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Resistance mechanisms in *Campylobacter jejuni*

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Abbreviations: FQ, fluoroquinolone; LOS, lipooligosaccharide; LPS, lipopolysaccharide; MIC, minimum inhibitory concentration; MOMP, major outer membrane protein; NARMS, National Antimicrobial Resistance Monitoring System

Campylobacter jejuni is a major cause of food-borne gastroenteritis worldwide. While mortality is low, morbidity imparted by post-infectious sequelae such as Guillain-Barré syndrome, Reiter syndrome/reactive arthritis and irritable bowel syndrome is significant. In addition, the economic cost is high due to lost productivity. Food animals, particularly poultry, are the main reservoirs of *C. jejuni*. The over-use of antibiotics in the human population and in animal husbandry has led to an increase in antibiotic-resistant infections, particularly with fluoroquinolones. This is problematic because *C. jejuni* gastroenteritis is clinically indistinguishable from that caused by other bacterial pathogens, and such illnesses are usually treated empirically with fluoroquinolones. Since *C. jejuni* is naturally transformable, acquisition of additional genes imparting antibiotic resistance is likely. Therefore, an understanding of the antibiotic resistance mechanisms in *C. jejuni* is needed to provide proper therapy both to the veterinary and human populations.

Introduction

Campylobacter jejuni is a small, Gram-negative, curved rod and is the most common cause of bacteria-mediated diarrheal disease globally.[1] For the first time in 2005, campylobacteriosis exceeded salmonellosis as the most commonly reported zoonosis in the European Union, and the number of cases continues to increase.[2,3] Campylobacteriosis is also the most common notifiable disease in New Zealand and Australia.[4,5] There is little human-to-human transmission, probably due to its microaerophilic nature. Instead, it is primarily a zoonosis because it is a commensal of food animals, particularly poultry, which serves as the main reservoir for human infection.[6] Meat becomes contaminated during the slaughtering process, and *C. jejuni* survives in the crevices of animal carcasses where oxygen tension is low.[7] Although implementation of Hazard Analysis and Critical Control Points (HACCP) in the food industry in the mid 1990s markedly reduced the rate of Campylobacter infections,[8] *C. jejuni* remains second only to Salmonella as the cause of food-borne disease in the United States.[9] However, other modes of transmission, such as drinking contaminated water, are also important means of disease spread.[10]

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The indiscriminate use of antibiotics in the human population as well as the use of antibiotics in animal husbandry, for treatment, growth promotion and off-label uses, has led to an increase in antibiotic-resistant Campylobacter infections, particularly with regard to fluoroquinolones (FQ).[9,11-16] There is evidence to support the hypothesis that resistance patterns in poultry may predict human resistance patterns; this has been most clearly shown with FQ.[9,11-20] Although not all cases of Campylobacter infection require treatment,[21] many cases of acute diarrhea are empirically treated with FQ, which likely further contributes to the emergence of FQ resistance.

The use of veterinary antibiotics varies greatly throughout the world. Of greatest concern are situations in which antibiotics can be used for growth-promotion purposes (as opposed to therapeutic) because the low levels of antibiotics used in this setting and over long periods of time set the stage for the emergence of resistant bacteria. In some areas including Indonesia, Thailand, India and parts of Africa, veterinary antibiotics can be obtained without prescription or other controls.[20,22] In contrast, the general use of antibiotics for growth promotion is banned in the European Union and Japan,[23] and FQ cannot be used in food producing animals in Australia.

Although Campylobacter has an extensive formidable restriction modification system that would tend to decrease the uptake of foreign genetic material, it is also naturally transformable, and the acquisition of resistance genes from other organisms has been described.[24-35] For all these reasons, the study of the resistance mechanisms present in *C. jejuni* is important to both human and veterinary health.

The genetic elements that underlie these mechanisms may be chromosomal or plasmid-borne, and represent a combination of endogenous and acquired genes. In general, mechanisms of antibiotic resistance include (**Table 1**):

(1) Modification of the antibiotic's target and/or its expression (i.e., DNA gyrase mutations)

(2) Inability of the antibiotic to reach its target (i.e., expression of the major outer membrane protein or MOMP)

(3) Efflux of the antibiotic (i.e., multidrug efflux pumps such as CmeABC)

(4) Modification or inactivation of the antibiotic (i.e., β-lactamase production).

Table 1. Antibiotic resistance mechanisms of Campylobacter

Antibiotic class	Resistance mechanisms
Aminoglycoside	Modification of the antibiotic by aminoglycoside-modifying enzymes (AphA, AadE, Sat) Contribution of efflux is not clear
Beta-Lactam	Enzymatic inactivation of the antibiotic by β-lactamase (penicillinase, OXA-61) Decreased membrane permeability of most anionic and MW > 360 kDa antibiotics due to MOMP Efflux through CmeABC and possibly others
Fluoroquinolone	Modification of the DNA gyrase target (Thr-86-Ile; also Asp-90-Asn, Ala-70-Thr) Efflux through CmeABC
Macrolide	Mutations in 23S rRNA Contribution of mutations in ribosomal proteins L4/L22 is likely minor Efflux through CmeABC and possibly others Decreased membrane permeability due to MOMP
Tetracycline	Modification of the target ribosomal A site by TetO binding Efflux through CmeABC and possibly others Contribution of decreased membrane permeability due to MOMP is not clear

In Campylobacter, a recurring theme is synergy between antibiotic efflux and a second mechanism. The best-described multidrug efflux pump in Campylobacter is CmeABC, consisting of three components: an outer membrane protein (encoded by *cmeC*), an inner membrane drug transporter (encoded by *cmeB*), and a periplasmic protein (encoded by *cmeA*) that bridges CmeB and CmeC.[36,37] This efflux pump also contributes to resistance to bile acids.[38] Other putative efflux pumps including CmeDEF and CmeG, may also contribute to antibiotic resistance.[39,40] Sequencing reveals that *C. jejuni* has a total of 14 possible efflux pumps, but most have not been characterized functionally.[41] In addition to intrinsic resistance mediated by efflux,[36,37,39,40,42-44] antibiotic exclusion [via the major outer membrane porin (MOMP),[45] lipooligosaccharide and possibly capsule][46] also contribute to intrinsic resistance. Campylobacter exhibits intrinsic resistance to novobiocin, bacitracin and vancomycin, polymyxin/colistin, presumably due to the absence of appropriate targets and/or low affinity binding to targets.[47-50] In the case of intrinsic resistance to trimethoprim,[26,47,51-53] variant forms of dihydrofolate reductases (encoded by *dfr1* most often but also by *dfr9*) that are not inhibited by trimethoprim are found in > 90% of *C. jejuni* that have been examined.[26]

Approximately 90% of Campylobacter infections in humans are caused by *C. jejuni* (*C. coli* accounts for ~9%),[54] and the majority of the literature on human infection focuses on *C. jejuni*. Therefore, this review will focus on the antibiotic resistance mechanisms found in *C. jejuni* for commonly-used antibiotics.

Fluoroquinolone Resistance

Fluoroquinolones manifest concentration-dependent, bactericidal activity against a wide variety of both Gram-negative and Gram-positive organisms, are available in both oral and intravenous forms, are conveniently dosed once or twice daily usually, and are well-tolerated; all these attributes make this a heavily-used class of antibiotic in humans. Nalidixic acid is the parent, non-fluorinated compound of this antibiotic class. The fluoroquinolones include the most commonly used antibiotics (i.e., ciprofloxacin) to treat acute bacterial diarrhea, although macrolides are the drug of choice if campylobacteriosis is strongly suspected.[21] However, campylobacteriosis is clinically indistinguishable from other causes of bacterial diarrheal illness, and so without epidemiology suggestive of Campylobacter infection, many cases are treated empirically with FQ. As such, FQ resistance is of great clinical concern.

Worldwide, FQ resistance was unusual in the late 1980s to early 1990s.[12,13,55] However, the combination of indiscriminate use of FQ in humans and increased FQ use in the poultry industry in particular, has contributed to an increase in the prevalence of FQ-resistance in both animals and humans.[11,12,14] The surveillance of FQ susceptibility in Campylobacter in animals is important not only for purposes of food production, but also because the emergence of resistant strains in animals portends an increase in resistant human infections.[11-14,56] Recognition of this connection has supported the limitation or outright banning of FQ for veterinary purposes in many countries including the United States,[57] Denmark, and Australia among other countries. Accordingly, FQ-resistance in > 150 Campylobacter isolates from broilers in Australia was reported to be between 0–2.4%,[58,59] which likely contributes to the similarly low-level of FQ-resistance (2%) in human isolates.[59] Additionally, data from the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) show that *C. jejuni* isolates from domestic broilers was 11%, compared with 57% from imported broilers,[55] and that while one-third of domestically-acquired Campylobacter infections were FQ-resistant in 2011, 84% of infections acquired abroad were FQ-resistant.[55] Similarly, 6.5% of human Campylobacter infections acquired in Norway were FQ-resistant, compared with 67% FQ-resistance in infections acquired abroad.[60]

However, the veterinary use of FQ varies widely throughout the world depending on the production setting (i.e., commercial vs. family-owned) as well as on a country-wide basis.[11,52,53,61] For example, as in many countries, antibiotics are used both

prophylactically and therapeutically in industrialized and commercial free-range poultry farms in South Africa, but not in small-scale family farming. The rates of FQ resistance were highest in commercial free-range broilers, at > 95%, but were lower in industrial broiler (16%) and lowest in poultry from family farms (8%).[62] Thailand also reports very high rates of FQ resistance in *C. jejuni* from broilers, upwards of 80%.[13,52,63] In Japan, the rate of nalidixic acid resistance in *C. jejuni* from broiler flocks was 55%, and for a veterinary FQ (enrofloxacin) the rate was 30%.[64] The experience in Europe has been quite variable, ranging from very low FQ-resistance (1.2%) in broilers in Norway,[60] intermediate in Belgium[56] and Poland,[65] (44% and 56%, respectively), to alarmingly high in Spain, where it was reported in 2000 that 99% of Campylobacter isolates from broilers were FQ-resistant.[66]

In the United States in 2004, the Federal Drug Administration reversed its prior approval for the therapeutic use of the veterinary FQ enrofloxacin because of concerns that the rising level of FQ-resistant Campylobacter in poultry was being reflected in increasing FQ resistance in human isolates.[12,57] However, it is not yet clear if the elevated rates of FQ resistance will decline after FQ restriction. Studies in several countries have shown that FQ-resistant Campylobacter persists in poultry populations after the withdrawal of FQ,[67-70] suggesting that there is little/no fitness cost to FQ-resistance in Campylobacter.[70,71] The latest available data from the United States shows that resistance to ciprofloxacin in human isolates of *C. jejuni* peaked in 2007 at nearly 26%, and has since declined somewhat to ~22% in 2010;[54] whether this is a true decline attributable even in part to the enrofloxacin ban is debatable.

