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MINIREVIEW

Mechanisms of Antibiotic Resistance in *Campylobacter* Species

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Members of the *Campylobacter* genus are gram-negative, microaerophilic bacteria which are major pathogens responsible for both human and animal diseases. It is our aim in this review to discuss what is known about the biochemical mechanisms and the genetic basis of antibiotic resistance in *Campylobacter* species and to endeavor to provide insights into how campylobacters could have acquired specific resistance determinants.

CAMPYLOBACTER SPECIES CONSIDERED IN THIS REVIEW

The majority (95 to 98%) of cases of *Campylobacter* gastroenteritis are caused by *C. jejuni*, with the closely related species *C. coli* responsible for about 2 to 5% of cases (16). A more distantly related species, *C. laridis*, is rarely isolated from stool specimens of patients with gastroenteritis (37, 39). *C. fetus* subsp. *fetus* is occasionally responsible for septicemic infections in humans, especially in immunocompromised individuals, although this species is also a significant animal pathogen since it causes abortions in sheep and cattle (6). The closely related *C. fetus* subsp. *venerealis* is an important cause of sterility in cattle but is not a human pathogen (6). *C. hyointestinalis* is found in the intestines of pigs and other animals (11), but its role in human pathogenesis is not clearly defined. Other *Campylobacter*-like organisms (CLOs) have been associated with enteritis and proctitis in homosexual men, with the establishment of two distinct species: "*C. cinaedi*" and "*C. fennelliae*" (53). One further *Campylobacter* species should be mentioned, namely *C. pylori*. These organisms, which are frequently isolated from gastric biopsies obtained from patients with chronic gastritis, also play some role in human gastrointestinal disease (7, 24).

INTRINSIC ANTIBIOTIC RESISTANCE IN *CAMPYLOBACTER* SPECIES

Most studies of antibiotic resistance in *Campylobacter* species have involved *C. jejuni* and, to a lesser extent, *C. coli*. Thus, we will focus on these two species predominantly, although other species will be mentioned where appropriate. In considering resistance, a distinction should be made between intrinsic resistance to an antibiotic, such that every strain in the species is resistant, and acquired resistance resulting from a chromosomal mutation or acquisition of foreign DNA (plasmid or transposon). All *C. jejuni* and *C. coli* isolates are intrinsically resistant to a number of antibiotics, including bacitracin, novobiocin, rifampin, streptogramin B, trimethoprim, vancomycin, and usually cephalothin (Table 1). Various combinations of these antibiotics are used in selective media for isolation of *C. jejuni* and *C. coli* strains from stool samples (6). No information is available on these intrinsic mechanisms of resistance, although some of them probably involve the inability of the drugs to penetrate the cells.

QUINOLONE RESISTANCE

C. jejuni and *C. coli* are usually susceptible to nalidixic acid (MIC, 2 to 16 μg/ml) (17); however, several *Campylobacter* species are resistant to this drug, including *C. laridis*, *C. fetus* subsp. *fetus*, *C. fetus* subsp. *venerealis*, and *C. hyointestinalis*, for which MICs are 128 to 256 μg/ml (48). One of us found *C. pylori* strains to be resistant to intermediate levels of nalidixic acid (MIC, 48 μg/ml) (46), although others (36) have noted a wider range of susceptibilities (MIC, 4 to 128 μg/ml). In vitro activities of the fluoroquinolones against *Campylobacter* species have been reported by a number of workers (8, 12, 13, 36). Both *C. jejuni* and *C. coli* strains are highly susceptible to ciprofloxacin, norfloxacin, and ofloxacin (13). In a representative study of *C. jejuni* strains, ciprofloxacin MICs were 0.125 to 0.5 μg/ml and norfloxacin MICs were 0.25 to 2 μg/ml (8). These agents therefore are potentially useful for the treatment of enteritis caused by *Campylobacter* species. However, nalidixic acid-resistant mutants of *C. jejuni* and *C. coli* could be selected at frequencies of 10^{-8}, and these mutants exhibited cross resistance to enoxacin and ciprofloxacin (48). *C. laridis* strains also show cross resistance to enoxacin and ciprofloxacin, although various other *Campylobacter* species (*C. fetus* subsp. *fetus*, *C. fetus* subsp. *venerealis*, and *C. hyointestinalis*), which are all intrinsically resistant to nalidixic acid, are uniformly susceptible to enoxacin (MIC, ≤2 μg/ml) (48). These results suggest that different resistance mechanisms may be operative in these two groups of *Campylobacter* species towards DNA gyrase subunit A inhibitors. Resistance may involve the DNA gyrase enzyme itself or could be due to the inability of the drug to penetrate. *C. pylori* strains are highly susceptible to the fluoroquinolone norfloxacin (MIC, 0.06 to 1 μg/ml) (36).

