ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1988, p. 844–847
0066-4804/88/060844-04$02.00/0

Vol. 32, No. 6

Ciprofloxacin Activity in Cyst Fluid from Polycystic Kidneys

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Received 30 November 1987/Accepted 24 March 1988

Renal cyst infection in patients with polycystic kidney disease (PKD) is often unresponsive to standard antimicrobial therapy, in part because of the failure of most antibiotics to adequately penetrate cyst fluid. Ciprofloxacin, a new quinolone antibiotic, possesses in vitro activity against most pathogens likely to be encountered in renal cyst infection. To study the potential usefulness of ciprofloxacin for the treatment of cyst infection, fluid from 70 cysts was obtained from seven patients with polycystic kidney disease who were receiving the drug. Cysts were categorized as nongradient or gradient by the sodium concentration in the fluid. The ciprofloxacin concentration within cysts was measured, and the cyst fluid bactericidal activity against likely cyst fluid pathogens was determined. The mean (± standard error) ciprofloxacin concentration was 12.7 ± 2.9 μg/ml. Preferential accumulation of ciprofloxacin occurred in gradient cysts; these levels exceeded levels in serum by more than fourfold. Cyst fluid bactericidal activity titers were uniformly high against *Escherichia coli* and *Proteus mirabilis*, while less activity was observed against *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*.

Polycystic kidney disease (PKD) encompasses a variety of disorders, the most common of which is inherited as an autosomal dominant trait (ADPKD). The course of disease in patients with ADPKD is frequently complicated by infection of the urinary tract (7, 9, 14, 20, 29). Upper-tract infection, with involvement of the renal cysts, remains a difficult diagnostic and therapeutic problem which frequently results in adverse clinical consequences for the patient (22, 30, 31). The refractory nature of cyst infection has been shown to be due, in part, to the failure of commonly used antibiotics to achieve therapeutic concentrations within cyst fluid (18). There is a major need, therefore, to identify antibiotics which attain reliable concentrations and antibacterial activity within cysts.

Ciprofloxacin, a new fluorinated quinolone, has potent bactericidal activity against a broad spectrum of bacterial pathogens (1, 4, 23, 33, 34). It is particularly active against gram-negative enteric bacteria, the pathogens most frequently implicated in cyst infections (27). Ciprofloxacin appears to have few side effects and possesses favorable pharmacokinetic properties, including adequate oral bioavailability and wide distribution into body fluids and tissues (5, 8, 12, 17). Ciprofloxacin, therefore, has potential application in the treatment of cyst infection in PKD.

In the present study, we obtained cyst fluid from seven patients with PKD who were receiving ciprofloxacin. Cyst fluid antibiotic levels were determined, and the in vitro antibacterial activity of the fluid against common urinary tract pathogens, representative of those most frequently encountered in cyst infection, was assessed.

(Preliminary results of this study were reported at the 19th Annual Meeting of the American Society of Nephrology, Washington, D.C., December 1986 [Kidney Int. 31:193, 1987].)

MATERIALS AND METHODS

Patients. Four men and three women, age 39 to 65 years (mean ± standard error = 47.3 ± 3.3 years), with PKD were studied. Among these seven patients, five had typical features of ADPKD, including bilaterally enlarged cystic kidneys and a family history of PKD. The two other patients, both of whom were receiving maintenance hemodialysis, had no associated features to confirm the autosomal dominant variety of PKD. Of the five patients with ADPKD, one was on chronic peritoneal dialysis and the others had advanced renal insufficiency as determined by inulin clearance or ^{99m}technetium-diethylenetriaminepentacetic acid clearance.

All patients received one 750-mg ciprofloxacin tablet (Miles Pharmaceuticals, West Haven, Conn.) by mouth every 12 h for 1 to 14 days (mean ± standard error = 8.5 ± 2 days), with the exception of patient 7, who received the ciprofloxacin tablet beginning at 12 h and then again at 6 h before sample collection. Patient 4 was referred to our institution after failing to respond clinically to successive courses of nitrofurantoin and cefaclor; cyst infection was diagnosed on the basis of recurring fever, pyuria, and a gallium-67 scintigraphic scan indicating discrete renal infection corresponding to an area of focal tenderness. The cefaclor was discontinued 2 days before the start of ciprofloxacin administration, a total of 9 days before sample collection. Similarly, patient 5 was referred during a prolonged course of clindamycin treatment for cyst infection with a streptococcal species. The clindamycin was stopped, and ciprofloxacin was begun. The other patients had not received any antibiotics within 1 month of entering this study. The clinical data for each patient are presented in Table 1.

