ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2003, p. 2946–2950 Vol. 47, No. 9
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.9.2946–2950.2003

In Vitro Activities of New Fluoroquinolones against *Campylobacter jejuni* and *Campylobacter coli* Isolates Obtained from Humans in 1980 to 1982 and 1997 to 2001

Rea Krausse* and Uwe Ullmann

Institute of Medical Microbiology and Virology, The University of Kiel, 24105 Kiel, Germany

Received 21 October 2002/Returned for modification 23 January 2003/Accepted 5 June 2003

The antibacterial activities of three newly developed fluoroquinolones (gatifloxacin, levofloxacin, and moxifloxacin) against a total of 307 gastrointestinal human isolates of *Campylobacter jejuni* and *Campylobacter coli* collected during 1980 to 1982 and 1997 to 2001 were examined and compared to those of ciprofloxacin and the unrelated antibacterial agents, clarithromycin, erythromycin, and tetracycline by using the agar plate dilution method. All of the fluoroquinolones exhibited a good activity against *Campylobacter*, and some of them were more active than ciprofloxacin, the macrolides, and tetracycline. Among the fluoroquinolones, gatifloxacin and moxifloxacin showed the highest anticampylobacter activity, with MICs at which 50% of the isolates tested are inhibited (MIC_{50}s) and MIC_{90}s of 0.125 and 4 μg/ml, respectively; the MIC_{50} for both levofloxacin and ciprofloxacin was 0.25, and the MIC_{90}s were 16 and 32 μg/ml, respectively. About 30% of the strains were found to be resistant to at least one fluoroquinolone. Resistance to gatifloxacin occurred in 9.8% of the isolates tested, and resistance to the other fluoroquinolones occurred in 19.9 to 27.4% of the isolates tested; the frequency of cross-resistance was 35.7 to 100%. An increase in fluoroquinolone resistance from 0% in 1980 to 1982 to 11.8 to 29% in 1997 and 1998, 8.2 to 31.8% in 1999 and 2000, and 12.1 to 30.3% in 2001 was found. A total of 61.4 to 73.2% of the *C. jenuni* strains resistant to erythromycin, clarithromycin, and/or tetracycline were susceptible to fluoroquinolones; gatifloxacin showed the highest percentage of inhibition. These results show that the newer fluoroquinolones with their potent activity could be used to treat infections with *C. jejuni* and *C. coli*. However, when these drugs are used, one must consider the increase in resistance and the high cross-resistance to these antimicrobial agents.

The thermotolerant *Campylobacter* species, especially *Campylobacter jejuni* and, rarely, *Campylobacter coli*, are frequent causes of acute bacterial gastroenteritis in humans worldwide. Although infections with these bacteria are usually self-limited so that a treatment with antibiotics is not required, clinical complications and systemic and postinfectious manifestations may occur (13, 14, 18, 22).

The new fluoroquinolones exhibit potent activities against a variety of both gram-negative and gram-positive bacteria and anaerobes (9, 15). Their activity against *Campylobacter* spp., however, has not been well studied. There is a great need for new antibiotics to treat infections caused by these bacteria, which do not respond to commonly used drugs (6–8, 13, 19, 25).

The objective of the present study was to investigate the in vitro activities of newer fluoroquinolone drugs (gatifloxacin [GAT], levofloxacin (LVX], and moxifloxacin [MXF]) developed during the 1990s and to compare these activities to those of ciprofloxacin (CIP; developed in the 1980s and used to treat human bacterial infections since 1986), clarithromycin (CLR), erythromycin (ERY), and tetracycline (TET) against 307 clinical isolates of *C. jejuni* and *C. coli* obtained from across Germany during the periods from 1980 to 1982 and from 1997 to 2001. Comparative studies were done to detect the increase in resistance to the fluoroquinolones and nonrelated antimicrobial agents, as well as the cross-resistance between the drugs.

(Part of this study was presented at the 10th International Workshop on *Campylobacter*, *Helicobacter*, and Related Organisms in Baltimore, Md., 12 to 16 September 1999.)

* Corresponding author. Mailing address: Institute of Medical Microbiology and Virology, The University of Kiel, Brunswiker Str. 4, 24105 Kiel, Germany. Phone: 49-431-5973298. Fax: 49-431-5973296. E-mail: r.krausse@medmicrobio.uni-kiel.de.

MATERIALS AND METHODS

Bacteria strains. A total of 308 strains of *C. jejuni* and *C. coli* were tested. The test organisms included 295 *C. jejuni* and 12 *C. coli* isolates from feces of patients with gastroenteritis and one type strain of *C. jejuni* (ATCC 33560). The investigated strains were nonduplicate isolates. A total of 277 of these were recent isolates, collected during the last 5 years from 1997 to 2001 at our department during routine diagnostic testing; the remaining 30 strains, with known biotypes and serotypes (Lior's scheme) (12), were older human isolates (1980 to 1982) received from microbiological laboratories located in different areas in Germany.

