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Ciprofloxacin Resistance in Clinical Isolates of *Salmonella typhimurium* Obtained from Two Patients

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Two patients (patients A and B) infected with *Salmonella typhimurium* failed ciprofloxacin therapy, and the posttherapy isolates had reduced susceptibilities to quinolones; 6 of 11 isolates from patient B were also cross-resistant to chemically unrelated agents. No transferable resistance, chloramphenicol-acetylating enzymes, or β-lactamases were detected. For 13 of 14 isolates, the concentrations of ciprofloxacin that inhibited DNA synthesis by 50% were similar to the MICs, suggesting a mutation in *gyrA*. Insertion of pNJR3-2 (*gyrA*) in the posttherapy isolate from patient A and 5 of 11 of the posttherapy isolates from patient B resulted in lower quinolone MICs, also suggesting that resistance was due to a mutation in *gyrA*. Three of the five isolates also had reduced levels of accumulation of quinolones. All six cross-resistant isolates from patient B had reduced levels of accumulation of quinolones, but only one isolate had increased susceptibility when pNJR3-2 was inserted. Despite the lack of OmpF seen in five isolates from patient B, there was no correlation with decreased levels of quinolone accumulation. All isolates had identical smooth lipopolysaccharide profiles. The mechanism of apparently reduced accumulation has yet to be determined.

The antimicrobial therapy of salmonella infections presents a therapeutic challenge to the clinician (7, 18). Although the course of salmonella enteritis is usually self-limiting and needs no antibacterial chemotherapy, patients who are severely ill, who are immunocompromised, or who have invasive infection require immediate antibiotic treatment (7, 18). Ampicillin, chloramphenicol, and co-trimoxazole have been the antibiotics of choice for the treatment of salmonellosis, but the increase in the number of strains that are resistant to these commonly used agents is disturbing (10). The emergence of multiresistant strains of salmonellae has led to the evaluation of the fluoroquinolones for the treatment of salmonellosis (7). Quinolones, such as ciprofloxacin, have potent activity in vitro against salmonellae (26) and have rapid bactericidal activity, even against multiresistant strains (18). Epidemics of multiresistant *Salmonella* spp. in developing countries have been managed successfully with quinolone therapy (22, 23).

However, the emergence of quinolone resistance in salmonellae is a matter of concern. There have been several reports of treatment failure because of the emergence of ciprofloxacin resistance in *Salmonella typhimurium* during therapy (6, 15). In addition, Hof et al. (4) described the isolation of a highly quinolone-resistant *S. typhimurium* isolate from the stool of a patient not previously exposed to quinolone therapy. Lewin et al. (8) have also reported on nalidixic acid-resistant strains of *S. typhimurium* isolated in India.

The mechanisms of quinolone resistance in other members of the family *Enterobacteriaceae* have been characterized, and in *Escherichia coli* resistance essentially falls into two classes: mutations in *gyrA* or *gyrB* affecting the interaction between the target enzyme, DNA gyrase, and the quinolone or from reduced levels of quinolone accumulation into the cell. This may be due to mutations in *marA* or *ompF* that affect the expression of OmpF or possibly may be due to unidentified mutations that affect non-porin pathways such as the lipopolysaccharide (LPS) (16).

Little is known of the mechanisms of quinolone resistance in salmonellae. In parallel to the present study, Howard et al. (6) found substantially reduced levels of expression of OmpF in a ciprofloxacin-resistant posttherapy strain of *S. typhimurium*, whereas Lewin et al. (8) found no difference in the Omp profiles of four nalidixic acid-resistant *S. typhimurium* strains compared with those of susceptible strains.

In the present study, we sought to characterize the mechanisms of quinolone resistance in the clinical isolates of *S. typhimurium* obtained from two patients who failed ciprofloxacin therapy (12, 15).

