Readers Insight
Publisher of open access books and journals

PJMLS

Print ISSN: 2707-4471. Online ISSN: 2707-448X

Review Article	Pak-Euro Journal of Medical and Life Sciences
DOI: 10.31580/pjmls.v4iSpecialIs.2632	Copyright © All rights are reserved by Corresponding Author
Vol. 4 No. Sp.1, 2022: pp. S166-S171	
www.readersinsight.net/pjmls	
Submission: January 03, 2021	**Revised:** June 13, 2022 **Accepted:** June 27, 2022

CAMPYLOBACTER JEJUNI AS AN EMERGING MULTIDRUG-RESISTANT (MDR) PATHOGEN

Nazia Naz[1]*, Abdul Samad[2], Sajjad Haider[1]

[1]**Department of Pharmacology,** Faculty of Pharmacy & Health Sciences, University of Balochistan, Quetta, Pakistan

[2]**Center for Advanced Studies in Vaccinology and Biotechnology,** University of Balochistan, Quetta, Pakistan

*Corresponding Author: Nazia Naz. nazn8806@gmail.com

Abstract

Antimicrobial resistance is a serious health problemworldwide, harming humans, environment and animals due to irrational and increase use of antibiotics in different areas (agriculture, farming, and human medicine). There are several factors contributing to the spread of drug resistance including the movement of diseased humans and animals, improper use of antibiotics, ineffective infection control measures, agricultural waste and environmental contaminants. Humans who are exposed to the Campylobacter get gastroenteritis, it is a gram negative bacteria needs microaerophilic environment for growth. ''Antibiotics such as fluoroquinolones and macrolides are the preferred medication for treating campylobacteriosis are losing their effectiveness against this food-borne zoonotic pathogen''. As a zoonotic pathogen the infection spreads to humans from animal reservior by contaminated food, water and milk. The use of antibiotics in agriculture, human medicine and in animals as growth promoters can result in the emergence of Campylobacter resistance but the clinically significant antibiotics are losing their effectiveness against Campylobacter and the health of general people is being harmed by this rising resistance. It is challenging to stop the emergence and spread of Campylobaceter that is resistant to antibiotics due to the zoonotic nature of the disease, which makes it susceptible to drugs utilized both in traditional remedy and livestock farming. The most common pathogen associated with human Food-borne outbreaks is thought to be Campylobacter jejuni. Several studies conducted in the recent years have revealed antimicrobial resistance (AMR) in C. jejuni strains. Concerns are growing as a result of the WHO's current designation of C. jejuni as a "high priority pathogen" since it has become resistant to a number of medications, including fluoroquinolones, macrolides, and other groups which has limited the options for treatment.

Keywords: *Antimicrobial resistance, Campylobacter spp, Campylobacteriosis, Food born pathogen,Irrational use of antibiotics, Zoonotic pathogen*

INTRODUCTION

Worldwide Antimicrobial Resistance (AMR) is the biggest health issue which best illustrates the human health concern (1) because of the irrational and increased usage of antibiotics many sectors (agriculture, farming and human medicine), each of these three factors has a connection to AMR (2, 3). The choice of antibiotics encourages bacteria to develop and spread resistance genes that can affect other organisms of the same or different species. When bacteria develop antibiotic resistance, they become more able to spread the disease to humans, animals and the environment. The mismanagement, insufficient infection control, agricultural debris, environmental toxins and the movement of infected people and animals with resistant bacteria all contribute to emergence of resistance (4, 5). Antimicrobial resistance is a major issue worldwide that influence human, environment and animals. AMR is such a complicated issue, it requires a multidisciplinary approach to handle to be handled (6, 7).

CAMPLOBACTER

According to the WHO, *Campylobacter* is one of the most common causes of gastroenteritis in both industrialized and developing countries (8-10). *Campylobacter jejuni* is a commensal bacteria found in chickens' digestive tracts, are the most prevalent specie that are thermotolerant (11). The majority of *Campylobacter* spp are seen in broilers, with the colonisation of their ceca reaching 109 cfu/g cecal content(12). Despite the fact that human campylobacteriosis is not require any treatment, although in certain cases first-line antibiotics like erythromycin (macrolide) and ciprofloxacin (fluoroquinolone) are administered. Various studies have shown that *Campylobacter* antimicrobial resistance is increasing particularly against fluoroquinolones(13, 14). Antibiotic usage in veterinary medicine as a growth stimulant for prophylactic measure or on therapeutic intervention has been associated with an increase in resistance(15, 16). As a result the resistant isolates of *Campylobacter* could spread across the world, putting public health at high risk (8, 17).