Specimen collection and analysis. Samples were collected 4 to 7 h (mean ± standard error = 5.1 ± 0.4 h) after the last ciprofloxacin dose. Cyst fluid was obtained from two patients by ultrasound-guided aspiration of two to four large cysts with a 22-gauge needle. Cyst fluid from the remaining five patients was aspirated during surgery under direct visualization. Care was taken to avoid blood contamination of the cyst fluid. Serum samples were obtained as close to the time of cyst aspiration as possible, usually within 15 to 30 min. After collection, samples were immediately placed on

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TABLE 1. Patient profile and number of cysts sampled

Patient no.	Age (yr)/sex[a]	Glomerular filtration rate (ml/min)	Circumstances of aspiration	Duration of treatment (days)	No. of cysts
1	47/M	Dialysis	Pretransplant bilateral nephrectomy	7	7
2	45/M	36	Symptomatic; cyst marsupialization	14	27
3	65/M	Dialysis	Symptomatic; percutaneous aspiration	8	4
4	39/F	16	Symptomatic; percutaneous aspiration	7	2
5	44/F	Dialysis	Pretransplant nephrectomy, solitary kidney	1	3
6	50/F	11	Unilateral cyst marsupialization	14	15
7[b]	41/M	22	Unilateral cyst marsupialization	0.5	12

[a] M, Male; F, female.
[b] Cyst results were analyzed separately; see text.

ice and subsequently stored at −70°C in tightly capped glass vials until analysis.

Cyst fluid sodium concentrations were measured by flame photometry (Beckman Instruments, Inc., Fullerton, Calif.). Cysts with cyst fluid/serum (CF/S) sodium ratios of 0.8 or greater were designated nongradient cysts, and those with CF/S ratios of less than 0.4 were categorized as gradient cysts (6). Cysts with a CF/S ratio between 0.4 and 0.8 or with insufficient volume for sodium determination were designated indeterminate. Ciprofloxacin in cyst fluid and serum was assayed by a standard agar diffusion method (24) with *Bacillus subtilis* as the test organism in antibiotic medium 5 (pH 7.9) (Difco Laboratories, Detroit, Mich.). The lower limit of sensitivity of the assay was 0.5 μg/ml, and the coefficient of variation was 10%. The value for each sample was reported as the mean of quadruplicate determinations. For patient 5, who had received clindamycin within 24 h of sample collection, a clindamycin-resistant *Pseudomonas aeruginosa* strain (clinical isolate) was used as the test organism. For patient 4, who had received cefaclor 9 days before cyst fluid collection, an alternate test organism was not required since no antibacterial activity was present in two cysts sampled 48 h after discontinuation of cefaclor (before ciprofloxacin administration). The plates were incubated in air at 35°C for 4 to 6 h.

Cyst fluid ciprofloxacin concentrations are reported as the mean ± standard error, and the concentrations in gradient and nongradient cysts were compared by utilizing the Mann-Whitney *U* rank sum test for nonparametric data. Significance was defined as $P < 0.05$. In patient 7, the opportunity for ciprofloxacin accumulation in cyst fluid was limited to 12 h; thus, the 12 cysts from this patient are excluded from the group analysis and are considered separately.