The *C. jejuni* and *C. coli* isolates were identified by Gram staining and determination of enzyme activities (catalase, oxidase, and urease activity; hippurate hydrolysis; nitrate and nitrite reduction; and desoxyribonuclease and lipolytic activity), as well as susceptibility to antibacterial agents (nalidixic acid and cephalothin) and growth at different temperatures (42 and 25°C) according to conventional methods (3) and as in previous studies (27). All of the strains were harvested by suspending them in brain heart infusion (BHI) broth supplemented with 10% horse serum and 0.25% yeast extract and then stored at −70°C until used.

Antimicrobial agents. The antimicrobial agents used were CIP and MXF (both from Bayer), GAT and TET (both from Grünenthal), LVX (Hoechst Marion Roussell), CLR (Abbott), and ERY (Durachemie). Each antimicrobial agent was prepared prior to use in accordance with the manufacturer's instructions with a stock solution of 12,800 μg/ml, which was stored at −70°C until used. We used 0.9% NaCl as a diluent for all of the drugs. In detail, CLR was dissolved in a minimal volume of ethanol and 0.9% NaCl, MXF was dissolved in 1.0 N NaOH and 0.9% NaCl, and GAT was dissolved in 0.1 N HCl–0.9% NaCl–0.1 N NaOH (1:8:1). For the remaining drugs (ERY, TET, CIP, and LVX), the solvent was

TABLE 1. Comparative MICs of four fluoroquinolones and other nonrelated antibiotics against 307 human strains of *C. jejuni* and *C. coli* collected during 1980 to 1982 and 1997 to 2001 in Schleswig-Holstein[a]

Antibiotic	No. of isolates inhibited by MIC (μg/ml):														Geometric mean of MICs (μg/ml)
	0.015	0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	16	32	64	128	
MXF	6	51	87	42	18	11	9	22	30	20	10	1	–	–	1.8
GAT	1	14	70	78	43	14	9	25	23	15	14	1	–	–	1.8
LVX	1	4	19	82	73	27	12	12	10	18	23	19	6	1	5.7
CIP	–	6	19	89	59	34	13	3	5	10	17	21	20	11	12.4
ERY	–	–	–	2	5	21	99	118	48	12	–	–	–	2	2.9
CLR	–	3	6	–	3	17	75	94	80	10	12	5	–	2	4.2
TET	–	4	3	2	13	63	65	53	16	4	5	5	4	24[b]	50.9

[a] A total of 295 *C. jejuni* and 12 *C. coli* strains were tested. –, negative.
[b] The MICs of 46 *C. jejuni* strains and 1 *C. coli* strain were >128 μg/ml.

0.9% NaCl. On the day of the test twofold serial dilutions (range, 0.01 to 1,280 μg/ml) were made in 0.9% NaCl.

MIC determination. The MICs were evaluated by the standard agar dilution method by using BHI agar supplemented with 7% sheep blood containing twofold serial dilutions of antibiotics (range, 0.001 to 128 μg/ml). Inocula were prepared from *C. jejuni* and *C. coli* cultures grown on a chocolate agar plate in BHI broth. The plates were inoculated with a bacterial suspension (ca. 5×10^6 CFU/ml) in BHI broth with a multipoint inoculator (Titertek; Flow Laboratories) and a volume of 10 μl per spot. Antibiotic-free agars made from the same media were used as controls. Inoculated plates were incubated at 37°C under microaerobic conditions and were examined after 3 days. The MIC was defined as the lowest antibiotic concentration that completely inhibited the development of visible growth on the agar plates and was determined in duplicate for each strain. Since no specific breakpoints have been established for *Campylobacter*, the tentative breakpoints used for susceptible (S), intermediate (I), and resistant (R) strains of *Campylobacter* to antibacterial agents were the MIC interpretive standards (in micrograms/milliliter) recommended by the National Committee for Clinical Laboratory Standards (NCCLS) for *Enterobacteriaceae* (for CIP, LVX, GAT, and TET), for *Staphylococcus* spp. (for ERY and CLR), and for *Streptococcus pneumoniae* (for MXF). These concentrations were defined as follows (S/I/R): for MXF and CIP, ≤1/2/≥4; for GAT, LVX, and CLR, ≤2/4/≥8; for ERY, ≤0.5/1 to 4/≥8; and for TET, ≤4/8/≥16 (20).