In Campylobacter, there are two well-described mechanisms that underlie resistance to FQ: (1) inactivation of the target of FQ; (2) efflux of FQ. These two mechanisms work together synergistically.[72-74] In general, the two intracellular enzymatic targets of FQ are DNA gyrase (encoded by *gyrA* and *gyrB*) and the structurally related topoisomerase IV (encoded by *parC* and *parE*).[75] Fluoroquinolones form a stable complex with these enzymes and traps them onto DNA, leading to decreased DNA replication, transcription, and ultimately to cell death.[76,77] However, several studies have demonstrated that *C. jejuni* and *C. coli* lack the *parC* and *parE* genes;[41,78-80] therefore, they cannot be a source of FQ resistance. Instead, FQ-resistance in *C. jejuni* and *C. coli* occurs via specific point mutations in the quinolone resistance-determining region (QRDR) of the *gyrA* gene, with the Thr-86-Ile mutation being both the most common. This single mutation in *gyrA* leads to high-level resistance to nalidixic acid and FQ (ciprofloxacin minimum inhibitory concentration (MIC) > 16 g/ml), unlike FQ resistance in *E. coli* or Salmonella, which requires the accumulation of several point mutations in the QRDR before high-level resistance is achieved.[81] Interestingly, the less common Thr-86-Ala mutation confers resistance only to nalidixic acid but not FQ.[82] Perhaps since only a single point mutation is required for high level resistance, FQ-resistant mutants appear rapidly both in animals and humans.[16,67,72,73,83-88] The less common Asp-90-Asn and Ala-70-Thr mutations in *gyrA* confer intermediate-level resistance to FQ (ciprofloxacin MIC 6–16 g/ml).[89,90] While mutations in *gyrB* have been reported, they do not confer FQ resistance.[78,80,91]

It is somewhat surprising that the Thr-86-Ile mutation in *gyrA* seems to increase the fitness of Campylobacter in a chicken model,[71] although this observation supported by the previously mentioned studies demonstrating that these resistant strains persist even after FQ are withdrawn from poultry flocks for several years.[67-69] Conflicting reports exist about whether this mutation translates into more severe infections in humans.[92-97]

Another mechanism of FQ-resistance that seems to work in concert with *gyrA* mutations is efflux via the chromosomally-encoded CmeABC multidrug efflux pump, which reduces the intracellular concentration of FQ and several other antibiotics.[36,37] This efflux pump acts synergistically with DNA gyrase mutations to effect high-level FQ-resistance;[72-74] for example, strains carrying DNA gyrase mutations that alone lead to intermediate-level FQ resistance manifest high-level resistance when CmeABC is also expressed.[73,74] Also, CmeABC assists in the emergence of *gyrA* mutants that otherwise could not survive selection by even low dose FQ.[74] Unlike efflux pump mechanisms in other Gram-negative bacteria which require overexpression to lead to clinically relevant resistance, the basal, constitutive expression of CmeABC is sufficient to mediate FQ resistance (although experimental overexpression does increase the level of FQ-resistance).[74]

An additional putative efflux pump, CmeG, has also recently been described as conferring both resistance to structurally unrelated antibiotics as well as oxidants.[40] Insertional mutagenesis of *cmeG* led to a 4-fold reduction in ciprofloxacin resistance vs. the wild-type parent, and an 8- to 32-fold increase in resistance to ciprofloxacin and other FQ when *cmeG* was overexpressed.[40]

Interestingly, FQ-resistance has emerged on poultry farms even in the absence of FQ administration.[64,98] Since the major mechanism of nalidixic acid and FQ-resistance in Campylobacter is via point mutations in *gyrA*, it is difficult to attribute this phenomenon to co-inheritance of multi-resistance mobile elements. It has been suggested that other antibiotics could select for FQ-resistance in Campylobacter,[98] but whether this occurs via expression of the CmeABC pump or other mechanism remains to be clarified.

Macrolide Resistance

Macrolide antibiotics and the closely-related ketolides are large molecules (MW > 700) that inhibit bacterial protein synthesis. The macrolide antibiotic erythromycin is the treatment of choice for campylobacteriosis.[21] Other members of this class of antibiotics include clarithromycin, azithromycin, telithromycin (technically a ketolide), tylosin and tilmicosin; the latter two are approved for veterinary use only (erythromycin also has a veterinary indication).[99] Macrolides inhibit protein synthesis by binding reversibly to the P site on the 50S subunit of bacterial ribosomes. The main mechanisms of resistance to macrolides in Campylobacter are (1) target modification, (2) efflux and (3) altered membrane permeability. The first two mechanisms act synergistically to confer high-level macrolide resistance.[100,101]

A fourth mechanism of macrolide resistance, enzymatic modification of macrolides, has not been described in Campylobacter.[102]

As in other bacteria, point mutations in the peptidyl encoding region in domain V of the 23S rRNA gene at positions 2074 and 2075 (corresponding to positions 2058 and 2059 in *E. coli* numbering) confer high-level macrolide resistance,[101,103-109] with the 2075 substitution being more common.[104,110] *C. jejuni* and *C. coli* carry three copies of 23s rRNA gene,[41,111] all of which are usually mutated in macrolide-resistant strains. However, some strains with lower MICs to macrolides have been found to have only two mutated gene copies, suggesting a gene dosage effect.[110,112,113] Strains harboring single mutations in 23S rRNA have not been reported. Mutations (usually insertions) in the ribosomal proteins L4 and L22 leading to macrolide resistance but are not the major means of tetracycline resistance.[100,106]

The barrier to the generation of macrolide resistance in Campylobacter appears to be much higher than that of FQ-resistance. In two studies, several weeks of tylosin administration to poultry at a growth-promotion dose was necessary to select for macrolide resistance.[101,114] In another departure from FQ-resistant Campylobacter, macrolide resistance imparts a fitness cost, at least when analyzed in competition experiments.[114-118] These two factors combined with a low spontaneous mutation rate leading to macrolide resistance (~10^{-10} per cell per generation)[101] and clinical efficacy, make macrolides the drug of choice to treat campylobacteriosis. Through 2008, there was concern in the US about increasing macrolide resistance in both *C. jejuni* and *C. coli* (2.3% and 10.1%, respectively), but there was a decline over the following two years to 1.2% and 4.3% for these strains.[54] As of 2010 in the European Union, the highest rates of macrolide resistance for *C. jejuni* is in Malta (10%), and Italy for *C. coli* (33%).[119] Unfortunately, rates are much higher in parts of Asia and Africa; for example, in Nigeria, nearly 80% of strains are macrolide-resistant.[120] Similar to observations made with FQ-resistance in South Africa, 88% of Campylobacter isolates from poultry raised commercially were erythromycin resistant vs. 0% for those isolates from small-scale family farms.[62]

The multidrug efflux pump CmeABC also contributes to macrolide resistance[36,37,101,107,113,121] and functions synergistically with 23S rRNA mutations to effect high-level macrolide resistance.[43,100,122] In mutants that are macrolide-resistant but lack 23S rRNA mutations, gene disruption of *cmeB* or antisense-mediated gene silencing of *cmeA* leads to inactivation of the CmeABC transporter and mediates reversion to a macrolide-susceptible phenotype.[100,123] The putative efflux pump CmeG may also contribute to macrolide resistance, as insertional mutagenesis of *cmeG* causes an 8-fold reduction in erythromycin resistance vs. the wild-type parent.[40] In addition, there is one study that suggests the existence of a second efflux system that contributes to low-level macrolide resistance, but it has not been further characterized.[107]

A third mechanism of macrolide resistance involves altered membrane permeability mediated by expression of the major outer membrane porin (MOMP), chromosomally encoded by *porA*.[44,45] In Gram-negative bacteria, porins are outer membrane proteins that form transmembrane pores and allow the passive diffusion of hydrophilic molecules, including many antibiotics. Properties of the pore including its size and charge characteristics underlie the selectivity for what can pass through it. In *C. jejuni* and *C. coli,* MOMP forms a cation-selective pore that is smaller than pores typically found in *E. coli*,[124] and therefore should limit the entry of most antibiotics with a molecular weight greater than 360 such as the macrolides (MW > 700).[45] However, since macrolides are known to be very effective against Campylobacter, these drugs must be able to cross the outer and cytoplasmic membranes. Whereas porins provide an aqueous environment for the transport of hydrophilic molecules, the relatively hydrophobic macrolides are thought to gain access to the cytoplasm of Gram-negative bacteria via a "hydrophobic pathway".[125,126] This pathway seems to be promoted in *E. coli* and Salmonella strains bearing mutations in lipopolysaccharide (LPS) synthesis genes that yield truncated LPS (lacking hydrophilic O-antigen sugars). The outer membranes of these mutant strains are therefore relatively more hydrophobic than the parent strains, and exhibit increased susceptibility to hydrophobic antibiotics including macrolides.[126] Given that Campylobacter naturally expresses lipooligosaccharide (LOS), which lacks the hydrophilic sugars expressed by full-length LPS in other Gram-negative bacteria,[127,128] it is reasonable to speculate that this comparatively increased outer membrane hydrophobicity promotes the uptake of macrolides. This is supported by the observation that LOS truncation increases the susceptibility of *C. jejuni* to erythromycin by 8-fold, an effect that was doubled in *C. jejuni* mutants also carrying the A2074G mutation.[46]

β-Lactam Resistance

The β-lactam antibiotics are a diverse class of compounds including penicillins, cephalosporins, carbapenems and monobactams, all of which contain the β-lactam ring required for antimicrobial activity. Individual members of this family are distinguished by various side chains that confer particular properties such as pharmacokinetics, resistance to stomach acid, hydrolysis by β lactamases, etc. By binding to and thereby inactivating the bacterial peptidoglycan transpeptidases (also known as penicillin-binding proteins) required to catalyze the final cross linking step, the resulting bacterial cell walls lack structural integrity and are subject to osmotic swelling and lysis. Exactly how this leads to bacterial cell death is not completely clear, but the unopposed action of autolysins, necessary for normal turnover and remodeling of peptidoglycan, may play a role.[129]

Three mechanisms mediate β-lactam resistance in Campylobacter: (1) enzymatic inactivation by chromosomally-encoded β-lactamases, (2) reduced uptake due to alterations in outer membrane porins and (3) efflux.

