Quinolone-Resistant *Salmonella typhi* in Viet Nam: Molecular Basis of Resistance and Clinical Response to Treatment

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Nalidixic acid–resistant *Salmonella typhi* (NARST) was first isolated in Viet Nam in 1993. Analysis of the quinolone resistance-determining region of *gyrA* in 20 NARST isolates by polymerase chain reaction and single-stranded conformational polymorphism yielded two novel patterns: pattern II corresponding to a point mutation at nucleotide 87 Asp → Gly (*n* = 17), and pattern III corresponding to a point mutation at nucleotide 83 Ser → Phe (*n* = 3). In trials of short-course ofloxacin therapy for uncomplicated typhoid, 117 (78%) of 150 patients were infected with multidrug-resistant *S. typhi*, 18 (15%) of which were NARST. The median time to fever clearance was 156 hours (range, 30–366 hours) for patients infected with NARST and 84 hours (range, 12–378 hours) for those infected with nalidixic acid–susceptible strains (*P* < .001). Six (33.3%) of 18 NARST infections required retreatment, whereas 1 (0.8%) of 132 infections due to susceptible strains required retreatment (relative risk = 44; 95% confidence interval = 5.6–345; *P* < .0001). We recommend that short courses of quinolones not be used in patients infected with NARST.

Typhoid is a major cause of morbidity in tropical countries. The development of antibiotic resistance in *Salmonella typhi* poses the considerable threat of increased mortality and morbidity to many communities of the world. In southern Viet Nam, multidrug resistance in *S. typhi* had become established by late 1992 and early 1993 [1–3]. These multidrug-resistant *S. typhi* isolates were resistant to the usual first-line antibiotics, chloramphenicol, ampicillin, and co-trimoxazole, but remained fully susceptible to the fluoroquinolones and third-generation cephalosporins.

To reduce cost and possible toxicity, courses of fluoroquinolones shorter than 1 week have been evaluated in patients with mild-to-moderate typhoid fever. Studies conducted in Viet Nam have shown that courses of treatment as short as 2 days are >90% effective [2–5], and detailed observations of children receiving this short-course treatment have shown no apparent short- or longer-term adverse effects [6]. Thus, the fluoroquinolone antibiotics have become the treatment of choice for multidrug-resistant typhoid fever. Indeed, they are the only effective orally active drugs for this common infection. Resistance to these compounds will therefore have serious public health consequences, particularly in areas where typhoid fever is endemic. We report the emergence of nalidixic acid resistance in isolates of *S. typhi* in southern Viet Nam and the effect of this resistance on the response to treatment with short courses of fluoroquinolones.

Quinolone resistance in other bacteria is usually associated with mutations of the target site, DNA gyrase, most commonly in the quinolone resistance–determining region (QRDR) of the A subunit [7]. In *Salmonella typhimurium*, resistance has been associated with a mutation in the *gyrA* gene, giving rise to amino acid changes at serine 83 and aspartic acid 87 [8–11]. Single-stranded conformational polymorphism (SSCP) analysis has been used to demonstrate mutations in *gyrA* of a number of bacterial species including *Mycobacterium tuberculosis* and *Staphylococcus aureus* [13, 14]. This technique is based on the differential mobility of single-stranded DNA in nondenaturing gels, where the mobility of DNA is dependent on the sequence and resulting conformation of the molecule. We have used PCR to amplify the QRDRs of the *gyrA* gene from a selection of nalidixic acid-resistant *S. typhi* (NARST) and nalidixic acid-susceptible *S. typhi* (NASST) from Viet Nam, and we have analyzed these QRDRs for point mutations using SSCP. The DNA of the *gyrA* QRDR of two NARST strains representative of each SSCP pattern was sequenced and compared with the DNA sequences of the same region of *gyrA*.
of *S. typhi* type A, NASST from Viet Nam, and other NASST and NARST serotypes [9].

**Methods**

Prospective diagnostic and treatment studies of typhoid fever have been in progress at the Centre for Tropical Diseases, Ho Chi Minh City, Viet Nam, since 1992. The hospital is a 500-bed referral center for patients with infectious diseases who reside in Ho Chi Minh City and the southern provinces of Viet Nam.