TETRACYCLINE RESISTANCE

The incidence of tetracycline resistance in *C. jejuni* has ranged from 0% reported in Sweden in 1978 to 55% reported in Japan in 1987 (17, 35, 55). Resistance in *C. jejuni* was shown in 1980 to be plasmid mediated (D. E. Taylor, S. A. De Grandis, M. A. Karmali, and P. C. Fleming, Letter, Lancet ii:797, 1980). Subsequently, plasmids encoding tetracycline resistance in *C. jejuni* and *C. coli* have been reported

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TABLE 1. Intrinsic resistance in *C. jejuni*[a]

Antibiotic	MIC range (μg/ml)[b]
Bacitracin	≥512
Cephalothin	64–≥512
Novobiocin	64–≥512
Rifampin	8–≥128
Streptogramin B	≥256
Trimethoprim	256–≥512
Vancomycin	128–≥512

[a] Information from references 5 and 17.

[b] MICs for other closely related *Campylobacter* species are within these ranges. In contrast, CLOs, including "*C. cinaedi*" and "*C. fennelliae*," are highly susceptible to rifampin (MIC, <1 μg/ml) and "*C. fennelliae*" strains are susceptible to 8 μg of cephalothin per ml (10).

in studies from Canada (1, 28, 42, 45), France (20), the United States (18, 50, 52), and Japan (35). Tetracycline resistance plasmids from *C. jejuni* and *C. coli* are usually self-transmissible but have a very restricted host range, as they can be transferred only to other species within the *Campylobacter* genus, namely *C. laridis*, *C. fetus* subsp. *fetus*, and *C. fetus* subsp. *venerealis* (see reference 43). Reciprocally, it has not been possible to transfer plasmids from members of the family *Enterobacteriaceae* to *Campylobacter* species. We have attempted to transfer plasmids of incompatibility groups F, N, P, and W from *Escherichia coli* to *C. jejuni* by conjugation without success. The conjugative transposon Tn*1545* from *Streptococcus pneumoniae* and plasmid pJH1 from *Enterococcus faecalis* also could not be transferred to *C. jejuni* (D. E. Taylor and P. Courvalin, unpublished observations).

Plasmid sizes ranged from 45 to 58 kilobases when measured by restriction endonuclease analysis or electron microscopy (35, 41, 42, 45, 51). Tetracycline resistance determinants from *C. jejuni* plasmids pUA466 and pKFT1025 and *C. coli* plasmid pIP1433 have been cloned, and tetracycline resistance has been expressed in *E. coli* (38, 41, 47, 51). The determinants from plasmids pIP1433 and pUA466 have been sequenced (23, 38), are 98% homologous at the nucleotide level (Fig. 1), and have been designated *tetO*. The *tetO* genes demonstrate 75 to 76% homology with the *tetM* gene of *S. pneumoniae* (25). In dot blot hybridizations, homology can be detected between *tetM* and *tetO* under conditions of standard stringency (T_m − 21°C), viz. 50% formamide at 37°C, but is not detected under conditions of moderate stringency (T_m − 15°C), viz. 50% formamide at 42°C (28, 38, 41, 47, 51). No homology was detected between *tetO* and genes *tetA* to *D* from members of the *Enterobacteriaceae* (21, 45, 51) or with *tetK*, *L*, or *N* from gram-positive cocci (28, 38, 51).