Expression of a penicillinase-type of β-lactamase in Campylobacter confers resistance to amoxicillin, ampicillin and ticarcillin, which can be overcome with the β-lactamase inhibitors tazobactam, clavulanic acid and sulbactam.[105] This enzyme does not affect susceptibility to the carbapenems or cephalosporins. More recently, a class D β-lactamase OXA-61, was identified in Campylobacter.[130] This enzyme shows similarity

to other OXA-type genes in Fusobacterium, Acinetobacter and Pseudomonas, and mediates resistance to penicillin, oxacillin, ampicillin, amoxicillin-clavulanate, piperacillin and carbenicillin.[130,131] While OXA-61 is highly prevalent in the veterinary and human populations studied,[131] pooled national data on the prevalence of β-lactam resistance in general is not available since the NARMS does not include the β-lactam class for Campylobacter.[54] However, it appears that the prevalence of β-lactamase varies widely in both poultry and human populations, but is usually greater than 20%.[105,131-134] Finally, two genes encoding a metallo-β-lactamase type of enzyme has been reported, although it is not yet clear if expression actually leads to β-lactamase resistance.[131,132,135]

As with macrolides, the cation-selective MOMP in *C. jejuni* and *C. coli* tend to exclude most β-lactams with a molecular weight greater than 360 or which are anionic.[45] The partial positive charge and small size of imipenem (MW 299), ampicillin (MW 333) and cefpirome (MW 347) are consistent with passage through MOMP, and susceptibility to these antibiotics in the absence of a second mechanism such as β-lactamase production. Amoxicillin's molecular weight of 365 would seem to preclude efficient passage through MOMP, although its partial positive charge might facilitate entry through MOMP; alternatively, a non-MOMP-dependent mechanisms may mediate its entry.[45]

The CmeABC efflux pump may also contribute to β-lactam resistance. Insertional mutagenesis of *cmeB* in *C. jejuni* strain 81-176[136] and another strain led to a 32-fold increase in ampicillin susceptibility.[36] In another study using NCTC strain 11168, the *cmeB* mutant was 4 times more susceptible to ampicillin compared with the parent strain, and overexpression of *cmeB* lead to a 4-fold increase in ampicillin resistance.[44] Inactivation of the putative efflux pump CmeDEF by insertional mutagenesis of *cmeF* only led to a 2-fold increase in ampicillin resistance in strain 11168 and a 2-fold increase in cefotaxime resistance in the well-described, invasive, human outbreak strain 81-176.[39] Also, inactivation of the putative efflux pump CmeG did not affect cefotaxime resistance *in C. jejuni* strain 11168.[40] Therefore, at this point it seems that CmeABC is the most potent efflux pump with regard to β-lactams.

Tetracycline Resistance

The tetracyclines were discovered in the 1940s and have activity against Gram-negative and Gram-positive organisms. Due to their heavy use in the past for both human and veterinary indications, widespread resistance has somewhat limited their use today. Commonly used members of this class are tetracycline, doxycycline and minocycline. The tetracyclines are lipophilic protein synthesis inhibitors that likely use a combination of the hydrophobic pathway described for macrolides as well as outer membrane porins to gain access to the bacterial ribosome; exactly how each pathway contributes to tetracycline entry in Campylobacter is not completely clear. Known mechanisms of tetracycline resistance in Campylobacter are (1) alteration of tetracycline's ribosomal target and (2) efflux.

In other Gram-negatives, tetracyclines form a complex with magnesium, which imparts a positive charge that facilitates passage of the complex through pores formed by OmpC and OmpE.[137] Although MOMP of Campylobacter shares an antigenically-related region to OmpC in *E. coli*,[138,139] it is not certain that the high molecular weight of tetracyclines (> 400) allows passage through the relatively small pores (MW exclusion ~360) imparted by MOMP.[45] Nevertheless, once inside the bacteria cytoplasm, tetracyclines reversibly bind to the 30S subunit of ribosomes and inhibit protein synthesis by preventing the attachment of charged aminoacyl-tRNA to the ribosomal A site.[140,141] The major mechanism of tetracycline resistance in Campylobacter as well as other Gram-negatives is protection of an unoccupied A site by the binding of bacterial protein TetO to that site.[142,143] TetO can be encoded on the chromosome,[144] or more commonly, on the plasmids pTet in *C. jejuni*[145] and pCC31 in *C. coli*.[146,147] According to 2010 NARMS data, 43% of *C. jejuni* and 49% of *C. coli* isolates are tetracycline-resistant,[54] making this class of antibiotic of little use in veterinary or human Campylobacter-mediated disease.[54,144,148]

Although high-level resistance to tetracyclines can be mediated by TetO alone, the contribution of efflux to tetracycline resistance is demonstrated by the increase in tetracycline MIC when efflux pumps are genetically inactivated. For example, disruption of the putative efflux pump *cmeG* rendered the mutant strain 4-fold more susceptible to tetracycline compared with the wild-type strain.[40] Also, inactivation of the CmeABC efflux pump by disruption of *cmeB* led to an 8-fold decrease in the tetracycline MIC in a TetO-minus poultry isolate,[36] and similar findings were described with the NCTC isolate 11168 when *cmeB* was disrupted.[37] In a different study of other *C. jejuni* strains including 81-176, *cmeB* disruption rendered strains 16- to 64-fold more susceptible to tetracycline compared with the parent strains.[112] These studies also suggested that when both CmeABC and TetO are functional, the impact on tetracycline resistance is synergistic.[36,37,112]

Aminoglycoside Resistance

Aminoglycosides are protein synthesis inhibitors of many Gram-positive and Gram-negative organisms. They contain amino-modified sugars, are positively charged, water-soluble and have molecular weights ranging from 445 to 600.[149,150] Commonly used members of this group include gentamicin, kanamycin, amikacin, neomycin, tobramycin and streptomycin. The initial binding of aminoglycosides to negatively charged bacterial membranes is electrostatic in nature and relatively slow compared with the second phase of rapid but reversible binding to the 30S segment of the ribosome.[151] Transfer of aminoglycosides across the bacterial cytoplasmic membranes requires oxygen, an intact electron transport system and ATP.[150,152,153] According to 2010 NARMS data, > 99% of *C. jejuni* and 88% of *C. coli* isolates are susceptible to aminoglycosides.[54] These data suggest that despite Campylobacter's microaerophilic nature, sufficient oxygen is present for the uptake of aminoglycosides.

There are two major means by which aminoglycosides exert antimicrobial activity: (1) interference with the translocation of the nascent peptide chain from the ribosomal A site to the P site leading to premature termination, and (2) interference with proof-reading, leading to incorporation of incorrect amino acids and dysfunctional protein.[154] The main mechanism of aminoglycoside resistance in *C. jejuni* is via aminoglycoside modifying enzymes, which are usually plasmid-borne.

Aminoglycoside resistance was first detected in *C. coli* and was mediated by a 3'-aminoglycoside phosphotransferase (encoded by *aphA*-3) that had been previously described as conferring kanamycin resistance in Streptococcus and Staphylococcus.[29] This *aphA-3* gene remains the most common source of aminoglycoside resistance in Campylobacter. In some strains, *aphA-3* is located downstream of an insertion sequence (IS607*) bearing similarity to IS607 found in *H. pylori*.[27] In other strains, *aphA-3* is found with genes encoding streptomycin resistance (encoded by *aadE*, a 6'-adenylyl transferase) and streptothricin resistance (encoded by *sat*, an acetyl transferase).[27] The existence of a similar resistance cluster in Enterococcus suggests that Campylobacter acquired these genes via horizontal transfer.[27] Other Campylobacter strains harbor mosaic plasmids that contain various aminoglycoside resistance genes and insertion or transposon sequences from Gram-negative (i.e., *H. pylori*, *E. coli* and Salmonella) and Gram-positive sources (i.e., Enterococcus), along with *tetO*.[24,25,27,28,30-32,34,35] Acquisition of such plasmids by susceptible *C. jejuni* confers a multi-drug-resistant phenotype and that can present a clinical challenge in both the veterinary and human populations.

Other genes which confer kanamycin resistance include *aphA-1* and *aphA-7*, which were detected on plasmids in *C. jejuni*.[155-157] Unlike *aphA-3* and *aphA-1*, which are thought have been horizontally acquired, *aphA-7* has a similar G-C content to *C. jejuni* chromosomal DNA, suggesting it is intrinsic in Campylobacter.[158] Finally, there is a single report of a mutation in ribosomal protein S12 (encoded by *rpsL*) in *C. coli* that confers streptomycin resistance, but a similar mutation has not yet been described in *C. jejuni*.[159]

The contribution of efflux to aminoglycoside resistance is less clear. In one study, the putative efflux pump inhibitors phenylarginine-β-naphthylamide and 1-(1-naphthylmethyl)-piperazine did not affect the MIC of kanamycin in 5 *C. jejuni* strains.[160] Another study which directly measured the effect of the putative efflux pump CmeG by insertional mutagenesis and comparison of MICs of various antibiotics found 16-fold reduction in gentamicin resistance in the mutated CmeG strain vs. the wild-type parent.[40] However, no effect on streptomycin resistance was noted, and overexpression did not lead to increased aminoglycoside resistance.[40] Therefore, the contribution of efflux to aminoglycoside resistance in Campylobacter is not completely clear but is likely to be less important than the plasmid-borne drug-modifying enzymes described previously.