**Microbiological methods.** All isolates of *S. typhi* were from blood and were identified with use of specific antisera (Wellcome Diagnostics, Dartford, UK) and with standard biochemical tests. Antibiotic susceptibilities were determined at the time of isolation by the modified Kirby-Bauer disk diffusion method [15] with disks containing ampicillin (10 µg), chloramphenicol (30 µg), trimethoprim-sulfamethoxazole (TMP-SMZ) (1.25/23.75 µg), ceftriaxone (5 µg) and ofloxacin (5 µg). Multidrug-resistant strains were defined as those resistant to ampicillin, chloramphenicol, and TMP-SMZ.

Isolates from these treatment studies, which had been stored on nutrient agar slopes at room temperature or on bacterial preservers at −20°C, were then tested retrospectively for susceptibility to nalidixic acid. This testing included isolates from a study performed between December 1992 and June 1993, in which a 5-day course of oral ofloxacin was compared with a 3-day course of intravenous ceftriaxone in adults with blood culture–confirmed, uncomplicated typhoid fever [2], as well as isolates from studies of short-course ofloxacin treatment in adults and children between October 1993 and December 1994 [5, 16]. All *S. typhi* isolates recovered from blood cultures at the Centre for Tropical Diseases during 1995 were tested for susceptibility to nalidixic acid. The MICs of ofloxacin and nalidixic acid were measured by an agar plate incorporation method [17] to select NASST and NARST isolates from these studies. *Escherichia coli* ATCC (American Type Culture Collection) 25922 was used as a control strain.

**PCR, SSCP, and DNA sequencing.** Twenty NARST and three NASST isolates of *S. typhi* were studied. *S. typhi* type A was purchased from the Division of Enteric Pathogens, Central Public Health Laboratory, Colindale, London. All other *Salmonella* strains have been described previously [9, 11].

DNA prepared from bacterial strains [18] was amplified by PCR with use of the oligonucleotide primers P1 (3’-TGTCCGAGATGGCCTGAAGC-5’) and biotinylated P2BIO (5’-TACCGTCTAGTTATCCACG-3’), described by Griggs et al. [9]. The amplified products were stored at 4°C until they were used for SSCP or DNA sequencing. SSCP was performed by using MDE high resolution gel (FMC Bioproducts, Rockland, ME) according to the manufacturer’s instructions, except that 2 µL of PCR product was loaded onto the gel in 4 µL of formamid loading buffer, and visualization of DNA bands was achieved by using a commercially available silver staining kit (Silver Sequence; Promega Biotech, Madison, WI). PCR products were purified by binding to streptavidin-coated magnetic beads (Dynal, Oslo, Norway) for direct sequencing of the DNA with use of Sequenase 2.0 (United States Biochemical Corporation).

**Studies of short-course treatment of typhoid fever.** Since October 1993, a series of studies of short-course ofloxacin therapy in adults and children with mild-to-moderate typhoid fever have been in progress at the Centre for Tropical Diseases [5, 16]. Patients with blood culture–confirmed, uncomplicated typhoid fever have been recruited for open randomized comparisons of ofloxacin given orally for 2 or 3 days.

Adults received ofloxacin either at a dosage of 10 mg/kg body weight in two daily divided doses for 3 days or 15 mg/kg body weight in two daily divided doses for 2 days. Children were given ofloxacin at a dosage of 15 mg/kg body weight in two daily divided doses for either 2 or 3 days. Clinical failure was defined as failure to clear fever 7 days after the start of treatment in association with persistence of symptoms and signs or the development of severe or complicated enteric fever. Repeated blood cultures were performed 48 hours after the last dose of ofloxacin was given and on day 7 if the patient was still febrile. Patients for whom treatment failed clinically were retreated with a further course of ofloxacin at the discretion of the attending physician or pediatrician. Microbiological treatment failure was defined as a second positive blood culture, with the second isolate of *S. typhi* having the same antibiotic susceptibility pattern as the initial isolate after the completion of treatment or within a 6-week follow-up period.

