Antimicrobial Susceptibilities of Multidrug-Resistant *Campylobacter jejuni* and *C. coli* Strains: *In Vitro* Activities of 20 Antimicrobial Agents[▽]

Mirva Lehtopolku,^{1,2*} Ulla-Maija Nakari,³ Pirkko Kotilainen,^{1,2} Pentti Huovinen,¹
Anja Siitonen,³ and Antti J. Hakanen^{1,2}

Antimicrobial Resistance Unit,¹ and Gastrointestinal Infections Unit,³ National Institute for Health and Welfare, Turku and Helsinki, Finland, and Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland²

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There is a paucity of information regarding antimicrobial agents that are suitable to treat severe infections caused by multidrug-resistant *Campylobacter* spp. Our aim was to identify agents that are potentially effective against multiresistant *Campylobacter* strains. The *in vitro* activities of 20 antimicrobial agents against 238 *Campylobacter* strains were analyzed by determining MICs by the agar plate dilution method or the Etest. These strains were selected from 1,808 *Campylobacter* isolates collected from Finnish patients between 2003 and 2005 and screened for macrolide susceptibility by using the disk diffusion test. The 238 strains consisted of 183 strains with erythromycin inhibition zone diameters of ≤ 23 mm and 55 strains with inhibition zone diameters of >23 mm. Of the 238 *Campylobacter* strains, 19 were resistant to erythromycin by MIC determinations (MIC ≥ 16 μ g/ml). Given that the resistant strains were identified among the collection of 1,808 isolates, the frequency of erythromycin resistance was 1.1%. All erythromycin-resistant strains were multidrug resistant, with 18 (94.7%) of them being resistant to ciprofloxacin (MIC ≥ 4 μ g/ml). The percentages of resistance to tetracycline and amoxicillin-clavulanic acid (co-amoxiclav) were 73.7% and 31.6%, respectively. All macrolide-resistant strains were susceptible to imipenem, meropenem, and tigecycline. Ten (52.6%) multiresistant strains were identified as being *Campylobacter jejuni* strains, and 9 (47.4%) were identified as being *C. coli* strains. These data demonstrate that the incidence of macrolide resistance was low but that the macrolide-resistant *Campylobacter* strains were uniformly multidrug resistant. In addition to the carbapenems, tigecycline was also highly effective against these multidrug-resistant *Campylobacter* strains *in vitro*. Its efficacy for the treatment of human campylobacteriosis should be evaluated in clinical trials.

Campylobacteriosis is usually a mild and self-limiting disease requiring no antimicrobial treatment (3, 5). Only rarely is it associated with extraintestinal manifestations, e.g., septicemia, skin and soft tissue infection, infective endocarditis, or meningitis (3). These infections usually require treatment with intravenous antimicrobial agents (3). Infections of immunocompromised patients and pregnant women as well as very young and very old patients or those with persisting symptoms (>1 week) also require antimicrobial treatment (3). Guillain-Barré syndrome and reactive arthritis are major postinfectious complications of campylobacteriosis (3, 24, 26).

For many years, macrolides and fluoroquinolones have been the first- and second-choice alternatives for the antimicrobial treatment of campylobacter enteritis. Since the late 1980s, however, the emergence of resistance to these antimicrobial groups has complicated the treatment of this disease (1). For example, in Thailand, the rate of resistance to the fluoroquinolones has been up to 80% (8, 14). In Finland, the rate of fluoroquinolone resistance increased between 1995 and 2000 from 40% to 60% among all travelers' isolates and from 45%

to 72% among those from Asia alone (11). So far, resistance to macrolides has remained at quite a low level and stable. According to our previous study (12), the frequency of macrolide resistance was 2% among 376 *Campylobacter jejuni* strains collected from Finnish patients during 1995 to 2000. However, there have been a few studies showing that in some countries, the rate of macrolide resistance may be slowly increasing (28). The emergence of macrolide resistance is of serious concern since macrolide-resistant strains are usually resistant to fluoroquinolones and other antimicrobial groups (12, 14). Very few alternatives with which to treat campylobacteriosis caused by these multidrug-resistant strains exist. Also, previous studies have shown that patients infected with a quinolone- or erythromycin-resistant *Campylobacter* strain have an increased risk of an adverse event compared with patients infected with a quinolone- and erythromycin-susceptible *Campylobacter* strain (9, 13, 27).