RESULTS

Table 1 shows the MICs of four fluoroquinolones and of other drugs for *C. jejuni* and *C. coli* ERY, CLR, and TET inhibited at each MIC, as well as the geometric mean of MICs in micrograms/milliliter for each antibacterial agent studied. The antibiotic concentrations at which at least 50% of the strains are inhibited (MIC_{50}s) and the MIC_{90}s, as well as the ranges of each compound, are shown in Table 2.

MXF and GAT were the most active substances against *Campylobacter*, with MIC_{50}s of 0.125 μg/ml, followed by CIP and LVX, with MIC_{50}s of 0.25 μg/ml. The MIC_{50}s of the macrolides (ERY and CLR) and TET were 2 μg/ml (Table 2). The highest MIC_{90}s (>128 μg/ml) were those of TET, and the lowest (4 μg/ml) were those of MXF, GAT, ERY, and CLR. MXF and GAT had the lowest mean of MICs compared to LVX and CIP (1.8 versus 5.7 and 12.4 μg/ml). At a concentration of ≤1 μg/ml, 74.6 and 73% of the isolates were inhibited by GAT and MXF, ca. 71 to 72% were inhibited by the other quinolones, and only 48.9, 41.4, and 33.9% were inhibited by TET, ERY, and CLR (Table 1).

A total of 30.6% (94 of 307) of *Campylobacter* strains were found to be resistant to at least one fluorquinolone; the highest percentage was that of strains resistant to CIP (27.4% [84 of 307 strains]), followed by those of strains resistant to LVX, MXF, and GAT (21.8, 19.9, and 9.8%, respectively [67, 61, and 30 of 307 strains]). The frequency of cross-resistance among the fluoroquinolones varied between 35.7 and 100%, with 27.7% (26 of 94) of the isolates showing multiple resistance to all of these. In general, all of the fluoroquinolones had the lowest cross-resistance with GAT (35.7 to 47.5%) and the highest cross-resistance with CIP (86.9 to 100%). CIP-resistant *Campylobacter* strains ($n = 84$) were in 35.7, 64.3, and 75% of strains (30, 54, and 63 strains, respectively) resistant to GAT, MXF, and LVX, respectively. The corresponding sensitivities were 42.9, 10.7, and 15.5% (36, 9, and 13 strains); 21.4, 25, and 9.5% of the strains were intermediate-susceptible to GAT, MXF, and LVX, respectively.

A higher frequency of resistance to TET, similar to that toward CIP, was found among the *Campylobacter* strains compared to the frequencies of resistance to ERY and CLR (27.4% [84 of 307] versus 4.6 and 9.4% [14 and 29 strains of 307, respectively]). ERY-, CLR-, and TET-resistant *C. jejuni* strains were found to be sensitive to fluoroquinolones in the 71.4 to 78.6% (10 to 11 of 14 strains), 72.4 to 79.3% (21 to 23 of 29 strains), and 54.8 to 72.6% (46 to 61 of 84 strains), respectively, with the higher percentage of sensitivity by GAT (72.6%) against TET-resistant strains. The nonrelated antibacterial agents exhibited the lowest frequency of cross-resistance with GAT (7.1 to 17.9%) and the highest frequency of cross-resistance with CIP (27.6 to 42.9%); the analogous data for LVX and MXF were 24.1 to 36.9% and 17.2 to 36.9%, respectively. The *C. jejuni* reference strain was sensitive to all of the fluoroquinolones (MIC = 0.125 to 0.5 μg/ml); the ranges of MICs of ERY and CLR were 1 to 2 μg/ml and 4 to 8 μg/ml, respectively (data not shown). Three (25%) of the twelve *C.*

TABLE 2. MIC_{50}s and MIC_{90}s of four fluoroquinolones and other nonrelated antibiotics against 307 human strains of *C. jejuni* and *C. coli* collected during 1980 to 1982 and 1997 to 2001[a]

Antibiotic	MIC (μg/ml)		
	Range	50%	90%
MXF	0.015–32.0	0.125	4.0
GAT	0.015–32.0	0.125	4.0
LVX	0.015–128	0.25	16.0
CIP	0.030–32.0	0.25	32.0
ERY	0.125–128	2.0	4.0
CLR	0.030–128	2.0	4.0
TET	0.030–>128	2.0	>128

[a] A total of 295 *C. jejuni* and 12 *C. coli* strains were tested.