**Statistical methods.** The clinical features and response to treatment of patients with NASST and NARST isolates and the laboratory features of the isolates were compared by using Student’s *t* test or *analysis of variance*. The Mann-Whitney *U* test was used for nonnormally distributed data. Proportions were compared with use of the *χ*² test with Yates’ correction or Fisher’s exact test. Fever clearance times were compared on the basis of survival analysis by using the Kaplan-Meier plot and logrank test and relative risk calculation. The statistical package SPSS for Windows version 6.1.1 (SPSS, Inc., Chicago) was used for these analyses.

**Results**

*S. typhi* isolates. Of the 41 isolates of *S. typhi* isolated in the first study, performed between December 1992 and June 1993 [2], 26 (63%) were multidrug resistant, but none was resistant to nalidixic acid. This is a significantly lower proportion of multidrug-resistant strains than were recovered from a comparable group of patients in subsequent years (*P* = .043).

In the short-course treatment studies performed between October 1993 and December 1994 [5, 16], there were 150 isolates of *S. typhi*, including 117 multidrug-resistant strains (78%), of
Table 1. MICs of ofloxacin and nalidixic acid for a range of nalidixic acid–susceptible and nalidixic acid–resistant *Salmonella typhi* isolates.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Nalidixic acid–susceptible*</th>
<th>Nalidixic acid–resistant²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum MIC</td>
<td>Maximum MIC</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

NOTE. Data are µg/mL.
* A total of 160 isolates were tested against ofloxacin; 47 were tested against nalidixic acid.
² Eighteen isolates were tested against ofloxacin and nalidixic acid.

which 18 (15%) were also nalidixic acid resistant. The first NARST isolate was detected in October 1993.

During 1995, 4,946 patients had blood cultures performed on admission to the Centre for Tropical Diseases. *S. typhi* was isolated from 720 cultures (14.5%), of which 662 (92%) were multidrug resistant and 14 (2.1%) were also NARST.

**Quinolone susceptibility.** The MICs of ofloxacin for the NARST isolates were generally two or three doubling dilutions higher than those for the NASST isolates, although there was some overlap between the two groups (table 1). The MIC of nalidixic acid for all NARST isolates was $\geq 32$ µg/mL, whereas an MIC of $\leq 8$ µg/mL was found for a range of NASST isolates. The mean (±SD) zone size with a 5-µg ofloxacin disk for 381 NASST multidrug-resistant isolates was 30.0 ± 3.0 mm (range, 20–43 mm), a size significantly greater than that for 14 NARST isolates (22.5 ± 1.9 mm; range, 20–26 mm) ($P < .001$). Of 51 isolates with an ofloxacin zone size of $\leq 26$ mm, 14 (27%) were nalidixic acid resistant, whereas none of 343 isolates with a ofloxacin zone of $> 26$ mm were resistant.

**SSCP and DNA sequencing.** A region of gyrA, corresponding to nucleotides 108–454 in *E. coli*, was amplified from the 20 selected *S. typhi* strains. The nalidixic acid–susceptible *S. typhi* type A control and *S. typhimurium* NCTC (National Collection of Type Cultures) 74 gave different SSCP patterns (figure 1, lanes 27 and 29, respectively). Nalidixic acid–susceptible isolates from Viet Nam (lanes 8, 9, and 28) gave the same SSCP pattern (I) as the control *S. typhi* type A strain (lane 27). None of the 20 nalidixic acid–resistant isolates had the same pattern as the susceptible strains. There were two novel patterns, designated II ($n = 17$) and III ($n = 3$). Three nalidixic acid–resistant serotypes, *Salmonella heidelberg* Gly 87 (lane 3), *S. typhimurium* Phe 83 (lane 2), and *S. typhimurium* Glu 119 (lane 26), all gave different SSCP patterns from each other and from *S. typhi*. Several other nalidixic acid–susceptible *Salmonella* serotypes (*S. seftenberg* NCTC 3158, *S. virchow* NCTC 5742, and *S. saintpaul* NCTC 6022) all gave the same pattern as *S. typhimurium* NCTC 74 (data not shown), whereas *S. enteritidis* NCTC 5188 gave a novel pattern.

