin (6 µg/ml), and gatifloxacin (12 µg/ml). Gemifloxacin was the most potent agent tested, with an MIC of 0.5 µg/ml.

Discussion

As the frequency of penicillin- and macrolide-resistant *S. pneumoniae* has continued to increase, fluoroquinolones have become an important drug class for treating community-acquired respiratory tract infections.[8, 9] Fluoroquinolones with enhanced pneumococcal activity are an option for empiric outpatient treatment of community-acquired pneumonia and may be a preferred choice for older patients or those with underlying disease.[8] However, some investigators do not advocate administration of fluoroquinolones for first-line treatment of community-acquired pneumonia because of concerns regarding emerging resistance in pneumococci.[22] They suggest that a fluoroquinolone may be administered to patients whose previous therapy has failed, who are allergic to alternative agents, or who have a documented infection with highly drug-resistant pneumococci.[22]

Fluoroquinolones exert their antibacterial activity by inhibiting DNA replication, forming cleavage complexes with DNA gyrase and topoisomerase IV. In *S. pneumoniae*, DNA gyrase and topoisomerase IV are tetrameric enzymes encoded by *gyrA-gyrB* and *parC-parE*, respectively.[23, 24] Fluoroquinolone resistance in *S. pneumoniae* has been associated with mutations in *gyrA* and *parC* (alone or in combination) and/or drug efflux.[21, 24–27] In general, high-level fluoroquinolone resistance has been associated with amino acid substitutions in both *gyrA* and *parC*.[21, 25–27] Mutations in *gyrB* have not been associated with decreased fluoroquinolone susceptibility, and the role of *parE* mutations on fluoroquinolone activity is controversial.[24, 25, 28]

The frequency of fluoroquinolone-resistant *S. pneumoniae* has increased as fluoroquinolone administration for treatment of respiratory tract infections has increased.[10–15] Factors associated with reduced fluoroquinolone susceptibility are patient age (≥ 65 yrs), respiratory tract source, resistance to penicillin, presence of chronic obstructive pulmonary disease, nosocomial origin of the bacteria, nursing home residence, and previous fluoroquinolone exposure.[11, 29] Respiratory tract source, resistance to penicillin, chronic obstructive pulmonary disease, and previous fluoroquinolone exposure were present in our patient. Previous fluoroquinolone therapy is an important factor because it may provide the necessary selective pressure for mutations to occur.[29] Our patient received three treatment courses of levofloxacin over an 8-month period before isolation of the levofloxacin-resistant isolate. However, the bacterial strains isolated from the previous treatment courses were not available for comparison with the resistant isolate by pulsed-field gel electrophoresis. Therefore, we do not know if resistance developed due to persistence of the same strain or if the patient became infected with a different pneumococcal strain. Also, susceptibility testing was not performed on the isolates from the previous treatment courses, so we do not know if they were initially susceptible to levofloxacin. However, these strains may have been susceptible to levofloxacin since the patient's condition improved after therapy was started. During the fourth treatment course, symptoms did not improve after 3 days of levofloxacin therapy, and the pneumococcal isolate was levofloxacin resistant. Mutations were present in both *gyrA* (Ser81→Phe) and *parC* (Ser79→Phe), and the organism was cross-resistant to other fluoroquinolones, except for gemifloxacin.

Levofloxacin treatment failures in patients with respiratory tract infections caused by *S. pneumoniae* have been reported.[17–20] A 58-year-old man infected with human immunodeficiency virus was given oral levofloxacin 500 mg/day for sinus congestion and fever.[17] After 4 days of therapy, he became increasingly lethargic, and cultures of cerebrospinal fluid were positive for *S. pneumoniae* that was penicillin susceptible and levofloxacin resistant. The patient died several days later despite a change in his antibiotic therapy. Levofloxacin treatment failures were described in three other patients with pneumococcal respiratory tract infections.[18] Two had a history of fluoroquinolone therapy, and all of the isolates had *gyrA* and *parC* mutations in the quinolone-resistance determining region.

Levofloxacin treatment failures and development of resistance during therapy also have been described in two patients with pneumococcal pneumonia.[19] A 64-year-old man was treated with levofloxacin for 10 days. One week after completing therapy, he returned to his

physician with recurrent pneumonia. Sputum cultures obtained at both visits were positive for *S. pneumoniae*, which were identical based on pulsed-field gel electrophoresis. The initial isolate was susceptible to levofloxacin, but the second was resistant (MIC 8 µg/ml), with mutations in *gyrA* and *parC*.

A 37-year-old woman with pneumonia was treated with levofloxacin 500 mg for 14 days but was hospitalized 3 days after therapy was begun. Her initial sputum culture was positive for *S. pneumoniae*, which was susceptible to levofloxacin by disk diffusion but intermediate by broth dilution (MIC 4 µg/ml). This isolate had a mutation in *parC* only. With pulse-field gel electrophoresis, the same organism grew in the subsequent culture; it was resistant to levofloxacin (MIC 16 µg/ml) and had developed an additional mutation in *gyrA*.[19]

Another levofloxacin treatment failure was described in a patient with pneumococcal pneumonia who was given intravenous levofloxacin 500 mg once/day.[20] The levofloxacin MIC was not determined on the initial isolate, but after 5 days of therapy, the isolate recovered had an MIC of 6 µg/ml (Etest). In this isolate, DNA sequencing of the quinolone-resistance determining region was not determined.

Conclusion

Although the prevalence of fluoroquinolone resistance in *S. pneumoniae* is low, clinicians must be cognizant of local resistance patterns and the potential for treatment failures, especially in patients with risk factors for fluoroquinolone resistance. Global and local surveillance testing are needed to monitor changes in fluoroquinolone susceptibility, and clinical laboratories should test patient-specific pneumococcal isolates routinely for susceptibility to fluoroquinolones. Close monitoring and follow-up of patients are essential to ensure successful treatment of pneumococcal respiratory tract infections.

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