The aim of this study was to identify antimicrobial agents that, based on *in vitro* activities, could be useful against infections caused by multidrug-resistant *Campylobacter* strains. To do so, we evaluated the antimicrobial susceptibilities of 238 *Campylobacter* strains collected in different laboratories in Finland between 2003 and 2005 to 20 antimicrobial agents.

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* Corresponding author. Mailing address: Antimicrobial Resistance Unit, National Institute for Health and Welfare (THL), Kiinamyllynkatu 13, 20520 Turku, Finland. Phone: 358 20 610 6600. Fax: 358 20 610 6699. E-mail: mirva.lehtopolku@utu.fi.

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MATERIALS AND METHODS

Study collection. Between May 2003 and July 2005, a total of 1,808 *Campylobacter* strains were isolated from human stool specimens of Finnish patients in 10 clinical microbiology laboratories in different parts of Finland and sent to the Gastrointestinal Infections Unit, National Institute for Health and Welfare, Helsinki, Finland. The cultivation of the stool samples and the preliminary identification of the isolates were carried out by standard microbiological methods. At the Gastrointestinal Infections Unit, a hippurate hydrolysis test was used to differentiate *C. jejuni* and *C. coli* strains. All hippurate-negative isolates were confirmed by PCR to be isolates of either *C. jejuni* or *C. coli* (20). All of the isolates were also screened for macrolide susceptibility by using an erythromycin disk (content of 15 µg; BBL, Becton Dickinson, Sparks, MD), which was added to the pure-culture sheep blood plates. The screening was aimed at distinguishing the evidently macrolide-susceptible population from the population that contained the macrolide-resistant strains. An inhibition zone diameter of >23 mm around the erythromycin disk was chosen to indicate macrolide susceptibility. This decision was supported, e.g., by the French Society for Microbiology (www.sfm.asso.fr), proposing a zone diameter of ≥22 mm as a breakpoint for susceptibility. Moreover, the recent results of Gaudreau et al. (10) suggested that zone diameters of ≥20 mm and 6 mm around the erythromycin disk in the disk diffusion testing could be considered breakpoints of susceptibility and resistance, respectively, for *C. jejuni* isolates. All isolates exhibiting inhibition zone diameters of ≤23 mm were sent to the Antimicrobial Resistance Unit, National Institute for Health and Welfare, Turku, Finland, for analyses of species and antimicrobial susceptibilities. In addition, 60 randomly selected *Campylobacter* isolates exhibiting zone diameters of >23 mm were sent for further analyses to be included as macrolide-susceptible control strains.

Isolates from patients traveling abroad within 2 weeks preceding their symptoms were classified as being of foreign origin, and all other isolates were classified as being of domestic origin.

Antimicrobial susceptibility testing. The MICs for the *Campylobacter* isolates were determined by the agar plate dilution method as described previously (12) or by the Etest. The MIC breakpoints used for resistance were those recommended by the Clinical and Laboratory Standards Institute (CLSI) for non-*Enterobacteriaceae* against those antimicrobials for which such recommendations are available (7). The antimicrobials evaluated using the agar plate dilution method were as follows: ampicillin, chloramphenicol, clarithromycin, clindamycin, amoxicillin-clavulanic acid (co-amoxiclav), erythromycin, gentamicin, nalidixic acid, norfloxacin, ofloxacin, and tetracycline, from Sigma (Steinheim, Germany); azithromycin, ciprofloxacin, and levofloxacin, from Fluka (Buchs, Switzerland); imipenem, from MSD (United Kingdom); meropenem, from AstraZeneca (Espoo, Finland); moxifloxacin, from Bayer (Wuppertal, Germany); sitafloxacin, from Daiichi Pharmaceutical (Tokyo, Japan); and telithromycin, from Aventis Pharma (France). The reagent powder for each of these agents was obtained from its manufacturer.

