

Brief Report

RESISTANCE TO LEVOFLOXACIN
AND FAILURE OF TREATMENT
OF PNEUMOCOCCAL PNEUMONIA

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THE emergence of *Streptococcus pneumoniae* that is resistant to the β -lactam and macrolide antimicrobial drugs has aroused concern about the use of these agents for the empirical treatment of community-acquired pneumonia.¹ Fluoroquinolones with increased activity against *S. pneumoniae*, such as levofloxacin, moxifloxacin, and gatifloxacin, are now being recommended for the treatment of patients with community-acquired pneumonia whose infection is likely to have been caused by multidrug-resistant strains.¹⁻⁶ However, there has been relatively little experience with the use of these agents, as compared with the β -lactam and macrolide antimicrobial agents, as monotherapy for community-acquired pneumonia.

We describe four patients with pneumococcal pneumonia in whom empirical treatment with oral levofloxacin failed. In all four cases, an organism that either was resistant to levofloxacin before therapy or acquired resistance during therapy was isolated. In the light of these failures, we investigated the use of antimicrobial agents according to prescription records and determined the frequency of routine testing for pneumococcal susceptibility to levofloxacin in clinical laboratories in Ontario.

CASE REPORTS

Patient 1

Patient 1 was a 64-year-old man from Nova Scotia who presented in the late winter of 2000 with a two-day history of productive cough, fatigue, dyspnea, and fever (temperature, 38.4°C). He had no history of treatment with fluoroquinolones. The clin-

ical findings were compatible with the presence of a right-sided pneumonia. A sputum specimen contained gram-positive diplococci and grew *S. pneumoniae* that was susceptible to levofloxacin. He was treated for community-acquired pneumonia with 500 mg of oral levofloxacin daily for 10 days. The day after his last dose was given, signs and symptoms of recurrent pneumonia developed. Another sputum culture grew *S. pneumoniae*, which was now resistant to levofloxacin (Table 1).

Patient 2

Patient 2 was a 37-year-old woman from Nova Scotia who presented to the emergency department in the spring of 2000 with cough and fever (temperature, 38.7°C). She had no history of treatment with fluoroquinolones. A radiograph of the chest revealed consolidation in the right middle lobe. A sputum specimen showed gram-positive diplococci and grew *S. pneumoniae* with susceptibility to levofloxacin according to the disk-diffusion method. She was treated for community-acquired pneumonia with 500 mg of oral levofloxacin daily. On the third day of treatment, her clinical condition had not improved, and repeated radiography of the chest showed progression of the infiltrates. Another sputum specimen contained gram-positive diplococci and grew *S. pneumoniae*, which was now resistant to levofloxacin (Table 1).

Patient 3

Patient 3 was a 66-year-old woman from Ontario who was admitted to the hospital because of community-acquired pneumonia. She had a history of chronic obstructive lung disease, allergy to penicillin, and chronic lymphocytic leukemia, which did not currently require treatment. She had received a 10-day course of ciprofloxacin 6 months earlier and a 10-day course of oral levofloxacin 1 month previously, both for the treatment of an acute exacerbation of chronic bronchitis.

Two weeks before admission, an upper respiratory tract infection developed. Eight days before admission, treatment with 500 mg of ciprofloxacin twice daily was begun because of her persistent respiratory symptoms. At the time of admission, her clinical condition had deteriorated, and she was found to have an infiltrate in the right lower and middle lobes and a small right-sided pleural effusion. Blood cultures grew *S. pneumoniae*. Treatment was switched to 500 mg of oral levofloxacin daily. Cultures of pleural fluid obtained on the fourth hospital day grew *S. pneumoniae*. On the fifth hospital day, septic shock developed. The patient was intubated and transferred to the intensive care unit. She died the following day. Testing of the isolates for susceptibility to the fluoroquinolones was not performed at the time of admission, since such testing was not routine. On subsequent susceptibility testing, however, the initial isolate was found to be resistant to levofloxacin (Table 1).

Patient 4

Patient 4 was an 80-year-old woman from British Columbia who presented to her doctor in the summer of 2001 with signs and symptoms of an acute exacerbation of chronic bronchitis. She had a history of chronic obstructive lung disease. Treatment was begun with 500 mg of ciprofloxacin twice daily. After six days of therapy, she returned to her physician because her symptoms had not improved. A radiograph of the chest showed changes compatible with the development of pneumonia, and treatment with 500 mg of oral levofloxacin daily was begun. After eight days of therapy, her condition still had not improved, and treatment was switched to a macrolide antimicrobial agent. Sputum cultures grew *S. pneumoniae* that was resistant to levofloxacin (Table 1).