TABLE 3. Susceptibility profiles of 307 human *C. jejuni* and *C. coli* isolates collected during 1980 to 1982 (n = 30), 1997 to 1998 (n = 93), 1999 to 2000 (n = 85), and 2001 (n = 99)[a]

Drug	Yr	Cumulative % of isolates inhibited by MIC (μg/ml):														GM of MICs (μg/ml)
		0.015	0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0	16	32	64	128	
MXF	1980–1982	–	20.0	66.7	80.0	**96.7**	100	–	–	–	–	–	–	–	–	0.1
	1997–1998	1.1	16.1	49.5	68.8	72.0	74.2	75.3	81.7	**90.3**	98.9	100	–	–	–	1.4
	1999–2000	4.7	30.6	54.1	62.4	65.9	68.2	72.9	83.5	**90.6**	95.3	98.8	100	–	–	1.9
	2001	1.0	10.1	32.3	45.5	52.5	58.6	62.6	69.7	85.9	**93.9**	100	–	–	–	2.5
GAT	1980–1982	–	–	10.0	66.7	**90.0**	100	–	–	–	–	–	–	–	–	0.2
	1997–1998	–	2.2	28.0	53.8	68.8	71.0	72.0	81.7	88.2	**92.5**	100	–	–	–	2.1
	1999–2000	–	10.6	41.2	57.6	67.1	69.4	72.9	83.5	**91.8**	95.3	98.8	100	–	–	1.9
	2001	1.0	4.0	21.2	44.4	58.6	65.7	70.7	77.8	87.9	**96.0**	100	–	–	–	2.0
LVX	1980–1982	–	–	–	6.7	66.7	86.7	**96.7**	100	–	–	–	–	–	–	0.4
	1997–1998	–	–	3.2	35.5	60.2	68.8	73.1	74.2	77.4	83.9	88.2	**98.9**	100	–	5.7
	1999–2000	–	3.5	12.9	40.0	62.4	68.2	70.6	72.9	78.8	85.9	**90.6**	96.5	98.8	100	6.6
	2001	1.0	2.0	10.1	37.4	50.5	58.6	61.6	69.7	71.7	77.8	**92.9**	97.0	100	–	6.5
CIP	1980–1982	–	–	–	33.3	76.7	**96.7**	100	–	–	–	–	–	–	–	0.3
	1997–1998	–	–	2.2	37.6	58.1	66.7	69.9	71.0	72.0	75.3	84.9	**90.3**	96.8	100	12.0
	1999–2000	–	7.1	17.6	43.5	55.3	62.4	68.2	68.2	71.8	78.8	82.4	**90.6**	96.5	100	12.4
	2001	–	–	8.1	32.3	49.5	63.6	67.7	69.7	70.7	71.7	76.8	85.9	**94.9**	100	16.4
ERY	1980–1982	–	–	–	–	–	6.7	36.7	73.3	**90.0**	100	–	–	–	–	2.5
	1997–1998	–	–	–	–	–	7.5	37.6	83.9	**94.6**	100	–	–	–	–	2.1
	1999–2000	–	–	–	2.4	7.1	12.9	42.4	72.9	**95.3**	98.8	98.8	98.8	98.8	100	3.6
	2001	–	–	–	–	1.0	8.1	45.5	83.8	**98.0**	99.0	99.0	99.0	99.0	100	3.2
CLR	1980–1982	–	–	–	–	–	10.0	30.0	50.0	**96.7**	100	–	–	–	–	2.8
	1997–1998	–	–	–	–	1.1	7.5	21.5	61.3	**91.4**	97.8	100	–	–	–	3.0
	1999–2000	–	3.5	10.6	10.6	10.6	14.1	40.0	62.4	80.0	82.4	**92.9**	98.8	98.8	100	6.7
	2001	–	–	–	–	2.0	7.1	41.4	73.7	**97.0**	98.0	99.0	99.0	99.0	100	3.5
TET	1980–1982	–	–	–	–	–	–	36.7	70.0	86.7	**90.0**	90.0	90.0	90.0	90.0*	27.6
	1997–1998	–	–	–	–	3.2	36.6	57.0	66.7	67.7	67.7	67.7	69.9	71.0	80.6*	63.9
	1999–2000	–	4.7	7.1	8.2	14.1	42.4	58.8	71.8	77.6	77.6	77.6	78.8	80.0	**90.6***	39.6
	2001	–	–	1.0	2.0	7.1	15.2	36.4	59.6	64.6	67.7	72.7	74.7	76.8	82.8*	55.6

[a] A total of 295 *C. jejuni* and 12 *C. coli* strains were tested. GM, geometric mean. *, the TET MICs for 3 *C. jejuni* strains, 17 *C. jejuni* strains and 1 *C. coli* strain, 8 *C. jejuni* strains, and 17 *C. jejuni* strains were >128 μg/ml, respectively; —, not detected. The MIC_{50} (underscore) and MIC_{90} (boldface) values of antibiotics against *Campylobacter* isolates are indicated.

coli isolates were resistant to all of the fluoroquinolones, and one of them was also resistant to TET. No resistance to CLR and ERY was detected.

