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Antimicrobial Resistance in *Campylobacter* spp.

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ABSTRACT *Campylobacter* is a major foodborne pathogen and has become increasingly resistant to clinically important antimicrobials. To cope with the selection pressure from antimicrobial use in both veterinary and human medicine, *Campylobacter* has developed multiple mechanisms for antibiotic resistance, including modification or mutation of antimicrobial targets, modification or inactivation of antibiotics, and reduced drug accumulation by drug efflux pumps. Some of these mechanisms confer resistance to a specific class of antimicrobials, while others give rise to multidrug resistance. Notably, new antibiotic resistance mechanisms continuously emerge in *Campylobacter*, and some examples include the recently discovered multidrug resistance genomic islands harboring multiple genes involved in the resistance to aminoglycosides and macrolides, a novel Cfr(C) conferring resistance to phenicols and other drugs, and a potent multidrug efflux pump CmeABC variant (RE-CmeABC) that shows a significantly enhanced function in multidrug resistance and is associated with exceedingly high-level resistance to fluoroquinolones. These newly emerged resistance mechanisms are horizontally transferable and greatly facilitate the adaptation of *Campylobacter* in the food-producing environments where antibiotics are frequently used. In this article, we will discuss how *Campylobacter* resists the action of various classes of antimicrobials, with an emphasis on newly discovered mechanisms.

INTRODUCTION

Campylobacter, a foodborne bacterial pathogen, is the leading cause of human gastroenteritis worldwide. According to data from the World Health Organization, the estimated incidence of gastroenteritis due to *Campylobacter* spp. in high-income countries is between 4.4 and 9.3 per 1,000 people (1). Most *Campylobacter* infections are mild and self-limiting and may not require antimicrobial therapy; however, antibiotic treatment is required for severe or prolonged infections. In clinical settings, fluoroquinolones and macrolides are the drugs of choice to treat campylobacteriosis (2–6), but in some cases, tetracyclines and gentamicin are used to treat systemic infection with *Campylobacter* (5, 6). In a report from the Centers for Disease Control and Prevention (CDC) on antibiotic resistance threats in the United States in 2013, drug-resistant *Campylobacter* was listed under "microorganisms with a threat level of serious" (http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf). The CDC indicated that almost 24% of *Campylobacter* strains tested were resistant to ciprofloxacin (fluoroquinolone) or azithromycin (macrolide), indicating that approximately 310,000 *Campylobacter* infections are caused by drug-resistant *Campylobacter* each year in the United States. Although contaminated undercooked poultry meat is a main source of infection for human campylobacteriosis (2, 7), ruminant *Campylobacter* is also a significant contributor for foodborne illnesses (8–15).

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As a foodborne pathogen transmitted via foodborne routes, *Campylobacter* is constantly exposed to antimicrobials used for food production. In dealing with antimicrobial selection, *Campylobacter* has evolved various mechanisms of resistance to antimicrobials. Some of the mechanisms confer resistance to a specific class of antimicrobials, while others may confer multidrug resistance. Previous publications have provided excellent reviews on antibiotic resistance in *Campylobacter* (5, 16–19). However, several new antibiotic resistance mechanisms have emerged in *Campylobacter* in recent years. Examples include the rRNA methylase Erm(B) (mediating macrolide resistance), a functionally enhanced multidrug efflux pump variant (RE-CmeABC), methylarsenite efflux permease ArsP conferring resistance to organoarsenicals, a novel *fosX*^{CC} gene conferring fosfomycin resistance, and the rRNA methyltransferase Cfr(C) mediating multidrug resistance. In this review, we will summarize the current state of antibiotic resistance in *Campylobacter*, with an emphasis on the newly emerged mechanisms.