MATERIALS AND METHODS

Bacteria. The clinical isolates of *S. typhimurium* were obtained from K. Whale, Monsall Hospital, University of Manchester School of Medicine, Manchester, United Kingdom. The strains originated from two patients who failed ciprofloxacin therapy (15). Isolates L1 and L2 were obtained from the urine of patient A before and after ciprofloxacin therapy. Strain L3 was isolated from a hematoma in patient B prior to a course of ciprofloxacin. Eleven resistant posttherapy isolates (L4 to L6, L10 to L16, L18) were obtained from patient B over a period of 4.5 months (15). All isolates were stored on infusion agar slopes with or without 5 μg of nalidixic acid per ml and at −20°C on beads (Protect Bacterial Preservers; TSC Ltd., Heywood, United Kingdom). Control strains were obtained from K. Sanderson at the Canadian Salmonella Genetic Stock Centre; L77 and L78 lacked OmpC (*ompB*); L80, L81, and L82 lacked OmpF (*ompD*); L85 and L86 lacked OmpC (*ompR*); L87 was *nalB* and L88 was *gyrA*.

Media, antibiotics, and susceptibility determination. All strains were cultured in Iso-Sensitest medium (Unipath, Basingstoke, United Kingdom). All of the following antibiotics were gifts and were made up and used according to the instructions of the respective manufacturers: ciprofloxacin

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and mezlocillin (Bayer AG), nalidixic acid (Sterling Winthrop), enoxacin and chloramphenicol (Warner-Lambert–Parke-Davis), norfloxacin and cefoxitin (Merck Sharpe & Dohme), ofloxacin (Hoechst), ampicillin (SmithKline-Beecham), piperacillin and tetracycline (Cyanamid-Lederle Laboratories), ceftazidime and cefuroxime (Glaxo), cefotaxime and gentamicin (Roussel Laboratories Ltd), cefsulodin and rifampin (CIBA-GEIGY), trimethoprim (Roche), and amikacin (Bristol Myers). The MIC of each agent for each strain was determined by a routine agar plate dilution method. For all strains, the inocula were prepared by growing the strains overnight in Iso-Sensitest broth to yield a viable count of 10^9 CFU/ml. The agar plates containing doubling dilutions of antibiotic were inoculated by transferring 1 μl of an undiluted culture or a 1:100 dilution to the surface of the agar with a multipoint inoculator (Denley Tech, Billingshurst, United Kingdom) to give final inocula of 10^4 and 10^6 CFU. All plates were incubated aerobically at 37°C overnight. The MIC of the antibiotic was defined as that concentration (in micrograms per milliliter of agar) at which no more than two colonies were detected. For the higher inoculum a slight haze of growth was ignored.

Preparation of OMPs, LPS, and electrophoresis. The outer membrane proteins (OMPs) of all isolates were prepared by differential centrifugation, sonication, and sarcosyl extraction as described by Piddock et al. (14). All samples were electrophoresed on sodium dodecyl sulfate (SDS)–10% vertical polyacrylamide gels by using 20 μg of protein per channel. The LPSs of all isolates were prepared by boiling the bacterial membrane preparation in sample buffer (0.5M Tris-HCl [pH 6.8], SDS, glycerol, bromophenol blue, mercaptoethanol), adding 50 μg of proteinase K, and incubating the samples overnight at 55°C. Electrophoresis was performed on SDS–4M urea polyacrylamide gels and were stained with silver by the procedure of Tsai and Frasch (21).

Accumulation of quinolones. The modified fluorescence method was used for measuring the accumulation of all quinolones essentially as described by Mortimer and Piddock (9). The accumulation data were converted and expressed as nanograms of quinolone per milligram (dry weight) of cells.

Assay of DNA synthesis. The procedure for measuring the inhibition of DNA synthesis by ciprofloxacin and nalidixic acid was that usually used to measure the incorporation of [^{3}H]adenine into *Pseudomonas aeruginosa*, and was performed essentially as described by Benbrook and Miller (1). The concentration of each drug that inhibited DNA synthesis by 50% was determined from the linear portion of the inhibition curve.