For four of the seven patients (patients 1 through 4) fluid was also obtained by percutaneous aspiration of one to four cysts before the administration of ciprofloxacin. This fluid served as a control. Cyst fluid bactericidal titers both before (control) and during ciprofloxacin treatment were determined against a variety of bacterial strains frequently involved in urinary tract infection. Titers were determined by twofold serial dilution of cyst fluid, from 1:2 to 1:256, using Mueller-Hinton broth as the diluent. Each dilution was inoculated with approximately 5×10^5 CFU of one of the test organisms per ml. The method used is similar to the serum bactericidal assay (25), except that cyst fluid was tested instead of serum. The bactericidal titer represented the highest dilution of the cyst fluid which provided 99.9% killing of the inoculum after overnight incubation in air at 35°C. The bacterial strains used as test organisms were *Escherichia coli*, *Proteus mirabilis*, *Streptococcus faecalis*, *P. aeruginosa*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. The MBCs of ciprofloxacin for these organisms, determined by a standard broth dilution method (19), were 0.016, 0.03, 4.0, 1.0, 1.0, and 0.25 μg/ml, respectively.

RESULTS

Among the seven patients, fluid was obtained from a total of 80 cysts. Of the 10 cysts sampled before antibiotic administration, 7 were nongradient, 2 were gradient, and 1 was indeterminate. Cysts sampled during the course of ciprofloxacin administration included 23 nongradient, 27 gradient, and 20 indeterminate cysts. While a few of the cysts contained large amounts of sediment, none were contaminated with fresh blood on gross inspection. All cyst fluid was sterile, including fluid from patient 4, who was undergoing treatment with ciprofloxacin for cyst infection. In addition, this patient experienced prompt clinical cure, continued on ciprofloxacin for an additional 5 weeks, and did not relapse after drug withdrawal.

Cyst fluid ciprofloxacin concentrations in nongradient, gradient, and indeterminate cysts are shown in Table 2. The average concentration was 12.7 ± 2.9 μg/ml ($n = 57$), although individual values varied widely (0.9 to 110 μg/ml). This excludes a single gradient cyst with a concentration of 293 μg/ml, since this value was well beyond 2 standard deviations from the mean. The ciprofloxacin concentration in gradient cysts was significantly greater than that in nongradient cysts ($P = 0.01$), exceeding the latter by nearly sixfold. Within individual patients, cyst antibiotic levels showed a wide range, particularly among the gradient cysts. Both the lowest (0.9 μg/ml) and highest (293 μg/ml) cyst ciprofloxacin concentrations occurred in the same patient. When these concentrations were compared with simultaneous concentrations in serum, the mean CF/S ciprofloxacin ratio was 2.5 ± 0.4. In nongradient cysts this ratio was 1.4 ± 0.3, while in gradient cysts it was 4.4 ± 1.2 ($P < 0.002$), again excluding the single gradient cyst with a level of 293 μg/ml. With the exception of one nongradient cyst with a concentration of 0.9 μg/ml, antibiotic levels achieved in cyst fluid exceeded the MIC of ciprofloxacin for all test organisms.

TABLE 2. Cyst fluid ciprofloxacin concentrations and CF/S ratios

Cyst type	*n*	Ciprofloxacin (μg/ml)[a]	CF/S[a]
Total[b]	57	12.7 ± 2.9 (0.9–11.0)	2.5 ± 0.4 (0.3–19.7)
Nongradient	18	4.5 ± 0.8 (0.9–11.2)	1.4 ± 0.3 (0.3–4.4)
Gradient[b]	19	25.1 ± 7.9 (1.8–110)	4.4 ± 1.2 (0.6–19.7)
Indeterminate	20	8.3 ± 2.1 (2.4–38)	1.5 ± 0.3 (0.6–5.4)

[a] Mean ± standard error. Numbers in parentheses indicate the range of values.
[b] Excludes a single gradient cyst with a ciprofloxacin concentration of 293 μg/ml.

Therapeutic levels were achieved within a short time, particularly in gradient cysts. This is demonstrated by patient 5, whose three cysts had a mean CF/S ratio of 7.3 ± 2.4 after three doses of the drug, a period inadequate to establish steady-state pharmacokinetics. Furthermore, patient 7 had detectable levels (>0.5 μg/ml) in 7 of 12 cysts (average level, 5.0 ± 1.5 μg/ml) within 12 h of initiation of treatment.

The absence of in vitro antibacterial activity was demonstrated in fluid from the cysts sampled before ciprofloxacin administration, as bactericidal titers were consistently less than 1:2, with the exception of two cysts from patient 2 that showed bactericidal titers to *E. coli* of 1:4 and 1:16, respectively. The reason for the observed bactericidal activity in these two cysts is unclear.