The 218-nucleotide fragment of *gyrA*, amplified from the nalidixic acid–susceptible reference strain *S. typhi* type A had a $> 99.5$% identity with the same fragment from *S. typhimurium* NCTC 74. For *S. typhimurium*, a single base difference at

![Figure 1](cid1997-25-december.png)
Figure 2. The quinolone resistance-determining region (QRDR) of gyrA of Salmonella typhi clinical isolates and controls. TY 84 is a nalidixic acid–susceptible strain isolated in the same period as CT 48, TY 66, 5182, and 5214. Amino acids written in bold indicate changes when these isolates were compared with the reference strain. NA = nalidixic acid; Ofx = ofloxacin; Cpx = ciprofloxacin; SSCP = single-stranded conformational polymorphism.
	nucleotide 283 gave rise to the codon GAA (glutamic acid), whereas S. typhi contained the codon GGA at this position (glycine). The type A control strain of S. typhi gave the same sequence for this region of the QRDR of gyrA as the nalidixic acid–susceptible strain of S. typhi TY84 from Viet Nam, confirming the difference in the SSCP patterns. Two isolates that gave SSCP pattern II (TY66 and CT48) and two isolates that gave pattern III (5182 and 5214) were chosen for DNA sequencing. Pattern II isolates had a point mutation at codon 87 (A to G), substituting glycine for aspartic acid, and pattern III had a point mutation at codon 83 (C to T), substituting phenylalanine for serine (figure 2).

Studies of short-course treatment of typhoid fever. The demographic and clinical features of the patients infected with NASST and NARST strains are shown in table 2. The only difference was that patients with NARST isolates were significantly younger. The response to ofloxacin treatment was considerably worse in patients with NARST infections than in those with NASST infections. The median fever clearance times among the patients with NARST isolates were nearly twice as long as those among the patients with NASST isolates, 156 hours (interquartile range, 83–242 hours; absolute range, 30–366 hours) vs. 84 hours (interquartile range, 66–108 hours; absolute range, 12–378 hours), respectively (P < .001). Figure 3 shows a Kaplan-Meier plot for a comparison of fever clearing the difference in the SSCP patterns. Two isolates that gave SSCP pattern II (TY66 and CT48) and two isolates that gave pattern III (5182 and 5214) were chosen for DNA sequencing. Pattern II isolates had a point mutation at codon 87 (A to G), substituting glycine for aspartic acid, and pattern III had a point mutation at codon 83 (C to T), substituting phenylalanine for serine (figure 2).

Table 2. Clinical and laboratory features and response to short-course ofloxacin treatment in adults and children infected with nalidixic acid–susceptible or nalidixic acid–resistant Salmonella typhi.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nalidixic acid–susceptible (n = 132)</th>
<th>Nalidixic acid–resistant (n = 18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (no. of males/no. of females)</td>
<td>68/64</td>
<td>9/9</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Median age in y (IR, AR)</td>
<td>12 (7–21, 1–55)</td>
<td>6.5 (5–14, 3–24)</td>
<td>.05</td>
</tr>
<tr>
<td>Median duration of illness in d (IR, AR)</td>
<td>11 (9–15, 4–33)</td>
<td>10.5 (9–14, 7–32)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Median admission temperature in °C (IR, AR)</td>
<td>38.8 (38.0–39.5, 37.0–41.0)</td>
<td>39.1 (38.0–40.0, 37.0–40.2)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>No. (%) of patients with hepatomegaly</td>
<td>85 (64)</td>
<td>13 (72)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>No. (%) of patients with splenomegaly</td>
<td>35 (27)</td>
<td>7 (39)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Median percentage hematocrit (IR, AR)</td>
<td>35 (31–38, 19–60)</td>
<td>33 (31–36, 28–41)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Median no. of WBCs ×10^9/L (IR, AR)</td>
<td>7.2 (6.0–9.2, 1.2–25.1)</td>
<td>6.1 (5.0–8.4, 3.0–14.4)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>No. who received treatment for 3 d/no. who received treatment for 2 d</td>
<td>69/63</td>
<td>9/9</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Median fever clearance time in h (IR, AR)</td>
<td>84 (66–108, 12–378)</td>
<td>156 (83–242, 30–366)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. (%) of patients with clinical failure</td>
<td>4 (3)</td>
<td>9 (50)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. (%) of patients with microbiological failure</td>
<td>0</td>
<td>1 (5.6)</td>
<td>.12</td>
</tr>
<tr>
<td>No. (%) of patients retreated</td>
<td>1 (0.8)</td>
<td>6 (33)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Note. AR = absolute range; IR = interquartile range.
isolates (table 2). In 1995, 2.1% of isolates were nalidixic acid resistant. It has already been shown in patients from other areas. Many of those infected were children, inhibitor, may be the harbinger of full fluoroquinolone resistance in vivo [21–24] have been reported from blood cultures performed before treatment in the hospital, and only one of these lower than the range seen for the NARST isolates [25]. During 1993 and 1994 there was a localized outbreak of multidrug-resistant typhoid in Tien Giang province; 12 (41%) of 29 patients from Tien Giang province had a NARST isolate recovered, compared with 6 (5%) of 121 patients from other areas. Many of those infected were children, which explains the younger age of the patients with NARST isolates (table 2). In 1995, 2.1% of isolates were nalidixic acid resistant.

