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Emergence of Fluoroquinolone Resistance in *Campylobacter jejuni* and *Campylobacter coli* in Subjects from Finland

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The in vitro susceptibilities of 102 human campylobacter strains isolated between 1978 and 1980 and 100 strains isolated in 1990 to ciprofloxacin, norfloxacin, erythromycin, gentamicin, and doxycycline were examined. The biotypes and heat-stable serotypes of the strains as well as antimicrobial treatments and travel history of the campylobacter-positive patients were also studied. The results indicated that susceptibility to erythromycin, gentamicin, and doxycycline has remained the same during the past 10 years. No gentamicin-resistant strains were found. Resistance to erythromycin was 3% in both groups of strains. However, the number of norfloxacin-resistant strains increased from 4 to 11% in the follow-up period, and ciprofloxacin-resistant strains, which had not occurred 10 years ago, composed 9% of the strains isolated in 1990. Thus, the increase of fluoroquinolone resistance in *Campylobacter jejuni* and *Campylobacter coli* has been significant in Finland in the past 10 years.

Campylobacter jejuni and *Campylobacter coli* are the commonest bacterial enteropathogens in developed countries (20, 24, 26). Although most infections with these pathogens are mild and self-limiting and do not require antimicrobial therapy, in prolonged diseases with severe symptoms, in relapses, and in pregnancy, drugs are called for, and the drug of choice for campylobacter enteritis has been erythromycin. In the last few years, the fluoroquinolones ciprofloxacin, norfloxacin, and ofloxacin have become important oral antimicrobial agents, especially in the treatment of infections caused by gram-negative bacteria. Because of their broad spectra of activity against campylobacters, salmonellae, shigellae, *Yersinia enterocolitica*, *Escherichia coli*, *Plesiomonas shigelloides*, and *Aeromonas* species (7, 9), these agents have been used in the treatment of enteritis (3, 5, 8, 18) and even in the prophylaxis of traveller's diarrhea (12, 19, 33). Also, salmonella carriers have been successfully treated with these new antimicrobial agents (14).

This study was undertaken in order to determine whether the in vitro susceptibility of campylobacters to ciprofloxacin, norfloxacin, erythromycin, gentamicin, and doxycycline has changed in the past 10 years. We found a significant increase in fluoroquinolone resistance in human *C. jejuni* and *C. coli* strains isolated in 1990 compared with those isolated between 1978 and 1980, before the clinical era of fluoroquinolones.

MATERIALS AND METHODS

***Campylobacter* strains.** A total of 102 consecutive *Campylobacter* strains isolated between 1978 and 1980 and 100 consecutive strains isolated from humans in 1990 were included in this study. All strains were fecal isolates except one, which was isolated from a blood culture, and in all cases, the primary diagnosis of campylobacteriosis was made in our laboratory. The strains from 1978 through 80 were originally isolated on Skirrow's blood agar (23), and the strains from 1990 were isolated on *Campylobacter* blood-free selective agar containing amphotericin and cefoperazone (Oxoid Ltd., Basingstoke, Hants, England). After the original isolation, the strains were stored at −70°C. All strains were gram-negative, oxidase- and catalase-positive bacteria. They did not grow at 25°C, but all grew at 37 and 43°C in an atmosphere of 5% O_2, 10% CO_2, and 85% N_2. Susceptibilities of the strains to nalidixic acid (30 μg/ml; AB Biodisk, Solna, Sweden) and cephalothin (32 μg/ml; AB Biodisk) were tested by disk diffusion. Urease activity was determined with Christensen's urea broth, and hippurate and H_2S production was tested in iron medium by the method of Skirrow and Benjamin (25).