The *tetO* open reading frame corresponds to a 72.3-kilodalton protein (23, 38). This value is consistent with an observed protein of 68 kilodaltons specified by the cloned *tetO* fragment of pUA466 in an *E. coli* in vitro transcription-translation system and in minicells (47), as well as in maxicell analysis of the cloned *tet* fragment from pFKT1025 (51). Tetracycline-susceptible transposon insertion mutants did not produce the 68-kilodalton protein (23, 47).

The TetM and TetO proteins have almost identical hydrophilicity profiles (23) and probably assume very similar secondary structures. Burdett (3) has shown that the TetM protein acts at the level of protein synthesis, and it is likely that TetO has a similar mechanism of resistance. This mode of resistance contrasts directly with the efflux mechanism found in members of the *Enterobacteriaceae* in which a cytoplasmic membrane protein actively pumps out tetracycline (21). The mean hydrophilicity value obtained for the TetO protein was much greater than that of a membrane-localized protein (TetA). In addition, preliminary studies on the mechanism of TetO-mediated resistance suggest that this protein is probably localized in the cytoplasm (23).

The G+C content of *tetO* is 40 mol%, which is close to that of *tetM* but significantly higher than those of *C. jejuni* and *C. coli* chromosomal (32.5 mol%) and plasmid (31 to 33 mol%) DNAs (23, 45). A strong preference for AT-rich codons is seen in *tetO*, *tetM*, and a chromosomal gene from *Enterococcus* species (38). The ribosomal binding sequence identified in *tetO* from pIP1433 is complementary to 8 of 10 bases of the 3′-OH terminus of the 16S rRNA of *Bacillus subtilis*. Also, *tetO* has been identified in both *Streptococcus* and *Enterococcus* species (38). Thus, all available evidence suggests that the *tetO* determinant was acquired by *Campylobacter* species, most likely from a gram-positive coccus. The acquisition event probably occurred some time ago in evolution, consistent with 25% divergence of the DNA sequences. In one *C. coli* strain, the *tetO* gene was found to reside in the chromosome rather than on a plasmid, suggesting that it could be carried on a transposon, although no direct evidence for this idea has been obtained (28). The *tetM* determinant was originally identified in *Enterococcus* species (4); however, it is now very widely disseminated, being found at a chromosomal location in *Staphylococcus* species (21), *Mycoplasma hominis* (34), *Ureaplasma urealyticum* (33), *Gardnerella vaginalis* (32), and *Clostridium difficile* (14) and on plasmids in *Neisseria gonorrhoeae* (27). To date, all tetracycline-resistant *Campylobacter* strains have hybridized to a *tetO*-specific probe (28, 38). None of the other *Campylobacter* species, including *C. pylori* (36, 46), have been reported to be tetracycline resistant.

AMINOGLYCOSIDE RESISTANCE

Kanamycin resistance. Resistance to kanamycin was initially described in *C. coli* BM2509 isolated in France (20) and another *C. coli* strain isolated in Spain (31). In Japan, 5 of 10 *C. coli* strains were kanamycin resistant, whereas none of 111 *C. jejuni* strains were resistant to this antibiotic (35). Thus, in general, kanamycin resistance appears to be more often associated with *C. coli* than with *C. jejuni*. Kanamycin resistance is often mediated by a plasmid which also encodes tetracycline resistance (18, 20, 35). Kotarski and co-workers (18) noted that kanamycin-susceptible, tetracycline-resistant segregants carried plasmids 4 kilobases smaller than the 59-kilobase parental plasmids. In contrast, kanamycin-resistant, tetracycline-susceptible derivatives contained no detectable plasmid DNA, suggesting that kanamycin was located on a transposable element. As with *tetO*, the evidence is circumstantial.

