MAJOR ARTICLE

A Randomized Trial of Ciprofloxacin versus Cefixime for Treatment of Gonorrhea after Rapid Emergence of Gonococcal Ciprofloxacin Resistance in The Philippines

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From 1994 through 1996–1997, high-level ciprofloxacin resistance (minimum inhibitory concentration [MIC], ⩾4.0 μg/mL) increased from 9% to 49% of gonococcal isolates recovered from consecutive female sex workers in Cebu and Manila, The Philippines ($P < .01$). During 1996–1997, 105 female sex workers with gonorrhea were prospectively randomized to receive treatment with oral ciprofloxacin, 500 mg, or cefixime, 400 mg, and followed for test of cure. *Neisseria gonorrhoeae* was reisolated within 28 days after treatment from 1 (3.8%) of 26 women given cefixime versus 24 (32.3%) of 72 women given ciprofloxacin ($P < .01$). Treatment failure (reisolation of pretreatment auxotype/serovar) occurred in 14 (46.7%) of 30 women infected with strains with MICs of ciprofloxacin ⩾4.0 μg/mL versus 1 (3.6%) of 28 infected by strains with MICs <4.0 μg/mL ($P < .01$). High-level, clinically significant gonococcal resistance to ciprofloxacin has rapidly emerged in The Philippines, and spread of fluoroquinolone resistance through commercial sex poses a threat to control of gonorrhea and prevention of human immunodeficiency virus infection and the acquired immunodeficiency syndrome.

The fluoroquinolones have been extensively used for treatment of gonorrhea [1], not only in industrialized countries but also in developing countries, where ciprofloxacin has been the least expensive of the highly effective drugs that are widely available for oral treatment of gonorrhea. The importance of gonorrhea in facilitating transmission of HIV infection [2–4] has made the fluoroquinolones critically important for HIV prevention as well. Despite sporadic reports of gonococcal fluoroquinolone resistance and treatment failure [5–9], fluoroquinolone treatment of infections caused by strains with decreased susceptibility (MICs of ciprofloxacin of 0.125–0.5 μg/mL) or with resistance (MIC, ⩾1.0 μg/mL) has not been prospectively studied [8, 9].

We initially investigated ciprofloxacin susceptibilities of gonococci recovered from female sex workers in Manila and Cebu, The Philippines, from August through October 1994, and we found documentation of either

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The Institutional Review Boards at the Cebu Institute of Medicine, Cebu City; the Research Institute of Tropical Medicine, Manila; and the University of Washington, Seattle, Washington, approved this project. Informed consent was obtained from all subjects.

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decreased ciprofloxacin susceptibility or resistance in 42 (46%) of 92 consecutive gonococcal isolates. We returned in 1996–1997 to reassess ciprofloxacin susceptibilities of *Neisseria gonorrhoeae* in the same populations of female sex workers and to compare the efficacy of ciprofloxacin versus cefixime for the oral treatment of gonorrhea caused by strains with decreased susceptibility or resistance to ciprofloxacin.

METHODS

Study design. In 1996, the Social Hygiene Clinics selected for this study performed routine vaginal speculum examinations on registered female sex workers every 2 weeks, collected cervicovaginal specimens for Gram stain (but not for culture) for *N. gonorrhoeae,* and used ciprofloxacin for routine treatment of gonococcal infections detected by means of Gram staining. From August 1996 through January 1997, female sex workers in Manila and Cebu City were recruited at these Social Hygiene Clinics and through street outreach. Endocervical specimens were collected for Gram stain and for inoculation onto modified Thayer-Martin medium for isolation of *N. gonorrhoeae.*

Women with positive results for *N. gonorrhoeae* by endocervical Gram staining or culture were offered participation in the treatment trial on receipt of the test results. Exclusion criteria included age <16 years, pregnancy, and signs suggestive of pelvic inflammatory disease. Individual women were randomly assigned (by means of computer-generated random assignment) to receive a single oral dose of 500 mg of ciprofloxacin or a single oral dose of 400 mg of cefixime (2:1 ratio for assignment to ciprofloxacin or cefixime) by means of masked medications (prepackaged in identical envelopes identified by study number only). The clinicians who administered the treatment were unaware of which drug was to be used until the envelope containing the medication was opened.