Table 3 compares the susceptibilities (cumulative percentages and geometric means of MICs) of *Campylobacter* strains isolated during 1980 to 1982, 1997 and 1998, 1999 to 2000, and 2001. An increase in the MIC_{90}s (from MIC_{90}s of 0.25 to 1.0 to MIC_{90}s of 4 to >32 μg/ml) and geometric mean was seen with all of the fluoroquinolones, especially CIP, among strains collected in 1997 to 2001 compared to strains isolated in 1980 to 1982. The MIC_{50}s were almost the same. However, more isolates collected in 1980 to 1982 were inhibited at these concentrations than isolates collected during the years 1997 to 2001. No significant difference in susceptibility to fluoroquinolones (except for susceptibility to CIP) was found through the last 5 years (1997 to 2001); however, an increase of the inhibitory concentration of CIP was detected in 2001. In contrast, no differences in MIC_{50}s or MIC_{90}s were detected for ERY and CLR between the older and newer isolates and through the studied period. Among the fluoroquinolones, the increases in resistance from the period from 1980 to 1982 to the period from 1997 to 2001 were as follows: to MXF, from 0% to 18.3 to 30.3%; to GAT, from 0% to 8.2 to 12.1%; to CIP from 0% to 29 to 31.8%; and to LVX, from 0% to 21.2 to 28.3%. All five of the *C. coli* strains collected from 1980 to 1982 were sensitive; three of the seven isolated in 1997 and 1998 were resistant to all of the quinolones.

DISCUSSION

The use of fluoroquinolones has proven to be a major advance in the management of many forms of moderate to severe enteric infections. Fluoroquinolones are effective in both the treatment, even in a single dose (23), and the prophylaxis of traveler's diarrhea (2, 23, 30, 31). They are also the agents of choice in the management of invasive salmonellosis in AIDS patients. Previous studies showed a good activity of fluoroquinolones against *Enterobacteriaceae* (4, 24) and *Campylobacter* (10).

In the present study the various fluoroquinolones showed different levels of activity against *Campylobacter* spp., and some of them were two- to fourfold more active than the reference drug CIP, the agent of choice for infections caused by enteric pathogens and commonly used to treat *Campy-*

lobacter infections (30). Comparison of the in vitro activities of the fluoroquinolones evaluated in the present study, demonstrated that GAT and MXF displayed the best activity, with the lower MICs against *C. jejuni* and *C. coli*, followed by LVX and CIP, which exhibited similar activities. Although GAT acitivity was very similar to that of MXF, it was somewhat more active against *Campylobacter* (concerning the CIP- and TET-resistant isolates). GAT was previously reported to be particularly active against the *Enterobacteriaceae* (11) and approximately 8- to 16-fold more potent than CIP (MIC_{90} = 4 μg/ml versus ≥32 μg/ml) against *Campylobacter* (10), as also shown in the present study. No difference was seen in the activity of fluoroquinolones and the unrelated drugs against *C. jejuni* compared to *C. coli*. However, the number of *C. coli* strains studied here was too small compared to the number of *C. jejuni* strains, which is also the most frequently isolated species from humans (14, 21, 25). As in several recent studies (6, 8, 10, 14, 19, 21, 25), a high frequency of resistance to CIP and to the other newer fluoroquinolones and other antibiotics was detected here among *C. jejuni* and *C. coli* isolates through the last period studied, namely, 1997 to 2001.