RESISTANCE MECHANISM

Multidrug resistance may arise as a result of the acquisition of several resistance factors and genetic mechanisms. It may be carried on chromosomes or plasmids showing a combination of endogenous and acquired genes (18-20). *Campylobacter* genes linked to antibiotic resistance have been identified by many researchers (21, 22). Following are the mechanisms that are responsible for resistance development.

1. Mutations in DNA gyrase that cause alteration of the antibiotics target and its expression.
2. Expression of the major outer membrane protein that make antibiotics unable to reach its target.
3. CmeABC multidrug efflux pumps for the efflux of antibiotics.
4. Beta lactamase production for the changing and inactivation of antibiotics.

RESISTANCE TO FLOROQUNOLONES (FQs)

FQs resistance in *Campylobacter* mostly occur due to point mutations in DNA gyrase A (GyrAquinolone)'s resistance-determining region (QRDR) (23, 24). *Campylobacter* has been found to have no alterations in DNA gyrase B that affect FQ resistance (25, 26). The topoisomerase IV (parC/parE) genes play a similar role in Gram-negative bacteria that have FQ resistance; however, *Campylobacter* lacks these genetic traits . Therefore, it is not unexpected that changes in parC/parE are unrelated to FQ antibiotic resistance in *Campylobacter* (27).

Contrary to other enteric pathogens (such as *Salmonella* and *E. coli*) *Campylobacter* sensitivity to FQ antibiotics can be significantly decreased by a single point mutation in gyrA's QRDR. For high-level FQ resistance, gyrA and parC point mutations must accumulate over time (23, 28, 29). The T86I substitution in the gyrase caused by the C257T mutation in the gyrA gene improves resistance to FQs, this mutation is most frequently seen in *Campylobacter* isolates that are FQ-resistant. Compared to the less common resistance-associated mutations T86K, A70T, D90N, the T86I mutation imparts FQ resistance to a larger extent (30). The multidrug efflux pump CmeABC lowers the drugs' percentage in *Campylobacter* cells, also contributes to FQ resistance. As a result, CmeABC and gyrA mutations work together to mediate FQ resistance. In *Campylobacter* in contrast to plasmid-mediated factors of FQ determinants like qnr, aac(6′)-Ib-cr, and qepA chromosome contains all identified FQ resistance genes (28, 29, 31).

RESISTANCE TO MACROLIDE

Target modification and active efflux are two mechanisms of macrolide resistance in *Campylobacter* (23, 32).*Campylobacter,* via gene mutation in the ribosomal proteins L4and/or L22, or by enzyme-mediated methylation of the 23S rRNA,could develop macrolide resistance by rRNA methylation. *Campylobacter* has been found to have macrolide resistance due to point mutations in the 23S rRNA, the ribosomal proteins L4 and L22, or enzyme-mediated methylation''. However, it has been discovered that in *C. jejuni* and *C. coli*, macrolide resistance is most frequently caused by point mutations in the 23S rRNA domain V (23, 32, 33) . Accordingly, these point mutations are found at locations 2074 and 2075 in the 23S rRNA, which correspond to the locations 2058 and 2059 of *E. coli*. Mutations in *C. jejuni* and *C. coli* A2074C, A2074G and A2075G (erythromycin MIC >128 g/ml lead to high levels of resistance to macrolide antibiotics (33-36).

A2075G is the most common mutation in clinical and field isolates (23, 32, 37). *Campylobacter's* 23S rRNA gene contains three copies. Certain mutations such as A2074T, which slightly increases, there may not be three copies of the gene encoding erythromycin resistance.

In *C. coli* and *C. jejuni*, the rrn operon is present in three copies (38). *Campylobacter's* resistance to macrolides is a result of both target alteration and active efflux (11,22,47,(39, 40). In isolates with low or moderate degrees of resistance macrolide susceptibility was fully recovered after CmeABC efflux pump deactivation (35).