RESISTANCE TO FLUOROQUINOLONES

The fluoroquinolones (e.g., ciprofloxacin, enrofloxacin, etc.) are a family of synthetic broad-spectrum antibacterial agents that are active against a wide range of Gram-positive and Gram-negative organisms (20, 21). To date, they are one of the drugs of choice to treat campylobacteriosis in humans as well as other bacterial diseases in both animals and humans (21–23). Fluoroquinolones target two essential enzymes, DNA gyrase and topoisomerase IV, and impair DNA replication (21, 24). Generally, mutations in the genes encoding the subunits of DNA gyrase (GyrA and GyrB), topoisomerase IV (ParC and ParE), or both are responsible for the resistance of bacteria to fluoroquinolones (25, 26). In *Campylobacter*, the main resistance mechanism to fluoroquinolones is mediated by point mutations in the quinolone resistance-determining region of GyrA (4, 5). To date, mutations in GyrB have not been associated with fluoroquinolone resistance in *Campylobacter* (27–29). The absence of genes encoding ParC and ParE implies that they are not involved in fluoroquinolone action and resistance in *Campylobacter* (27–32). Notably, a single point mutation in the quinolone resistance-determining region of *gyrA* is sufficient to substantially reduce the susceptibility of *Campylobacter* to fluoroquinolone antimicrobials (5, 30, 33, 34). Multiple resistance-associated mutations, including T86I, T86K, A70T, and D90N, have been reported in *Campylobacter* (4, 5, 33, 35). The C257T change in the *gyrA* gene, which leads to the T86I substitution in gyrase, is the most frequently observed mutation conferring resistance to fluoroquinolones in *Campylobacter* (4, 5, 36). In addition to mutations in GyrA, the functional multidrug efflux pump, CmeABC, is also required for fluoroquinolone resistance in *Campylobacter*. Inactivation of *cmeABC* in fluoroquinolone-resistant mutants (carrying specific GyrA mutations) made the resistant mutants susceptible to fluoroquinolones (30). Until now, mutations in GyrA together with CmeABC have been the only identified mechanisms of fluoroquinolone resistance in *Campylobacter*. Plasmid-mediated quinolone-resistance determinants, such as *qnr*, *aac(6')-Ib-cr*, and *qepA*, have not been reported in *Campylobacter*.

RESISTANCE TO MACROLIDES

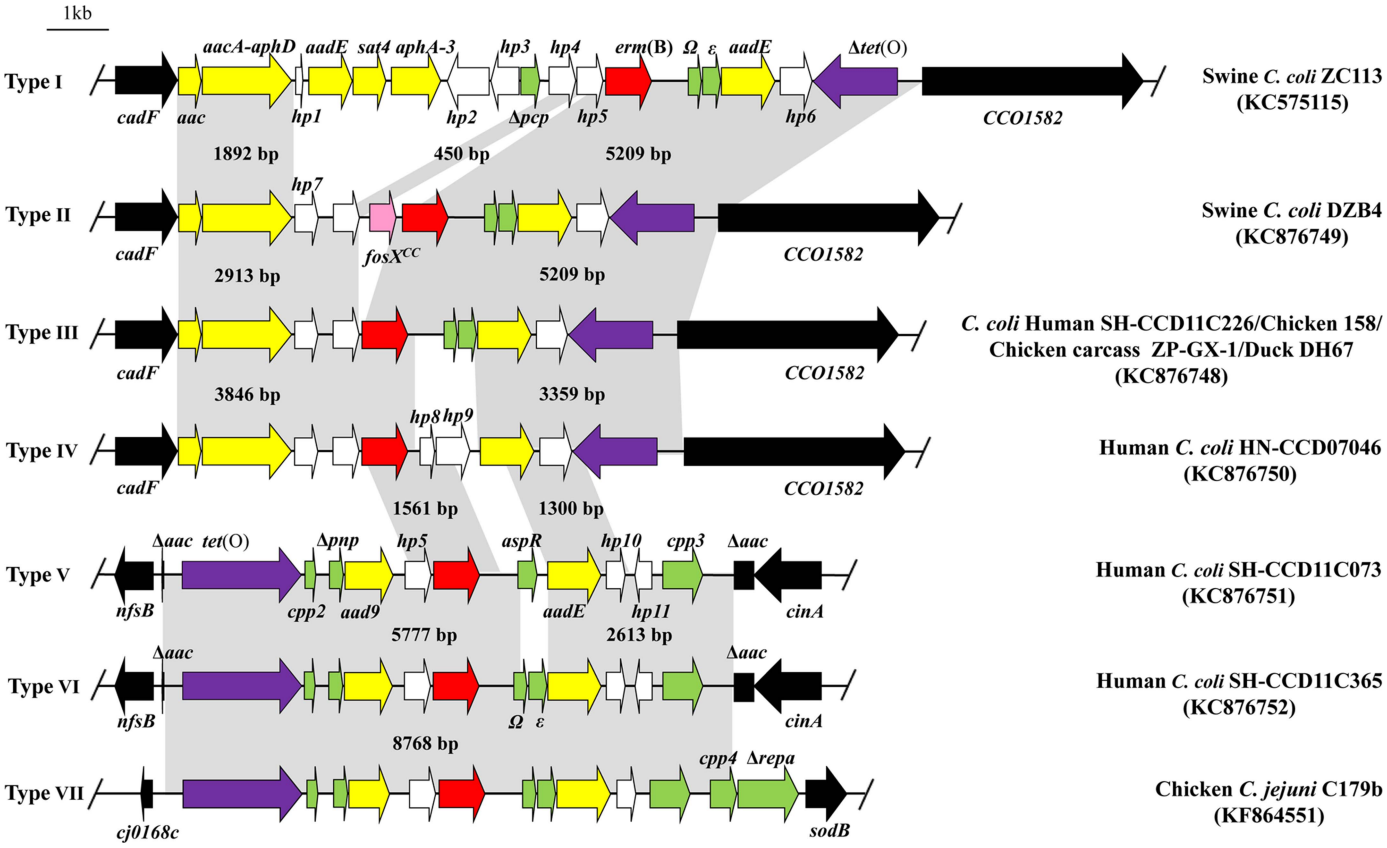
The macrolide antibiotics (azithromycin, clarithromycin, erythromycin, telithromycin, etc.) are a class of drugs for the treatment of gastric diseases caused by *Helicobacter pylori* and *Campylobacter* and for respiratory tract infections in humans (37). Antibiotics in this class, including erythromycin, tylosin, spiramycin, tilmicosin, and roxithromycin, are also approved for growth promotion and therapeutic purposes in animals (38). Macrolides target the 50S subunit of the bacterial ribosome and inhibit protein synthesis through interference with the peptide translocation step (39, 40). Generally, bacterial resistance to macrolides is mediated by three mechanisms: enzymatic inactivation of macrolides, modification or point mutations in the target, and enhanced drug efflux (5, 41). In *Campylobacter*, modification of the ribosomal target, leading to macrolide resistance, can occur either by enzyme-mediated methylation or by point mutation in the 23S rRNA and/or ribosomal proteins L4 and L22 (4, 5, 41). Although an early report suggested the presence of rRNA methylation genes in *Campylobacter rectus* isolates based on the result of Southern hybridization (42), an rRNA methylating enzyme was not formally identified until recently, when Erm(B) was identified in both *Campylobacter jejuni* and *Campylobacter coli* from various sources, including swine, chicken, ducks, and humans (43–45). The *erm*(B) gene was either located in the chromosomal DNA or carried by a plasmid (43). This gene alone is able to confer high-level resistance to macrolides (44). It is worth noting that the *erm*(B) gene is associated with multidrug resistance genomic islands (MDRGIs), which include several resistance genes [*aacA-aphD*, *sat4*, *aphA-3*, *fosX*^{CC}, *aad9*, and *tet*(O)] and mediate resis-