Cyst fluid sampled during ciprofloxacin administration consistently demonstrated high bactericidal activity against *E. coli* and *P. mirabilis*. The geometric mean bactericidal titers against these organisms were 1:188 and 1:86, respectively; titers in all cysts were greater than or equal to 1:32, with the exception of a single cyst having a titer of 1:16 against *P. mirabilis*. Cyst fluid activity against the other test bacteria was more variable, reflecting the lower susceptibility of these organisms to ciprofloxacin. While 80% of the bactericidal titers were greater than or equal to 1:8 for *S. epidermidis*, titers against *S. faecalis*, *P. aeruginosa*, and *S. aureus* were less reliable. A total of 48% of the cyst fluids had bactericidal titers of ≤1:2 against *S. faecalis*, and only 10% showed titers of ≥1:8. Similar results were observed with *P. aeruginosa* and *S. aureus*. The geometric mean bactericidal titer against *P. aeruginosa* was 1:3, with 52% of the cysts having titers of ≤1:2. Against *S. aureus* the geometric mean titer was 1:5, and 44% of the cysts had titers of ≤1:2. In patient 7, despite the absence of measurable levels of ciprofloxacin in several cysts (i.e., <0.5 μg/ml), bactericidal activity was present, with titers against the highly susceptible *E. coli* (MBC, 0.016 μg/ml) greater than or equal to 1:16 in all of these cysts (data not shown).

DISCUSSION

Renal cysts in ADPKD are derived from nephron segments whose epithelial lining maintains many of the functional and histologic properties of the nephron segment of origin (6, 11, 15). Thus, nongradient cysts are typically lined by cells with leaky intracellular junctions and contain fluid with a composition similar to that of fluid of the proximal tubule (6). In contrast, gradient cysts are characterized by tight junctional complexes which permit the maintenance of steep transepithelial solute gradients typical of the distal tubule (6, 11, 15). It has generally been assumed that cyst fluid in ADPKD is largely derived from the glomerular filtrate (3). Several recent observations, however, have led to a reevaluation of this widely held concept (13, 16, 21, 32), with some workers concluding that the fluid in most cysts results from the transepithelial movement of solutes and water (13). These observations have clinical relevance in terms of antibiotic entry into cyst fluid. Moreover, studies examining the ability of various antibiotics to gain entry into cysts have contributed to our knowledge of cyst fluid dynamics (18, 28).

Most antibiotics, including the aminoglycosides, penicillins, and cephalosporins, penetrate polycystic renal cysts poorly (2, 18, 28); this may explain, in part, the frequent failure of these commonly used antibiotics to eradicate cyst infection. Based on observations of preferential accumulation of clindamycin in the acidic environment of gradient cysts, Schwab and associates predicted similar behavior for other nonpolar and lipid-soluble drugs due to nonionic diffusion and ion trapping (28). Unfortunately, most antibiotics fulfilling these criteria, including clindamycin, are ineffective against gram-negative aerobes, the most commonly encountered pathogens in cyst infection (27). This is the reason for the need to identify agents with reliable cyst penetration and a favorable spectrum of activity; chloramphenicol is one such agent (26). We have shown that trimethoprim-sulfamethoxazole attains adequate concentrations in both gradient and nongradient cysts and, once there, is active against common cyst pathogens (10).