The MICs of tigecycline were determined by the Etest (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. In brief, after culturing of the isolates according to standard microbiological methods, inocula, prepared in NaCl at a density adjusted to a 1.0 McFarland turbidity standard, were delivered onto 5% sheep blood Mueller-Hinton agar plates. An Etest strip with a tigecycline concentration range from 0.016 to 256 µg/ml was applied onto each plate. The plates were incubated at 35°C for 48 h in a microaerobic atmosphere (CampyPak BBL). The MIC was read at the point of the intersection between the growth zone edge and the Etest strip. *C. jejuni* DSM 4688 was used as a control for susceptibility testing and also as a growth control strain. In addition, *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 35218 were used as controls for susceptibility testing. The results were interpreted by using the non-species-related EUCAST (<http://www.eucast.org/>) breakpoints for susceptibility (MIC ≤ 0.25 µg/ml) and resistance (MIC > 0.5 µg/ml).

Multidrug resistance was defined as resistance to three or more antimicrobial groups. The antimicrobial groups were as follows: (i) quinolones; (ii) macrolides, clindamycin, and telithromycin; (iii) tetracycline and tigecycline; (iv) β-lactams; (v) gentamicin; and (vi) chloramphenicol.

Data analysis. The susceptibility data were analyzed by using the WHONET5.4 computer program (available from <http://www.who.int/drugresistance/whonetsoftware/en/>). Comparisons of the susceptibility data between erythromycin-resistant and -susceptible *Campylobacter* strains as well as between *C. jejuni* and *C. coli* strains were performed by using Fisher's exact test. *P* values of less than 0.05 were considered to be significant.

RESULTS

Strain collection. Of the 1,808 *Campylobacter* isolates, all 202 isolates exhibiting inhibition zone diameters of ≤23 mm in erythromycin screenings were included in this study. In addition, we randomly selected 60 isolates exhibiting erythromycin zone diameters of >23 mm to serve as erythromycin-susceptible control strains. From those 262 isolates, 24 did not grow after freezing and storage. Thus, our strain collection consisted of 238 *Campylobacter* strains, 183 of which exhibited erythromycin inhibition zone diameters of ≤23 mm and 55 of which exhibited zone diameters of >23 mm. Of these strains, 122 were of foreign origin and 92 were of domestic origin. The origin was unknown for 24 strains. There were 220 (92.4%) strains identified as being *C. jejuni* strains and 18 (7.6%) strains identified as being *C. coli* strains. Only four (22.2%) *C. coli* strains were domestic, while 88 (40%) *C. jejuni* strains were domestic.

Erythromycin susceptibility. Of the 183 *Campylobacter* strains with inhibition zone diameters of ≤23 mm in the erythromycin disk screening, 19 were classified by the agar plate dilution method as being erythromycin resistant (MIC ≥ 16 µg/ml) and 164 were classified as being erythromycin susceptible (MIC < 16 µg/ml). All of the 55 strains with inhibition zone diameters of >23 mm were classified by the agar plate dilution method as being erythromycin susceptible. Thus, the final study collection consisted of 219 erythromycin-susceptible and 19 erythromycin-resistant *Campylobacter* strains. Given that the 19 erythromycin-resistant strains were identified among the initial study collection of 1,808 isolates, it can be estimated that the frequency of erythromycin resistance in *Campylobacter* spp. was 1.1%. To confirm the adequacy of our screening approach, the results of the erythromycin disk screening were compared with the erythromycin MICs. All 19 strains classified as being erythromycin resistant based on MIC determinations had erythromycin inhibition zone diameters of ≤20 mm, while all strains exhibiting zone diameters of ≥21 mm were classified by MIC determination as being erythromycin susceptible.

Among the erythromycin-resistant strains, 17 (89.5%) were foreign, one was domestic, and for one strain, the origin was unknown. Ten (52.6%) resistant strains were identified as being *C. jejuni* isolates, and nine (47.4%) strains were identified as being *C. coli* strains. Erythromycin resistance was significantly more common among *C. coli* than among *C. jejuni* strains (*P* < 0.001). Compared to the *C. jejuni* strains, the *C. coli* strains were also significantly more commonly resistant to several other antimicrobial agents (Table 1).