Resistance to kanamycin in *Campylobacter* species appears to have been acquired from two different sources. Trieu-Cuot and co-workers (54) cloned from plasmid pIP1433, harbored in *C. coli* BM2509, a 1,427-base-pair DNA fragment which conferred kanamycin resistance in *E. coli*. The fragment specified a 3′-aminoglycoside phosphotransferase of type III encoded by *aphA-3*, a gene found previously only in gram-positive cocci, in which it is extremely common. Moreover, the *aphA-3* gene has been shown to be transcribed in *B. subtilis* (54). Therefore, resistance to kanamycin in *C. coli* is probably due to in vivo acquisition of a gene from a gram-positive coccus (20, 54). In contrast, a CLO (BM2196) of undetermined species was

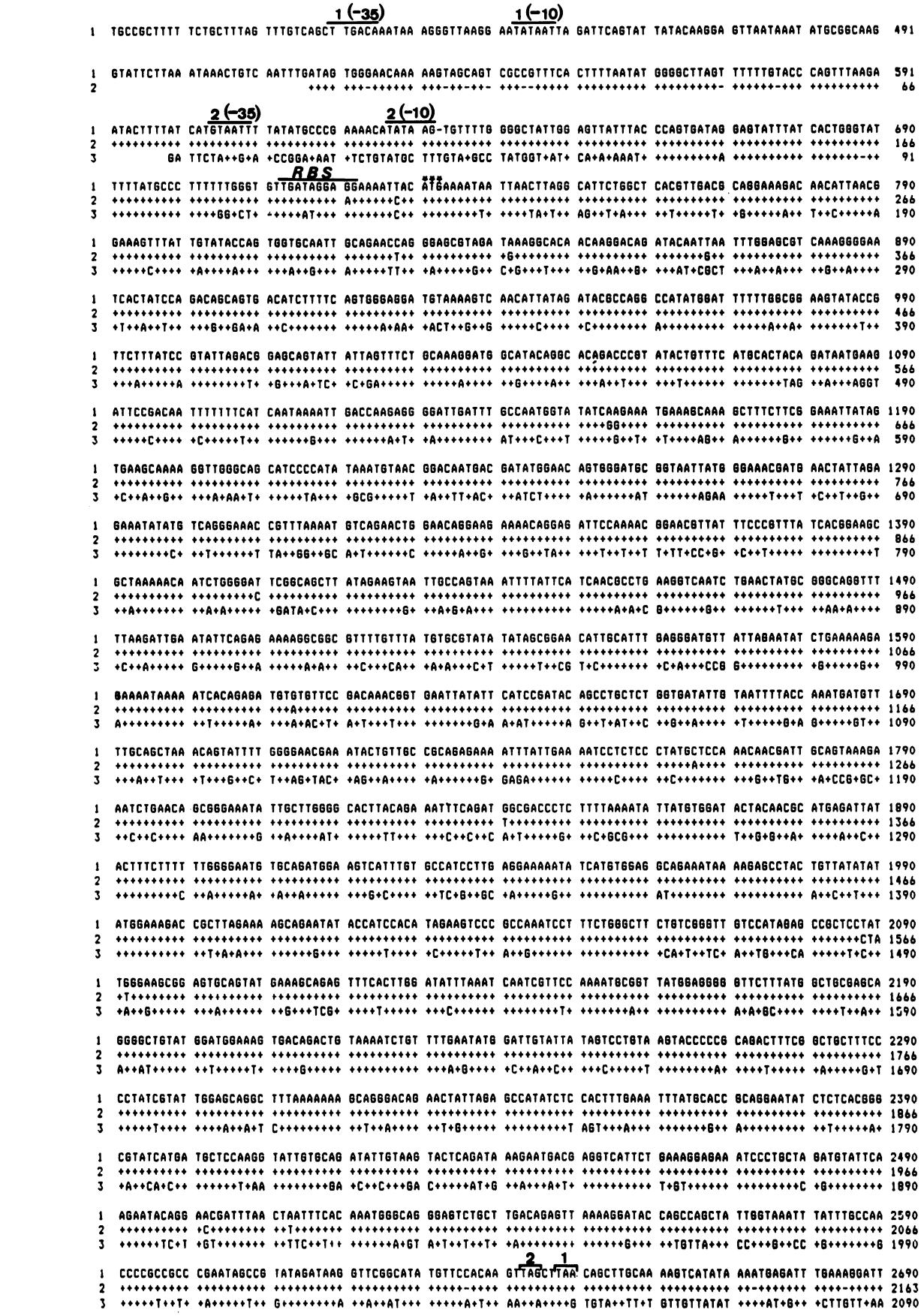

FIG. 1. Nucleotide sequences of *tetO* and *tetM*. 1, *tetO* from *C. coli* plasmid pIP1433; 2, *tetO* from *C. jejuni* plasmid pUA466; 3, *tetM* from Tn*1545* (based on information in references 38, 23, and 25, respectively). Identity with the DNA sequence of pIP1433 is indicated by +. Dashes represent gaps introduced to ensure maximum homology. The first base pair in the *C. coli tetO* sequence is defined as position 392. The presumed ribosomal binding site (RBS) for all three sequences is marked by an upper line. The start codon (ATG) is marked by ***. The putative −10 and −35 regions of *tetO* from *C. coli* and *C. jejuni* are as indicated. Similarly, positions of putative stop codons for the two *tetO* sequences are marked by brackets.

TABLE 2. Acquired antibiotic resistance in *Campylobacter* species

Antibiotic	MIC (μg/ml)	Gene	Location	Mechanism	Reference(s)
Tetracycline[a]	≤1,024	*tetO*[b]	Plasmid	Ribosomal protection	23, 28, 35, 38, 40–42
Minocycline	≤32				43, 45, 47, 50, 52
Kanamycin	>4,000	*aphA-3*[b]	Plasmid	3′-Aminoglycoside phosphotransferase	18, 20, 35
		aphA-1[c]	Chromosome	3′-Aminoglycoside phosphotransferase	20, 25, 30
Chloramphenicol	100	?	Plasmid	?	35
Streptomycin and spectinomycin	>4,096	*aadA*[c]	Chromosome	3″-9-Aminoglycoside nucleotidyltransferase	30; H. Pinto-Alphandary and P. Courvalin, unpublished data