Identification of isolates with mutations in *gyrA* with pNJR3-2 containing wild-type *E. coli gyrA*. *E. coli* S17-1 with plasmid pNJR3-2 containing *gyrA* encoding a quinolone-susceptible DNA gyrase (19) was conjugated with all resistant isolates essentially as described by Piddock and Zhu (17). After conjugation, the transconjugants were harvested into ML broth (10 g of tryptone, 5 g of yeast extract, 5 g of sodium chloride, 2 g of dipotassium hydrogen phosphate per liter) containing 2 μg of tetracycline per ml, and the mixture was incubated overnight at 37°C. Dilutions of the recovery-phase broth were used to inoculate ML agar selection plates containing 10, 20, and 100 μg of tetracycline per ml, and the plates were incubated overnight at 37°C. Replica plates were made on MacConkey agar (Unipath) and fresh ML agar with 10, 20, and 100 μg of tetracycline per ml, and the plates were incubated overnight at 37°C. Donor (lactose-fermenting) and salmonella transconjugate (non-lactose-fermenting) colonies could be easily distinguished on MacConkey agar. Ten transconjugate colonies were identified from the selection plates, and the susceptibility of each putative transconjugant was determined. Ten micrograms of tetracycline per milliliter was added to all media for susceptibility testing of the transconjugant to maintain the plasmid. The plasmid pLA2917, which is identical to pNJR3-2 except that it lacks the *gyrA* gene, was used as a control. The presence of the plasmids pNJR3-2 and pLA2917 in transconjugants was confirmed by agarose gel electrophoresis. Plasmid DNA was extracted by alkaline lysis (2) and electrophoresed in 0.7% agarose gels in TBE buffer (20) for 2.5 h at 94 V. Plasmids were visualized under UV light after staining in 0.5 μg of ethidium bromide solution per ml.

RESULTS

Reinfection or development of resistance? All isolates were identified at Monsall Hospital, and the serotype and phage type were confirmed by the Public Health Salmonella Reference Laboratory, London. Both isolates from patient A were phage type 67 and were considered to be identical to each other but distinct from the isolates from patient B and the standard *S. typhimurium* NCTC 74. Only 9 of 11 isolates from patient B had the same phage type (type 12). The reactions that were used to determine the phage types of isolates L12 and L15 (phage types 135 and 15a, respectively) suggested that these isolates were derived from a similar strain. The isolates from patient A had one plasmid of 34.2 MDa. All isolates from patient B contained three plasmids of approximately 34.2, 4.7, and 2.3 MDa. The chromosomal DNAs of all isolates were digested with the restriction enzyme *Hin*dIII. Identical profiles were obtained for the digested DNAs from both isolates from patient A and from all isolates from patient B, although the patterns of the digested DNAs from the isolates from the two patients were different (data not shown). The serotype, phage type, plasmid profiles, and restriction digest data showed that (i) the isolates from the two patients were distinct from each other and from the National Collection of Type Cultures (NCTC) type strain (L19), (ii) the isolates from patient A could be considered isogenic, (iii) 9 of 11 isolates from patient B could be considered isogenic, and (iv) the remaining two isolates were probably derived from the pretherapy isolate L3. There was no clinical evidence of reinfection in patient B. Both isolates from patient A had a mean doubling time of 43.5 min, whereas the NCTC type strain and all isolates from patient B had mean doubling times of 20 min.

Susceptibility. The posttherapy isolate L2 from patient A was 64-fold less susceptible to ciprofloxacin than was isolate L1 (Table 1). However, except for isolate L5 the susceptibilities of the posttherapy isolates from patient B fell into three groups: first, those (L4, L11, L14) that required a high concentration (MIC, 256 μg/ml) of nalidixic acid to be inhibited and that had no cross-resistance to unrelated antibacterial agents (tetracycline, chloramphenicol, cefoxitin); second, those (L13, L16) with intermediate susceptibilities to nalidixic acid (MIC, 32 μg/ml) but no cross-resistance to unrelated agents; and third, those (L6, L10, L12, L15, L18) with intermediate susceptibilities to nalidixic acid and cross-resistance to unrelated agents (Table 1). Isolate L5 was the exception because it had a high level of resistance to quinolones and unrelated agents. Increased MICs of ceftazidime, cefsulodin, cefotaxime, cefuroxime, and carbenicillin were also seen for the cross-resistant isolates (data not shown). The MICs of gentamicin, amika-