tance to multiple classes of antibiotics (43, 44) (Fig. 1). Generally, MDRGIs are located in the region between *cadF* and *CCO1582*, *nfsB* and *cinA*, or *cj0168c* and *sodB* (43–45) and are transferrable among different *Campylobacter* spp. by natural transformation under laboratory conditions (43).

Point mutations in domain V of the 23S rRNA have been recognized as the most common mechanism for macrolide resistance in *Campylobacter* (4, 5, 41, 46). These point mutations occur at positions 2074 and 2075 of the 23S rRNA in *Campylobacter*, which correspond to positions 2058 and 2059, respectively, in *Escherichia coli*. Among the reported resistance-associated mutations, the A2074C, A2074G, and A2075G mutations confer high-level resistance to macrolide antibiotics (erythromycin MIC >128 μg/ml) in *Campylobacter* (46–50), with A2075G being the predominant mutation in clinical and field isolates (4, 5, 41, 46). *Campylobacter* contains three copies of 23S rRNA genes (51), and usually, macrolide resistance-associated mutations occur in all three copies for most *Campylobacter* isolates with high-level resistance (47, 48, 52).

In addition to target modification, active efflux also contributes to macrolide resistance in *Campylobacter* (48–50, 53–56). The CmeABC efflux system functions synergistically with target mutations, and inactivation of CmeABC significantly reduces the resistance to macrolide antibiotics in isolates with high-, intermediate-, or low-level macrolide resistance (19). Additionally, the synergy between the CmeABC efflux pump and

FIGURE 1 Chromosomal organization and comparison of seven types (I to VII) of MDRGIs containing the *erm*(B) gene (modified from references 43–45). *erm*(B) is in red, aminoglycoside resistance genes are in yellow, the streptothricin resistance gene (*sat4*) is in blue, the tetracycline resistance gene [*tet*(O)] is in purple, genes with predicted functions are in green, and genes coding hypothetical proteins are in white. The *tet*(O) gene is intact in types V and VI but is truncated in other types. The border genes of the MDRGIs are depicted by black box arrows. The gray shading indicates regions sharing more than 98% DNA identity. A representative strain for each type of MDRGI is indicated on the right side of the panel.



mutations in the ribosomal proteins L4 (G74D) and L22 (inserted at position 86 or 98) also confers macrolide resistance in *Campylobacter* (50, 53).

RESISTANCE TO TETRACYCLINES

Tetracyclines, discovered in the 1940s, are an important class of antibiotics that are widely used in both human and animal medicine. Tetracyclines have broad-spectrum activity against Gram-positive and Gram-negative bacteria, as well as chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites (57). It is well established that tetracyclines inhibit bacterial protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site (58, 59). Because of the long history and widespread use of tetracyclines, a number of resistance determinants to this class of drugs have been observed in a variety of bacteria (60, 61). Generally, the resistance to tetracyclines is mediated by one of four mechanisms: efflux pumps, chemical modification of tetracyclines, ribosomal protection proteins, and mutations in rRNA (60).

