In Vitro Susceptibilities of Aerotolerant *Campylobacter* Isolates to 22 Antimicrobial Agents

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We evaluated the in vitro activities of 22 antimicrobial agents against 78 human and animal isolates belonging to two aerotolerant *Campylobacter* species, *C. cryaerophila* and *C. butzleri*, using a broth microdilution technique. An additional 10 antimicrobial agents were included at concentrations found in selective *Campylobacter* media. Strains of *C. cryaerophila* belonged to two DNA hybridization groups: DNA hybridization group 1A, which includes the type strain of *C. cryaerophila*, and DNA hybridization group 1B. The aminoglycosides, fluoroquinolones, and one tetracycline (minocycline) demonstrated the most activity against all DNA hybridization groups (*C. cryaerophila* DNA groups 1A and 1B and *C. butzleri*). Most isolates were resistant to cephalosporin antibiotics, with the exception of cefotaxime, and were variably susceptible to trimethoprim-sulfamethoxazole. *C. cryaerophila* DNA hybridization group 1A isolates were generally susceptible to the tetracyclines, chloramphenicol, nalidixic acid, azithromycin, erythromycin, and roxithromycin and moderately susceptible to clindamycin, trimethoprim-sulfamethoxazole, ampicillin, and ampicillin-sulbactam. The MICs of tetracyclines were higher for *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B isolates than for *C. cryaerophila* DNA hybridization group 1A isolates, but most strains were still susceptible to doxycycline and tetracycline; all isolates were susceptible to minocycline. *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B isolates were generally resistant to the macrolide antibiotics (including erythromycin), chloramphenicol, clindamycin, nalidixic acid, ampicillin, and trimethoprim-sulfamethoxazole. Differences in antimicrobial susceptibility between aerotolerant *Campylobacter* species and more common *Campylobacter* species, e.g., *C. jejuni*, suggest that different treatment strategies may be necessary. Strains of all three DNA hybridization groups of aerotolerant *Campylobacter* isolates were susceptible to colistin, polymyxin B, and rifampin at concentrations commonly used in selective media. These results suggest that primary isolation methods for *Campylobacter* species may need to be modified to include aerotolerant *Campylobacter* strains.

Previous investigations in our laboratory using DNA hybridization revealed two aerotolerant *Campylobacter* species, *C. butzleri* (previously designated DNA hybridization group 2) and *C. cryaerophila* (previously designated DNA hybridization group 1) (24). DNA hybridization data further separated strains of *C. cryaerophila* into two groups: DNA hybridization group 1A (containing the type strain of *C. cryaerophila*) and DNA hybridization group 1B. Two strains of DNA hybridization group 1B phenotypically resembled the type strain of *C. cryaerophila* (24). All strains from the United States belonged to *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B; strains were most frequently isolated from fecal specimens from human and nonhuman primates with diarrheal illness (24, 39). *C. cryaerophila* DNA hybridization group 1A strains have been isolated only from animals in Ireland (24), whereas *C. cryaerophila* DNA hybridization group 1B contains three human strains from the United States and five animal isolates from Ireland. More recently, strains of *C. cryaerophila* DNA hybridization group 1B have been isolated from aborted porcine and equine fetuses in the United States (41). Other investigators have proposed that *C. cryaerophila* be renamed *Arcobacter cryaerophilus*. Under this proposal, *C. butzleri* would become *Arcobacter butzleri* (52). This study was designed to

provide information regarding the antimicrobial susceptibilities of these aerotolerant *Campylobacter* organisms. Ten antimicrobial agents typically found in selective media were also included in this study to determine selective media that might be appropriate for primary isolation of these organisms. The third goal of this study was to determine whether antimicrobial susceptibility patterns could be used to differentiate these DNA hybridization groups, particularly those associated with human illness (*C. butzleri* and *C. cryaerophila* DNA hybridization group 1B).