A significant increase in the geometric mean of the MICs and the percent resistance to all of the fluoroquinolones was observed among *C. jejuni* and *C. coli* isolates collected in 1997 to 2001 compared to those observed for isolates collected in 1980 to 1982, and this corresponded to recent data (5); the reported increase of resistant strains isolated in 1998 to 2000 to CIP and nalidixic acid was 30.6% compared to 0% in 1987 and 1988. *C. jejuni* isolates were initially uniformly susceptible to the fluoroquinolone drugs introduced in the late 1980. CIP has been used to treat human bacterial infections since 1986, whereas the other newer fluoroquinolones developed during the 1990s have only been used for a short period; this is an explanation for the general susceptibility of the strains collected in 1980 to 1982. Several studies conducted worldwide have noted emerging resistance in *C. jejuni* strains in the last decade (5, 6, 8, 21, 25). Gaudreau reported a low percentage of (0.6%) and no strains resistant to nalidixic acid and CIP, respectively, among 161 *C. jejuni* isolates in 1980 to 1983 compared to those collected in 1995 to 1996 (16.3%) (8). An increase in the incidence of nalidixic acid resistance among human *C. jejuni* isolates from 1.3 to 3.8% in 1992 to 10.2 to 11% was noted in 1996 and 1998 (19, 25). All of these strains were also resistant to CIP. A two- to threefold-higher incidence of resistance toward CIP, LVX, and MXF was found in the present study among the strains isolated in 1997 to 2001 in Schleswig-Holstein, northern Germany, a finding similar to those reported elsewhere (1, 5, 6, 26). In contrast, GAT resistance was about twofold lower than that of the other fluoroquinolones (~11% versus 22 to 30%), as noted in a previous study (10) and comparable with that of CLR. An extremely high frequency of resistance of 72% was found previously among 641 *C. jejuni* human isolates from 1997 to 1998 in Spain (21). In China the resistance increased significantly from 9% in 1995 to 97% in 2001 (13). Such a high increase in fluoroquinolone resistance was not found in our region. The development of quinolone resistance, which involves mainly changes in the *gyrA* gene in *C. jejuni* (7, 29), appears to be linked to the veterinary use of these agents, as well as to the overuse of these antibacterial agents to treat infections caused by these pathogens (7, 16, 17, 19, 21, 25, 28). It was not possible to find out if defined *C. jejuni* serotypes were associated with an increase of resistance, since only strains collected in 1980 to 1982 were serotyped, and these were all susceptible. In contrast, a slight decrease in the percentage of resistance to macrolides was found, whereas the geometric mean MICs were less affected; the percentage of strains with reduced susceptibility to ERY and CLR isolated in 1980 to 1982 and through the years 1997 to 2001 either declined at ca. 6% or even remained nearly unchanged, as noted in recent studies (5). Strains resistant to TET have shown a two- to threefold increase in recent years, although the frequency has remained constant. Compared to the frequency of resistant strains collected in 1997 to 1998, 1999 to 2000, and 2001, there has been a trend toward an increase in the geometric mean MICs, as well as the percentages of resistance to all of the fluoroquinolones, especially in the last year, except for resistance to GAT.

A high frequency of cross-resistance was detected between the fluoroquinolones. Several studies (8, 10, 16, 19, 21, 25), like our own results, showed a high degree of cross-resistance between fluoroquinolones by thermophilic campylobacters. In a small sample of 20 human *C. jejuni* isolates from 1997, Smith et al. found that CIP-resistant isolates were generally resistant to LVX (25). We found 75 and 64.3% of CIP-resistant strains to be simultaneously resistant to LVX and MXF. Only a small percentage of these strains were susceptible to one of the new fluoroquinolones. GAT had here the higher effect, inhibiting ca. 43% of the strains compared to MXF and LVX (~11 to 16%). Previous studies reported a percentage of 25% of CIP-resistant *C. jejuni* strains to be susceptible to GAT (10).

Among the non-fluoroquinolone-related drugs, ERY was the most effective, with the lowest and most stable levels of resistance among campylobacters, followed by CLR. This suggests that ERY continues to be the drug of choice for the treatment of campylobacteriosis in Schleswig-Holstein, and this also supports other findings (1, 5, 7). Resistance of *C. jejuni* to ERY occurred rarely (1, 26); the prevalence was reported to be ≤2 to 7% (6, 8, 10, 21, 25), findings similar to our results. The incidence of TET resistance found in the present studies was lower than that of Gaudreau (40.7%) (8) and Smith et al. (61%) (25). A much lower frequency of 2.4, 27.1, and 17.9% in 1988, 1993, and 1996, respectively, was found by Murphy et al. (19). The different methods used for the determination of resistance, the differences in the breakpoints, which varied from ≥2 to >8 μg/ml and from ≥4 to >8 μg/ml for quinolones and macrolide-TETs, respectively (5, 8, 10, 14, 25, 26), made a direct comparison of the data presented here with those of other studies difficult. This supports the urgency of developing standardized methods for testing the anticampylobacter activity in vitro.

In conclusion, these results suggest that all of the newer fluoroquinolones, especially GAT and MXF, with their good to excellent activities may have a role to play in the therapy of *Campylobacter*-associated disease. However, because a high rate of resistance may occur, this must be taken into consideration during treatment of these infections with these antibacterial agents. Furthemore, in already known CIP-resistant strains in *Campylobacter* infection, treatment with another of the new fluoroquinolones must be avoided because of the high cross-resistance among these antibiotics, or else a resistance

test is recommended once treatment is begun. Even so, clinical trials would still have to be performed in order to determine the role of these new fluoroquinolones against such an infection when such treatment is indicated.

ACKNOWLEDGMENTS

We thank Antje Braas-Lipka and Ursula Hammer-Uschtrin for excellent technical assistance.