Discussion

Multidrug-resistant typhoid is an important problem in tropical countries. It is endemic in Viet Nam and has the potential for epidemic spread [3]. Until recently, infections with multidrug-resistant S. typhi have remained uniformly susceptible to the quinolones and third-generation cephalosporin antibiotics, although the clinical response to the cephalosporins is significantly inferior [1, 2]. The quinolones have proved remarkably effective when given for 5 and 7 days and retain excellent cure rates, even with treatment courses as short as 2 and 3 days [4, 5, 16]. These drugs have been well tolerated, and concerns over possible toxicity to bones and joints in children have not been substantiated in careful studies with ≤2 years of follow-up [6]. There are no safe, orally active alternatives that are as reliably effective.

S. typhi isolates with reduced susceptibility [19, 20] or resistance to fluoroquinolones in vivo [21–24] have been reported on the Indian subcontinent, and quinolone resistance has now also emerged in Viet Nam. Strains of S. typhi isolated before late 1993 were all susceptible to nalidixic acid; if they were not tested, the fluoroquinolone MICs for these strains were lower than the range seen for the NARST isolates [25]. During 1993 and 1994 there was a localized outbreak of multidrug-resistant typhoid in Tien Giang province in the Mekong Delta; 12 (41%) of 29 patients from Tien Giang province had a NARST isolate recovered, compared with 6 (5%) of 121 patients from other areas. Many of those infected were children, which explains the younger age of the patients with NARST isolates (table 2). In 1995, 2.1% of isolates were nalidixic acid resistant.

The MICs of ofloxacin for 18 of the NARST isolates were slightly higher than those for the 160 susceptible strains but still below the recommended breakpoint (2–8 μg/mL) [26]. However, “susceptible” infections with these strains responded poorly to short-course treatment with ofloxacin. The treatment failure rate among patients with NARST isolates was 50%, whereas it was <5% if the isolate was nalidixic acid susceptible. Although the in vivo susceptibility of S. typhi can generally be predicted by the in vitro susceptibility, there are well-known exceptions, such as gentamicin. The third-generation cephalosporins are also not as active in vivo as the in vitro data would suggest. The results of the present study suggest that the response of salmonella infections to treatment with fluoroquinolones may not be predicted accurately by the MIC and that the breakpoint for resistance may need to be revised.