Susceptibility of the macrolide-resistant and -susceptible strains to other antimicrobials. The susceptibilities of the erythromycin-resistant and -susceptible *Campylobacter* strains to 19 additional antimicrobial agents were different (Table 2). As determined by the agar plate dilution method, the MIC₅₀ and MIC₉₀ of erythromycin for the 19 erythromycin-resistant strains were >128 µg/ml. The MIC₅₀s and MIC₉₀s were 32 and >128 µg/ml for telithromycin and 64 and 64 µg/ml for clindamycin, respectively, with these being lower than those for azithromycin and clarithromycin. The respective MIC₅₀s and MIC₉₀s were 16 and >32 µg/ml for ciprofloxacin, 4 and 64 µg/ml for co-amoxiclav, and 8 and 128 µg/ml for ampicillin.

TABLE 1. Comparison of the antimicrobial susceptibilities between *Campylobacter jejuni* and *C. coli* strains

Antimicrobial agent	Resistance breakpoint ^b (μg/ml)	No. (%) of resistant strains		P value
		<i>C. jejuni</i> (n = 220) ^a	<i>C. coli</i> (n = 18)	
Erythromycin	16	10 (4.5)	9 (50)	<0.001
Azithromycin	4	11 (5)	7 (38.9)	<0.001
Clindamycin	8	11 (5)	9 (50)	<0.001
Nalidixic acid	32	91 (41.4)	15 (83.3)	<0.001
Ciprofloxacin	4	92 (42.4)	15 (83.3)	<0.001
Norfloxacin	16	90 (40.9)	15 (83.3)	<0.001
Ofloxacin	8	90 (40.9)	15 (83.3)	<0.001
Levofloxacin	8	76 (34.5)	13 (72.2)	0.002
Ampicillin	32	40 (18.2)	4 (22.2)	0.751
Co-amoxiclav	32	42 (19.1)	4 (22.2)	0.757
Chloramphenicol	32	1 (0.5)	0	1.000
Imipenem	16	0	0	Not applicable
Meropenem	16	0	0	Not applicable
Gentamicin	16	2 (0.9)	0	1.000
Tetracycline	16	61 (28.1)	12 (66.7)	0.002
Tigecycline	0.5	0	0	Not applicable

^a For ciprofloxacin and tetracycline, data were available for 216 strains. For tigecycline, data were available for 211 strains. For meropenem, data were available for 189 strains. For imipenem, data were available for 118 strains.

^b Resistance breakpoints according to the CLSI were as follows: ciprofloxacin, ≥4 μg/ml; norfloxacin, ≥16 μg/ml; ofloxacin, ≥8 μg/ml; levofloxacin, ≥8 μg/ml; imipenem, 16 μg/ml; meropenem, ≥16 μg/ml; tetracycline, ≥16 μg/ml; gentamicin, ≥16 μg/ml; and chloramphenicol, ≥32 μg/ml. Resistance breakpoints according to our previous work were as follows: erythromycin, ≥16 μg/ml; azithromycin, ≥4 μg/ml; clindamycin, ≥8 μg/ml; nalidixic acid, ≥32 μg/ml; ampicillin, ≥32 μg/ml; and co-amoxiclav, ≥32 μg/ml. The resistance breakpoint for tigecycline according to EUCAST was >0.5 μg/ml.

Imipenem, meropenem, gentamicin, and sitafloxacin exhibited the lowest MIC₅₀s and MIC₉₀s. As determined by the Etest, the MIC₅₀s and MIC₉₀s of tigecycline were 0.008 and 0.023 μg/ml for the erythromycin-resistant strains and 0.008 and 0.032 μg/ml for the erythromycin-susceptible strains, respectively. Compared to the erythromycin-susceptible *Campylobacter* strains, the erythromycin-resistant strains were significantly more commonly resistant to several antimicrobial agents presented in Table 2.

Of the 19 erythromycin-resistant strains, 17 (89.5%) were highly resistant (MIC ≥ 128 μg/ml) and also resistant to azithromycin (MIC ≥ 4 μg/ml) and clindamycin (MIC ≥ 8 μg/ml). Eighteen (94.7%) strains had telithromycin MICs of ≥8 μg/ml, including 14 strains with MICs of >32 μg/ml. All 19 erythromycin-resistant strains were multidrug resistant, with 18 (94.7%) of them being resistant to ciprofloxacin (MIC ≥ 4 μg/ml). Six strains had MICs of co-amoxiclav of between 32 and 64 μg/ml, and seven strains had MICs of ampicillin of between 32 and >128 μg/ml. There were 14 (73.7%) strains that were resistant to tetracycline (MIC ≥ 16 μg/ml).