METHODS

Susceptibility testing was performed on a pair of isolates from each patient according to the guidelines of the National Commit-

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TABLE 1. MICROBIOLOGIC CHARACTERISTICS OF *STREPTOCOCCUS PNEUMONIAE* ISOLATED BEFORE, DURING, OR AFTER THERAPY WITH ORAL LEVOFLOXACIN FROM FOUR PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA.*

PATIENT NO.	SOURCE AND TIME OF CULTURE	SERTYPE	PFGE PATTERN†	SUSCEPTIBILITY TO LEVOFLOXACIN‡	MINIMAL INHIBITORY CONCENTRATIONS§			AMINO ACID SUBSTITUTION	
					LEVO-FLOXACIN	MOXI-FLOXACIN	GATI-FLOXACIN	IN PARC	IN GYRA
					μg/ml				
1	Sputum, before treatment	23F	A	S	1 (S)	0.12 (S)	0.25 (S)	—	—
	Sputum, after treatment	23F	A	R	8 (R)	1 (S)	2 (I)	S79F	S81F
2	Sputum, before treatment	6A	B	S	4 (I)	0.25 (S)	0.5 (S)	S79F	—
	Sputum, during treatment	6A	B	R	16 (R)	4 (R)	4 (R)	S79F	S81F
3	Blood, before treatment	14	C	R	16 (R)	4 (R)	2 (I)	S79F	S81Y
	Pleural fluid, during treatment	14	C	R	16 (R)	4 (R)	2 (I)	S79F and D83Y	S81Y
4	Sputum, during treatment	ND	ND	R	16 (R)	4 (R)	8 (R)	S79Y	E85K

*PFGE denotes pulsed-field gel electrophoresis, S susceptible, R resistant, I having intermediate susceptibility, and ND not done. Dashes indicate that no mutation was found.

†Unique PFGE patterns are designated by arbitrary single letters.

‡Susceptibility was tested by the disk-diffusion method.

§The degree of susceptibility is indicated in parentheses.

tee for Clinical Laboratory Standards.⁷ All the isolates were serotyped at the National Centre for Streptococcus (Edmonton, Alta., Canada). The isolates were also examined by pulsed-field gel electrophoresis after the digestion of bacterial DNA with *SmaI*, according to methods described by Murray et al.⁸ Amplification of the *parC* and *gyrA* genes and DNA sequencing were performed as previously described, as was the determination of active efflux (a mechanism of resistance mediated by a membrane protein that transports levofloxacin out of the cell).⁹

After the death of Patient 3, the Quality Management Program–Laboratory Services of the Ontario Medical Association deemed it necessary to determine how frequently laboratories were performing routine testing of the susceptibility of pneumococci to levofloxacin. In the fall of 2000, we sent a pure culture of *S. pneumoniae* from a patient with community-acquired pneumonia to 109 participating laboratories in Ontario for blinded assessment of the proficiency of each laboratory in identifying the organism. The Quality Management Program–Laboratory Services promulgates the standards of the National Committee for Clinical Laboratory Standards in microbiology. IMS Health (Montreal) provided an estimate of the total number of prescriptions for antimicrobial agents dispensed in Canadian retail pharmacies.

RESULTS

Each of the two isolates from Patients 1, 2, and 3 had the same pattern on pulsed-field gel electrophoresis and the same serotype, but the pattern and serotype of the isolates differed among the patients (Table 1). The results of DNA sequencing of the fluoroquinolone-resistance–determining region of the *parC*

and *gyrA* genes are shown in Table 1. All the isolates were susceptible to penicillin and erythromycin. Active efflux did not contribute to the reduced fluoroquinolone susceptibility observed in any of the isolates.

According to the results of the Quality Management Program–Laboratory Services survey, all 109 laboratories correctly identified the challenge organism as *S. pneumoniae*. However, only 15 of these laboratories performed levofloxacin-susceptibility testing.

Levofloxacin was approved for use in Canada in the fall of 1997. In 1998, 51,908 prescriptions for oral levofloxacin were written for adults; in 1999 this number increased to 161,277, and in 2000 it increased to 316,467. In 2000, 1.3 levofloxacin prescriptions per 100 persons were written, as compared with 14.7 prescriptions for macrolides per 100 persons and 6.2 prescriptions for amoxicillin–clavulanate or second-generation cephalosporins per 100 persons.