Women were asked to return for evaluation 4–7 days after treatment. At all posttreatment evaluations, examination and culture procedures were repeated, and a course of doxycycline was then provided to all women for possible chlamydial coinfection. Women who had positive culture results for *N. gonorrhoeae* at follow-up were recalled and treated with cefixime, 400 mg given orally, if they had been initially treated with ciprofloxacin; or with ceftriaxone, 125 mg given im, if they had been initially treated with cefixime. When clinicians identified a participant as possibly having treatment failure, 1 investigator (M. R. A. or V. P.-M.) was called, and that investigator checked the randomization log to identify the appropriate second medication for treatment.

Microbiological procedures. Isolates that were presumptively identified in The Philippines in 1994 and in 1996–1997 as *N. gonorrhoeae* on the basis of colony morphology, oxidase reaction, and Gram stain appearance were confirmed by means of carbohydrate utilization tests in The Philippines. Isolates were subsequently shipped to Seattle for reconfirmation as *N. gonorrhoeae* by means of carbohydrate utilization tests (all such isolates were confirmed as *N. gonorrhoeae*), testing for β-lactamase production by use of established methods, and determination of MICs of penicillin G, tetracycline HCl, ceftriaxone, cefixime, ciprofloxacin, and spectinomycin by means of agar dilution [10]. During 1996–1997, such MICs were determined by means of agar dilution for pretreatment isolates from 115 patients; in addition, MICs of ciprofloxacin and ceftriaxone that were determined by use of Etest (AB Biodisk) [11] alone in The Philippines were used in data analyses for 5 pretreatment isolates that did not survive shipment to Seattle. Resistance to tetracycline HCl was defined by MICs of tetracycline of $\geq$2 μg/mL, and plasmid-mediated tetracycline resistance was presumptively identified by MICs $\geq$16 μg/mL [7]. To distinguish possible treatment failure from reinfection by a new strain of *N. gonorrhoeae,* auxotype and porin serovar of pretreatment isolates and any posttreatment isolates were determined by use of established methods for viable isolates received in Seattle [12, 13].

Ciprofloxacin susceptibilities were classified as follows: "fully susceptible," for strains with an MIC of ciprofloxacin $\leq$0.06 μg/mL; "decreased susceptibility," for strains with an MIC of 0.125–0.5 μg/mL; "resistant," for strains with an MIC of 1.0–2.0 μg/mL; and "highly resistant," for strains with an MIC $\geq$4.0 μg/mL [14].

Analysis. Desired sample sizes were calculated at 180 patients to be treated with ciprofloxacin and 90 to be treated with cefixime, sufficient to detect a difference ($\alpha = .05$; $\beta = .2$) between an estimated 2.5% failure rate with treatment with cefixime and at least a 10% higher failure rate (12.5%) with treatment with ciprofloxacin. The χ^2 test and Fisher's exact test were used to compare dichotomous variables. Continuous variables were compared by use of parametric or nonparametric tests as appropriate. Unexpectedly high levels of gonococcal ciprofloxacin resistance found in the first set of isolates sent to Seattle during the 1996–1997 study, coupled with reports of therapy failures, led to midpoint analysis of treatment results by investigators who were not involved in patient recruitment. On completion of that review in February 1997, recruitment of participants was stopped before the study end point had been reached.

RESULTS

In the 1994 study, *N. gonorrhoeae* had been recovered from 101 (16.8%) of 594 female sex workers. During the 1996–1997 study, *N. gonorrhoeae* was recovered from 120 (8%) of 1499 female sex workers. Of all isolates, 92 (91%) of those from the 1994 study and 115 pretreatment isolates (96%) from the

1996–1997 study were available for antimicrobial susceptibility testing, as described above.

Emergence of gonococci with high-level ciprofloxacin resistance during a 2 year period. In the 1994 study, 34% of gonococcal isolates had MICs of ciprofloxacin of 0.125–0.5 μg/mL, and 12% had MICs ⩾1.0 μg/mL, including 9% that had MICs ⩾4 μg/mL. The highest MIC of ciprofloxacin in the 1994 study was 8 μg/mL.