To date, resistance to tetracyclines in *Campylobacter* is conferred by the ribosomal protection protein Tet(O) and efflux pumps (CmeABC and CmeG). Tet(O) belongs to one of the characterized ribosomal protection proteins (61), several of which are paralogs of the translational GTPase EF-G and actively remove tetracycline from the ribosome in a GTP hydrolysis-dependent fashion (62–64). The well-documented action mode is that Tet(O) recognizes and binds to an open A site on the bacterial ribosome and then induces a conformational change that results in the sequential release of the bound tetracycline molecule (60, 64). This conformational change is able to persist and allows the A site to function in protein elongation (60, 64). A recent study indicated that several critical residues located in the three loops of Tet(O) disrupt the binding of tetracycline to the ribosome complex (59). The *tet*(*O*) gene, which is widely present in *C. jejuni* and *C. coli* (65, 66), can be located either in the chromosomal DNA or on a plasmid (e.g., pTet and pCC31) (67–69). Based on the G-C content, sequence homology, codon usage, and hybridization analysis, it appears that the *Campylobacter tet*(*O*) gene was probably acquired from a Gram-positive origin by horizontal gene transfer (66, 68). The CmeABC and CmeG multidrug efflux pumps contribute to both intrinsic and acquired resistance to tetracycline in *Campylobacter* (55, 70–72). CmeABC functions synergistically with Tet(O) to confer high-level resistance to tetracycline (70). Inactivation of either CmeABC or CmeG increases the susceptibility of *Campylobacter* to tetracyclines (70, 72).

RESISTANCE TO AMINOGLYCOSIDES

Aminoglycosides are bactericidal antibiotics that bind to ribosomes and inhibit protein synthesis (73). They are structurally characterized by an aminocyclitol ring bound to one or more amino sugars by pseudoglycosidic bonds (74–76). This class of antimicrobials is generally considered to have broad-spectrum bacteriocidal activity and is clinically used to treat acute and systemic *Campylobacter* infections (77, 78), although they have limited activity in anaerobic environment. On the basis of the *in vitro* susceptibility of many *Campylobacter* strains to aminoglycosides (79, 80), oxygen levels in the microaerophilic environments preferred by *Campylobacter* are sufficient to allow the transport of compounds into the intracellular environment (18). A total of five mechanisms of aminoglycoside resistance in bacteria have been described (74, 76, 81): (i) reduced accumulation of the drug in the intracellular environment, conferred by a multidrug efflux pump that transports the drug back into the extracellular environment or due to decreased permeability of the bacterial cellular membrane to the drug (74), (ii) methylation of 16S rRNA in sites that interfere with drug binding (75, 82), (iii) mutations in the binding sites of rRNA, especially in *Mycobacterium* spp. with a single copy of the ribosomal operon (75), (iv) active swarming, a nonspecific mechanism in *P. aeruginosa* cells that exhibits adaptive antibiotic resistance against several antibiotics, including gentamicin (83), and (v) enzymatic modification at the -OH or -NH_2 groups of the 2-deoxystreptamine nucleus or sugar moieties of the antibiotic, which is considered the most important mechanism (81). Among the known mechanisms of aminoglycoside resistance, modification of the aminoglycoside structure by enzymes such as aminoglycoside acetyltransferases, aminoglycoside phosphotransferases, and aminoglycoside nucleotidyltransferases is the most significant and prevalent in several bacterial species, including *Campylobacter* spp. (16, 78, 84). In *Campylobacter*, each of the above-mentioned aminoglycoside-modifying enzymes has been detected.

Aminoglycoside phosphotransferases constitute the majority of aminoglycoside-modifying enzymes identified in *Campylobacter* spp. and are responsible for phosphorylation of the 3′ hydroxyl group of aminoglycosides. They also mediate kanamycin and neomycin resistance. Aminoglycoside phosphotransferases are