Patients. Only cases of sporadic enteritis were included in the study. Family members and participants who had travelled on the same trips abroad were excluded. Males constituted 56 of the 102 patients from 1978 through 1980 and 45 of the 100 patients from 1990. The age range for patients was from 3 months to 82 years for those found campylobacter-positive in 1978 through 1980 and from 1 to 67 years for those from 1990. Mean ages for these two groups of patients were 33 and 29 years, respectively. Outpatients were the majority in both groups (64 and 86%, respectively, of individuals). After the isolation of campylobacter, a questionnaire regarding recent travel abroad and recent antimicrobial therapy was sent to the patients.

Serotyping. Campylobacter isolates were serotyped on the basis of heat-stable antigens by the method of Penner and coworkers (17). Ten additional sera not included in the Penner system were also used in typing.

Determination of MICs. The antimicrobial agents studied were erythromycin (Orion, Espoo, Finland), ciprofloxacin (Bayer, Leverkusen, Switzerland), norfloxacin (Astra, Södertälje, Sweden), gentamicin (Orion), and doxycycline (Orion). Erythromycin was initially dissolved in a 50% solution of ethanol, ciprofloxacin, and norfloxacin in 0.1 N NaOH; gentamicin was dissolved in sterile water; and doxycycline was dissolved in 0.1 M phosphate buffer solution (pH 4.5). Serial dilutions of all of the study drugs were prepared with sterile water. Antibacterial agent-containing medium was prepared within 24 h of use and stored overnight at room temperature.

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TABLE 1. MICs of five antimicrobial agents in agar dilutions and percentages of antimicrobial resistance in campylobacter strains

Antimicrobial agent	Yr strains were isolated[a]	MIC (μg/ml)[b]			Breakpoint[c] concn (μg/ml)	% Resistant
		Range	50%	90%		
Erythromycin	1978–1980	0.125–8	1	4	8	3
	1990	0.125–1024	1	4	8	3
Ciprofloxacin	1978–1980	0.03–4	0.25	1	8	0
	1990	0.03–128	0.25	2	8	9[d]
Norfloxacin	1978–1980	0.125–32	0.5	2	8	4
	1990	0.125–>128	1	8	8	11[e]
Gentamicin	1978–1980	0.25–2	0.5	0.5	8	0
	1990	0.125–1	0.25	0.5	8	0
Doxycycline	1978–1980	0.06–64	0.125	8	4	15
	1990	0.06–64	0.125	16	4	17

[a] Between 1978 and 80, 102 organisms were tested. In 1990, 100 were tested.
[b] 50% and 90%, MICs for 50 and 90% of isolates, respectively.
[c] Breakpoints for resistance as defined by the Reference Group for Antibiotics in Sweden, March 1990.
[d] $P = 0.0015$ for increase in resistance (Fisher's exact two-tailed test).
[e] $P = 0.048$ for increase in resistance (Fisher's exact two-tailed test).

MICs were determined by using an agar dilution method with Mueller-Hinton agar plates (BBL, Cockeysville, Md.). The turbidities of suspensions of *Campylobacter* strains grown in Mueller-Hinton broth in a microaerobic atmosphere at 43°C for 24 h were adjusted to MacFarland standard 0.5 by Cobas Inocheck (Roche Oy, Espoo, Finland), and a multipoint inoculator (Mast) was used to apply 10^5 CFU per spot. Isolates of *Staphylococcus aureus* ATCC 29213, *E. coli* ATCC 25922, and *C. jejuni* NCTC 143483 were included on each plate to serve as control organisms. The plates were incubated in an atmosphere of 5% O_2, 10% CO_2, and 85% N_2 for 48 h. The MIC was defined as the lowest concentration of the drug that inhibited visible growth completely. Breakpoints of resistance for each antimicrobial agent were determined according to the Reference Group for Antibiotics in Sweden, March 1990.