By the time that the 1996–1997 study was conducted, the distribution had shifted dramatically toward greater resistance; 72 (63%) of 115 isolates had MICs of ciprofloxacin ⩾1.0 μg/mL, including 49% with MICs ⩾4.0 μg/mL (figure 1). In the 1996–1997 study, the highest MIC of ciprofloxacin was 64 μg/mL. The proportion of isolates with intermediate susceptibility actually decreased significantly ($P < .05$) and the proportion with high-level resistance increased significantly ($P < .001$) between the 2 time periods. In the 1996–1997 study, the isolates from Cebu exhibited MICs of ciprofloxacin ⩾4.0 μg/mL somewhat less frequently than did isolates from Manila (37.5% vs. 54.7%; $P = .1$).

Between the 1994 and the 1996–1997 studies, the proportion of strains producing β-lactamase and those with presumptive plasmid-mediated tetracycline resistance did not change substantially. However, chromosomal tetracycline resistance (MIC, 2–8 μg/mL) increased from 18.5% to 40.0% ($P < .05$). All strains in both time periods were fully susceptible in vitro to ceftriaxone and cefixime (MICs, ⩽0.06 μg/mL for both) as well as to spectinomycin (MICs, <128 mg/mL).

Outcome of therapy. Of 120 women with positive culture results, a total of 105 were randomized to receive treatment; 77 were randomly allocated to receive ciprofloxacin therapy and 28 to receive cefixime therapy (figure 2). Another 6 had culture results that were negative for *N. gonorrhoeae*, despite positive results of Gram staining; these women were randomized to receive ciprofloxacin (4 patients) or cefixime (2 patients) but excluded from further analysis. Of the 105 women with positive results of culture who were randomized to receive treatment, 7 had no follow-up, and 98 (93.3%) returned for posttreatment assessment within 28 days. One woman returned at 61 days; results of posttreatment culture were negative. Of the 98 who returned within 28 days (including 85 who returned within 14 days), 72 had received ciprofloxacin and 26 had received cefixime. Participants assigned to receive ciprofloxacin and those assigned to receive cefixime treatment had similar characteristics (mean age ± SD, 23.0 ± 3.9 and 22.3 ± 4.2 years; percentage registered with the Social Hygiene Clinic, 54.0% and 44.4%; and percentage recruited in Manila, 52.7% and 48.2%, respectively).

N. gonorrhoeae was isolated from posttreatment cultures performed within 28 days from 24 (32.3%) of 72 women who received ciprofloxacin and 1 (3.8%) of 26 women who received cefixime ($P < .01$). The posttreatment isolate differed by auxotype/serovar class from the pretreatment isolate for 2 of 24 women who were given ciprofloxacin and for the 1 strain that was isolated after the patient received cefixime treatment.

Among all women treated with ciprofloxacin for whom both pre- and posttreatment isolates were available, a strain identical by auxotype/serovar class to the pretreatment isolate was re-