In the present study, we demonstrated that ciprofloxacin achieves therapeutic concentrations within the cyst fluid of polycystic kidneys, attaining levels above the MIC for most ciprofloxacin-susceptible organisms (1, 4, 23, 33, 34). These data were obtained despite the inclusion of some patients with end-stage renal failure who were receiving dialysis. Moreover, adequate levels were obtained within a short period of time, as was demonstrated with patients 5 and 7, whose cysts were sampled well before steady-state pharmacokinetics could be established. Preferential accumulation of ciprofloxacin occurred in gradient cysts, where drug levels exceeded those in serum by more than fourfold. Such behavior is predictable, based on the observations of Schwab et al. (28), as ciprofloxacin is a lipid-soluble dipolar ion which is isoelectric at pH 7.4. The efficacy of ciprofloxacin for cyst infection was further documented by demonstrating the bactericidal properties of the cyst fluid from treated patients. Whereas antibacterial activity was generally absent from cyst fluid obtained before antibiotic administration, such activity was regularly present after therapy. Uniformly high cyst fluid bactericidal titers were observed against *E. coli* and *P. mirabilis*, reflecting the fact that the cyst fluid ciprofloxacin level was substantially higher than the MBC. While high titers (≥1:8) were generally obtained against *S. epidermidis*, titers against *S. faecalis*, *P. aeruginosa*, and *S. aureas* were lower in most cases. The reason for the low cyst fluid bactericidal activity against these organisms is readily apparent. With the MBCs for *P. aeruginosa*, *S. aureus*, and *S. faecalis* being 1.0 to 4.0 μg/ml, no more than a one- or twofold dilution would be necessary to cause the concentration of ciprofloxacin in many of the cysts to fall below the MBC. Therefore, low bactericidal activity would be expected in these cysts.

In summary, ciprofloxacin appears to be very promising in the treatment of cyst infections in patients with PKD, based on achievable drug concentrations and demonstrated antibacterial activity against likely pathogens in both gradient and nongradient cysts. Establishment of its appropriate role in the treatment of cyst infection will await further use of this agent in this setting.

ACKNOWLEDGMENTS

This work was supported in part by a grant from the Polycystic Kidney Research Foundation, Kansas City, Mo. L. W. Elzinga is a National Kidney Foundation Research Fellow.

We appreciate the secretarial skills of Kelli L. Conachan Brock.

LITERATURE CITED

1. **Barry, A. L., R. N. Jones, C. Thornsberry, L. W. Ayers, E. H. Gerlach, and H. M. Sommers.** 1984. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. Antimicrob. Agents Chemother. **25**:633–637.
2. **Bennett, W. M., L. Elzinga, J. P. Pulliam, A. L. Rashad, and J. M. Barry.** 1985. Cyst fluid antibiotic concentrations in auto-