RESULTS

According to the biotyping scheme of Skirrow and Benjamin (25), 76 of the 102 strains isolated between 1978 and 1980 were *C. jejuni* biotype 1, nine were *C. jejuni* biotype 2, and 16 were *C. coli*. One strain was hippurate negative, produced H_2S in iron medium, and was nalidixic acid resistant and thus was *Campylobacter lari* (formerly *Campylobacter laridis*) (30). Seventy-eight of the strains from 1990 were *C. jejuni* biotype 1, 4 strains were biotype 2, and 16 strains were *C. coli*. Furthermore, two strains were hippurate negative and produced H_2S but were susceptible to nalidixic acid and thus did not fulfill the criteria for *C. lari*. All campylobacter strains were urease negative and cephalothin resistant.

The MICs for erythromycin, ciprofloxacin, norfloxacin, gentamicin, and doxycycline are presented in Table 1. The only blood culture isolate included in this study was susceptible to all antimicrobial agents tested. No gentamicin-resistant strains were found. The percentage of erythromycin-resistant strains had remained unchanged in the past 10 years, as had the percentage of doxycycline-resistant strains. However, the percentage of norfloxacin-resistant strains more than doubled in the follow-up period, and ciprofloxacin-resistant strains that had not existed 10 years ago now composed 9% of the 1990 strains tested. The MICs of norfloxacin for 1978 through 1980 and for 1990 are shown in Fig. 1.

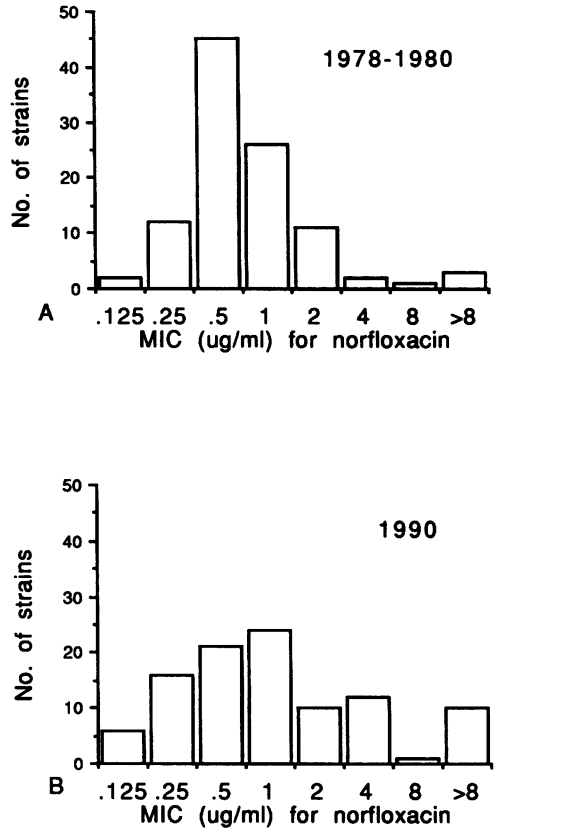

FIG. 1. MICs of norfloxacin for 102 human campylobacter strains isolated from 1978 through 1980 (A) and for 100 strains isolated in 1990 (B).

None of the nalidixic acid-susceptible strains showed resistance to norfloxacin or ciprofloxacin. Of the 32 nalidixic acid-resistant strains, 15 had MICs of norfloxacin of ≥8 μg/ml, 8 had MICs of 4 μg/ml, 6 had MICs of 2 μg/ml, and 3 had MICs of 1 μg/ml. All ciprofloxacin-resistant strains were also resistant to norfloxacin, and 9 of 16 norfloxacin-resistant strains had MICs of ciprofloxacin of ≥8 μg/ml. One strain showed resistance to norfloxacin, ciprofloxacin, and erythromycin, whereas the rest of the erythromycin-resistant strains were resistant only to this one antimicrobial agent. Twenty-four of 33 doxycycline-resistant strains were susceptible to all other antibiotics tested, whereas 7 strains were resistant to one or both of the quinolones.