RESISTANCE TO TETRACYCLINE

Tetracycline resistance in *Campylobacter* is caused by the presence of Tet (O), which is commonly detected in samples from a variety of animal taxa (41). *Campylobacter* has not yet been found to contain any other tet resistance genes. This gene encodes the ribosomal protective protein tet (O) (42). According to recent findings, this protein identifies and binds to an open A site on the bacterial ribosome in a way that alters the structure of the ribosome, releasing the attached tetracycline molecule (43). Furthermore, the conformational shift lasts for a long time, allowing for effective protein elongation (43) . Tet(O) in *Campylobacter* was most likely derived from *Streptomyces*, *Streptococcus*, or *Enterococcus spp*. through horizontal gene transfer (HGT), as determined by G-C content, sequence homology, codon usage, and hybridization studies (44). The majority of strains have plasmid-encoded tet(O) genes (45). Although some isolates do possess a copy that is chromosomally encoded (46, 47) .

RESISTANCE TO AMINOGLYCOSIDES

There has been little focus on *Campylobacter* resistance to other antibiotics than *Campylobacter* resistance to FQs, macrolides and tetracyclines. Drug alteration proteins confer aminoglycoside resistance in *Campylobacter.* Numerous aminoglycoside-modifying enzymes from *Campylobacter* have been discovered, including the 3'aminoglycoside phosphotransferases types I, III, IV, and VII, the 3',9-aminoglycoside adenyltransferase, and the 6'aminoglycoside adenyl transferase (24).

RESISTANCE TO BETA-LACTAMS AND OTHER ANTIBIOTICS

In general, beta-lactam antibiotics are ineffective against *Campylobacter* species, and it appears that both intrinsic resistance and the formation of β-lactamase are responsible for this class of medication's resistance(24, 48). *Campylobacter* is essentially resistant to a number of antibiotics including bacitracin, novobiocin, rifampin, streptogramin B, trimethoprim and vancomycin(49, 50). Although the causes of intrinsic resistance are unknown, it is thought that the important factors include the poor membrane permeability of *Campylobacter* and the active efflux provided by multidrug-efflux transporters (26).

FUTURE PERSPECTIVES AGAINST MDR CAMPYLOBACTER

Toward the future perspectives antibiotic resistance to *Campylobacter* is still a problem for public health and food safety. A greater understanding of the additional mechanisms influencing its necessity for FQ-resistant *Campylobacter* to spread and persist among different hosts and ecosystems. FQ medications are becoming less effective at treating human campylobacteriosis due to rising prevalence of FQ resistance exploring the impact of FQ resistance on *Campylobacter* fitness and whether eliminating FQ antibiotics from animal production, it will be interesting if the prevalence of FQ-resistant *Campylobacter* decreases. Additionally, it is critical to research more contemporary innovative therapeutic approaches that prevent the selection of FQ-resistant mutations as well as FQs that successfully combat ciprofloxacin resistant. Despite the fact that erythromycin resistance has been discovered recently in some *C. coli* and *C. jejuni* strains, caution should be taken when using macrolides, which are still the most useful drugs for treating *Campylobacter* infections. More study is required to understand how selection pressure leads to the emergence of macrolide-resistant *Campylobacter* bacteria. Although the functions of other efflux transporters in antibiotic resistance are yet unknown, *Campylobacter* antibiotic resistance has been shown to be significantly influenced by CmeABC, Understanding the role of these efflux transporters in *Campylobacter*

physiology will require more study. Antibiotic-resistant *Campylobacter* can be controlled using contemporary techniques that focus on drug efflux transporters or prevent the establishment and spread of resistance determinants.

CONCLUSION

In order to combat AMR and MDR pathogens like *Campylobacter*, it is essential to never use antibiotics as growth promoters and infrequently for prophylaxis and must only use as a treatment. The types and quantities of antimicrobials used in medical procedures must be strictly and appropriately regulated. Resistant *Campylobacter* must also be monitored and controlled as it spreads throughout the environment.