Streptomycin	>1,024	*aadE*[b]	Chromosome	6-Aminoglycoside nucleotidyltransferase	20; Pinto-Alphandary and Courvalin, unpublished data
Erythromycin[d]	≥1,024	?	Chromosome	?	5, 40, 44
Ampicillin	≥128	?	Chromosome	β-Lactamase	9, 22, 43
Nalidixic acid	256	?	Chromosome	?	48

[a] The tetracycline MIC for most strains was 64 μg/ml.
[b] Likely to have been acquired from a gram-positive source.
[c] Likely to have been acquired from a gram-negative source.
[d] Accompanied by cross resistance to spiramycin (MIC, ≥256 μg/ml), tylosin (MIC, 512 μg/ml), and clindamycin (MIC, ≥8 μg/ml).

shown to have acquired the gene for a 3′-aminoglycoside phosphotransferase of type I, an enzyme specific for gram-negative bacteria (30). Since no plasmid DNA was detected in BM2196, this gene is believed to be located on the chromosome. Ouellette et al. (30) cloned and partially sequenced a 2.2-kilobase fragment of BM2196 DNA in *E. coli* and determined that its sequence was almost identical to that of Tn*903*, which was originally derived from *E. coli* (29). The insertion sequence IS*15*-Δ, which is widespread in gram-negative bacteria (19), was adjacent to the kanamycin resistance gene in BM2196, suggesting that *Campylobacter* species can also act as a recipient for genes from members of the family *Enterobacteriaceae* (30).

Conjugative and nonconjugative plasmids were shown to encode kanamycin resistance, as well as tetracycline and chloramphenicol resistance, in strains of *C. coli* from Japan. The kanamycin resistance determinants from three plasmids were cloned, and the determinants were expressed in *E. coli* (35).

Streptomycin and spectinomycin resistance. A few *Campylobacter* strains appear to be resistant to streptomycin and spectinomycin. For example, *C. coli* BM2509 and CLO strain BM2196 are resistant to both antibiotics (20, 30). CLO strain BM2196 is resistant to both antibiotics due to the production of 3″-9-aminoglycoside nucleotidyltransferase, whereas *C. coli* BM2509 is resistant to streptomycin due to the production of a 6-aminoglycoside nucleotidyltransferase (Table 2).