A history of recent travel was reported by 84 campylobacter-positive patients from the period 1978 through 1980. Twenty-one of these patients had undertaken no trips outside Finland within a month before the illness, whereas 63 had travelled abroad. In 1990, 51 patients had been abroad, 9 were known not to have travelled, and information was lacking for 40. The most popular destinations at the end of the 1970s among these patients were Spain (16 patients), Morocco (13 patients), other parts of Africa (12 patients), Soviet Union (7 patients), and India (4 patients), whereas the patients of 1990 had most frequently visited Spain (12 patients), Turkey (9 patients), Portugal (5 patients), Soviet Union (5 patients), and France (5 patients). Of the nine

TABLE 2. Most common heat-stable serotypes of 202 human campylobacter strains

Heat-stable serotype	No. of campylobacter strains isolated in[a]:	
	1978–1980	1990
1,44	14 (2; Morocco, 2[b])	8 (1)
2	13	8 (1; France)
3,4,59	13 (1; Spain)	3 (1)
6,25	8	2 (1; Spain)
3	2	8
37,56	3	5
5	0	7 (2; Malaysia, 1[c])
34	3	1
21	2	2
45	3	1
11,15	0	3 (2; Spain, 1[c])
Not typeable	7 (1)	5
Other	34	47 (3)

[a] Data in parentheses are the numbers and origins, if known, of norfloxacin-resistant isolates.
[b] Two norfloxacin-resistant strains, both from Morocco, one isolated in 1978 and the other isolated in 1979.
[c] Two norfloxacin-resistant strains, one from the indicated country.

strains resistant to ciprofloxacin, two were isolated after trips to Spain and one each was isolated after trips to France and Malaysia. Norfloxacin-resistant but ciprofloxacin-susceptible and intermediately susceptible strains were isolated after trips to Spain (two patients), and Morocco (two patients), and in two cases, the travel history was not known. Of the six erythromycin-resistant strains, one was of domestic origin, two probably originated in Spain, and one originated in Tunisia, judged by travel of patients to these countries prior to their illnesses. For about one-third of patients with doxycycline-resistant strains, travel information was not available, and for two-thirds, travel implied that the resistant strains originated in another country, resulting in strains from 11 different foreign countries in all.

Twenty patients from the period 1978 through 1980 had been treated with antibiotics, 44 had not been treated, and data were missing for 38. Similarly, 40 patients in 1990 had undertaken antimicrobial therapy, 21 had not had any antibiotics, and information was lacking for 39. Three patients received some kind of antimicrobial agent at their travel destination, but the precise nature of these treatments remained unknown; in these three cases, the isolated campylobacter strains were susceptible to all antibiotics tested. In the other cases, it is unlikely that the patients would have received antimicrobial therapy before stool cultures were taken. No patient reported any prophylactic treatment. Of those patients treated with antimicrobial agents from 1978 through 1980, 8 of 20 patients had been treated with erythromycin. Other reported antimicrobial agents used for treatment included nitrofurantoin, tinidazole, tetracyclines, ampicillin, and trimethoprim with sulfamethoxazole. Of the 40 patients from 1990 whose enteritis was treated with antibiotics, 15 were treated with erythromycin, 16 were treated with ciprofloxacin, norfloxacin, or ofloxacin, 1 was treated with both erythromycin and norfloxacin, and 1 each was treated with tinidazole, tetracycline, and roxithromycin. In five cases, the antibiotic used remained unknown.

Heat-stable serotypes were determined for all isolates, and 64 different serotypes were found. Twelve strains remained untypeable. In Table 2, the most common serotypes found are listed. Four strains that could not be serotyped by using Penner's system were typeable with our own sera.

Of the six erythromycin-resistant strains, all three isolated from 1978 through 1980 were *C. jejuni* biotype 1. Two of these three belonged to heat-stable serotype 2, and one belonged to serotype 1,44. In contrast, the three strains isolated in 1990 were all *C. coli* and belonged to serotypes 5, 28, and 30. Three of the norfloxacin-resistant strains isolated from 1978 through 1980 were *C. jejuni* biotype 1, and one was *C. lari*. All 11 norfloxacin-resistant isolates from 1990 except 1 *C. coli* isolate were *C. jejuni* biotype 1. The distribution of norfloxacin-resistant isolates among the heat-stable serotypes is shown in Table 2. The doxycycline-resistant isolates belonged to 16 different serotypes, and three strains remained untypeable.