Of all 238 *Campylobacter* strains, 107 (45.0%) were ciprofloxacin resistant; of them, 35 (32.7%) were multidrug resistant. The proportion of tetracycline resistance was 30.7% (73/238) in the whole study population.

DISCUSSION

In the present study, the macrolide-resistant *Campylobacter* strains were uniformly multidrug resistant. There is a paucity of information regarding antimicrobial agents that could be used for serious infections if caused by these multidrug-resis-

TABLE 2. MICs of 20 antimicrobial agents for 238 *Campylobacter* strains and comparison of erythromycin-resistant and -susceptible *Campylobacter* strains

Antimicrobial agent	Erythromycin-resistant strains (n = 19) ^c			Erythromycin-susceptible strains (n = 219) ^a			P value
	MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)	% Resistance ^b	MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)	% Resistance ^b	
Erythromycin	>128	>128	100	2	4	0	<0.001
Azithromycin	>128	>128	89.5	0.25	0.5	0.5	
Clarithromycin	>128	>128		2	4		
Telithromycin	32	>128		2	8		<0.001
Clindamycin	64	64	89.5	0.5	1	1.4	
Nalidixic acid	128	128	94.7	8	256	40.1	
Ciprofloxacin	16	>32	94.7	0.25	32	40.7	<0.001
Norfloxacin	64	>64	94.7	1	>64	39.6	<0.001
Ofloxacin	16	64	84.2	0.5	32	40.6	<0.001
Levofloxacin	8	>64	78.9	0.25	16	33.6	<0.001
Moxifloxacin	2	16		0.125	8		0.054
Sitafloxacin	0.125	0.5		0.016	0.25		
Ampicillin	8	128	36.8	4	64	16.6	
Co-amoxiclav	4	64	31.6	4	64	18.0	0.216
Chloramphenicol	4	16	0	2	8	0.5	1.000
Imipenem	0.25	0.5	0	0.064	0.25	0	Not applicable
Meropenem	≤0.03	0.25	0	≤0.03	0.125	0	Not applicable
Gentamicin	0.5	0.5	0	0.5	1	0.9	0.154
Tetracycline	128	>128	73.7	0.25	128	26.9	<0.001
Tigecycline	0.008	0.023	0	0.008	0.032	0	Not applicable

^a For clarithromycin, ciprofloxacin, and tetracycline, data were available for 216 strains. For tigecycline, data were available for 211 strains. For meropenem, data were available for 189 strains. For imipenem, data were available for 118 strains. Erythromycin susceptibility was defined as an MIC of <16 μg/ml.

^b Resistance breakpoints according to the CLSI were as follows: ciprofloxacin, ≥4 μg/ml; norfloxacin, ≥16 μg/ml; ofloxacin, ≥8 μg/ml; levofloxacin, ≥8 μg/ml; imipenem, ≥16 μg/ml; meropenem, ≥16 μg/ml; tetracycline, ≥16 μg/ml; gentamicin, ≥16 μg/ml; and chloramphenicol, ≥32 μg/ml. Resistance breakpoints according to our previous work were as follows: erythromycin, ≥16 μg/ml; azithromycin, ≥4 μg/ml; clindamycin, ≥8 μg/ml; nalidixic acid, ≥32 μg/ml; ampicillin, ≥32 μg/ml; and co-amoxiclav, ≥32 μg/ml. The resistance breakpoint for tigecycline according to EUCAST was >0.5 μg/ml.