REFERENCES

1. **Afset, J. E., and J. A. Maeland.** 2001. Erythromycin and ciprofloxacin resistant *Campylobacter jejuni.* Tidsskr. Nor. Laegeforen. **121:**2152–2154.
2. **Akalin, H. E.** 1995. Role of quinolones in the treatment of diarrhoeal diseases. Drugs **49**(Suppl. 2)**:**128–131.
3. **Anonymous.** 1997. *Campylobacter*, *Helicobacter*, *Wolinella*, *Arcobacter*, and related bacteria, p. 322–338. *In* E. W. Koneman, S. D. Allen, W. M. Janda, P. C. Schreckenberger, and W. C. Winn (ed.), Color atlas and textbook of diagnostic microbiology, 5th ed. Lippincott, Philadelphia, Pa.
4. **Bauernfeind, A.** 1997. Comparison of antibacterial activities of the quinolones BAY12–8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin, and ciprofloxacin. J. Antimicrob. Chemother. **40:**639–651.
5. **Chatzipanagiotou, S., E. Papavasileiou, A. Lakumenta, A. Makri, C. Nicolaou, K. Chantzis, S. Manganas, and N. I. Legakis.** 2002. Antimicrobial susceptibility patterns of *Campylobacter jejuni* strains isolated from hospitalized children in Athens, Greece. J. Antimicrob. Chemother. **49:**803–805.
6. **Devaster, J.-M., L. Vlaes, R. Tridiani, A. Dediste, O. Vandenberg, Y. Glupczynski, and J.-P. Butzler.** 1998. In vitro activity of ofloxacin, ketolides RU 004 and 647, and four other antibiotics against four different *Campylobacter* spp., p. 137–142. *In* A. J. Lastovica, D. G. Newell, and E. E. Lastovica (ed.), *Campylobacter*, *Helicobacter*, and related organisms. Institute of Child Health, University of Cape Town, Cape Town, South Africa.
7. **Engberg, J., F. M. Aarestrup, D. E. Taylor, P. Gerner-Smidt, and I. Nachamkin.** 2001. Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: resistance mechanisms and trends in human isolates. Emerg. Infect. Dis. **7:**24–34.
8. **Gaudreau, C.** 1998. Antimicrobial resistance trends of *Campylobacter jejuni* subsp. *jejuni* and *Campylobacter coli* isolated in Quebec from 1980 to 1996, p. 145. *In* A. J. Lastovica, D. G. Newell, and E. E. Lastovica (ed.), *Campylobacter*, *Helicobacter*, and related organisms. Institute of Child Health, University of Cape Town, Cape Town, South Africa.
9. **Goldstein, E. J. C., D. M. Citron, C. V. Merriam, K. Ryrrell, and Y. Warren.** 1999. Activity of gatifloxacin compared to those of five other quinolones versus aerobic and anaerobic isolates from skin and soft tissue samples of human and animal bite wound infections. Antimicrob. Agents Chemother. **43:**1475–1479.
10. **Hayward, C. L., M. E. Erwin, M. S. Barrett, and R. N. Jones.** 1999. Comparative antimicrobial activity of gatifloxacin tested against *Campylobacter jejuni*, including fluoroquinolone-resistant clinical isolates. Diagn. Microbiol. Infect. Dis. **34:**99–102.
11. **Jones, R. N., M. A. T. Croco, M. A. Pfaller, M. L. Beach, K. C. Kugler, et al.** 1999. Antimicrobial activity evaluations of gatifloxacin, a new fluoroquinolone: contemporary pathogen results from a global antimicrobial resistance surveillance program (SENTRY, 1997). Clin. Microbiol. Infect. **5:**540–546.
12. **Krausse, R., W. Bär, and U. Ullmann.** 1991. In vitro stimulation and phagocytosis of polymorphonuclear granulocytes (PMNG) by different serotypes of *Campylobacter jejuni*, p. 218–220. *In* G. M. Ruitz-Palacios, E. Calva, and B. R. Ruitz-Palacios (ed.), *Campylobacter* V. National Institute of Nutrition, Mexico City, Mexico.
13. **Lau, S. K. P., P. C. Y. Woo, K. W. Leung, and K. Y. Yuen.** 2002. Emergence of cotrimoxazole- and quinolone-resistant *Campylobacter* infections in bone marrow transplant recipients. Eur. J. Clin. Microbiol. Infect. Dis. **21:**127–129.
14. **Liassine, N., A. P. Burnens, C. Fournier, and R. Auckenthaler.** 1999. Species identification and antimicrobial susceptibility of *Campylobacter* spp. and related organisms: a 2-year survey in a tertiary university hospital. Clin. Microbiol. Infect. **5:**718–723.