References:

1. Organization WH. Antimicrobial resistance: global report on surveillance: World Health Organization; 2014.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N. Antibiotic resistance—the need for global solutions. The Lancet infectious diseases. 2013;13(12):1057-98.
3. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. 2016.
4. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. The Lancet Planetary Health. 2018;2(9):e398-e405.
5. Bürgmann H, Frigon D, H Gaze W, M Manaia C, Pruden A, Singer AC. Water and sanitation: an essential battlefront in the war on antimicrobial resistance. FEMS microbiology ecology. 2018;94(9):fiy101.
6. Collignon PJ, McEwen SA. One health—its importance in helping to better control antimicrobial resistance. Tropical medicine and infectious disease. 2019;4(1):22.
7. Shrestha K, Acharya KP, Shrestha S. One health: The interface between veterinary and human health. International Journal of One Health. 2018;4(47):8-14.
8. Organization WH. Global diffusion of eHealth: making universal health coverage achievable: report of the third global survey on eHealth: World Health Organization; 2017.
9. Natsos G, Koutoulis K, Sossidou E, Chemaly M, Mouttotou N. Campylobacter spp. infection in humans and poultry. Journal of the Hellenic Veterinary Medical Society. 2016;67(2):65-82.
10. Pedersen SK, Wagenaar JA, Vigre H, Roer L, Mikoleit M, Aidara-Kane A. Proficiency of WHO global foodborne infections network external quality assurance system participants in identification and susceptibility testing of thermotolerant Campylobacter spp. from 2003 to 2012. Journal of Clinical Microbiology. 2018;56(11):e01066-18.
11. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of Campylobacter infection. Clinical microbiology reviews. 2015;28(3):687-720.
12. Boelaert F, Amore G, Van der Stede Y, Hugas M. EU-wide monitoring of biological hazards along the food chain: achievements, challenges and EFSA vision for the future. Current Opinion in Food Science. 2016;12:52-62.
13. Steiner TJ, Birbeck GL, Jensen R, Katsarava Z, Martelletti P, Stovner LJ. The global campaign, world health organization and lifting the burden: collaboration in action. Springer; 2011. p. 273-4.
14. Wieczorek MA, Neumann GA, Nimmo F, Kiefer WS, Taylor GJ, Melosh HJ. The crust of the Moon as seen by GRAIL. Science. 2013;339(6120):671-5.
15. Radostits OM, Rubinstein E. The therapeutic use of fluoroquinolones in poultry: the effect on Campylobacter and the potential human health consequences. International journal of infectious diseases. 2002;6:S49-S52.
16. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and therapeutics. 2015;40(4):277.
17. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors—United States, 2005–2013. 2014.
18. Wilson M, O'Hanlon R, Prasad S, Deighan A, MacMillan P, Oxborough D. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. Journal of applied physiology. 2011.
19. Selinger E, Whyte K. Is there a right way to nudge? The practice and ethics of choice architecture. Sociology Compass. 2011;5(10):923-35.