somal-dominant polycystic kidney disease. Am. J. Kidney Dis. **6**:400–404.
3. **Bricker, N. S., and J. F. Patton.** 1955. Cystic disease of the kidneys: a study of dynamics and chemical composition of cyst fluid. Am. J. Med. **18**:207–219.
4. **Chin, N.-X., and H. C. Neu.** 1984. Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. 25:319–326.
5. **Crump, B., R. Wise, and J. Dent.** 1983. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob. Agents Chemother. **24**:784–786.
6. **Cuppage, F. E., R. A. Huseman, A. Chapman, and J. J. Grantham.** 1980. Ultrastructure and function of cysts from human adult polycystic kidneys. Kidney Int. **17**:372–381.
7. **Dalgaard, O. Z.** 1957. Bilateral polycystic disease of the kidneys: a follow-up of two hundred and eighty-four patients and their families. Acta Med. Scand. Suppl. **328**:1–255.
8. **Daschner, F. D., M. Westenfelder, and A. Dalhoff.** 1986. Penetration of ciprofloxacin into kidney, fat, muscle, and skin tissue. Eur. J. Clin. Microbiol. **5**:212–213.
9. **De Bono, D. P., and D. B. Evans.** 1977. The management of polycystic kidney disease with special reference to dialysis and transplantation. Q. J. Med. **183**:353–363.
10. **Elzinga, L. W., T. A. Golper, A. L. Rashad, M. E. Carr, and W. M. Bennett.** 1987. Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys. Kidney Int. **32**:884–888.
11. **Gardner, K. D.** 1969. Composition of fluid in twelve cysts of a polycystic kidney. N. Engl. J. Med. **281**:985–988.
12. **Gonzalez, M. A., F. Uribe, S. D. Moisen, A. P. Fuster, A. Selen, P. G. Welling, and B. Painter.** 1984. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob. Agents Chemother. **26**:741–744.
13. **Grantham, J. J., J. L. Geiser, and A. P. Evan.** 1987. Cyst formation and growth in autosomal dominant polycystic kidney disease. Kidney Int. **31**:1145–1152.
14. **Higgens, C. C.** 1952. Bilateral polycystic kidney disease: review of 94 cases. Arch. Surg. **65**:318–329.
15. **Huseman, R., A. Grady, D. Welling, and J. Grantham.** 1980. Micropuncture study of polycystic disease in adult human kidneys. Kidney Int. **18**:375–385.
16. **Jacobsson, L., B. Lindqvist, G. Michaelson, and P. Bjerle.** 1977. Fluid turnover in renal cysts. Acta Med. Scand. **202**:327–329.
17. **Le Bel, M., F. Vallee, and M. G. Bergeron.** 1986. Tissue penetration of ciprofloxacin after single and multiple doses. Antimicrob. Agents Chemother. **29**:501–505.
18. **Muther, R. S., and W. M. Bennett.** 1981. Cyst fluid antibiotic concentrations in polycystic kidney disease: differences between proximal and distal cysts. Kidney Int. **20**:519–522.
19. **National Committee for Clinical Laboratory Standards.** 1985. Standard methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically. Approved standard M7-A. National Committee for Clinical Laboratory Standards. Villanova, Pa.
20. **Oppenheimer, G. D.** 1934. Polycystic disease of the kidney. Ann. Surg. **100**:1136–1158.
21. **Perrone, R. D.** 1985. In vitro function of cyst epithelium from human polycystic kidney. J. Clin. Invest. **76**:1688–1691.
22. **Rothermel, F. J., F. J. Miller, E. Sanford, J. Drago, and T. J. Rohner.** 1977. Clinical and radiographic findings of focally infected polycystic kidneys. Urology **9**:580–585.
23. **Rudin, J. E., C. W. Norden, and E. M. Shinners.** 1984. In vitro activity of ciprofloxacin against aerobic gram-negative bacteria. Antimicrob. Agents Chemother. **26**:597–598.
24. **Sabath, L. D., and J. P. Anhalt.** 1980. Assay of antimicrobics, p. 485–490. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and J. P. Truant (ed.), Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.
25. **Schoenknecht, F. D., L. D. Sabath, and C. Thornsberry.** 1985. Susceptibility tests: special tests, p. 1000–1008. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and H. J. Shadomy (ed.), Manual of Clinical Microbiology, 4th ed. American Society for Microbiology, Washington, D.C.
26. **Schwab, S. J.** 1985. Efficacy of chloramphenicol in refractory cyst infections in autosomal dominant polycystic kidney disease. Am. J. Kidney Dis. **5**:258–261.
27. **Schwab, S. J., S. J. Bander, and S. Klahr.** 1987. Renal infection in autosomal dominant polycystic kidney disease. Am. J. Med. **82**:714–718.
28. **Schwab, S. J., D. Hinthorn, D. Diederich, F. Cuppage, and J. Grantham.** 1983. pH-dependent accumulation of clindamycin in a polycystic kidney. Am. J. Kidney Dis. **3**:63–66.
29. **Simon, H. B., and G. J. Thompson.** 1955. Congenital renal polycystic disease: a clinical and therapeutic study of three hundred sixty-six cases. J. Am. Med. Assoc. **159**:657–662.
30. **Sweet, R., and W. F. Keane.** 1979. Perinephric abscess in patients with polycystic kidney disease undergoing chronic hemodialysis. Nephron **23**:237–240.
31. **Waters, W. B., H. Hershman, and L. A. Klein.** 1979. Management of infected polycystic kidneys. J. Urol. **122**:383–385.
32. **Wickre, C. G., and W. M. Bennett.** 1983. Renal cyst epithelial transport in nonuremic polycystic kidney disease. Kidney Int. **23**:514–518.
33. **Wise, R., J. M. Andrews, and L. J. Edwards.** 1983. In vitro activity of Bay 09867, a quinolone derivative, compared with those of other antimicrobial agents. Antimicrob. Agents Chemother. **23**:559–564.
34. **Wolfson, J. S., and D. C. Hooper.** 1985. The fluroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob. Agents Chemother. **28**:581–586.