TABLE 1. Phenotypes of pre- and posttherapy isolates from patients A and B

Patient and isolate	MIC (μg/ml)[a]								OMPs[b]	Accumulation as SSC (μg/ml) of ciprofloxacin[c]	DNA synthesis as IC_{50} (μg/ml) of ciprofloxacin[d]	pNJR3-2 present	Proposed mechanism of resistance
	NAL	CIP	NOR	ENX	OFX	TET	CHL	FOX					
L19	2	0.008	0.06	≤0.06	0.03	2	2	1	37 kDa	88.9	0.018	ND	
Patient A													
L1	8	0.03	0.25	0.5	0.12	8	64	4	37 kDa	87.3	0.06	ND[e]	
L2	256	2	8	8	4	16	64	4	37 kDa	93.1	1.37	+	*gyrA*
L2pNJR3-2	2	0.015	0.03	0.06	0.015	>128							
Patient B													
L3	8	0.03	0.06	0.5	<0.06	4	8	1	F^+ C^+	100.6 ± 19.6	0.03	ND	
L4	>256	0.12	1	2	1	8	16	1	F^- C^+	72.5 ± 5.6	0.22	+	*gyrA*[f]
L4pNJR3-2	2	0.015	0.03	0.06	0.03	>128							
L5	256	0.25	1	4	0.5	16	64	64	F^- C^+	28.3 ± 8.4	0.07	+	*gyrA*[f]
L5pNJR3-2	1	0.015	0.03	0.06	0.015	>128							
L6	64	0.25	1	4	1	16	32	16	F^+ C^+	64.2 ± 11.6	0.65	+	Unknown[f]
L10	32	0.06	0.5	1	0.5	16	32	16	F^- C^+	22.1 ± 4.1	0.04	+	Unknown[f]
L11	256	0.5	0.25	4	0.5	4	8	4	F^- C^-	84.2 ± 4.7	0.21	+	*gyrA*
L11pNJR3-2	2	0.015	0.03	0.06	0.015	>128							
L12	32	0.25	2	4	2	16	32	16	F^+ C^+	55.2	0.49	−	Unknown[f]
L13	32	0.03	0.25	1	0.06	2	8	1	F^- C^+	63.9 ± 11.1	0.05	+	*gyrA*[f]
L13pNJR3-2	2	0.015	0.03	0.06	0.015	>128							
L14	>256	0.25	2	4	1	4	8	1	F^- C^+	49.3 ± 1.7	0.17	+	*gyrA*[f]
L14pNJR3-2	2	0.015	0.03	0.06	0.015	>128							
L15	32	0.25	2	4	1	16	32	8	F^+ C^+	20.3 ± 6.0	0.04	+	Unknown[f]
L16	32	0.12	1	1	0.12	4	4	1	F^+ C^+	87.0 ± 1.8	0.15	+	*gyrA*
L16pNJR3-2	2	0.03	0.06	0.5	0.06	>128							
L18	32	0.5	2	4	2	16	32	32	F^+ C^+	70.1 ± 15.5	0.6	−	Unknown[f]

[a] NAL, nalidixic acid; CIP, ciprofloxacin; NOR, norfloxacin; ENX, enoxacin; OFX, ofloxacin; TET, tetracycline; CHL, chloramphenicol; FOX, cefoxitin.
[b] F, OmpF; C, OmpC.
[c] SSC, steady-state concentration (mean ± standard deviation).
[d] IC_{50}, 50% inhibitory concentration.
[e] nd, not done.
[f] The isolate also had decreased levels of accumulation.

cin, rifampin, and trimethoprim were similar in pre- and posttherapy isolates.