DISCUSSION

Since the 1970s, the roles of *C. jejuni* and, to a lesser extent, *C. coli* as the most important bacterial enteropathogens in developed countries have been verified (20, 24, 26). In general, these thermophilic campylobacters are susceptible to erythromycin, tetracyclines, clindamycin, aminoglycosides, and chloramphenicol (29). Resistance to erythromycin has been reported to be 1 to 8% (1, 15, 29, 31). In this study, the percentage of erythromycin-resistant strains was 3% both in the campylobacter isolates recovered from 1978 through 1980 and in those from 1990. All three such isolates from 1990 were *C. coli*, resulting in an overall resistance of 19% in this group. This is in agreement with the findings of several other researchers, who have reported a more frequent erythromycin resistance in *C. coli* than in *C. jejuni* (6, 22, 32). In contrast, none of the erythromycin-resistant isolates recovered from 1978 through 1980 were *C. coli*. Compared with the clinical situation, the small number of strains resistant to erythromycin may actually be too high, especially since strains with MICs no higher than 8 μg/ml are considered, because CO_2 in the atmosphere decreases the pH of the test medium and thus increases the MICs of erythromycin. Nevertheless, two strains of *C. coli* were highly resistant to erythromycin, with MICs of 256 and 1,024 μg/ml. This is concordant with previous studies in which high-level erythromycin resistance has been demonstrated, especially in *C. coli* (27).

In the group of patients who had had campylobacteriosis at the end of the 1970s, 20 of 64 from whom information was available had been treated with antimicrobial agents, and in almost half of the cases, erythromycin had been the drug of choice. In 1990, the number of patients whose campylobacter enteritis had been treated with antibiotics had doubled, and besides erythromycin, fluoroquinolones were the most common antimicrobial agents used, even though fluoroquinolones have always been less effective against campylobacters than against other enteropathogens (7, 9). In general, the MICs of fluoroquinolones have been about 10 times greater for campylobacters than for, e.g., *E. coli*.

In recent reports from Sweden (16) and Austria (11), no in vitro resistance of campylobacters to ciprofloxacin or norfloxacin was found. However, in reports from The Netherlands (4) and Spain (21), the emergence of fluoroquinolone resistance already has been emphasized. In our studies, ciprofloxacin-resistant strains did not occur from 1978 through 1980, but in 1990, the proportion of ciprofloxacin-resistant campylobacter strains was 9%. In Finland, ciprofloxacin was the first fluoroquinolone to be available for clinical use, becoming available in July 1987. Norfloxacin followed in October 1988, and ofloxacin followed in January 1989. However, even before the introduction of fluoroqui-

nolones onto the Finnish market, some natural resistance occurred, since 4% of the strains isolated from 1978 through 1980 had MICs of norfloxacin of ≥8 μg/ml. In 1990, the proportion of norfloxacin-resistant isolates had almost tripled (11%) compared with the situation from 1978 through 1980. In a Spanish report (21), 3.4% of human campylobacter strains isolated in 1989 showed resistance to quinolones, whereas our present percentage of quinolone resistance was the same as in the Dutch study (4), even if the breakpoint of resistance was slightly different from theirs (4 μg/ml). We chose a breakpoint concentration of 8 μg/ml for both ciprofloxacin and norfloxacin according to the Reference Group for Antibiotics in Sweden. The concentration of fluoroquinolones in feces is high (2), and thus the use of the higher breakpoint concentration in this study is justified.