Conclusions

Antibiotic resistance in *C. jejuni* is an increasing problem, as it is in many other microorganisms. Due to Campylobacter's natural competence and hypervariable genomic sequences,[41] there is considerable genomic plasticity that supports the emergence of resistant mutants. Because Campylobacter is a commensal of many animal species that are exposed to veterinary antimicrobials, ample opportunity exists for Campylobacter to continue to evolve additional resistance mechanisms. Furthermore, the over-use of antibiotics in the human population is an additional important source of selective pressure. Both scenarios contribute to the current problem of FQ resistance in Campylobacter. In this regard, the lack of a fitness cost (and perhaps even a fitness advantage[71]) of FQ-resistant *C. jejuni* is an issue that must be remembered when future resistance mutations arise in *C. jejuni* against other antimicrobials. Of greatest clinical concern would be the emergence of widespread macrolide resistance, since this class is the current treatment of choice for campylobacteriosis. A better understanding of the mechanism of macrolide entry (possibly via the hydrophobic pathway) may be useful in eventually mitigating the impact of acquired macrolide resistance. Also, the contribution of efflux pumps to antibiotic resistance warrants further study, since this mechanism acts synergistically with other mechanisms of antibiotic resistance to confer high-level resistance in many instances. Furthermore, genome sequencing predicts 14 potential efflux pumps,[41] but only CmeABC and CmeG have been studied functionally,[40,44,161] making this a fertile area for future research.

The antibiotic resistance mechanisms discussed herein are summarized in **Figure 1**.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Zilbauer M, Dorrell N, Wren BW, Bajaj-Elliott M. Campylobacter jejuni-mediated disease pathogenesis: an update. Trans R Soc Trop Med Hyg 2008; 102:123-9; PMID:18023831; http://dx.doi.org/10.1016/j.trstmh.2007.09.019
2. Eurosurveillance editorial team. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2010. Euro Surveill 2012; 17:20113; PMID:22433599.
3. EFSA. The Community Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union in 2008. Eur Food Safety Auth J 2010; 8:1658-919.
4. OzFoodNet Working Group. Monitoring the incidence and causes of diseases potentially transmitted by food in Australia: annual report of the OzFoodNet Network, 2009. Commun Dis Intell 2010; 34:396-426; PMID:21413526.
5. Notifiable and Other Diseases in New Zealand. Annula Report 2011. In: The Institute of Environmental Science and Research Ltd. Porirua, New Zealand; 2012.
6. Allos BM, Blaser MJ. Campylobacter jejuni and related species. In: Mandell, ed. Principles and Practice of Infectious Diseases. Philadelphia: Churchill Livingstone; 2010:2793-802.
7. Blaser MJ, Taylor DN, Feldman RA. Epidemiology of Campylobacter jejuni infections. Epidemiol Rev 1983; 5:157-76; PMID:6357819.
8. Centers for Disease Control and Prevention (CDC). Incidence of foodborne illnesses: preliminary data from the Foodborne Diseases Active Surveillance Network (FoodNet)--United States, 1998. MMWR Morb Mortal Wkly Rep 1999; 48:189-94; PMID:10208124.
9. FoodNet - Foodborne Diseases Active Surveillance Network. Centers for Disease Control and Prevention, 2012. (Accessed March 14, 2012, at http://www.cdc.gov/foodnet/.)

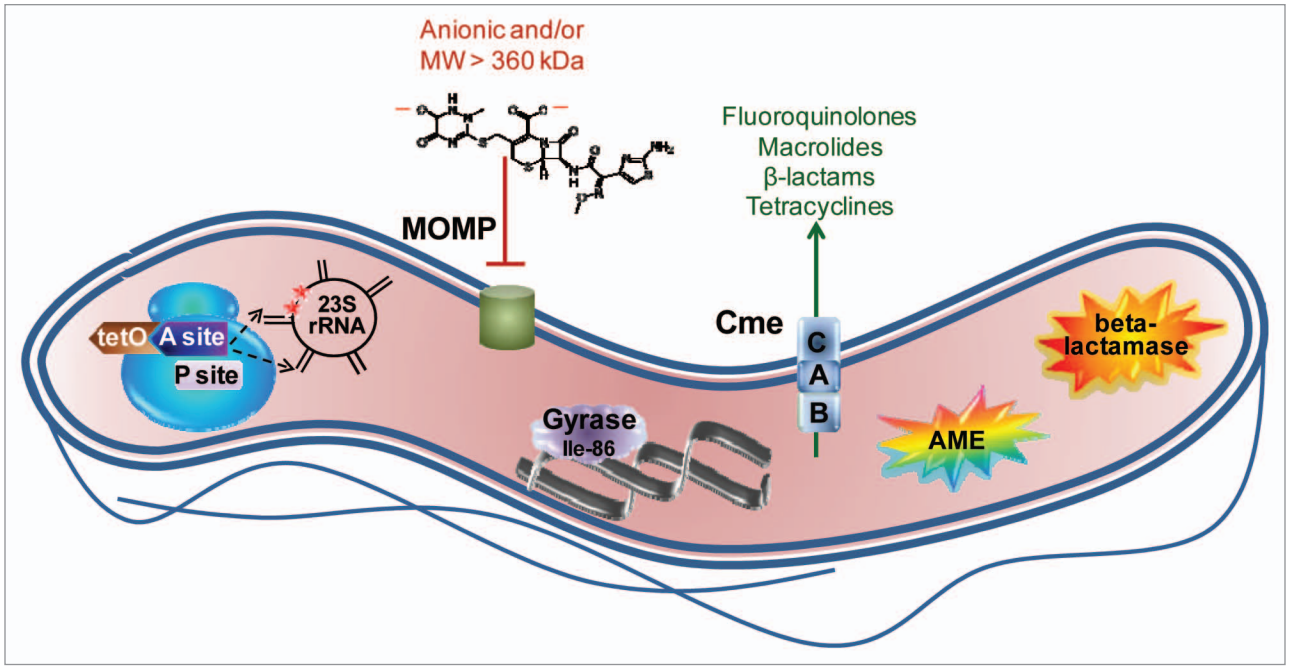

Figure 1. Summary of major antibiotic resistance mechanisms in Campylobacter. The ribosome, shown in blue at the left, is the site of two major resistance mechanisms. Binding of the TetO protein (shown in brown) to the A site (shown in dark purple) prevents tetracycline from occupying that site but stills allows access of the aminoacyl tRNA so that protein synthesis continues. Point mutations in 23S rRNA in the domain V region (shown in black) at position 2,075 principally and less often at position 2,074 (indicated by red stars) decrease the binding affinity for macrolides and lead to resistance. The major outer membrane protein (MOMP, shown in green), limits the entry of most antibiotics that are negatively charged or with a molecular weight larger than 360 kDa; the structure of the 552 kDa, dianionic antibiotic ceftriaxone is shown as an example. The Thr-86-Ile substitution in DNA gyrase (shown in light purple), is the main means of fluoroquinolone resistance, and this single mutation also confers high level resistance to this antibiotic class. The multi-drug efflux pump CmeABC (shown as stacked blue squares) contributes to resistance against fluoroquinolones, macrolides, β-lactams and tetracyclines, and works synergistically with other resistance mechanisms, often leading to high-level resistance. Aminoglycoside-modifying enzymes (AME; shown as the multi-colored star burst), principally of the aminoglycoside phosphotransferase family, are the main means of aminoglycoside resistance. Finally, β-lactamases (shown as the orange star burst) of the penicillinase type as well as the Ambler class D OXA-61 contribute to β-lactam resistance.

10. Thomas C, Gibson H, Hill DJ, Mabey M. Campylobacter epidemiology: an aquatic perspective. J Appl Microbiol 1998; 85(Suppl 1):168S-77S; PMID:21182706; http://dx.doi.org/10.1111/j.1365-2672.1998.tb05296.x
11. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J Antimicrob Chemother 1991; 27:199-208; PMID:2055811; http://dx.doi.org/10.1093/jac/27.2.199
12. Gupta A, Nelson JM, Barrett TJ, Tauxe RV, Rossiter SP, Friedman CR, et al.; NARMS Working Group. Antimicrobial resistance among Campylobacter strains, United States, 1997-2001. Emerg Infect Dis 2004; 10:1102-9; PMID:15207064; http://dx.doi.org/10.3201/eid1006.030635
13. Luangtongkum T, Jeon B, Han J, Plummer P, Logue CM, Zhang Q. Antibiotic resistance in Campylobacter: emergence, transmission and persistence. Future Microbiol 2009; 4:189-200; PMID:19257846; http://dx.doi.org/10.2217/17460913.4.2.189
14. Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB, Wicklund JH, et al.; Investigation Team. Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998. N Engl J Med 1999; 340:1525-32; PMID:10332013; http://dx.doi.org/10.1056/NEJM199905203402001
15. Threlfall EJ, Ward LR, Frost JA, Willshaw GA. Spread of resistance from food animals to man--the UK experience. Acta Vet Scand Suppl 2000; 93:63-8, discussion 68-74; PMID:10822859.
16. van Boven M, Veldman KT, de Jong MC, Mevius DJ. Rapid selection of quinolone resistance in Campylobacter jejuni but not in Escherichia coli in individually housed broilers. J Antimicrob Chemother 2003; 52:719-23; PMID:12951353; http://dx.doi.org/10.1093/jac/dkg402
17. Hooper DC. Emerging mechanisms of fluoroquinolone resistance. Emerg Infect Dis 2001; 7:337-41; PMID:11294736; http://dx.doi.org/10.3201/eid0702.010239
18. Moore JE, Barton MD, Blair IS, Corcoran D, Dooley JS, Fanning S, et al. The epidemiology of antibiotic resistance in Campylobacter. Microbes Infect 2006; 8:1955-66; PMID:16716632; http://dx.doi.org/10.1016/j.micinf.2005.12.030
19. Kittl S, Kuhnert P, Hächler H, Korczak BM. Comparison of genotypes and antibiotic resistance of Campylobacter jejuni isolated from humans and slaughtered chickens in Switzerland. J Appl Microbiol 2011; 110:513-20; PMID:21143711; http://dx.doi.org/10.1111/j.1365-2672.2010.04906.x
20. Monitoring antimicrobial usage in food animals for the protection of human health: Report of a WHO consultation. World Health Organization Department of Communicable Disease, Surveillance and Response 2001.
21. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, et al.; Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001; 32:331-51; PMID:11170940; http://dx.doi.org/10.1086/318514
22. Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 2006; 65:725-59; PMID:16677683; http://dx.doi.org/10.1016/j.chemosphere.2006.03.026
23. Council regulation (EC) No. 2821/98 of 17 December 1998 amending, as regards withdrawal of the authorization of certain antibiotics, Directive 70/524/EEC concerning additives in feedingstuffs. Official Journal of the European Communities 1998; 351:4-8.
24. Ansary A, Radu S. Conjugal transfer of antibiotic resistances and plasmids from Campylobacter jejuni clinical isolates. FEMS Microbiol Lett 1992; 70:125-8; PMID:1587459; http://dx.doi.org/10.1111/j.1574-6968.1992.tb05196.x
25. Bradbury WC, Munroe DL. Occurrence of plasmids and antibiotic resistance among Campylobacter jejuni and Campylobacter coli isolated from healthy and diarrheic animals. J Clin Microbiol 1985; 22:339-46; PMID:4044793.
26. Gibreel A, Sköld O. High-level resistance to trimethoprim in clinical isolates of Campylobacter jejuni by acquisition of foreign genes (dfr1 and dfr9) expressing drug-insensitive dihydrofolate reductases. Antimicrob Agents Chemother 1998; 42:3059-64; PMID:9835491.
27. Gibreel A, Sköld O, Taylor DE. Characterization of plasmid-mediated aphA-3 kanamycin resistance in Campylobacter jejuni. Microb Drug Resist 2004; 10:98-105; PMID:15256024; http://dx.doi.org/10.1089/1076629041310127