Unfortunately, the isolates from patient B were not received in the same order as they were isolated from the patient, and so the strain numbers are not representative of the order in which the isolates were obtained. However, when the isolates are placed in consecutive order there is no relationship between phenotype and date of isolation. In fact, isolates L4 and L10 were isolated on the same day (2 April 1987), as were isolates L14 and L15 (same site on 21 April 1987).

During the study it was noticed that some isolates became more susceptible to some agents, and so the ability to select revertants from the four isolates (L11, L12, L13, L15) that exhibited this phenomenon was examined. After four subcultures on antibiotic-free agar, revertants with increased susceptibilities to nalidixic acid, chloramphenicol (L12), ampicillin (L11, L13, L14), and cefuroxime (L12) occurring in parallel could be obtained. Three plasmids were seen in the resistant isolates and all revertants.

Resistance to unrelated agents. Because multiply resistant salmonellae are becoming increasingly prevalent, it was thought that several different mechanisms of resistance were the cause of the multiple resistance seen in some of the isolates. However, no β-lactamases were detected in crude cell-free extracts by using nitrocefin as a substrate. In addition, no chloramphenicol acetyltransferase (CAT) activity was detected in a bioassay or a spectrophotometric assay of our *Salmonella* isolates and cell-free lysates when compared with that the CAT activity of *E. coli* expressing CAT I, II, or III (NCTC 50055, NCTC 500128, NCTC 50022). Because the plasmid profiles demonstrated the presence of several plasmids, the isolates were conjugated with *E. coli* HB101 in attempts to transfer resistance. However, none of the plasmids were transferred. Plasmids were prepared and transformation was performed with competent *E. coli* HB101, but no resistant transformants were obtained. In both sets of experiments, control plasmid RK2 was successfully transferred.

OMP and LPS profiles. The different phage types obtained for some of the posttherapy isolates from patient B suggested that the mutations conferring resistance also conferred changes at the cell surface, affecting phage suscepti-

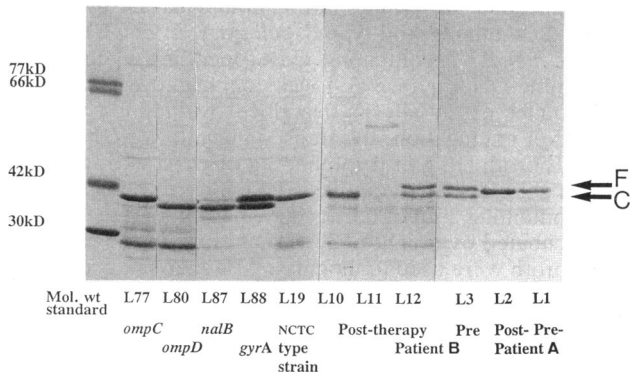

FIG. 1. OMP profiles of selected *S. typhimurium* isolates and control strains. F, OmpF; C, OmpC.

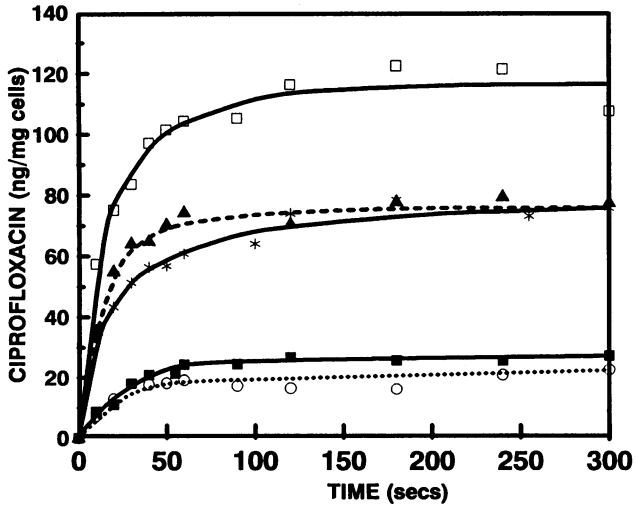

FIG. 2. Accumulation of ciprofloxacin in five isolates from patient B. □, L3; ▲, L4; ○, L5; *, L6; ■, L10.