The target site of the fluoroquinolones, DNA gyrase, is made up of two subunits—A and B—coded for by gyrA and gyrB genes. The amino acid sequence of the QRDR of gyrA has been shown to be conserved in several bacterial species ranging from E. coli and nonenteric salmonellae to staphylococci and mycobacteria [7]. The nucleic acid sequence reported herein demonstrates that this finding is also true for S. typhi. The results of our analysis of amplified DNA fragments of the QRDR of gyrA by use of SSCP and DNA sequencing revealed two mutations in nalidixic acid–resistant strains of S. typhi from Viet Nam, as compared with a standard strain of NASST (pattern I, figure 1). Pattern II (Ser83→Phe) was found in 17 of 20 of the examined strains, and pattern III (Asp87→Gly) was found in 3 of 20 strains, confirming the role of these mutations in quinolone resistance in S. typhi. Similar mutations have been reported in 12 NARST isolates from southern India [27]. Nine of these isolates had the substitution Ser83→Phe (our type II pattern), and two isolates had Asp87→Tyr, a different mutation at the same site as our pattern III isolates. One further isolate had a combination of both mutations. The clinical response to treatment of these infections was not described.

Previous reports [8, 24] have described the development of resistance in Salmonella during treatment with fluoroquinolones. The NARST strains in the present study were isolated from blood cultures performed before treatment in the hospital, and none of the 20 patients whose NARST isolates were examined by SSCP had a definite history of taking quinolones. One had taken ceftriaxone, one had taken co-trimoxazole, and 10 had taken an unknown drug. Urine samples from all 20 patients were tested on admission to the hospital, and only one of these samples showed antibiotic activity consistent with the use of a fluoroquinolone. This finding suggests infection with NARST, rather than mutation of the isolates during treatment.

Resistance to nalidixic acid, a first-generation DNA gyrase inhibitor, may be the harbinger of full fluoroquinolone resistance caused by an additional mutation in the same organism. It has already been shown in E. coli that a double mutation in gyrA can increase the MIC of ciprofloxacin from 0.5 μg/mL.
to 64 μg/mL [28] and that gyrB and other genes are involved in resistance to quinolones [7]. In one study, the mean peak level, after oral administration, of ofloxacin in the blood of Vietnamese children with typhoid was 6.7 μg/mL [29], and thus further mutations, if viable, in the relevant genes would probably lead to clinical resistance. The effect on virulence of a double mutation in the DNA gyrase of S. typhi is unknown, and as yet, we have not encountered fully fluoroquinolone-resistant infections; however, double mutations have been reported in clinical isolates from India [27]. The emergence of strains highly resistant to fluoroquinolones (MIC, >32 μg/mL) would create a major health problem, leaving only the less-effective third-generation cephalosporins for treatment in many countries where enteric fever is endemic. Before the introduction of chloramphenicol in 1948, the mortality associated with typhoid fever was 30% [30]. The control of resistant strains is therefore of the utmost importance.

Why have these quinolone-resistant strains emerged, and will they spread? In many tropical countries, including the Indian subcontinent and Viet Nam, there is widespread availability and uncontrolled use of antibiotics, including quinolones. Public health measures and education programs are limited by finances, and typhoid fever is endemic. Therefore, there is selective pressure on a large bacterial population that is mobile. Understanding how these factors affect the spread of nontransmissible resistance to antimicrobial agents is crucial to the chemotherapeutic control of infection. As has been verified herein, molecular methods, such as SSCP, especially if combined with bacterial typing at the strain level, provide powerful tools in helping to explain the emergence and spread of antibiotic resistance.

There are several direct clinical implications of these observations. First, all S. typhi isolates should be screened for nalidixic acid resistance with a 30-μg nalidixic acid disk, as other investigators have suggested [20], and they should be tested against a clinically appropriate quinolone. Although the zone of inhibition for NARST isolates around a 5-μg ofloxacin disk was significantly smaller than that for the susceptible isolates, screening for NARST strains by using a zone of inhibition of <26 mm was only partially successful. All NARST strains were detected, but the zone of inhibition was <26 mm for 11% of the NASST strains as well. Use of a 30-μg nalidixic acid disk is a more direct and reliable method for detecting resistance.

Second, if the isolate is resistant to nalidixic acid, short-course (i.e., <5 days) fluoroquinolone therapy should not be given. Furthermore, during 1995, not all patients with NARST isolates who were treated for 7–10 days with ofloxacin responded satisfactorily, and as most NARST isolates are multidrug resistant, the range of alternative drugs is very limited. The optimum treatment for these infections remains to be determined, especially in the countries where typhoid fever is endemic.

Acknowledgments

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