DISCUSSION

In the treatment of pneumococcal pneumonia with β -lactam, tetracycline, and macrolide antimicrobial drugs, pneumococcal resistance usually results from the acquisition of a resistance gene before therapy. However, reduced susceptibility or resistance to the fluoroquinolones may develop during therapy. Such

a change could adversely affect the pharmacodynamics of the drug. As the prevalence of resistant pneumococci increases, so does the likelihood that treatment will fail if susceptibility testing is not performed. In our opinion, the current data indicate that recent exposure to a fluoroquinolone should be a contraindication to the use of another fluoroquinolone for the empirical treatment of community-acquired pneumonia. Finally, other risk factors for infection with a resistant strain may need to be taken into consideration before one of these agents is prescribed.¹⁰

Decreased susceptibility to the fluoroquinolones develops primarily as a result of mutations in the *parC* and *gyrA* genes, which encode the targets of fluoroquinolones, the topoisomerase enzymes.¹¹ These spontaneous mutations occur at a frequency of 1 in 10⁶ to 1 in 10⁹. This is analogous to the development of resistance to rifampin and streptomycin in *Mycobacterium tuberculosis*, which occurs as a result of mutations in the *rpoB* and *str* genes, the genes that encode the respective target proteins.¹² In patients with pneumonia, there may be more than 10¹⁰ infecting organisms in the lung parenchyma.^{13,14} Thus, not only may a fluoroquinolone-resistant strain of pneumococcus be acquired from another person (as in cases of primary resistance),¹⁵ but resistance may also develop during treatment or as a result of previous fluoroquinolone exposure (as in cases of acquired resistance). Acquired resistance probably explains the resistance to levofloxacin in Patients 1 and 2 in this report. The ratio of the peak concentration to the minimal inhibitory concentration (MIC) for the infecting pathogen or the ratio of the area under the concentration–time curve (AUC) to the MIC has been directly linked to the probability of a successful clinical or microbiologic outcome in *S. pneumoniae* infections when the ratio is greater than 30.^{16,17} The AUC:MIC ratio may have been as low as 6 in Patient 1 and as low as 3 in Patients 2, 3, and 4.¹⁸

In some countries, there have been reports suggesting that fluoroquinolone resistance in *S. pneumoniae* may be increasing,^{19,20} but in the United States, the incidence of such resistance remains below 1 percent.²¹ Therefore, the National Committee for Clinical Laboratory Standards does not recommend that levofloxacin, moxifloxacin, or gatifloxacin be included in the routine panel of agents used in susceptibility testing of pneumococci.⁷ According to the results of the assessment of proficiency of 109 laboratories in Ontario, laboratories in that province are not routinely performing fluoroquinolone-susceptibility testing. Since fluoroquinolones are being recommended in some situations for the empirical treatment of community-acquired pneumonia, it may now be appropriate to consider recommending routine testing and reporting of the susceptibility of pneumococci to

these agents. Although routine testing reliably detects high-level resistance to levofloxacin, it may not always detect low-level resistance, such as that in Patient 2.^{9,22}

Since *S. pneumoniae* can develop resistance to fluoroquinolones during therapy and since cross-resistance to other fluoroquinolones is likely to occur,¹⁹ physicians should be aware of the consequences of substituting one fluoroquinolone compound for another if a patient does not have a response to the initial therapy, as was the case for Patients 3 and 4. In a case–control study by Ho et al.,¹⁰ it was found that the presence of chronic obstructive lung disease, a nosocomial origin of the bacteria, residence in a nursing home, and exposure to fluoroquinolones were all independently associated with colonization or infection by levofloxacin-resistant pneumococci. Ironically, it is for patients with these same factors that fluoroquinolones are recommended as first-line therapy.³ None of the position papers published on community-acquired pneumonia since the introduction of fluoroquinolones for the treatment of pneumococcal pneumonia have suggested that a history of fluoroquinolone use should be a reason for caution in using one of these antimicrobials.¹⁻⁴

The volume of levofloxacin consumed in Canada is small in comparison with the volume of other agents used to treat lower respiratory tract infections. Nevertheless, we identified four patients in whom resistance to fluoroquinolones was associated with the failure of bacterial eradication and the lack of a clinical response. This finding suggests that routine testing of pneumococci for susceptibility to fluoroquinolones should now be considered. Such testing would identify patients who are infected with a resistant strain, although physicians should be aware that resistance may develop during therapy.

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