divided into eight groups according to the resistance of additional specific aminoglycosides (I to VIII) (76, 81). To date, only types I, III, IV, and VII, which mainly mediate kanamycin resistance, have been detected in *Campylobacter*. The *aphA-1* gene, also known as *aph (3')-Ia*, was identified adjacent to the insertion sequence IS*15*-delta commonly found in Gram-negative bacteria, suggesting that it may have originated from the *Enterobacteriaceae* family of organisms (85). Sequence analysis showed identical homology to the kanamycin resistance gene of the Tn*903* transposon in *E. coli* (85). The *aphA-1* gene is also commonly used as a resistance marker gene in cloning vehicles (81). Different from *aphA-1*, the *aphA-3* gene is commonly detected in Gram-positive bacteria, such as *Staphylococcus*, and has been identified in clinical *Campylobacter* isolates. It is located on plasmids or chromosomes (80, 84). Some plasmids in *C. jejuni* harbor the *aphA-3* gene as part of the resistance cluster that includes the *aadE* and *sat4* genes, which originated from Gram-positive bacteria (86). Subsequently, the *aadE-sat4-aphA-3* cluster together with additional aminoglycoside resistance genes, including *aacA-aphD* and *aac*, was identified in a genomic island on a chromosome of *C. coli* (87). Clonal expansion and horizontal transmission have been involved in dissemination of this novel aminoglycoside resistance genomic island (87). The identification of the *aphA-3* gene in *Campylobacter* provides another piece of evidence suggesting the transfer of antibiotic resistance genes from Gram-positive bacteria to Gram-negative bacteria. The plasmid-encoded *aphA-7* gene, mediating kanamycin resistance, may be an indigenous gene of *Campylobacter* based on its G+C content at 32.8%, which is similar to that of the *Campylobacter* genome (88). The *aphA-7* gene was found on small plasmids of 9.5 and 11.5 kb in *C. jejuni* (89), and the presence of this gene in *C. coli* has also been documented (87).

The *aacA4* gene encodes aminoglycoside *6'-N*-acetyltransferase, AAC(6')-Ib7, conferring resistance to tobramycin, kanamycin, and neomycin (90). Additionally, the *aacA4* gene was associated with class 1 integron and found in *C. jejuni* isolated from the water lines of a broiler chicken house environment (91). The plasmid-borne gene *aac(6')-Ie/aph(2")-Ia* (also named *aacA/aphD* and encoding a bifunctional enzyme) was described in a clinical isolate of *C. jejuni* from a U.S. soldier deployed to Thailand. It was found to encode phosphotransferase activity and was named *aph(2")-If* (92). Gentamicin resistance, conferred by *aacA/aphD* that is associated with an aminoglycoside resistance genomic island, was reported in *C. coli* from China, and clonal expansion may be involved in dissemination of this entire resistance island (87). Subsequently, the gentamicin resistance-related gene *aph(2")-Ig* (encoding a phosphotransferase) was detected in a *C. coli* isolate from retail chicken meat (93). Recently, several variants of gentamicin resistance genes [*aph(2")-Ib*, *Ic*, *If1*, *If3*, *Ih*, and *aac(6')-Ie/aph(2")-If2*] were identified in *Campylobacter* isolates from humans and retail meats in the United States. The same resistance profile and similar pulsed-field gel electrophoresis patterns shared by isolates from human and retail chicken indicated that retail chicken is a potential source for gentamicin-resistant *C. coli* that causes infections in humans (94). The increasing prevalence and emergence of novel genes of gentamicin resistance has led to an increasing number of studies on gentamicin resistance mechanisms.

The *sat4* gene encoding a streptothricin acetyltransferase is present either as a single gene or in the *aadE-sat4-aphA-3* cluster in streptothricin-resistant *Campylobacter* spp. (87, 95). The aminoglycoside 3-adenyltransferase gene (*aadA*) confers resistance to streptomycin and spectinomycin, while the aminoglycoside 6-adenyltransferase gene (*aadE*) only confers resistance to streptomycin. The *aadA* gene was identified in the multidrug resistance plasmid pCG8245, which contains various aminoglycoside resistance genes in *C. jejuni* (95). In contrast, *aadE* was commonly associated with the *aadE-sat4-aphA-3* gene cluster that was detected on the plasmid or chromosome of *C. jejuni* and *C. coli* (87, 94, 95). The 286-amino-acid streptomycin resistance protein, ANT(6)-Ib, encoded by *ant(6)-Ib*, belongs to a family of aminoglycoside nucleotidyltransferases and was identified in *Campylobacter fetus* subsp. *fetus* (96). Recently, a novel streptomycin resistance gene was described, and its widespread presence among *C. coli* isolates may partly account for the prevalence of streptomycin resistance in *C. coli* (97).

RESISTANCE TO β-LACTAMS

β-Lactam antibiotics are a class of broad-spectrum antibiotics that inhibit bacterial cell wall biosynthesis. This class of antibiotic agents contains a β-lactam ring in their molecular structures. β-lactam antibiotics are the most widely used antibiotics and account for more than half of the total antibiotic market worldwide (98). For the past decades, the prevalence of β-lactam-resistant bacteria has greatly increased (99, 100). To date, three mechanisms contributing to β-lactam resistance in *Campylobacter* have been identified: enzymatic inactivation, reduced uptake, and efflux pump. A previous study

showed that β-lactamase-positive *Campylobacter* were more resistant than β-lactamase-negative *Campylobacter* to amoxicillin, ampicillin, and ticarcillin (101). OXA-61 (Cj0299) is the only identified and characterized β-lactamase in *C. jejuni* (102–104). Notably, almost half of OXA-61-carrying *Campylobacter* are susceptible to ampicillin, suggesting that the expression level of OXA-61 modulates the resistance phenotype (102). Indeed, a recent study indicated that a G → T transversion in the OXA-61 promoter enhances the expression of β-lactamase and is linked to high-level β-lactam resistance in *C. jejuni* isolates (104). The porins of *C. jejuni* and *C. coli* form a relatively small cation-selective pore that may contribute to intrinsic resistance to antimicrobial agents. These cation-selective pores in *C. jejuni* and *C. coli* are able to exclude most β-lactams with a molecular weight greater than 360 or that are anionic (105). The CmeABC and CmeDEF efflux pumps may also contribute to β-lactam resistance. Inactivation of these efflux pumps results in increased susceptibility to ampicillin (70, 106, 107).