MATERIALS AND METHODS

Bacterial isolates. A total of 78 isolates, belonging to the three DNA hybridization groups of aerotolerant *Campylobacter* isolates were included in this study. These isolates and their sources have been described in detail elsewhere (24). These isolates included 64 strains of *C. butzleri* (DNA hybridization group 2) and 14 *C. cryaerophila* isolates (6 isolates belonging to DNA hybridization group 1A and 8 strains belonging to DNA hybridization group 1B). Each isolate was stored at $-70°C$ in tryptic soy broth containing 20% glycerol. Isolates were removed from the freezer and subcultured onto heart infusion agar containing 5% rabbit blood (BBL Microbiology Systems, Cockeysville, Md.), and plates were incubated at 30°C in an atmosphere of 5% O_2, 7.5% CO_2, 7.5% H_2, and 80% N_2. Organisms were subcultured one additional time prior to antimicrobial susceptibility testing.

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Antimicrobial susceptibility test. The antimicrobial agents used are listed in Table 1. The drugs were diluted, as previously described (32), in cation-supplemented Mueller-Hinton broth with 5% lysed horse blood (in contrast to cation-adjusted Mueller-Hinton broth [33]), and dispensed into U-bottom microdilution trays. Quality control for the completed trays was done at the time of preparation by using *Escherichia coli* ATCC 25922 and ATCC 35218, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Pseudomonas aeruginosa* ATCC 27853. Trays were stored at −70°C until needed. In addition, control organisms were tested under the same incubation conditions (both microaerobic atmosphere and length of incubation) as the test organisms; all results were within acceptable limits. The trays were removed from the freezer and thawed at room temperature for at least 1 h prior to inoculation.

Growth from one plate of heart infusion agar containing 5% rabbit blood was harvested into Mueller-Hinton broth and adjusted to the turbidity of a MacFarland standard no. 0.5 (50). Inoculation was performed by using a Dynatech Disposable Inoculator (Dynatech Laboratories, Inc. Alexandria, Va.), which provided a final inoculum of approximately 5×10^5 CFU/ml. At least one control strain was included with each run. Trays were incubated at 35°C in anaerobic jars (BBL) containing the atmosphere described above. Additional trays were inoculated with *C. cryaerophila* (DNA hybridization groups 1A and 1B) organisms, which were incubated at 30°C. Growth was recorded at 20 h and again at 48 h for those strains that did not exhibit satisfactory growth at 20 h. Results were interpreted by using published breakpoints for susceptibility and resistance for rapidly growing aerobic organisms (32); ampicillin results were interpreted using criteria for members of the family *Enterobacteriaceae*, azithromycin and roxithromycin breakpoints were interpreted according to erythromycin breakpoints, and ofloxacin breakpoints were interpreted as previously described (33). Susceptibility of *C. butzleri* strains was determined after 20 h of incubation at 35°C; however, it was necessary to incubate *C. cryaerophila* strains for 48 h at 35°C.

RESULTS

The results of MIC testing of three hybridization groups of aerotolerant *Campylobacter* isolates are expressed in Table 1 as range, mode, MIC_{50} (MIC for 50% of strains), and MIC_{90} (MIC_{90}s are not listed for *C. cryaerophila* DNA hybridization groups because of the small number of isolates tested). The MICs for strains D2883 and D2884 are listed separately, because they do not clearly belong to either hybridization group. In general, *C. cryaerophila* DNA hybridization group 1A isolates were more susceptible to the agents tested than were *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B isolates.

All 78 isolates tested were susceptible to minocycline, the aminoglycosides (amikacin and gentamicin), and the quinolones (ciprofloxacin, enoxacin, norfloxacin, and ofloxacin). The cephalosporins were the least active against aerotolerant *Campylobacter* strains; most strains were resistant to cephalothin, cefuroxime, and cefoperazone. Cefotaxime was the most active cephalosporin tested; however, 30% of *C. butzleri* isolates were resistant to this expanded-spectrum cephalosporin. Variable susceptibility was noted for the macrolide antibiotics: most *C. butzleri* isolates included in this study were resistant to erythromycin (52%), azithromycin (75%), roxithromycin (95%), clindamycin (98%), and chloramphenicol (81%), whereas most *C. cryaerophila*