15. **Lode, H., and M. Allewelt.** 2002. Role of newer fluoroquinolones in lower respiratory tract infections. J. Antimicrob. Chemother. **49:**709–712.
16. **Malorny, B., A. Schroeter, and R. Helmuth.** 1999. Incidence of quinolone resistance over the period 1986 to 1998 in veterinary *Salmonella* isolates from Germany. Antimcrob. Agents Chemother. **43:**2278–2282.
17. **McDermott, P. F., S. M. Bodeis, L. L. English, D. G. White, R. D. Walker, S. Zhao, S. Simjee, and D. D. Wagner.** 2002. Ciprofloxacin resistance in *Campylobacter jejuni* evolves rapidly in chickens treated with fluoroquinolones. J. Infect. Dis. **185:**837–840.
18. **Mishu-Allos, B., and M. Blaser.** 1995. *Campylobacter jejuni* and the expanding spectrum of related infectious. Clin. Infect. Dis. **20:**1092–1101.
19. **Murphy, P. G., E. Crothers, and J. E. Moore.** 1998. Antibiotic resistance patterns in clinical *Campylobacter* spp. isolated in Northern Ireland during the period 1990–1996: a review, p. 150–151 *In* A. J. Lastovica, D. G. Newell, and E. E. Lastovica (ed.), *Campylobacter*, *Helicobacter*, and related organisms. Institute of Child Health, University of Cape Town, Cape Town, South Africa.
20. **National Committee for Clinical Laboratory Standards.** 2002. Performance standards for antimicrobial susceptibility testing. Twelfth informational supplement. Approved standard M7-A5. NCCLS document M100-S12, vol. 22, no. 1. National Committee for Clinical Laboratory Standards, Wayne, Pa.
21. **Saenz, Y., M. Zarazaga, M. Lantero, M. J. Gastanares, F. Baquero, and C. Torres.** 2000. Antibiotic resistance in *Campylobacter* strains isolated from animals, foods, and humans in Spain in 1997–1998. Antimicrob. Agents Chemother. **44:**267–271.
22. **Sakran, W., R. Raz, Y. Levi, R. Colodner, and A. Koren.** 1999. *Campylobacter* bacteremia and pneumonia in two splenectomized patients. Eur. J. Clin. Microbiol. Infect. Dis. **18:**496–498.
23. **Salam, I., P. Katelaris, S. Leigh-Smith, and M. J. G. Farthing.** 1994. Randomised trial of single-dose ciprofloxacin for traveller's diarrhoea. Lancet **344:**1537–1539.
24. **Schubert, S., U. Ullmann, and R. Krausse.** 1999. The in vitro activity of moxifloxacin (BAY12–8039) in comparison to other newer fluoroquinolones against enteropathogenic bacteria. Clin. Microbiol. Infect. **5**(Suppl. 3)**:**142.
25. **Smith, K. E., J. M. Besser, C. W. Hedeberg, F. T. Leano, J. B. Bender, J. H. Wicklung, B. P. Johnson, K. A. Moore, M. T. Osterholm, et al.** 1999. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992–1998. N. Engl. J. Med. **340:**1525–1532.
26. **Thwaites, R. T., and J. A. Frost.** 1999. Drug resistance in *Campylobacter jejuni*, *C. coli*, and *C. lari* isolated from humans in North West England and Wales, 1997. J. Clin. Pathol. **52:**812–814.
27. **Ullmann, U., and R. Krausse.** 1986. Diagnostic procedures in *Campylobacter* infections, p. 59–68. *In* C. Simon and P. Wilkinson (ed.), Diagnosis of infectious diseases: new aspects. Schattauer, Stuttgart, Germany.
28. **Van Looveren, M., G. Daube, L. De Zutter, J. M. Dumont, C. Lammens, M. Wijdooghe, P. Vandamme, M. Jouret, M. Cornelis, and H. Goossens.** 2001. Antimicrobial susceptibilities of *Campylobacter* strains isolated from food animals in Belgium. J. Antimicrob. Chemother. **48:**235–240.
29. **Wang, Y., W. M. Huang, and D. E. Taylor.** 1993. Cloning and nucleotide sequence of the *Campylobacter jejuni gyrA* gene and characterization of quinolone resistance mutations. Antimicrob. Agents Chemother. **37:**457–463.
30. **Wilson, A. P. R., and R. N. Grüneberg.** 1997. Antibacterial activity/gastrointestinal and intra-abdominal infections, p. 155–165. *In* Ciprofloxacin: 10 years of clinical experience. Maxim Medical, Oxford, United Kingdom.
31. **Wistrom, J., and R. Norrby.** 1990. Antibiotic prophylaxis of traveller's diarrhoea. Scand. J. Infect. Dis. **22**(Suppl. 70)**:**111–129.