RESISTANCE TO PHENICOLS

Nonfluorinated (chloramphenicol) or fluorinated phenicols (florfenicol) are highly effective against a wide variety of Gram-positive and Gram-negative bacteria. Phenicols were once widely applied in both human and veterinary practices for the prevention and treatment of many bacterial infections. Resistance to phenicols in *Campylobacter* is mediated by enzymatic inactivation via chloramphenicol acetyltransferases, target site mutations in 23S rRNA, target site modification in 23S rRNA via the rRNA methyltransferase Cfr(C), or enhanced extrusion by efflux pumps. Acetylation of the drug by chloramphenicol acetyltransferases (encoded by *cat*) confers resistance to chloramphenicol but not to florfenicol (108). The G2073A mutation in the 23S rRNA gene of *Campylobacter* (corresponding to position 2057 in the 23S rRNA gene of *E. coli*) is associated with chloramphenicol and florfenicol resistance (109). The first *cfr* gene was discovered in a bovine *Staphylococcus sciuri* isolate in 2000 (110). It encodes an rRNA methyltransferase that methylates the adenine at position 2503 in the 23S rRNA, resulting in resistance to five chemically unrelated antimicrobial classes: phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A (known as the PhLOPSA phenotype) (111). Since its discovery, the *cfr* gene has been detected in a variety of Gram-positive and Gram-negative bacteria (110, 112–116). A recent study identified a novel plasmid-borne *cfr*-like gene, designated *cfr*(C), in multidrug-resistant *C. coli* isolates of cattle origin. Similar to *cfr* and *cfr*(B), the *cfr*(C) gene was found to confer transferable resistance to phenicols and oxazolidinones (linezolid) as well as lincosamides and pleuromutilins (*Campylobacter* is naturally resistant to streptogramin) in both *C. jejuni and C. coli* (117). Additionally, the recently identified multidrug efflux pump variant RE-CmeABC alone can confer elevated resistance to phenicols (see details in "CmeABC" below) (118).

RESISTANCE TO FOSFOMYCIN

Fosfomycin is a broad-spectrum antibiotic with bactericidal activity against both Gram-positive and Gram-negative bacteria (119). Fosfomycin inhibits bacterial cell wall synthesis by inactivating the essential enzyme for the catalysis of bacterial peptidoglycan biosynthesis (120). *Campylobacter* resistance to fosfomycin is rare, and the resistance rate has remained low (121, 122). To date, the only mechanism of fosfomycin resistance identified in *Campylobacter* is the $fosX^{CC}$ gene, which encodes a protein that shares 63.9% identity to fosfomycin resistance determinant FosX, found in *Listeria monocytogenes*. FosX inactivates fosfomycin by catalyzing the addition of groups to its epoxide (120, 123). The $fosX^{CC}$ gene is contained in the MDRGI in *C. coli*, and is transferrable to *C. jejuni* by natural transformation (43, 123).

RESISTANCE TO ARSENICS

Arsenic compounds have been commonly used in the poultry industry for promoting growth and controlling diseases. Due to their potential risk to human health and the environment, they were recently withdrawn from poultry use in the United States. However, the organic form of arsenic, roxarsone, is still used as a feed additive in other countries. To survive in the poultry production environment, *Campylobacter* has developed ways to resist the action of arsenic compounds. *Campylobacter* isolates from conventional poultry products showed significantly higher levels of arsenic resistance than those from antimicrobial-free poultry products (124). Recently, several arsenic detoxification mechanisms have been identified in *C. jejuni*, including arsenate reductase ArsC, arsenite efflux transporters Acr3 and ArsB, and methylarsenite efflux permease ArsP (125–128). The two arsenite transporters (Acr3 and ArsB) belong to different families (129) and extrude toxic AS(III) out of bacterial cells. The ArsB family has been found only in