(DNA hybridization groups 1A and 1B) isolates were intermediately susceptible to these antimicrobial agents. Resistance to ampicillin and ampicillin-sulbactam was common in *C. butzleri* isolates (83 and 69%, respectively) but less common in *C. cryaerophila* DNA hybridization group 1A (17% resistance to ampicillin). Many isolates were also resistant to trimethoprim-sulfamethoxazole; 33% of *C. cryaerophila* DNA hybridization group 1B isolates and 80% of *C. butzleri* isolates were resistant to this combination. Some isolates of *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B were intermediately susceptible to doxycycline and tetracycline. Three concentrations of metronidazole were tested against aerotolerant *Campylobacter* isolates; *C. cryaerophila* DNA hybridization group 1A isolates did not grow in 4 μg of metronidazole per ml; however, 53% of *C. butzleri* isolates and all *C. cryaerophila* DNA hybridization group 1B isolates (except D2883 and D2884) grew at this concentration. Most *C. butzleri* isolates were susceptible to 32 and 64 μg of metronidazole per ml, whereas *C. cryaerophila* DNA hybridization group 1B isolates were generally susceptible to metronidazole only at 64 μg/ml.

An additional 10 antimicrobial agents were included at concentrations found in commercially available selective media for primary isolation of *Campylobacter* organisms. The susceptibilities of aerotolerant *Campylobacter* organisms to these agents are shown in Table 2. Aerotolerant *Campylobacter* organisms were resistant to amphotericin B, bacitracin, cefazolin, cycloheximide, novobiocin, trimethoprim, or vancomycin at concentrations found in selective media. Organisms were generally susceptible to polymyxin B and rifampin at concentrations used in selective media, and *C. cryaerophila* and most *C. butzleri* isolates were also susceptible to colistin.

C. cryaerophila DNA hybridization groups 1A and 1B, in addition to selected strains of *C. butzleri*, were tested in parallel at both 30 and 35°C. MICs obtained following incubation at both temperatures were generally within one dilution of each other. Strains that did not grow well overnight were incubated for 48 h, along with representative strains that did grow well. For strains that grew well, results were comparable at 20 and 48 h. Three subsets of organisms were present within *C. butzleri*, strains isolated from animals ($n = 15$), strains isolated from children in Thailand with diarrhea ($n = 15$), and strains of human origin isolated in the United States ($n = 34$). Comparison of the range, mode, MIC_{50} and MIC_{90} failed to reveal significant differences among the three subsets of *C. butzleri* organisms; the value for each differed by no more than two dilutions among the three groups (data not shown).

DISCUSSION

The antimicrobial susceptibility patterns of aerotolerant *Campylobacter* organisms found in this study were quite different from that previously described for other *Campylobacter* species. Aerotolerant *Campylobacter* strains associated with human illness appeared resistant to antimicrobial agents typically used in treatment of diarrheal illness caused by other *Campylobacter* species, e.g., erythromycin, other macrolide antibiotics, tetracycline, and chloramphenicol. In addition, aerotolerant *Campylobacter* isolates were typically resistant to clindamycin, a finding which has been previously described only for *C. coli* (25, 55). Increased MICs of erythromycin have been described only for isolates of *C. coli* (3, 8, 11, 14, 48, 55), *C. fetus* subsp. *fetus* (14), *C. cinaedi* (15), and animal strains of *C. hyointestinalis* (17). Human

TABLE 1. Susceptibilities of aerotolerant *Campylobacter* spp.