^c Erythromycin resistance was defined as an MIC of ≥16 μg/ml.

tant *Campylobacter* strains. Since extraintestinal manifestations are uncommon in campylobacteriosis, data on their antimicrobial therapy are based only on anecdotal case reports (4, 18, 21) and small retrospective case series (15, 16). Thus, the most appropriate protocols for antimicrobial treatment for bacteremic infections, whether caused by susceptible or resistant strains, have not been established. Successful outcomes have been reported previously, especially with the carbapenems (4, 15, 16, 18). In previous studies, this antimicrobial group has also shown excellent *in vitro* activities against *Campylobacter* spp. (12, 25). Correspondingly, in the present study, all macrolide-resistant strains were susceptible to meropenem and imipenem. Among the older antimicrobial agents, gentamicin was effective, but it is not suitable for use, e.g., for meningitis or during pregnancy. However, gentamicin may be effective against septicemia and other systemic infections in conjunction with carbapenem antibiotics. It is of note that here, tigecycline was also highly active against all *Campylobacter* strains, including the macrolide- and multidrug-resistant strains. We consider this an important finding due to the limited number of other agents that are potentially effective for the treatment of multidrug-resistant campylobacteriosis.

In campylobacter enteritis, antimicrobial treatment is required at least for immunocompromised patients and during pregnancy (3). The treatment is also required if the patient has severe or persisting symptoms and in cases of bloody diarrhea (3). In enteric infections, the administration of antimicrobials by the peroral route is usually preferable to the intravenous route. Based on the results of the present study, no currently available peroral antimicrobial agent reliably covers the macrolide-resistant *Campylobacter* strains. All but one erythromycin-resistant strain were resistant to ciprofloxacin here, with the majority of them also being resistant to telithromycin and tetracycline. Co-amoxiclav may offer the best alternative, with only one-third of our strains being resistant. Among the fluoroquinolones, sitafloxacin exhibited low MICs against the macrolide-resistant isolates, and these results were consistent with our previous findings (17). However, sitafloxacin is not presently on that market and is thus of no clinical consequence. In addition, all macrolide-resistant strains were susceptible to chloramphenicol, which is no longer available in Finland for systemic use.

The present study provides information on the frequency of macrolide resistance in campylobacters in Finland between 2003 and 2005. The finding that 19 of the 1,808 *Campylobacter* isolates initially included proved to be erythromycin resistant by MIC determinations indicates that the frequency of macrolide resistance was 1.1%. We trust this material to be representative of the macrolide resistance situation in our country during that period, as these isolates comprised about one-fifth of all campylobacters recovered from Finnish patients throughout the study. We also trust that our screening approach was appropriate to identify at least a great majority, if not all, of the macrolide-resistant strains present in the initial study population. The adequacy of the methodology was verified by comparing the results of the screening tests to the results of MIC determinations, with a finding that all isolates with inhibition zone diameters of ≥ 21 mm were determined by MICs to be susceptible.

Among the 238 strains undergoing species determination,

7.6% were identified as being *C. coli* strains, and yet almost half (47.4%) of the macrolide-resistant strains were identified as being *C. coli* strains. This finding is consistent with data from previous studies showing that the *C. coli* strains are macrolide resistant more often than *C. jejuni* strains (8, 23). Because of the increasing trend of resistance among *Campylobacter* spp., routine susceptibility testing is an important tool to choose an appropriate antimicrobial treatment for the patient. Also, species identification may have therapeutic implications.

The *in vitro* activity of tigecycline against the *Campylobacter* spp. has been analyzed in one previous study (22), in which it exhibited the lowest MICs against resistant *Campylobacter* strains. Clinically, the drug has shown excellent activity, e.g., for the treatment of complicated skin and soft tissue infections (6), which is known to be one manifestation of extraintestinal campylobacteriosis (15, 18). Tigecycline circulates primarily as unchanged drug, and its major route of elimination is through the feces, likely via biliary excretion (2, 19). On this basis, it seems reasonable to assume that tigecycline might be effective even for patients with gastroenteritis.

In conclusion, the incidence of macrolide resistance among *Campylobacter* spp. was low, but the macrolide-resistant strains were uniformly multidrug resistant. *C. coli* was significantly more frequently macrolide resistant than *C. jejuni*. Thus, rapid species identification may have therapeutic implications. Based on our results, no perorally administered antimicrobial agent reliably covers the macrolide-resistant *Campylobacter* strains. Co-amoxiclav appears to offer the best treatment alternative, with only one-third of our isolates being resistant. In addition to imipenem and meropenem, tigecycline was also highly effective *in vitro* against multidrug-resistant *Campylobacter* strains. The efficacy of tigecycline for the treatment of human campylobacteriosis should be evaluated in clinical trials.

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