bacteria and archaea, while the Acr3 family exists in prokaryotes and fungi, as well as in plant genomes (129–132). As an arsenate reductase, ArsC converts As(V) to AS(III) in the cytoplasm (130, 133), which is subsequently extruded by Acr3 or ArsB transporters (125, 130). Acr3 in *C. jejuni* consists of 347 amino acids and contains 10 predicted transmembrane helices. The presence of the *acr3*-containing operon is significantly associated with elevated resistance to arsenite and arsenate in *Campylobacter*. Furthermore, inactivation of *acr3* leads to reductions in the MICs of both arsenite and arsenate. Acr3 is not involved in the resistance to other classes of antibiotics in *Campylobacter* (125). ArsB in *C. jejuni* consists of 428 amino acids and contains 11 probable transmembrane helices. The amino acid sequence of ArsB is homologous to ArsB in *Shewanella* sp. ANA-3 (134), *S. aureus* (135), *E. coli* (136–138), and *Acidithiobacillus caldus* (139). Inactivation of *arsB* resulted in increased susceptibility of *Campylobacter* to both arsenite and arsenate, but not to other heavy metals and antibiotics (126). Interestingly, analysis of various *Campylobacter* isolates of different animal origins for the distribution of *arsB* and *acr3* genes indicated that all of the tested strains contained at least one of the two genes (126). ArsP in *C. jejuni* consists of 315 amino acids and contains 8 probable transmembrane helices. *arsP* is the first gene in the four-gene *ars* operon, which contains *arsP*, *arsR*, *arsC*, and *acr3*. The presence of ArsP is associated with elevated MIC of roxarsone. Inactivation of *arsP* results in reduced resistance to several organic arsenics including arsanilic acid, nitarsone, and roxarsone (127). It was also revealed that ArsP is an efflux permease for trivalent organoarsenicals including methylarsenite and trivalent forms of aromatic arsenicals (128). ArsP does not play a role in the resistance to inorganic arsenic.

MULTIDRUG EFFLUX PUMPS

The antibiotic efflux transporters play an essential role in the intrinsic and acquired resistance to structurally diverse antimicrobials. In *Campylobacter*, several multidrug efflux pumps (CmeABC, CmeDEF, and CmeG) have been functionally characterized for their contributions to antimicrobial resistance.

CmeABC

CmeABC is the predominant antibiotic efflux system in *C. jejuni* and belongs to the resistance-nodulation-cell division superfamily of multidrug efflux transporters. This efflux system is encoded by a three-gene operon comprising *cmeA*, *cmeB*, and *cmeC* (70) and consists of a membrane fusion protein (CmeA), an inner membrane transporter (CmeB), and an outer membrane protein (CmeC) (70). CmeABC extrudes toxic compounds and contributes to *Campylobacter* resistance to structurally diverse antimicrobials (70, 71). It should be noted that every component of the CmeABC system is required for its full function as an efflux pump. As mentioned above, CmeABC functions synergistically with other mechanisms in conferring high-level resistance to antibiotics (30, 48, 50, 53, 55, 70, 140, 141). These examples illustrate the important role of CmeABC in conferring resistance to clinically important antibiotics such as macrolide and fluoroquinolone. Interestingly, CmeABC also contributes to resistance to bacteriocins, antimicrobial peptides produced by bacteria (142, 143). As the predominant efflux system in *Campylobacter*, *cmeABC* is conserved among different *Campylobacter* spp. and is widely distributed in *Campylobacter* isolates (144). This efflux system has been functionally characterized in *C. jejuni* (70, 71, 145), *C. coli* (33, 141), *Campylobacter lari*, *C. fetus*, and *Campylobacter hyointestinals* (144) and has been shown to contribute to antibiotic resistance in all examined species. In general, the sequences of *cmeABC* are highly conserved within a species, but significant sequence polymorphisms are observed in the *cmeABC* genes among different *Campylobacter* spp. (144, 146–148). The expression of *cmeABC* is modulated by a transcriptional regulator called CmeR (149) that functions as a repressor for *cmeABC*. The *cmeABC* operon is inducible by bile salts and salicylate (150, 151), and the induction by bile is due to conformational changes in the DNA binding motif of CmeR, releasing its repression on the *cmeABC* promoter (152–154).

Notably, a potent variant of CmeABC, named RE-CmeABC, has recently emerged in *C. jejuni* (118). This variant CmeABC is much more powerful in conferring multidrug resistance and is especially potent to florfenicol and chloramphenicol. The RE-CmeABC operon has a unique CmeB sequence that shows only ~80% amino acid sequence identity to CmeB in other *C. jejuni* strains. The sequence variation in CmeB contributed mostly to the enhanced function of RE-CmeABC. In addition to the enhanced resistance to various antibiotics, RE-CmeABC also promotes the emergence of fluoroquinolone-resistant mutants under selection pressure. In the presence of GyrA mutations, RE-CmeABC confers exceedingly high-level resistance (ciprofloxacin MIC $\geq$ 128 μg/ml) to fluoroquinolone (118). Additionally, Re-CmeABC is increasingly prevalent in *C. jejuni*

isolates in China, suggesting that it facilitates the adaptation of *Campylobacter* to antibiotic selection pressure.