Antimicrobial agent	MIC (μg/ml)[a]												
	C. butzleri (n = 64)				*C. cryaerophila*								
					DNA hybridization group 1A (n = 6)			DNA hybridization group 1B (n = 6)			D2883[b]	D2884[b]
	Range	Mode	50%	90%	Range	Mode	50%	Range	Mode	50%		
Aminoglycosides												
Amikacin	≤0.5–2	1	1	1	≤0.5	≤0.5	≤0.5	≤0.5–2	≤0.5	≤0.5	≤0.5	≤0.5
Gentamicin	≤0.12–0.5	0.5	0.5	0.5	≤0.12–0.25	0.25	0.25	≤0.12–0.5	0.5	0.5	≤0.12	0.25
Cephalosporins												
Cephalothin	32–>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Cefuroxime	8–>32	>32	>32	>32	32–>32	>32	>32	16–>32	>32	>32	32	16
Cefoperazone	16–>32	>32	>32	>32	>32	>32	>32	16–>32	>32	>32	>32	4
Cefotaxime	4–>64	32	32	64	8–>64	16, 32	16	8–32	16	16	8	16
Chloramphenicol	8–>32	>32	32	>32	4–16	8	8	8–>32	16	16	2	8
Clindamycin	2–>8	>8	>8	>8	0.5–8	1	1	4–>8	>8	8	0.25	2
Macrolides												
Azithromycin	1–>16	16	16	>16	≤0.12–0.5	0.5	0.25	0.5–2	1	1	≤0.12	≤0.12
Erythromycin	2–16	4	8	16	≤0.12–1	≤0.12	≤0.12	1–4	2	2	0.25	0.25
Roxithromycin	4–>16	>16	16	>16	0.5–2	0.5	0.5	2–8	4	4	0.25	0.5
Penicillins												
Ampicillin	4–>32	>32	>32	>32	8–>32	16	16	16–>32	32	32	16	8
Ampicillin-sulbactam[c]	2–>32	32	32	>32	4–16	8	8	4–16	4, 8, 16	8	4	2
Quinolones												
Nalidixic acid	8–>32	>32	32	>32	4–>32	8	8	8–>32	32, >32	32	4	4
Ciprofloxacin	≤0.03–0.25	0.12	0.12	0.25	≤0.03–0.25	≤0.03	≤0.03	0.06–0.25	0.12	0.12	≤0.03	0.12
Enoxacin	0.25–0.5	0.25	0.25	0.5	0.25–0.5	0.25	0.25	0.25–1	0.25, 0.5, 1	0.5	0.25	0.25
Norfloxacin	0.25–2	1	1	1	0.25–0.5	0.5	0.5	0.5–2	0.5	0.5	0.25	0.25
Ofloxacin	0.25–2	0.5	0.5	1	0.25–0.5	0.5	0.5	≤0.12–2	0.5	0.5	≤0.12	≤0.12
Trimethoprim-sulfamethoxazole[d]	0.5–>4	>4	>4	>4	0.25–>4	0.25, 4	0.5	0.5–>4	>4	>4	4	0.5
Tetracyclines												
Doxycycline	0.5–8	2	2	4	≤0.12–1	0.5	0.5	0.5–4	0.5, 2, 4	1	0.25	≤0.12
Minocycline	0.25–1	0.5	0.5	1	0.25–1	0.5	0.5	0.25–4	2	2	≤0.12	≤0.12
Tetracycline	0.25–8	1	1	2	0.5–2	0.5	0.5	0.5–8	0.5	1	0.25	0.25

[a] 50% and 90%, MICs for 50 and 90% of strains tested, respectively.
[b] Strains D2883 and D2884 belong to DNA hybridization group 1B; however, they phenotypically resemble *C. cryaerophila* DNA hybridization group 1A.
[c] Ampicillin concentrations are shown; ampicillin-sulbactam was tested in a 2:1 ratio.
[d] Trimethoprim concentrations are shown; trimethoprim-sulfamethoxazole was tested in a 1:19 ratio.

strains of *C. hyointestinalis* (10), *C. jejuni*, *C. fennelliae* (15), *C. upsaliensis* (37), *C. fetus* subsp. *fetus* (14, 19, 30), and *C. lari* (31, 43, 47) are generally susceptible to erythromycin. Although the microaerobic atmosphere used in this study may decrease the level of activity of erythromycin and the aminoglycosides (7, 12, 40), this does not appear to have affected results in this study. In a similar study using the same conditions and media, 49 of 50 *C. jejuni* isolates had MICs to erythromycin ranging from 0.25 to 2.0 μg/ml (mode = 0.5 μg/ml) (2). This range is in accord with results established by other investigators.