28. Gibreel A, Tracz DM, Nonaka L, Ngo TM, Connell SR, Taylor DE. Incidence of antibiotic resistance in Campylobacter jejuni isolated in Alberta, Canada, from 1999 to 2002, with special reference to tet(O)-mediated tetracycline resistance. Antimicrob Agents Chemother 2004; 48:3442-50; PMID:15328109; http://dx.doi.org/10.1128/AAC.48.9.3442-3450.2004
29. Lambert T, Gerbaud G, Trieu-Cuot P, Courvalin P. Structural relationship between the genes encoding 3'-aminoglycoside phosphotransferases in Campylobacter and in gram-positive cocci. Ann Inst Pasteur Microbiol 1985; 136B:135-50; PMID:3002237; http://dx.doi.org/10.1016/S0769-2609(85)80040-5
30. Lee MD, Sanchez S, Zimmer M, Idris U, Berrang ME, McDermott PF. Class 1 integron-associated tobramycin-gentamicin resistance in Campylobacter jejuni isolated from the broiler chicken house environment. Antimicrob Agents Chemother 2002; 46:3660-4; PMID:12384387; http://dx.doi.org/10.1128/AAC.46.11.3660-3664.2002
31. Nirdnoy W, Mason CJ, Guerry P. Mosaic structure of a multiple-drug-resistant, conjugative plasmid from Campylobacter jejuni. Antimicrob Agents Chemother 2005; 49:2454-9; PMID:15917546; http://dx.doi.org/10.1128/AAC.49.6.2454-2459.2005
32. O'Halloran F, Lucey B, Cryan B, Buckley T, Fanning S. Molecular characterization of class 1 integrons from Irish thermophilic Campylobacter spp. J Antimicrob Chemother 2004; 53:952-7; PMID:15128721; http://dx.doi.org/10.1093/jac/dkh193
33. Pinto-Alphandary H, Mabilat C, Courvalin P. Emergence of aminoglycoside resistance genes aadA and aadE in the genus Campylobacter. Antimicrob Agents Chemother 1990; 34:1294-6; PMID:2168151; http://dx.doi.org/10.1128/AAC.34.6.1294
34. Sagara H, Mochizuki A, Okamura N, Nakaya R. Antimicrobial resistance of Campylobacter jejuni and Campylobacter coli with special reference to plasmid profiles of Japanese clinical isolates. Antimicrob Agents Chemother 1987; 31:713-9; PMID:3038005; http://dx.doi.org/10.1128/AAC.31.5.713
35. Velázquez JB, Jiménez A, Chomón B, Villa TG. Incidence and transmission of antibiotic resistance in Campylobacter jejuni and Campylobacter coli. J Antimicrob Chemother 1995; 35:173-8; PMID:7768766; http://dx.doi.org/10.1093/jac/35.1.173
36. Lin J, Michel LO, Zhang Q. CmeABC functions as a multidrug efflux system in Campylobacter jejuni. Antimicrob Agents Chemother 2002; 46:2124-31; PMID:12069964; http://dx.doi.org/10.1128/AAC.46.7.2124-2131.2002
37. Pumbwe L, Piddock LJ. Identification and molecular characterisation of CmeB, a Campylobacter jejuni multidrug efflux pump. FEMS Microbiol Lett 2002; 206:185-9; PMID:11814661; http://dx.doi.org/10.1111/j.1574-6968.2002.tb11007.x
38. Lin J, Sahin O, Michel LO, Zhang Q. Critical role of multidrug efflux pump CmeABC in bile resistance and in vivo colonization of Campylobacter jejuni. Infect Immun 2003; 71:4250-9; PMID:12874300; http://dx.doi.org/10.1128/IAI.71.8.4250-4259.2003
39. Akiba M, Lin J, Barton YW, Zhang Q. Interaction of CmeABC and CmeDEF in conferring antimicrobial resistance and maintaining cell viability in Campylobacter jejuni. J Antimicrob Chemother 2006; 57:52-60; PMID:16303882; http://dx.doi.org/10.1093/jac/dki419
40. Jeon B, Wang Y, Hao H, Barton YW, Zhang Q. Contribution of CmeG to antibiotic and oxidative stress resistance in Campylobacter jejuni. J Antimicrob Chemother 2011; 66:79-85; PMID:21081547; http://dx.doi.org/10.1093/jac/dkq418
41. Parkhill J, Wren BW, Mungall K, Ketley JM, Churcher C, Basham D, et al. The genome sequence of the food-borne pathogen Campylobacter jejuni reveals hypervariable sequences. Nature 2000; 403:665-8; PMID:10688204; http://dx.doi.org/10.1038/35001088
42. Corcoran D, Quinn T, Cotter L, Fanning S. An investigation of the molecular mechanisms contributing to high-level erythromycin resistance in Campylobacter. Int J Antimicrob Agents 2006; 27:40-5; PMID:16318913; http://dx.doi.org/10.1016/j.ijantimicag.2005.08.019
43. Kurincic M, Botteldoorn N, Herman L, Smole Mozina S. Mechanisms of erythromycin resistance of Campylobacter spp. isolated from food, animals and humans. Int J Food Microbiol 2007; 120:186-90; PMID:17889390; http://dx.doi.org/10.1016/j.ijfoodmicro.2007.03.012
44. Pumbwe L, Randall LP, Woodward MJ, Piddock LJ. Expression of the efflux pump genes cmeB, cmeF and the porin gene porA in multiple-antibiotic-resistant Campylobacter jejuni. J Antimicrob Chemother 2004; 54:341-7; PMID:15201231; http://dx.doi.org/10.1093/jac/dkh331
45. Page WJ, Huyer G, Huyer M, Worobec EA. Characterization of the porins of Campylobacter jejuni and Campylobacter coli and implications for antibiotic susceptibility. Antimicrob Agents Chemother 1989; 33:297-303; PMID:2543277; http://dx.doi.org/10.1128/AAC.33.3.297
46. Jeon B, Muraoka W, Scupham A, Zhang Q. Roles of lipooligosaccharide and capsular polysaccharide in antimicrobial resistance and natural transformation of Campylobacter jejuni. J Antimicrob Chemother 2009; 63:462-8; PMID:19147521; http://dx.doi.org/10.1093/jac/dkn529
47. Karmali MA, De Grandis S, Fleming PC. Antimicrobial susceptibility of Campylobacter jejuni with special reference to resistance patterns of Canadian isolates. Antimicrob Agents Chemother 1981; 19:593-7; PMID:7247381; http://dx.doi.org/10.1128/AAC.19.4.593
48. Keo T, Collins J, Kunwar P, Blaser MJ, Iovine NM. Campylobacter capsule and lipooligosaccharide confer resistance to serum and cationic antimicrobials. Virulence 2011; 2:30-40; PMID:21266840; http://dx.doi.org/10.4161/viru.2.1.14752
49. Taylor DE, Ng LK, Lior H. Susceptibility of Campylobacter species to nalidixic acid, enoxacin, and other DNA gyrase inhibitors. Antimicrob Agents Chemother 1985; 28:708-10; PMID:3004325; http://dx.doi.org/10.1128/AAC.28.5.708
50. van Mourik A, Steeghs L, van Laar J, Meiring HD, Hamstra HJ, van Putten JP, et al. Altered linkage of hydroxyacyl chains in lipid A of Campylobacter jejuni reduces TLR4 activation and antimicrobial resistance. J Biol Chem 2010; 285:15828-36; PMID:20351099; http://dx.doi.org/10.1074/jbc.M110.102061
51. Akhtar SQ. Antimicrobial sensitivity and plasmid-mediated tetracycline resistance in Campylobacter jejuni isolated in Bangladesh. Chemotherapy 1988; 34:326-31; PMID:3208549; http://dx.doi.org/10.1159/000238587
52. Boonmar S, Sangsuk L, Suthivarakom K, Padungtod P, Morita Y. Serotypes and antimicrobial resistance of Campylobacter jejuni isolated from humans and animals in Thailand. Southeast Asian J Trop Med Public Health 2005; 36:130-4; PMID:15906655.
53. Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Echeverria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. Clin Infect Dis 1998; 26:341-5; PMID:9502453; http://dx.doi.org/10.1086/516303
54. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). Human Isolates Final Report, 2010. U.S. Department of Health and Human Services, CDC, 2012. (Accessed at http://www.cdc.gov/narms/reports.htm.)
55. DANMAP. 2011. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. In: The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; 2012.
56. Van Looveren M, Daube G, De Zutter L, Dumont JM, Lammens C, Wijdooghe M, et al. Antimicrobial susceptibilities of Campylobacter strains isolated from food animals in Belgium. J Antimicrob Chemother 2001; 48:235-40; PMID:11481294; http://dx.doi.org/10.1093/jac/48.2.235
57. Davidson D. In the matter of enrofloxacin for poultry: Withdrawal of approval of Bayer Corporation's new animal drug application 1 (NADA) 140-828 (Baytril). In: FDA Docket No 00N-1571 2004; 2004.
58. Miflin JK, Templeton JM, Blackall PJ. Antibiotic resistance in Campylobacter jejuni and Campylobacter coli isolated from poultry in the South-East Queensland region. J Antimicrob Chemother 2007; 59:775-8; PMID:17392353; http://dx.doi.org/10.1093/jac/dkm024
59. Unicomb LE, Ferguson J, Stafford RJ, Ashbolt R, Kirk MD, Becker NG, et al.; Australian Campylobacter Subtyping Study Group. Low-level fluoroquinolone resistance among Campylobacter jejuni isolates in Australia. Clin Infect Dis 2006; 42:1368-74; PMID:16619147; http://dx.doi.org/10.1086/503426
60. Norström M, Hofshagen M, Stavnes T, Schau J, Lassen J, Kruse H. Antimicrobial resistance in Campylobacter jejuni from humans and broilers in Norway. Epidemiol Infect 2006; 134:127-30; PMID:16409659; http://dx.doi.org/10.1017/S0950268805004814
61. Jain D, Sinha S, Prasad KN, Pandey CM. Campylobacter species and drug resistance in a north Indian rural community. Trans R Soc Trop Med Hyg 2005; 99:207-14; PMID:15653123; http://dx.doi.org/10.1016/j.trstmh.2004.09.006
62. Bester LA, Essack SY. Observational study of the prevalence and antibiotic resistance of Campylobacter spp. from different poultry production systems in KwaZulu-Natal, South Africa. J Food Prot 2012; 75:154-9; PMID:22221370; http://dx.doi.org/10.4315/0362-028X.JFP-11-237
63. Chokboonmongkol C, Patchanee P, Gölz G, Zessin KH, Alter T. Prevalence, quantitative load, and antimicrobial resistance of Campylobacter spp. from broiler ceca and broiler skin samples in Thailand. Poult Sci 2013; 92:462-7; PMID:23300314; http://dx.doi.org/10.3382/ps.2012-02599
64. Haruna M, Sasaki Y, Murakami M, Ikeda A, Kusukawa M, Tsujiyama Y, et al. Prevalence and antimicrobial susceptibility of Campylobacter in broiler flocks in Japan. Zoonoses Public Health 2012; 59:241-5; PMID:22103704; http://dx.doi.org/10.1111/j.1863-2378.2011.01441.x
65. Wardak S, Szych J, Zasada AA, Gierczynski R. Antibiotic resistance of Campylobacter jejuni and Campylobacter coli clinical isolates from Poland. Antimicrob Agents Chemother 2007; 51:1123-5; PMID:17210776; http://dx.doi.org/10.1128/AAC.01187-06
66. Sáenz Y, Zarazaga M, Lantero M, Gastanares MJ, Baquero F, Torres C. Antibiotic resistance in Campylobacter strains isolated from animals, foods, and humans in Spain in 1997-1998. Antimicrob Agents Chemother 2000; 44:267-71; PMID:10639348; http://dx.doi.org/10.1128/AAC.44.2.267-271.2000
67. Griggs DJ, Johnson MM, Frost JA, Humphrey T, Jørgensen F, Piddock LJ. Incidence and mechanism of ciprofloxacin resistance in Campylobacter spp. isolated from commercial poultry flocks in the United Kingdom before, during, and after fluoroquinolone treatment. Antimicrob Agents Chemother 2005; 49:699-707; PMID:15673754; http://dx.doi.org/10.1128/AAC.49.2.699-707.2005