bility. The OMP profiles of all isolates were compared with those of the NCTC type strain (L19), a *gyrA* mutant (L88), and a *nalB* mutant (L87) (Fig. 1). Both isolates from patient A and the NCTC type strain L19 contained only one major OMP at 37 kDa. The pretherapy isolate from patient B, L3, had the typical OMP profile associated with salmonellae; two OMPs at 36 and 38 kDa, presumably, OmpF and OmpC, respectively. A profile that was the same as that of the wild type was seen for isolates L6, L12, L15, L16, and L18. Isolates L4, L5, L10, L13, and L14 lacked OmpF. Isolate L11 lacked both major OMPs. Smooth LPS profiles were obtained from both isolates from patient A and were identical to each other (data not shown). The smooth LPS profiles of all the isolates from patient B were also identical to each other but were distinct from those from patient A (data not shown).

Accumulation of quinolones. The kinetics of accumulation of norfloxacin and ciprofloxacin into all isolates were typical of those of members of the family *Enterobacteriaceae*. Both isolates from patient A accumulated both agents to a similar extent (Table 1). However, some isolates from patient B had reduced levels of accumulation (Fig. 2). Six isolates (L4, L6, L12, L13, L14, L18) accumulated approximately one-half to three-quarters the concentration accumulated in the pretherapy isolate L3. Three isolates (L5, L10, L15) accumulated approximately one-half to one-third the concentration accumulated in isolate L3. The remaining two isolates (L11 and L16) accumulated concentrations similar to those accumulated by isolate L3. However, there was no clear relationship between decreased levels of expression of some OMPs and quinolone accumulation. For instance, isolate L15, which had reduced levels of accumulation of quinolones, had a wild-type OMP profile, and isolate L11, which lacked both OmpF and OmpC, accumulated quinolones to the same level as the wild type. Interestingly, the accumulation of proline was also reduced in isolate L5 compared with that in isolate L3 and the NCTC wild-type isolate L19 (data not shown).

Inhibition of DNA synthesis by quinolones. Thymidine was accumulated and incorporated into the DNAs of both isolates from patient A, and the concentration of quinolone that inhibited DNA synthesis by 50% could be calculated. However, all isolates from patient B poorly incorporated thymidine; the addition of EDTA further decreased the level of accumulation (data not shown). Therefore, an alternative method for measuring DNA synthesis was used. The method of Benbrook and Miller (1) for *P. aeruginosa* which measures the incorporation of [^{3}H]adenine into DNA was successfully used (Table 1). For all the isolates except isolate L15, the concentrations of quinolones that inhibited DNA synthesis by 50% correlated well with the MICs (±1 dilution) of the same agents.

Conjugation with *E. coli* containing quinolone-susceptible *gyrA*. All isolates were conjugated with *E. coli* S17-1 containing pNJR3-2 and pLA2917. None of the transconjugants containing pLA2917 had increased susceptibility to quinolones (data not shown). Those isolates that contained pNJR3-2 and that had increased susceptibilities to nalidixic acid, ciprofloxacin, norfloxacin, enoxacin, and ofloxacin were presumed to possess a mutation in *gyrA* (Table 1). For the transconjugants of the posttherapy isolate (L2) from patient A and six posttherapy isolates (L4, L5, L11, L13, L14, L16) from patient B, the MICs of quinolones (but not those of chloramphenicol or cefoxitin) were reduced when pNJR3-2 was inserted (Table 1). Five of these six isolates were not cross-resistant to other agents. Three cross-resistant isolates (L10, L15, L18) contained pNJR3-2 but had no increased susceptibility. In the two remaining isolates, L6 and L12, pNJR3-2 could not be clearly seen on agarose electrophoresis, and the susceptibilities of these two isolates were unchanged.