In this study, the most active classes of antimicrobial agents against aerotolerant *Campylobacter* organisms were the aminoglycosides and quinolones in addition to minocycline. Other *Campylobacter* species are also generally susceptible to aminoglycosides (11, 14, 16, 26, 29, 42, 53) and the 4-fluoroquinolones (14, 18, 20, 26, 54). In contrast to other *Campylobacter* species, which demonstrate cross-

resistance between nalidixic acid and other quinolones (1, 49), most strains of *C. butzleri* and *C. cryaerophila* DNA hybridization group 1B were resistant to nalidixic acid but not to other quinolones.

In addition, variable susceptibility was noted for trimethoprim-sulfamethoxazole, ampicillin, and ampicillin-sulbactam. Variable activities of tetracyclines, trimethoprim-sulfamethoxazole, and ampicillin toward *C. jejuni* strains, similar to that seen for aerotolerant *Campylobacter* organisms, have been reported (7, 11, 14, 16, 22, 26, 29, 42, 46, 54). However, other *Campylobacter* species (*C. fetus* subsp. *fetus* [30], *C. cinaedi*, and *C. fennelliae* [15]) are generally considered susceptible to these antimicrobic agents. Isolates of *C. lari* are generally susceptible to tetracycline, but like aerotolerant *Campylobacter* organisms, demonstrate variable susceptibility toward trimethoprim-sulfamethoxazole (31, 43, 47). Increased levels of resistance of aerotolerant *Campylobacter* organisms to ampicillin (range, 4 to 32) were

TABLE 2. Susceptibilities to agents commonly used in selective media

Antimicrobial agent	Concn tested	No. (%) of strains susceptible to antimicrobial agent			D2883[a]	D2884[a]
		C. butzleri (n = 64)	C. cryaerophila			
			DNA hybridization group 1A (n = 6)	DNA hybridization group 1B (n = 6)		
Amphotericin B	2 μg/ml	0 (0)	0 (0)	0 (0)	R	R
Bacitracin	25 U/ml	0 (0)	2 (33)	0 (0)	R	R
Cefazolin	15 μg/ml	0 (0)	0 (0)	0 (0)	R	R
Colistin	10 U/ml	60 (94)	6 (100)	5 (83)	R	R
Cycloheximide	50 μg/ml	0 (0)	1 (17)	0 (0)	S	S
Novobiocin	5 U/ml	0 (0)	0 (0)	0 (0)	R	R
Polymyxin B	5 U/ml	59 (92)	6 (100	5 (83)	S	S
	2.5 U/ml	44 (69)	6 (100)	2 (33)	S	S
Rifampin	10 U/ml	38 (59)	3 (50)	1 (17)	S	S
Trimethoprim	5 μg/ml	0 (0)	0 (0)	0 (0)	R	R
	10 μg/ml	0 (0)	0 (0)	0 (0)	R	R
	50 μg/ml	0 (0)	0 (0)	0 (0)	R	R
Vancomycin	10 μg/ml	0 (0)	0 (0)	0 (0)	R	R
Metronidazole	4 μg/ml	30 (47)	6 (100)	0 (0)	S	S
	32 μg/ml	59 (92)	6 (100)	1 (17)	S	S
	64 μg/ml	61 (95)	6 (100)	3 (50)	S	S

[a] Strains D2883 and D2884 belong to DNA hybridization group 1B; however, they phenotypically resemble C. cryaerophila DNA hybridization group 1A. R, resistant; S, susceptible.

also noted, which is not typical of levels obtained when testing other *Campylobacter* species. The activity of ampicillin was not enhanced significantly by the addition of sulbactam for the study organisms; similar results have been noted for *C. jejuni* and *C. fetus* subsp. *fetus* (14, 51).