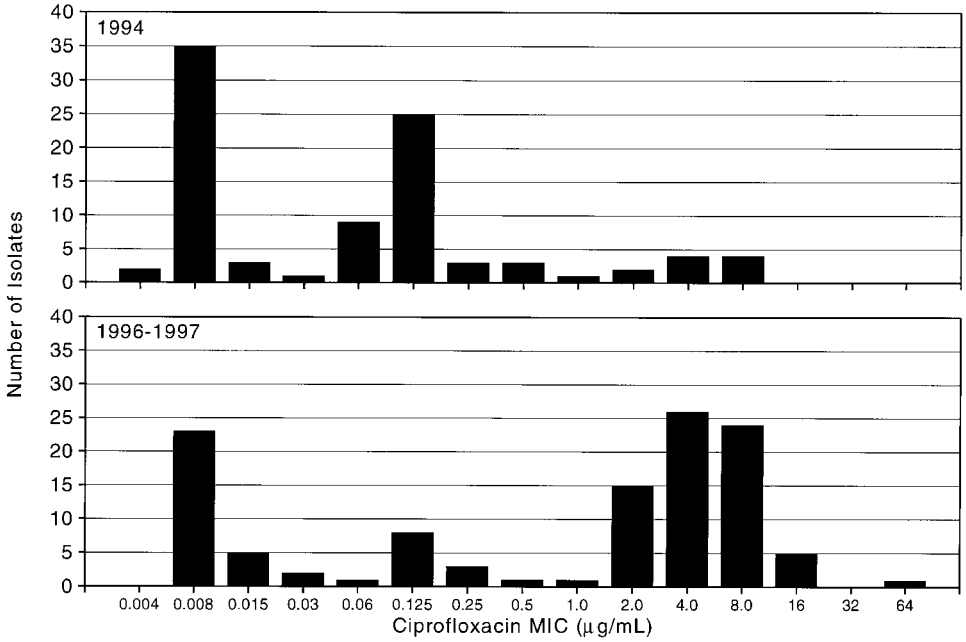

Figure 1. Ciprofloxacin susceptibilities among gonococci recovered from female sex workers in Manila and Cebu City, The Philippines, including 92 consecutive isolates in 1994 and 115 consecutive isolates in 1996–1997.

isolated after treatment from 14 (46.7%) of 30 women who were infected with strains with MICs of ciprofloxacin ⩾4.0 μg/mL versus only 1 (3.6%) of 28 who were infected with strains with MICs <4 μg/mL. The small number of infections caused by strains with MICs of ciprofloxacin of 0.125–2.0 μg/mL precluded reliable estimates of probabilities of treatment failure for such infections (table 1).

Table 1. Posttreatment culture results, according to MICs of ciprofloxacin, for pretreatment gonococcal isolates among women who were treated with ciprofloxacin, 500 mg given orally.

MIC of ciprofloxacin, μg/mL	No. of positive culture results/ total no. of cultures performed (%)
⩽0.06	2/18 (11.1)
0.125–0.5	0/4
1.0–2.0	0/6
⩾4.0	15/30 (50.0)[a]

NOTE. Auxotype/serovar of posttreatment and pretreatment isolates differed for 1 patient with pretreatment MIC ⩽0.06 and for 1 with pretreatment MIC ⩾4.0 (not all isolates from those treated with ciprofloxacin who had posttreatment cultures done were available for serotyping and auxotyping).

[a] $P < .01$ compared with all other MICs.

DISCUSSION

Resistance to ciprofloxacin has become widespread throughout many parts of Asia [15–17]. Rapid emergence of high-level resistance in a high proportion of gonococcal isolates during a 2-year period has now been documented in The Philippines, and continued spread of highly resistant isolates is likely. This randomized trial documented an unacceptably high rate of failure (45%) after patients received ciprofloxacin treatment for cervical infections caused by gonococci with high-level ciprofloxacin resistance. Ciprofloxacin is no longer a useful drug for treatment of gonorrhea in The Philippines. In a recent retrospective analysis, Kam et al. [18] found a failure rate of 27.9% among men and women in Hong Kong who were treated for gonorrhea with a single 600-mg dose of ofloxacin, given orally. The loss of the only effective and inexpensive oral medication available for treatment of gonorrhea in many developing countries in Asia is particularly unfortunate.

A separate analysis of the gonococci with decreased susceptibility or resistance to fluoroquinolones recovered from par-