CmeDEF

CmeDEF is another resistance-nodulation-cell division-type efflux pump identified in *C. jejuni*. CmeD (Cj1031) is an outer membrane protein of 424 amino acids which shares low but significant sequence homology to HefA of *H. pylori* and TolC of *E. coli*, the outer membrane components of antibiotic efflux systems (1). CmeE (Cj1032) is a membrane fusion protein composed of 246 amino acids, which shares significant homology with the membrane fusion protein of HefB in *H. pylori*. CmeF is an inner membrane transporter and is predicted to contain a 12-transmembrane helical domain structure. The sequence of CmeF (1,005 amino acids) shares certain homology with many other resistance-nodulation-cell division-type efflux transporters such as HefC of *H. pylori* and AcrB, AcrD, and AcrF of *E. coli* (1, 155). The low sequence identity between CmeDEF and CmeABC suggests that these two efflux systems may have different functions and abilities to extrude antibiotics and other toxic compounds. Several studies have determined the contribution of *cmeDEF* to antimicrobial resistance. Pumbwe et al. (106) reported that the insertional mutation of *cmeF* in *Campylobacter* resulted in increased susceptibility to structurally unrelated antimicrobial compounds, including ampicillin, ethidium bromide, acridine orange, SDS, sodium deoxycholate, bile, detrimide, and triclosan. Akiba et al. (107) also reported that the *cmeF* mutant of *C. jejuni* NCTC 11168 showed a 2-fold decrease in resistance to ampicillin and ethidium bromide, but the authors did not observe any changes in the susceptibility to other tested antimicrobials, including bile salts. Another study, by Ge et al. (33), found that inactivation of *cmeF* in *C. jejuni* 81-176 had no effects on susceptibility to ciprofloxaxin, erythromycin, tetracycline, and chloramphenicol. In general, CmeDEF appears to play a modest role in antibiotic resistance in a strain-dependent manner, and its natural function in *Campylobacter* physiology remains unknown.

CmeG

CmeG (Cj1375) is one of the predicted MFS (major facilitator superfamily) transporters and is present in all the *C. jejuni* strains sequenced to date. Analysis of its amino acid sequence revealed that CmeG is a homolog of Bmr of *B. subtilis* and NorA of *S. aureus* (72), both of which contribute to multidrug resistance in bacteria (72). In addition, CmeG is predicated to be an inner membrane protein and possesses 12 transmembrane domains. Inactivation of *cmeG* significantly reduced resistance to various classes of antimicrobials, including ciprofloxacin, erythromycin, tetracycline, gentamicin, ethidium bromide, and cholic acid, while overexpression of *cmeG* enhanced the resistance to various fluoroquinolone antimicrobials, including ciprofloxacin, enrofloxacin, norfloxacin, and moxifloxacin but not to the other antibiotics tested in the study (72). Accumulation assays demonstrated that the *cmeG* mutant accumulated more ethidium bromide and ciprofloxacin than the wild-type strain (72). These results indicate that CmeG is a functional efflux transporter in *Campylobacter*. The expression of *cmeG* appears to be regulated by the Fur protein and iron concentrations, because inactivation of Fur or iron depletion resulted in the upregulation of *cmeG* (156–158). The detailed mechanism underlying *cmeG* regulation remains to be determined.

SUMMARY AND PERSPECTIVES

Campylobacter is a major foodborne pathogen, and its resistance to clinically important antibiotics is increasingly prevalent. Particularly, rising fluoroquinolone resistance in *Campylobacter* has been reported in many countries (6), limiting its usage for the treatment of campylobacteriosis. *Campylobacter* is highly mutable to fluoroquinolone treatment, and acquisition of resistance does not incur a fitness cost, contributing to the rapid development and persistence of fluoroquinolone-resistant *Campylobacter* (159). In contrast, development of macrolide resistance in *Campylobacter* occurs slowly and incurs a significant fitness cost in the absence of selection pressure, contributing to the overall low prevalence of macrolide-resistant *Campylobacter*. However, a horizontally transferable *erm*(B) has recently emerged in *Campylobacter* (43–45), which may significantly influence the epidemiology of macrolide-resistant *Campylobacter*. This possibility warrants enhanced efforts to monitor its further spread in *Campylobacter* isolates. Importantly, several new multidrug resistance mechanisms, including MDRGIs, Cfr(C), and RE-CmeABC, have been detected in *Campylobacter*, which greatly increases its ability to cope with selection pressure from multiple antibiotics. These examples illustrate the extraordinary ability of *Campylobacter* to acquire new mechanisms for adaptation to antimicrobial usage. With that said, it is likely that new antibiotic resistance mechanisms will continue to emerge in *Campylobacter*. Thus, innovative strategies are needed to curb the rise and spread of antibiotic-resistant *Campylobacter*.

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