An additional goal of this study was to discriminate between strains belonging to *C. cryaerophila* DNA hybridization group 1B and *C. butzleri*. These groups are currently difficult to distinguish using phenotypic tests (24). However, overlapping MICs were noted between the hybridization groups. The MICs of strains D2883 and D2884, which genetically belong to DNA hybridization group 1B but phenotypically more closely resemble hybridization group 1A, were similar to those of isolates of *C. cryaerophila* DNA hybridization group 1A. In addition, differences were not noted among the three subsets of *C. butzleri* strains, including U.S. animal isolates (primarily of macaque origin), strains isolated in Thailand, and U.S. isolates submitted to the Centers for Disease Control for identification. This is in contrast to reports showing that strains of *C. jejuni* and *C. coli* isolated from locations outside the United States demonstrate higher MICs to antimicrobial agents such as erythromycin, chloramphenicol, and tetracycline, that are more readily available in these countries than they are in the United States (29, 36, 48).

Previous investigations in our laboratory noted that aerotolerant *Campylobacter* organisms generally did not grow on a selective medium (Campy-BAP) commonly used in primary isolation of *Campylobacter* organisms (24). To determine which antimicrobial agents might be responsible for this, we included 10 additional antimicrobial agents at con-

centrations commonly used in commercial media. Aerotolerant *Campylobacter* isolates were typically susceptible to colistin, polymyxin B, and rifampin. These antimicrobial agents are included in commercially available media based on several formulations, namely, those of Skirrow (containing trimethoprim, polymyxin B, and vancomycin) (44), Butzler and Skirrow (containing bacitracin, cycloheximide, colistin, cefazolin, and novobiocin) (9), Blaser et al. (Campy-BAP; containing vancomycin, polymyxin B, trimethoprim, amphotericin B, and cephalothin) (4), Bolton and Robertson (Preston medium containing polymyxin B, rifampin, trimethoprim, and cycloheximide) (6) and modification thereof (5], and Fennell and colleagues' modification of Skirrow's formulation by the addition of amphotericin B (13). These antimicrobial agents are not present in commercially available formulations of CVA (containing cefoperazone, vancomycin, and amphotericin B) (38), Karmali (containing cefoperazone, vancomycin, and cycloheximide) (23), or a modified Preston formula (CCDA; containing cefoperazone) (28). Some formulations of selective media for *Helicobacter pylori* may also be suitable for isolation of aerotolerant *Campylobacter* organisms; however, each formulation must be carefully evaluated for the presence of colistin, polymyxin B, and rifampin. An additional and important consideration when isolating these organisms is that most aerotolerant *Campylobacter* strains will not grow at 42°C (24). Lack of growth on certain selective media has been reported for other *Campylobacter* species, such as *C. upsaliensis* (37, 45), *C. fennelliae*, and *C. cinaedi* (13), in addition to a few strains of *C. jejuni* and *C. coli* (21, 27, 34, 35). An increasing recognition of the clinical significance of these organisms, in

addition to aerotolerant *Campylobacter* strains, should prompt investigation of alternative media or additional procedures for primary isolation of *Campylobacter* species.

In conclusion, human and most animal isolates of aerotolerant *Campylobacter* organisms were generally not susceptible to antimicrobial agents commonly used to treat other diarrheogenic campylobacters, e.g., erythromycin, other macrolide antibiotics, cephalosporins, ampicillin and ampicillin-sulbactam, clindamycin, chloramphenicol, and trimethoprim-sulfamethoxazole. In vitro laboratory data suggest that these antimicrobial agents may not be appropriate for treatment of diarrheal illness associated with aerotolerant *Campylobacter* organisms and that minocycline, the quinolones, or an aminoglycoside should be considered. Additionally, isolates are susceptible to antimicrobial agents used in commercially available *Campylobacter* media (colistin, polymyxin B, and rifampin). Laboratories interested in isolating aerotolerant *Campylobacter* organisms must modify existing procedures, and laboratories that isolate aerotolerant *Campylobacter* organisms from diarrheal stools need to be aware of the unusual antimicrobial susceptibility patterns.

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