68. Price LB, Johnson E, Vailes R, Silbergeld E. Fluoroquinolone-resistant Campylobacter isolates from conventional and antibiotic-free chicken products. Environ Health Perspect 2005; 113:557-60; PMID:15866763; http://dx.doi.org/10.1289/ehp.7647
69. Price LB, Lackey LG, Vailes R, Silbergeld E. The persistence of fluoroquinolone-resistant Campylobacter in poultry production. Environ Health Perspect 2007; 115:1035-9; PMID:17637919; http://dx.doi.org/10.1289/ehp.10050
70. Zhang Q, Lin J, Pereira S. Fluoroquinolone-resistant Campylobacter in animal reservoirs: dynamics of development, resistance mechanisms and ecological fitness. Anim Health Res Rev 2003; 4:63-71; PMID:15134291; http://dx.doi.org/10.1079/AHR200356
71. Luo N, Pereira S, Sahin O, Lin J, Huang S, Michel L, et al. Enhanced in vivo fitness of fluoroquinolone-resistant Campylobacter jejuni in the absence of antibiotic selection pressure. Proc Natl Acad Sci U S A 2005; 102:541-6; PMID:15634738; http://dx.doi.org/10.1073/pnas.0408966102
72. Ge B, McDermott PF, White DG, Meng J. Role of efflux pumps and topoisomerase mutations in fluoroquinolone resistance in Campylobacter jejuni and Campylobacter coli. Antimicrob Agents Chemother 2005; 49:3347-54; PMID:16048946; http://dx.doi.org/10.1128/AAC.49.8.3347-3354.2005
73. Luo N, Sahin O, Lin J, Michel LO, Zhang Q. In vivo selection of Campylobacter isolates with high levels of fluoroquinolone resistance associated with gyrA mutations and the function of the CmeABC efflux pump. Antimicrob Agents Chemother 2003; 47:390-4; PMID:12499221; http://dx.doi.org/10.1128/AAC.47.1.390-394.2003
74. Yan M, Sahin O, Lin J, Zhang Q. Role of the CmeABC efflux pump in the emergence of fluoroquinolone-resistant Campylobacter under selection pressure. J Antimicrob Chemother 2006; 58:1154-9; PMID:17023497; http://dx.doi.org/10.1093/jac/dkl412
75. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev 1997; 61:377-92; PMID:9293187.
76. Shea ME, Hiasa H. Interactions between DNA helicases and frozen topoisomerase IV-quinolone-DNA ternary complexes. J Biol Chem 1999; 274:22747-54; PMID:10428858; http://dx.doi.org/10.1074/jbc.274.32.22747
77. Willmott CJ, Critchlow SE, Eperon IC, Maxwell A. The complex of DNA gyrase and quinolone drugs with DNA forms a barrier to transcription by RNA polymerase. J Mol Biol 1994; 242:351-63; PMID:7932695; http://dx.doi.org/10.1006/jmbi.1994.1586
78. Bachoual R, Ouabdesselam S, Mory F, Lascols C, Soussy CJ, Tankovic J. Single or double mutational alterations of gyrA associated with fluoroquinolone resistance in Campylobacter jejuni and Campylobacter coli. Microb Drug Resist 2001; 7:257-61; PMID:11759087; http://dx.doi.org/10.1089/10766290152652800
79. Cooper R, Segal H, Lastovica AJ, Elisha BG. Genetic basis of quinolone resistance and epidemiology of resistant and susceptible isolates of porcine Campylobacter coli strains. J Appl Microbiol 2002; 93:241-9; PMID:12147072; http://dx.doi.org/10.1046/j.1365-2672.2002.01650.x
80. Payot S, Cloeckaert A, Chaslus-Dancla E. Selection and characterization of fluoroquinolone-resistant mutants of Campylobacter jejuni using enrofloxacin. Microb Drug Resist 2002; 8:335-43; PMID:12523631; http://dx.doi.org/10.1089/10766290260469606
81. Gootz TD, Martin BA. Characterization of high-level quinolone resistance in Campylobacter jejuni. Antimicrob Agents Chemother 1991; 35:840-5; PMID:1649570; http://dx.doi.org/10.1128/AAC.35.5.840
82. Jesse TW, Englen MD, Pittenger-Alley LG, Fedorka-Cray PJ. Two distinct mutations in gyrA lead to ciprofloxacin and nalidixic acid resistance in Campylobacter coli and Campylobacter jejuni isolated from chickens and beef cattle. J Appl Microbiol 2006; 100:682-8; PMID:16553723; http://dx.doi.org/10.1111/j.1365-2672.2005.02796.x
83. Farnell MB, Donoghue AM, Cole K, Reyes-Herrera I, Blore PJ, Donoghue DJ. Campylobacter susceptibility to ciprofloxacin and corresponding fluoroquinolone concentrations within the gastrointestinal tracts of chickens. J Appl Microbiol 2005; 99:1043-50; PMID:16238734; http://dx.doi.org/10.1111/j.1365-2672.2005.02712.x
84. McDermott PF, Bodeis SM, English LL, White DG, Walker RD, Zhao S, et al. Ciprofloxacin resistance in Campylobacter jejuni evolves rapidly in chickens treated with fluoroquinolones. J Infect Dis 2002; 185:837-40; PMID:11920303; http://dx.doi.org/10.1086/339195
85. Takahashi T, Ishihara K, Kojima A, Asai T, Harada K, Tamura Y. Emergence of fluoroquinolone resistance in Campylobacter jejuni in chickens exposed to enrofloxacin treatment at the inherent dosage licensed in Japan. J Vet Med B Infect Dis Vet Public Health 2005; 52:460-4; PMID:16364022; http://dx.doi.org/10.1111/j.1439-0450.2005.00890.x
86. Ellis-Pegler RB, Hyman LK, Ingram RJ, McCarthy M. A placebo controlled evaluation of lomefloxacin in the treatment of bacterial diarrhoea in the community. J Antimicrob Chemother 1995; 36:259-63; PMID:8537277; http://dx.doi.org/10.1093/jac/36.1.259
87. Segreti J, Gootz TD, Goodman LJ, Parkhurst GW, Quinn JP, Martin BA, et al. High-level quinolone resistance in clinical isolates of Campylobacter jejuni. J Infect Dis 1992; 165:667-70; PMID:1313069; http://dx.doi.org/10.1093/infdis/165.4.667
88. Wretlind B, Strömberg A, Ostlund L, Sjögren E, Kaijser B. Rapid emergence of quinolone resistance in Campylobacter jejuni in patients treated with norfloxacin. Scand J Infect Dis 1992; 24:685-6; PMID:1465591; http://dx.doi.org/10.3109/00365549209054659
89. Ruiz J, Goñi P, Marco F, Gallardo F, Mirelis B, Jimenez De Anta T, et al. Increased resistance to quinolones in Campylobacter jejuni: a genetic analysis of gyrA gene mutations in quinolone-resistant clinical isolates. Microbiol Immunol 1998; 42:223-6; PMID:9580533.
90. Wang Y, Huang WM, Taylor DE. Cloning and nucleotide sequence of the Campylobacter jejuni gyrA gene and characterization of quinolone resistance mutations. Antimicrob Agents Chemother 1993; 37:457-63; PMID:8384814; http://dx.doi.org/10.1128/AAC.37.3.457
91. Piddock LJ, Ricci V, Pumbwe L, Everett MJ, Griggs DJ. Fluoroquinolone resistance in Campylobacter species from man and animals: detection of mutations in topoisomerase genes. J Antimicrob Chemother 2003; 51:19-26; PMID:12493783; http://dx.doi.org/10.1093/jac/dkg033
92. Engberg J, Neimann J, Nielsen EM, Aerestrup FM, Fussing V. Quinolone-resistant Campylobacter infections: risk factors and clinical consequences. Emerg Infect Dis 2004; 10:1056-63; PMID:15207057; http://dx.doi.org/10.3201/eid1006.030669
93. Feodoroff FB, Lauhio AR, Sarna SJ, Hänninen ML, Rautelin HI. Severe diarrhoea caused by highly ciprofloxacin-susceptible Campylobacter isolates. Clin Microbiol Infect 2009; 15:188-92; PMID:19154485; http://dx.doi.org/10.1111/j.1469-0691.2008.02657.x
94. Helms M, Simonsen J, Olsen KE, Mølbak K. Adverse health events associated with antimicrobial drug resistance in Campylobacter species: a registry-based cohort study. J Infect Dis 2005; 191:1050-5; PMID:15747238; http://dx.doi.org/10.1086/428453
95. Nelson JM, Smith KE, Vugia DJ, Rabatsky-Ehr T, Segler SD, Kassenborg HD, et al. Prolonged diarrhea due to ciprofloxacin-resistant campylobacter infection. J Infect Dis 2004; 190:1150-7; PMID:15319866; http://dx.doi.org/10.1086/423282
96. Sonnevend A, Kovács J, Pál T, Akawi N, Nagelkerke N, Schneider G. Lack of correlation between the 257C-to-T mutation in the gyrA gene and clinical severity of Campylobacter jejuni infection in a region of high incidence of ciprofloxacin resistance. Scand J Infect Dis 2011; 43:905-11; PMID:21905953; http://dx.doi.org/10.3109/00365548.2011.603743
97. Wassenaar TM, Kist M, de Jong A. Re-analysis of the risks attributed to ciprofloxacin-resistant Campylobacter jejuni infections. Int J Antimicrob Agents 2007; 30:195-201; PMID:17420115; http://dx.doi.org/10.1016/j.ijantimicag.2007.01.019
98. Asai T, Harada K, Ishihara K, Kojima A, Sameshima T, Tamura Y, et al. Association of antimicrobial resistance in Campylobacter isolated from food-producing animals with antimicrobial use on farms. Jpn J Infect Dis 2007; 60:290-4; PMID:17881869.
99. Animal Drugs @ FDA. Center for Veterinary Medicine, 2012. (Accessed at http://www.accessdata.fda.gov/scripts/animaldrugsatfda/index.cfm.)
100. Cagliero C, Mouline C, Cloeckaert A, Payot S. Synergy between efflux pump CmeABC and modifications in ribosomal proteins L4 and L22 in conferring macrolide resistance in Campylobacter jejuni and Campylobacter coli. Antimicrob Agents Chemother 2006; 50:3893-6; PMID:16940070; http://dx.doi.org/10.1128/AAC.00616-06
101. Lin J, Yan M, Sahin O, Pereira S, Chang YJ, Zhang Q. Effect of macrolide usage on emergence of erythromycin-resistant Campylobacter isolates in chickens. Antimicrob Agents Chemother 2007; 51:1678-86; PMID:17353243; http://dx.doi.org/10.1128/AAC.01411-06
102. Payot S, Bolla JM, Corcoran D, Fanning S, Mégraud F, Zhang Q. Mechanisms of fluoroquinolone and macrolide resistance in Campylobacter spp. Microbes Infect 2006; 8:1967-71; PMID:16713726; http://dx.doi.org/10.1016/j.micinf.2005.12.032
103. Egger R, Korczak BM, Niederer L, Overesch G, Kuhnert P. Genotypes and antibiotic resistance of Campylobacter coli in fattening pigs. Vet Microbiol 2012; 155:272-8; PMID:21899961; http://dx.doi.org/10.1016/j.vetmic.2011.08.012
104. Gibreel A, Taylor DE. Macrolide resistance in Campylobacter jejuni and Campylobacter coli. J Antimicrob Chemother 2006; 58:243-55; PMID:16735431; http://dx.doi.org/10.1093/jac/dkl210
105. Lachance N, Gaudreau C, Lamothe F, Larivière LA. Role of the beta-lactamase of Campylobacter jejuni in resistance to beta-lactam agents. Antimicrob Agents Chemother 1991; 35:813-8; PMID:1854162; http://dx.doi.org/10.1128/AAC.35.5.813
106. Lehtopolku M, Kotilainen P, Haanperä-Heikkinen M, Nakari UM, Hänninen ML, Huovinen P, et al. Ribosomal mutations as the main cause of macrolide resistance in Campylobacter jejuni and Campylobacter coli. Antimicrob Agents Chemother 2011; 55:5939-41; PMID:21911571; http://dx.doi.org/10.1128/AAC.00314-11
107. Mamelli L, Prouzet-Mauléon V, Pagès JM, Mégraud F, Bolla JM. Molecular basis of macrolide resistance in Campylobacter: role of efflux pumps and target mutations. J Antimicrob Chemother 2005; 56:491-7; PMID:16055509; http://dx.doi.org/10.1093/jac/dki253
108. Pérez-Boto D, López-Portolés JA, Simón C, Valdezate S, Echeita MA. Study of the molecular mechanisms involved in high-level macrolide resistance of Spanish Campylobacter jejuni and Campylobacter coli strains. J Antimicrob Chemother 2010; 65:2083-8; PMID:20647243; http://dx.doi.org/10.1093/jac/dkq268
109. Ren GW, Wang Y, Shen Z, Chen X, Shen J, Wu C. Rapid detection of point mutations in domain V of the 23S rRNA gene in erythromycin-resistant Campylobacter isolates by pyrosequencing. Foodborne Pathog Dis 2011; 8:375-9; PMID:21166562; http://dx.doi.org/10.1089/fpd.2010.0676