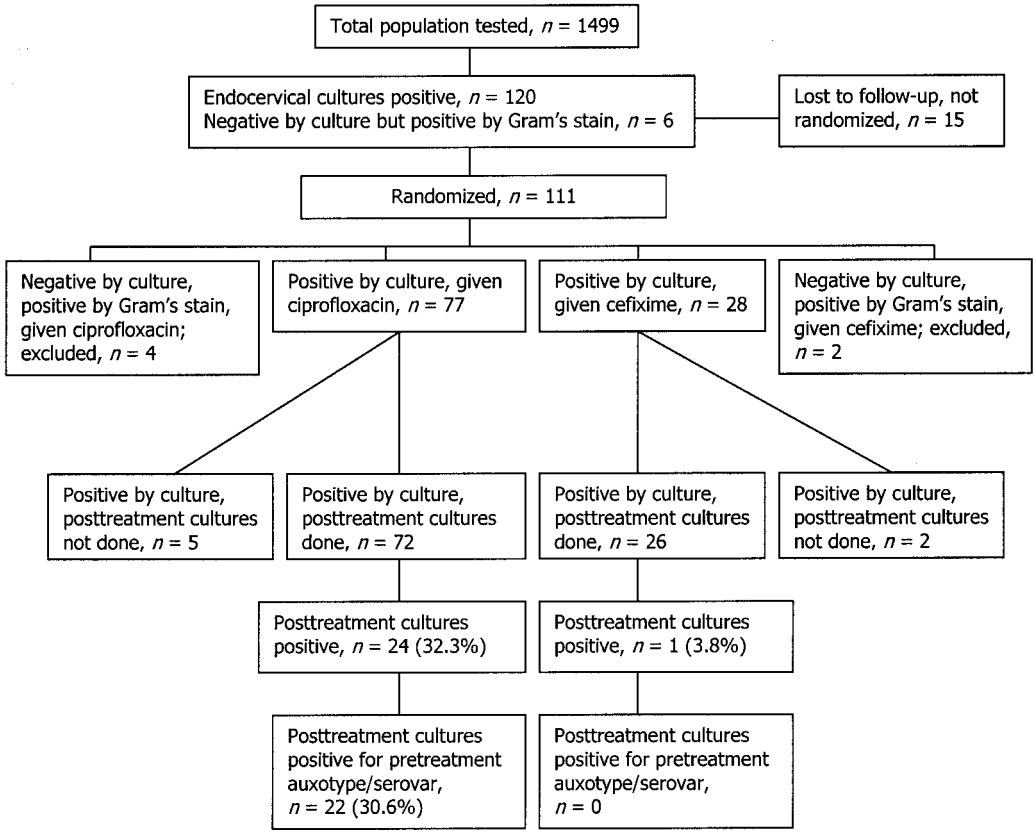

Figure 2. Summary of trial participant flow, indicating number of female sex workers tested for gonorrhea, results of culture and Gram staining, numbers randomized and retested, and treatment results.

ticipants in this study has demonstrated mutations in both the *gyrA* and *parC* genes [19], with multiple separate mutations present concurrently in most of the 1996–1997 isolates with high-level fluoroquinolone resistance. Apparently, additive *gyrA* and *parC* mutations increase fluoroquinolone resistance from low to moderate-to-high levels, as is described elsewhere [20].

Selection of these mutations and emergence of these ciprofloxacin-resistant gonococci may be the result of several factors, including extensive use of quinolones. Use of rosoxacin for gonorrhea treatment was unusually extensive in The Philippines during the early 1980s, and resistance to it became common as early as 1983 [21]. Subsequently, norfloxacin and then ciprofloxacin became primary therapy for gonorrhea in many facilities, often given at relatively low doses (e.g., 250 mg of ciprofloxacin, given in a single dose). As many as 30% of female sex workers in The Philippines have reported taking prophylactic antibiotics, often in a low dosage and often consisting of a quinolone, during the 2 weeks before scheduled routine examinations [22]. During the late 1980s, one study in The Philippines found that a concentration of ciprofloxacin of 0.25 μg/mL was required to inhibit 90% of gonococcal strains, with a peak MIC $\geq$4.0 μg/mL for a single strain [23]. Use of less than the recommended 500-mg dose of ciprofloxacin for treatment and for prophylaxis and extensive use of less active quinolones, such as rosoxacin and norfloxacin, probably have contributed to the selection of fluoroquinolone resistance. In fact, we found that self-prescribed prophylaxis with antimicrobial agents was associated with increased prevalence of ciprofloxacin-resistant gonococcal infection among the female sex workers in this study [24].

Cefixime remains effective for single-dose oral treatment of gonorrhea in The Philippines. However, cefixime and other newer oral cephalosporins are more expensive than is ciprofloxacin, and cefixime is less affordable in many health care systems. Inexpensive alternatives are needed in those developing countries where gonococcal fluoroquinolone resistance has become common. Furthermore, because cefixime and other third-generation cephalosporins remain the most reliable class of antibiotics throughout the world for treatment of gonorrhea, it is particularly important that these drugs not be used in lower-than-recommended doses to save money, nor should they be used prophylactically, particularly by persons who engage in commercial sex. Also, the less active congeners of these drugs should not be widely used by persons with gonorrhea. It is particularly important to emphasize the use of condoms during commercial sex to prevent development and spread of gonococci resistant to the cephalosporins. This is extremely important in The Philippines and in other parts of Asia, where persons who seek treatment now depend on cephalosporins, and further development of resistance of *N. gonorrhoeae* to this class of antimicrobial agents would be disastrous.

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