Endtz and coworkers (4) speculated that the increase of quinolone resistance from 0 to 11% in their campylobacter strains of human origin, which was paralleled by a similar rise in quinolone resistance in campylobacter strains isolated from poultry, probably reflected the veterinary use of quinolones. In our study, travel implied that 2 of the 11 quinolone-resistant strains from 1990 originated in Spain, 1 originated in France, 1 originated in Malaysia, and for 7, the travel history of the patient was not known. None of the resistant strains were known for certain to be of domestic origin. Because about 80% of campylobacter strains are isolated in Finland after patients have travelled abroad (13), the increased quinolone resistance found in this study probably reflects the overall quinolone susceptibility of strains from other countries rather than the veterinary use of quinolones in Finland. Nor did the prior use of fluoroquinolones by the individuals explain the resistance to these drugs. Although it is most unlikely that quinolones were used in their treatment, no patient treated at the travel destination harbored fluoroquinolone-resistant strains. Only 3 of 17 patients treated with fluoroquinolones in Finland had strains resistant to these antibiotics, and it is most probable that the patients had not been treated until positive stool cultures were taken. It was not possible or our intention in this study to determine the origin of the fluoroquinolone-resistant campylobacter strains.

Thermophilic campylobacters are, in general, susceptible to nalidixic acid. Nalidixic acid has played a major role in the identification of naturally nalidixic acid-resistant strains of *C. lari* which show cross-resistance to other quinolones. In our samples, only one *C. lari* strain was found; this strain was also resistant to both fluoroquinolones tested. However, several other nalidixic acid-resistant strains were found in this study, and most of them showed lowered susceptibility to fluoroquinolones. Taylor and coworkers (28) have selected nalidixic acid-resistant mutants of *C. jejuni* and *C. coli* at frequencies of 10^{-8}, and these mutants have shown cross-resistance to enoxacin and ciprofloxacin. These observations have been confirmed by Gootz and Martin (10), who selected in vitro ciprofloxacin- and norfloxacin-resistant mutants of *C. jejuni* with MICs considerably higher than those demonstrated in *E. coli*. Furthermore, they isolated DNA gyrase from *C. jejuni* and showed that antibiotic resistance was due to a change in the A subunit of this enzyme (10).

The cross-resistance between nalidixic acid and fluoroquinolones has also been found in nalidixic acid-resistant clinical isolates of *C. jejuni* and *C. coli* (28). Because the number of nalidixic acid-resistant campylobacters has increased, the importance of testing the susceptibility of campylobacter strains to nalidixic acid routinely in order to find *C. lari* has lost its original meaning. However, susceptibility to nalidixic acid can give valuable information concerning the susceptibility of the isolates to fluoroquinolones, which is not routinely tested in laboratories. In our study, none of the nalidixic acid-susceptible strains showed resistance to the fluoroquinolones tested.

Heat-stable serotypes were determined for all the isolates in this study to determine whether there was any association with a certain serotype and antimicrobial resistance. Four (2; 3; 5; and 1,44) of the 11 most common serotypes found in the Dutch study (4) were among the most frequent serotypes detected in the present study. The Dutch study found that quinolone resistance was particularly common in serotype 3; in our study, no quinolone-resistant strain with this serotype could be found. In the present study, norfloxacin-resistant strains were most frequently found to be serotypes 11 and 5 (Table 2). The number of isolates in the different serotypes was small, however, and thus the significance of this finding remains to be determined.

Campylobacter enteritis is a common disease in which antimicrobial therapy is seldom needed. Additional studies will be required in order to determine the benefits of antibiotics in the clinical course of the disease. Meanwhile, the emergence of fluoroquinolone-resistant campylobacters calls into question the use of these drugs in the treatment of campylobacteriosis, especially in the prophylaxis of bacterial enteritis. Even if strains resistant to erythromycin occur, their percentage is lower than that of quinolones and has remained at the same level for the past 10 years. If antimicrobial treatment of campylobacter enteritis is needed at all, the drug of choice is erythromycin.

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