20. Nguyen D, Rieu I, Mariani C, van Dam NM. How plants handle multiple stresses: hormonal interactions underlying responses to abiotic stress and insect herbivory. Plant Molecular Biology. 2016;91(6):727-40.
21. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. The Lancet Planetary Health. 2017;1(8):e316-e27.
22. Iovine NM. Resistance mechanisms in Campylobacter jejuni. Virulence. 2013;4(3):230-40.
23. Payot S, Bolla J-M, Corcoran D, Fanning S, Mégraud F, Zhang Q. Mechanisms of fluoroquinolone and macrolide resistance in Campylobacter spp. Microbes and Infection. 2006;8(7):1967-71.
24. Nachamkin I, Szymanski CM, Blaser MJ. Campylobacter: ASM Press; 2008.
25. Payot S, Cloeckaert A, Chaslus-Dancla E. Selection and characterization of fluoroquinolone-resistant mutants of Campylobacter jejuni using enrofloxacin. Microbial drug resistance. 2002;8(4):335-43.
26. Bachoual R, Ouabdesselam S, Mory F, Lascols C, Soussy C-J, Tankovic J. Single or double mutational alterations of gyrA associated with fluoroquinolone resistance in Campylobacter jejuni and Campylobacter coli. Microbial drug resistance. 2001;7(3):257-61.
27. Parkhill J, Wren B, Mungall K, Ketley J, Churcher C, Basham D. The genome sequence of the food-borne pathogen Campylobacter jejuni reveals hypervariable sequences. Nature. 2000;403(6770):665-8.
28. 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. Antimicrobial agents and chemotherapy. 2003;47(1):390-4.
29. Ge B, McDermott PF, White DG, Meng J. Role of efflux pumps and topoisomerase mutations in fluoroquinolone resistance in Campylobacter jejuni and Campylobacter coli. Antimicrobial agents and chemotherapy. 2005;49(8):3347-54.
30. Engberg J, Aarestrup FM, Taylor DE, Gerner-Smidt P, Nachamkin I. Quinolone and macrolide resistance in Campylobacter jejuni and C. coli: resistance mechanisms and trends in human isolates. Emerging infectious diseases. 2001;7(1):24.
31. Lin J, Michel LO, Zhang Q. CmeABC functions as a multidrug efflux system in Campylobacter jejuni. Antimicrobial agents and chemotherapy. 2002;46(7):2124-31.
32. Prachantasena S, Charununtakorn P, Muangnoicharoen S, Hankla L, Techawal N, Chaveerach P. Distribution and genetic profiles of Campylobacter in commercial broiler production from breeder to slaughter in Thailand. PLoS One. 2016;11(2):e0149585.
33. Corcoran D, Quinn T, Cotter L, Fanning S. An investigation of the molecular mechanisms contributing to high-level erythromycin resistance in Campylobacter. International journal of antimicrobial agents. 2006;27(1):40-5.
34. Gibreel A, Kos VN, Keelan M, Trieber CA, Levesque S, Michaud S. Macrolide resistance in Campylobacter jejuni and Campylobacter coli: molecular mechanism and stability of the resistance phenotype. Antimicrobial agents and chemotherapy. 2005;49(7):2753-9.
35. Mamelli L, Prouzet-Mauléon V, Pagès J-M, Mégraud F, Bolla J-M. Molecular basis of macrolide resistance in Campylobacter: role of efflux pumps and target mutations. Journal of Antimicrobial Chemotherapy. 2005;56(3):491-7.
36. Lin J, Yan M, Sahin O, Pereira S, Chang Y-J, Zhang Q. Effect of macrolide usage on emergence of erythromycin-resistant Campylobacter isolates in chickens. Antimicrobial agents and chemotherapy. 2007;51(5):1678-86.
37. Kurinčič M, Botteldoorn N, Herman L, Možina SS. Mechanisms of erythromycin resistance of Campylobacter spp. isolated from food, animals and humans. International Journal of Food Microbiology. 2007;120(1-2):186-90.
38. Fouts DE, Mongodin EF, Mandrell RE, Miller WG, Rasko DA, Ravel J. Major structural differences and novel potential virulence mechanisms from the genomes of multiple Campylobacter species. PLoS biology. 2005;3(1):e15.
39. Gibreel A, Wetsch NM, Taylor DE. Contribution of the CmeABC efflux pump to macrolide and tetracycline resistance in Campylobacter jejuni. Antimicrobial agents and chemotherapy. 2007;51(9):3212-6.
40. 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. International journal of antimicrobial agents. 2004;23(5):468-72.

41. Moore JE, Barton MD, Blair IS, Corcoran D, Dooley JS, Fanning S. The epidemiology of antibiotic resistance in Campylobacter. Microbes and Infection. 2006;8(7):1955-66.
42. Taylor D, Hiratsuka K, Ray H, Manavathu EK. Characterization and expression of a cloned tetracycline resistance determinant from Campylobacter jejuni plasmid pUA466. Journal of bacteriology. 1987;169(7):2984-9.
43. Hashimi H, Kaltenbrunner S, Zíková A, Lukeš J. Trypanosome mitochondrial translation and tetracycline: no sweat about Tet. PLoS pathogens. 2016;12(4):e1005492.
44. 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(10):3507-17.
45. Taylor DE, Garner RS, Allan BJ. Characterization of tetracycline resistance plasmids from Campylobacter jejuni and Campylobacter coli. Antimicrobial agents and chemotherapy. 1983;24(6):930-5.
46. 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. Journal of medical microbiology. 2007;56(6):833-7.
47. Pratt A, Korolik V. Tetracycline resistance of Australian Campylobacter jejuni and Campylobacter coli isolates. Journal of Antimicrobial Chemotherapy. 2005;55(4):452-60.
48. Tian G-B, Wang H-N, Zhang A-Y, Zhang Y, Fan W-Q, Xu C-W. Detection of clinically important β-lactamases in commensal Escherichia coli of human and swine origin in western China. Journal of medical microbiology. 2012;61(2):233-8.
49. Taylor DE, Courvalin P. Mechanisms of antibiotic resistance in Campylobacter species. Antimicrobial agents and chemotherapy. 1988;32(8):1107-12.
50. Vieira A, Seddon AM, Karlyshev AV. Campylobacter–Acanthamoeba interactions. Microbiology. 2015;161(5):933-47.