110. Vacher S, Menard A, Bernard E, Santos A, Megraud F. Detection of mutations associated with macrolide resistance in thermophilic Campylobacter spp. by real-time PCR. Microb Drug Resist 2005; 11:40-7; PMID:15770093; http://dx.doi.org/10.1089/mdr.2005.11.40
111. Fouts DE, Mongodin EF, Mandrell RE, Miller WG, Rasko DA, Ravel J, et al. Major structural differences and novel potential virulence mechanisms from the genomes of multiple campylobacter species. PLoS Biol 2005; 3:e15; PMID:15660156; http://dx.doi.org/10.1371/journal.pbio.0030015
112. Gibreel A, Wetsch NM, Taylor DE. Contribution of the CmeABC efflux pump to macrolide and tetracycline resistance in Campylobacter jejuni. Antimicrob Agents Chemother 2007; 51:3212-6; PMID:17606685; http://dx.doi.org/10.1128/AAC.01592-06
113. Payot S, Avrain L, Magras C, Praud K, Cloeckaert A, Chaslus-Dancla E. Relative contribution of target gene mutation and efflux to fluoroquinolone and erythromycin resistance, in French poultry and pig isolates of Campylobacter coli. Int J Antimicrob Agents 2004; 23:468-72; PMID:15120725; http://dx.doi.org/10.1016/j.ijantimicag.2003.12.008
114. Logue CM, Danzeisen GT, Sherwood JS, Thorsness JL, Mercier BM, Axtman JE. Repeated therapeutic dosing selects macrolide-resistant Campylobacter spp. in a turkey facility. J Appl Microbiol 2010; 109:1379-88; PMID:20497488; http://dx.doi.org/10.1111/j.1365-2672.2010.04765.x
115. Almofti YA, Dai M, Sun Y, Haihong H, Yuan Z. Impact of erythromycin resistance on the virulence properties and fitness of Campylobacter jejuni. Microb Pathog 2011; 50:336-42; PMID:21377522; http://dx.doi.org/10.1016/j.micpath.2011.02.009
116. Han F, Pu S, Wang F, Meng J, Ge B. Fitness cost of macrolide resistance in Campylobacter jejuni. Int J Antimicrob Agents 2009; 34:462-6; PMID:19651494; http://dx.doi.org/10.1016/j.ijantimicag.2009.06.019
117. Hao H, Dai M, Wang Y, Peng D, Liu Z, Yuan Z. 23S rRNA mutation A2074C conferring high-level macrolide resistance and fitness cost in Campylobacter jejuni. Microb Drug Resist 2009; 15:239-44; PMID:19857128; http://dx.doi.org/10.1089/mdr.2009.0008
118. Zeitouni S, Collin O, Andraud M, Ermel G, Kempf I. Fitness of macrolide resistant Campylobacter coli and Campylobacter jejuni. Microb Drug Resist 2012; 18:101-8; PMID:22324770; http://dx.doi.org/10.1089/mdr.2011.0188
119. EFSA. The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2010. Eur Food Safety Auth J 2012; 10:2598-830.
120. Smith SI, Sansa TI, Coker AO. Antibiotic susceptibility patterns and beta-lactamase production of animal and human isolates of Campylobacter in Lagos, Nigeria. Z Naturforsch C 1999; 54:583-6; PMID:10488568.
121. Gibreel A, Kos VN, Keelan M, Trieber CA, Levesque S, Michaud S, et al. Macrolide resistance in Campylobacter jejuni and Campylobacter coli: molecular mechanism and stability of the resistance phenotype. Antimicrob Agents Chemother 2005; 49:2753-9; PMID:15980346; http://dx.doi.org/10.1128/AAC.49.7.2753-2759.2005
122. Caldwell DB, Wang Y, Lin J. Development, stability, and molecular mechanisms of macrolide resistance in Campylobacter jejuni. Antimicrob Agents Chemother 2008; 52:3947-54; PMID:18779354; http://dx.doi.org/10.1128/AAC.00450-08
123. Jeon B, Zhang Q. Sensitization of Campylobacter jejuni to fluoroquinolone and macrolide antibiotics by antisense inhibition of the CmeABC multidrug efflux transporter. J Antimicrob Chemother 2009; 63:946-8; PMID:19279049; http://dx.doi.org/10.1093/jac/dkp067
124. Huyer MP, Hancock T, Page RW. Outer membrane porin protein of *Campylobacter jejuni.* FEMS Microbiol Lett 1986; 37:247-50; http://dx.doi.org/10.1111/j.1574-6968.1986.tb01803.x
125. Hancock RE, Bell A. Antibiotic uptake into gram-negative bacteria. Eur J Clin Microbiol Infect Dis 1988; 7:713-20; PMID:2850910; http://dx.doi.org/10.1007/BF01975036
126. Vaara M. Outer membrane permeability barrier to azithromycin, clarithromycin, and roxithromycin in gram-negative enteric bacteria. Antimicrob Agents Chemother 1993; 37:354-6; PMID:8383945; http://dx.doi.org/10.1128/AAC.37.2.354
127. Logan SM, Trust TJ. Structural and antigenic heterogeneity of lipopolysaccharides of Campylobacter jejuni and Campylobacter coli. Infect Immun 1984; 45:210-6; PMID:6203838.
128. Naess V, Hofstad T. Isolation and chemical composition of lipopolysaccharide from Campylobacter jejuni. Acta Pathol Microbiol Immunol Scand B 1982; 90:135-9; PMID:7080831.
129. Giesbrecht P, Kersten T, Maidhof H, Wecke J. Staphylococcal cell wall: morphogenesis and fatal variations in the presence of penicillin. Microbiol Mol Biol Rev 1998; 62:1371-414; PMID:9841676.
130. Alfredson DA, Korolik V. Isolation and expression of a novel molecular class D beta-lactamase, OXA-61, from Campylobacter jejuni. Antimicrob Agents Chemother 2005; 49:2515-8; PMID:15917560; http://dx.doi.org/10.1128/AAC.49.6.2515-2518.2005
131. Griggs DJ, Peake L, Johnson MM, Ghori S, Mott A, Piddock LJ. Beta-lactamase-mediated beta-lactam resistance in Campylobacter species: prevalence of Cj0299 (bla OXA-61) and evidence for a novel beta-Lactamase in C. jejuni. Antimicrob Agents Chemother 2009; 53:3357-64; PMID:19506058; http://dx.doi.org/10.1128/AAC.01655-08
132. Lachance N, Gaudreau C, Lamothe F, Turgeon F. Susceptibilities of beta-lactamase-positive and -negative strains of Campylobacter coli to beta-lactam agents. Antimicrob Agents Chemother 1993; 37:1174-6; PMID:8390812; http://dx.doi.org/10.1128/AAC.37.5.1174
133. Tajada P, Gomez-Graces JL, Alós JI, Balas D, Cogollos R. Antimicrobial susceptibilities of Campylobacter jejuni and Campylobacter coli to 12 beta-lactam agents and combinations with beta-lactamase inhibitors. Antimicrob Agents Chemother 1996; 40:1924-5; PMID:8843305.
134. Wright EP, Knowles MA. Beta-lactamase production by Campylobacter jejuni. J Clin Pathol 1980; 33:904-5; PMID:6968758; http://dx.doi.org/10.1136/jcp.33.9.904-b
135. Alfredson DA, Korolik V. Identification of putative zinc hydrolase genes of the metallo-beta-lactamase superfamily from Campylobacter jejuni. FEMS Immunol Med Microbiol 2007; 49:159-64; PMID:17266723; http://dx.doi.org/10.1111/j.1574-695X.2006.00197.x
136. Potter ME, Blaser MJ, Sikes RK, Kaufmann AF, Wells JG. Human Campylobacter infection associated with certified raw milk. Am J Epidemiol 1983; 117:475-83; PMID:6837559.
137. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. [second page, table of contents.]. Microbiol Mol Biol Rev 2001; 65:232-60; PMID:11381101; http://dx.doi.org/10.1128/MMBR.65.2.232-260.2001
138. Bolla JM, Loret E, Zalewski M, Pagés JM. Conformational analysis of the Campylobacter jejuni porin. J Bacteriol 1995; 177:4266-71; PMID:7543469.
139. Kervella M, Fauchère JL, Fourel D, Pagès JM. Immunological cross-reactivity between outer membrane pore proteins of Campylobacter jejuni and Escherichia coli. FEMS Microbiol Lett 1992; 78:281-5; PMID:1337053; http://dx.doi.org/10.1111/j.1574-6968.1992.tb05582.x
140. Epe B, Woolley P, Hornig H. Competition between tetracycline and tRNA at both P and A sites of the ribosome of Escherichia coli. FEBS Lett 1987; 213:443-7; PMID:3104093; http://dx.doi.org/10.1016/0014-5793(87)81539-9
141. Goldman RA, Hasan T, Hall CC, Strycharz WA, Cooperman BS. Photoincorporation of tetracycline into Escherichia coli ribosomes. Identification of the major proteins photolabeled by native tetracycline and tetracycline photoproducts and implications for the inhibitory action of tetracycline on protein synthesis. Biochemistry 1983; 22:359-68; PMID:6337627; http://dx.doi.org/10.1021/bi00271a020
142. Manavathu EK, Hiratsuka K, Taylor DE. Nucleotide sequence analysis and expression of a tetracycline-resistance gene from Campylobacter jejuni. Gene 1988; 62:17-26; PMID:2836268; http://dx.doi.org/10.1016/0378-1119(88)90576-8
143. Salyers AA, Speer BS, Shoemaker NB. New perspectives in tetracycline resistance. Mol Microbiol 1990; 4:151-6; PMID:2181236; http://dx.doi.org/10.1111/j.1365-2958.1990.tb02025.x
144. Dasti JI, Gross U, Pohl S, Lugert R, Weig M, Schmidt-Ott R. Role of the plasmid-encoded tet(O) gene in tetracycline-resistant clinical isolates of Campylobacter jejuni and Campylobacter coli. J Med Microbiol 2007; 56:833-7; PMID:17510271; http://dx.doi.org/10.1099/jmm.0.47103-0
145. Taylor DE. Plasmid-mediated tetracycline resistance in Campylobacter jejuni: expression in Escherichia coli and identification of homology with streptococcal class M determinant. J Bacteriol 1986; 165:1037-9; PMID:3005233.
146. Batchelor RA, Pearson BM, Friis LM, Guerry P, Wells JM. Nucleotide sequences and comparison of two large conjugative plasmids from different Campylobacter species. Microbiology 2004; 150:3507-17; PMID:15470128; http://dx.doi.org/10.1099/mic.0.27112-0
147. Taylor DE, Courvalin P. Mechanisms of antibiotic resistance in Campylobacter species. Antimicrob Agents Chemother 1988; 32:1107-12; PMID:3056250; http://dx.doi.org/10.1128/AAC.32.8.1107
148. Sahin O, Plummer PJ, Jordan DM, Sulaj K, Pereira S, Robbe-Austerman S, et al. Emergence of a tetracycline-resistant Campylobacter jejuni clone associated with outbreaks of ovine abortion in the United States. J Clin Microbiol 2008; 46:1663-71; PMID:18322054; http://dx.doi.org/10.1128/JCM.00031-08
149. Bérdy J. CRC handbook of antibiotic compounds. Boca Raton, Fla.: CRC Press; 1980.
150. Jana S, Deb JK. Molecular understanding of aminoglycoside action and resistance. Appl Microbiol Biotechnol 2006; 70:140-50; PMID:16391922; http://dx.doi.org/10.1007/s00253-005-0279-0
151. Taber HW, Mueller JP, Miller PF, Arrow AS. Bacterial uptake of aminoglycoside antibiotics. Microbiol Rev 1987; 51:439-57; PMID:3325794.
152. Bryan LE, Kwan S. Roles of ribosomal binding, membrane potential, and electron transport in bacterial uptake of streptomycin and gentamicin. Antimicrob Agents Chemother 1983; 23:835-45; PMID:6351731; http://dx.doi.org/10.1128/AAC.23.6.835
153. Bryan LE, Van Den Elzen HM. Gentamicin accumulation by sensitive strains of Escherichia coli and Pseudomonas aeruginosa. J Antibiot (Tokyo) 1975; 28:696-703; PMID:810469; http://dx.doi.org/10.7164/antibiotics.28.696
154. Hermann T. Aminoglycoside antibiotics: old drugs and new therapeutic approaches. Cell Mol Life Sci 2007; 64:1841-52; PMID:17447006; http://dx.doi.org/10.1007/s00018-007-7034-x
155. Ouellette M, Gerbaud G, Lambert T, Courvalin P. Acquisition by a Campylobacter-like strain of aphA-1, a kanamycin resistance determinant from members of the family Enterobacteriaceae. Antimicrob Agents Chemother 1987; 31:1021-6; PMID:2821885; http://dx.doi.org/10.1128/AAC.31.7.1021