MACROLIDE, LINCOSAMIDE, AND STREPTOGRAMIN RESISTANCE

In Canada and the United Kingdom, 1% or fewer *Campylobacter* strains were resistant to erythromycin (2, 15, 42), although higher frequencies have been reported in other countries (26, 35, 49, 55, 56). Several studies have emphasized that erythromycin resistance is more likely to be associated with *C. coli* than *C. jejuni* (5, 15, 35, 49). Macrolide resistance appears to be widespread in *C. coli* strains from pigs in the United Kingdom (5). This common incidence may relate to the use of tylosin and virginiamycin as growth promoters in agriculture (5). Of untreated pigs or those treated with antibiotics other than tylosin, 55% contained *C. coli* strains resistant to tylosin, and the figure rose to 70% of pigs to which tylosin had been administered. Thus, it appears that erythromycin resistance is still infrequent in the majority of cases of *Campylobacter* gastroenteritis but that in the United Kingdom a large animal reservoir of macrolide-resistant *C. coli* exists. Moreover, in some communities such as Thailand (49), the frequency of erythromycin-resistant strains may constitute a treatment problem.

C. jejuni and *C. coli* strains which are erythromycin resistant are uniformly cross resistant to spiramycin, tylosin, and clindamycin (5, 17). All *C. jejuni* and *C. coli* strains appear to be intrinsically resistant to streptogramin B (Table 1). Burridge et al. attempted to divide erythromycin-resistant *Campylobacter* strains, most of which proved to be *C. coli*, into groups based on their patterns of susceptibility to macrolides, lincosamides, and streptogramins (5). However, susceptibility patterns appear to be less clear-cut than those noted in gram-positive cocci, which express the well-characterized macrolide-lincosamide-streptogramin resistance phenotype (57). Studies of erythromycin-resistant strains of *C. coli* with and without tetracycline resistance plasmids demonstrate that erythromycin resistance is unrelated to the presence of plasmid DNA (40, 44). Thus, macrolide resistance appears to be chromosomally determined.

BETA-LACTAM RESISTANCE

Ampicillin resistance was noted in approximately 15% of clinical isolates of *C. jejuni* (17) and is associated with β-lactamase production in these strains (9). Four distinct β-lactamases have been identified based on various criteria, including activity against a number of beta-lactams, relative rates of hydrolysis, immunological specificity, and isoelectric point. However, one type (A) was much more common than the others (22). Ampicillin resistance is not cotransferred with tetracycline resistance in strains of *C. jejuni* and *C. coli* resistant to both ampicillin and tetracycline that contain a single tetracycline resistance plasmid (43). Therefore, ampicillin resistance and the associated β-lactamase production in *Campylobacter* strains appear to be chromosomally encoded.

CONCLUSIONS AND DIRECTIONS FOR FUTURE STUDIES

The mechanisms of antibiotic resistance in *Campylobacter* species are summarized in Table 2. The *Campylobacter* genus, with its gram-negative cell wall but very low G+C content, has apparently been able to acquire resistance determinants from both gram-positive and gram-negative organisms, although the former seem to be the more common source. Genes such as *tetO*, *aphA-1*, and *aphA-3* have been able to become integrated into a plasmid, which was probably indigenous to *C. jejuni* and *C. coli*, or occasionally into the chromosome (28). *Campylobacter* and *Enterococcus* species occupy a common ecosystem, namely the human and animal gastrointestinal tracts. It is possible that DNA exchange occurs in this environment. Consistent with this idea, direct transfer of plasmid DNA from gram-positive cocci (*Enterococcus* species) to gram-negative bacteria (*E. coli*) was recently obtained under laboratory conditions (P. Trieu-Cuot, C. Carlier, and P. Courvalin, submitted for publication).

A glance at Table 2 shows that much work remains. Detailed studies of almost all of the resistance mechanisms in *Campylobacter* species are still needed. It is especially important to investigate the biochemical mechanism involved in resistance to macrolides, since erythromycin is the drug of choice for treatment of serious *Campylobacter* infections (17, 55). It will also be interesting to determine the biochemical basis of tetracycline resistance, which is common in *Campylobacter* species.

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