DISCUSSION

The preliminary report of the isolates described here was the first publication documenting quinolone resistance arising in salmonellae during quinolone therapy (15). The data from the typing methods suggested that the isolates from each patient were distinct but that those from each patient were derived from the same strain. The coincidental development of ciprofloxacin resistance associated with therapeutic failure in two patients is worrying. Of most concern is the susceptibility data, because the posttherapy isolates from patient B were inhibited by concentrations of ciprofloxacin well below the recommended breakpoint concentration for this agent in the United Kingdom (1 μg/ml). Patient B did not have abnormal pharmacokinetics, and the correct dose of ciprofloxacin was given (25); therefore, the reason for the failure of therapy is presumably the decrease in the susceptibilities of the infecting organisms. The management of patient B was further compromised by the cross-resistance of some of the isolates to unrelated agents.

The biochemical data and the data obtained in the conjugation experiments suggest that the posttherapy isolate from patient A contained a mutation in *gyrA*. However, for the posttherapy isolates from patient B, the data suggest that several phenotypes arose during treatment. First, the data suggest that all five isolates that were resistant to quinolones alone had mutations in *gyrA*. However, three of these five isolates also had reduced levels of accumulation of quinolones. Second, all six isolates that were cross-resistant to other agents had reduced levels of accumulation of quinolones. pNJR3-2 was inserted in four of these six isolates, but the data suggested that only one isolate had a mutation in *gyrA*. pNJR3-2 could not be inserted into the remaining two isolates. Bacteria with mutations in *gyrA* are usually stably resistant to quinolones; however, four isolates in the present study easily reverted to susceptibility. This suggests the involvement of another gene that causes the resistance.

The mechanism of quinolone resistance in five of the isolates remains unclear. Despite the reproducible observation of reduced levels of quinolone accumulation for several of the isolates, this did not correlate with a consistent decrease or absence of OmpF or any other OMP, unlike other quinolone-resistant members of the family *Enterobacteriaceae* (3, 5, 13). In fact, the lack of OmpF or OmpC in salmonellae would seem to be misleading and unrelated to susceptibility. However, the reduced steady-state concentrations were apparently not due to altered LPS profiles, since our analysis failed to reveal differences in the LPSs from these isolates. Enhanced quinolone efflux from these isolates as a mechanism of resistance must be considered, but it has not yet been identified in other gram-negative bacteria.

Despite insertion of the probe pNJR3-2 (*gyrA*) and DNA synthesis data suggesting a mutation affecting the target enzyme, two isolates that contained pNJR3-2 did not appear to have mutations in *gyrA*. Recently, Weidemann (24) has shown that some quinolone-resistant salmonellae contain mutations in *gyrB* alone or in addition to those in *gyrA*. The concentration of quinolone required to inhibit the DNA synthesis of the remaining isolate (L15) did not correlate with the MIC, but it was similar to the concentration that inhibited the pretherapy isolate. In addition, this strain accumulated quinolones poorly and L15(pNJR3-2) had unchanged susceptibility. These data suggest that this isolate was a permeability mutant.

To confirm the data obtained in the present study, amplification of *gyrA* and DNA sequencing is under way. However, the primers used for amplification of *gyrA* from *E. coli* (11) did not amplify *gyrA* from the salmonellae from either patient or control strains. By using mixed oligonucleotide primers, a fragment of *gyrA* was amplified from the NCTC type strain and L88 (the control *gyrA* mutant). The precise identification of the mutation(s) in *gyrA* and/or *gyrB* will greatly enhance the clinical relevance of the present study, because it may be that multiple mutations are responsible, which may be rare.

It was thought that ciprofloxacin-resistant clinical isolates of salmonellae failing fluoroquinolone therapy would occur very rarely, first, because of the high concentrations achievable at various body sites and, second, because this species is extremely susceptible to fluoroquinolones. However, until epidemiological information is available, clinicians should be aware that quinolone therapy may not be the most appropriate therapy for multiply resistant salmonellae.

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