156. Tenover FC, Fennell CL, Lee L, LeBlanc DJ. Characterization of two plasmids from Campylobacter jejuni isolates that carry the aphA-7 kanamycin resistance determinant. Antimicrob Agents Chemother 1992; 36:712-6; PMID:1503433; http://dx.doi.org/10.1128/AAC.36.4.712

157. Tenover FC, Filpula D, Phillips KL, Plorde JJ. Cloning and sequencing of a gene encoding an aminoglycoside 6'-N-acetyltransferase from an R factor of Citrobacter diversus. J Bacteriol 1988; 170:471-3; PMID:2826403.

158. Tenover FC, Gilbert T, O'Hara P. Nucleotide sequence of a novel kanamycin resistance gene, aphA-7, from Campylobacter jejuni and comparison to other kanamycin phosphotransferase genes. Plasmid 1989; 22:52-8; PMID:2550983; http://dx.doi.org/10.1016/0147-619X(89)90035-8

159. Olkkola S, Juntunen P, Heiska H, Hyytiäinen H, Hänninen ML. Mutations in the rpsL gene are involved in streptomycin resistance in Campylobacter coli. Microb Drug Resist 2010; 16:105-10; PMID:20370506; http://dx.doi.org/10.1089/mdr.2009.0128

160. Hannula M, Hänninen ML. Effect of putative efflux pump inhibitors and inducers on the antimicrobial susceptibility of Campylobacter jejuni and Campylobacter coli. J Med Microbiol 2008; 57:851-5; PMID:18566143; http://dx.doi.org/10.1099/jmm.0.47823-0

161. Pumbwe L, Piddock LJV. Identification and molecular characterisation of CmeB, a Campylobacter jejuni multidrug efflux pump. FEMS Microbiol Lett 2002; 206:185-9; PMID:11814661; http://dx.doi.org/10.1111/j.1574-6968.2002.tb11007.x