Campylobacter and It's Role in Gastroenteritis: Review Article

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Abstract

Rotavirus is the main causative organisms causing diarrhea in children younger than 5 years. It is involved in many episodes of gastroenteritis across the world, and yearly thousands of deaths, mostly in the developing countries. Co-infection between Rotavirus and Campylobacter have been previously reported worldwide. There are different techniques for diagnosis of Rotavirus and Campylobacter infection with wide range of sensitivities and specificities. Determining the exact cause of acute diarrhea is required to predict the disease progression and decide the optimal treatment. In addition, adequate knowledge and information on local burden, trends, and age distribution of Rotavirus gastroenteritis is needed to help decision-makers consider the introduction of a Rotavirus vaccine as part of their immunization programs. In addition, continuous surveillance of rotavirus genotypes is required to determine if the vaccines could be used to cover the prevalent genotypes.

KeyWords: Campylobacter, Gastroenteritis,Rotavirus .

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Introduction.

Historical background:

Theodor Escherich was the first to identify what are now known as Campylobacters in 1886 in infants' stool samples who had died from a condition he called "cholera infantum." Numerous papers detailing the incidence of such "spirilla" in cases of "cholera-like" and "dysenteric" sickness occurred over the years up until the turn of the century. In diarrhoeal stool samples, these organisms were mostly detected in the colon. ***(1).***

In 1913, Sir John McFadyean and Stockman reported finding bacteria similar to Vibrio in the embryonic tissues of lambs that had been aborted. Campylobacters were consistently referred to as "Vibrio-like organisms" for a number of years before Sebald and Veron gave the genus the name "Campylobacter" in 1963 after demonstrating significant biological differences with Vibrio species and based on the shape and requirement for microaerophilic growth ***(2).***

Structure and properties of Campylobacter:

The word "*Campylobacter*" is derived from the Greek *Campylo*("curved") and *bacter* ("rod")**(3).**

The majority of Campylobacter spp. have comma- or curved-shaped gram negativerod-like shapes and can move by means of unipolar or bipolar flagella.The size of bacterial cells is small and ranges from 0.2 to 0.9 µm in width and 0.5 to 5 µm in length. In a microaerophilic atmosphere, they thrive between 37 and 42 °C. C. jejuni can transform into a coccus form when exposed to breathable oxygen. Most Campylobacter species can reduce nitrate and are found to be positive for the oxidase and catalase tests. ***(4).***

Campylobacter spp. are non-fermentative, oxidase and catalase tests positive. They can survive in the environment with low oxygen concentration. However,

C. jejuni can be changed to coccal form when exposed to the atmospheric oxygen. Campylobacters spp. are best cultured at 42°C and can survive for a short time at a refrigerator temperature up to 15 times than at 20°C. However, their survival is poor at room temperature and die out slowly through freezing as well as the cells are heat sensitive and are destroyed at a temperature greater than 48 °C ***(5).***

Genomics:

Starting with C. jejuni in 2000, the genomes of various Campylobacter species have been sequenced. These genome analyses have discovered molecular markers unique to Campylobacter species. Genomes of Campylobacter ssp. range in size from 1.60 to 1.90 Mbp, making them relatively tiny in comparison to those of other gastrointestinal infections. Hypervariable sections are a common feature of Campylobacter genomes, and they can vary significantly between strains ***(2).***

The genes in Campylobacter species that control motility have been the subject of studies. Two flagellin genes, flaA and flaB, are present in some Campylobacter species in tandem for motility. These genes are subject to intergenic recombination, which increases their pathogenicity ***(1).***

Virulence factors and Pathogenesis:

Campylobacteriosis, a gastrointestinal infection, can be brought on by campylobacter. After infection, the incubation period lasts for 24 to 72 hours. Consisting primarily of cramps, fever, and pain, this is characterised by an inflammatory, occasionally bloody diarrhoea or dysentery condition ***(6).***

However, since antacids reduce natural gastric acid, those who take them (such as those with gastritis or stomach ulcers) are more likely to get sickness from a smaller number of germs ***(2).***

The jejunum, ileum, and colon are among the tissue injury sites. The majority of C jejuni strains produce cytolethal distending toxin, which prevents cell division and immune system activation. This enables the bacteria to avoid detection by the immune system and endure for a brief period of time inside intestinal cells ***(1).***

Mode of transmission:

Fecal-oral transmission, consumption of tainted food or drink, and consumption of raw meat are the most frequent modes of transmission. Foods linked to campylobacteriosis include contaminated fruit, raw dairy products, and undercooked or raw chicken. Campylobacter rarely causes sickness when a person is exposed to less than 10,000 organisms because the bacteriais sensitive to the stomach's natural production of hydrochloric acid. As a result, the infectious dosage is quite large ***(4).***

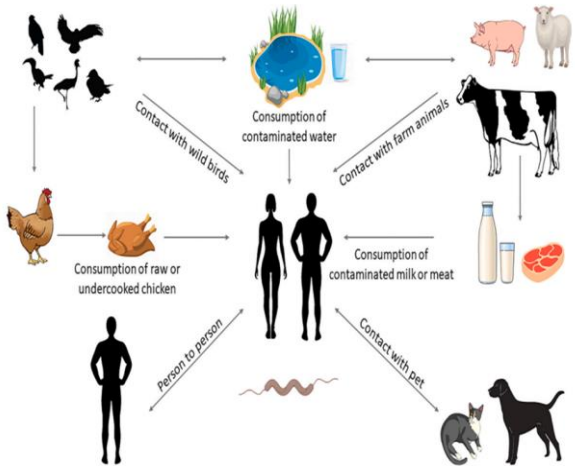

Fig (1): Reservoirs and routes of transmission associated with Campylobacter species. The microorganism can be transmitted to humans through consumption of raw or undercooked contaminated food, consumption of contaminated water, via contact with food-producing animals, wild animals, companion animals, and person to person transmission (fecal-oral or via fomites) ***(7).***

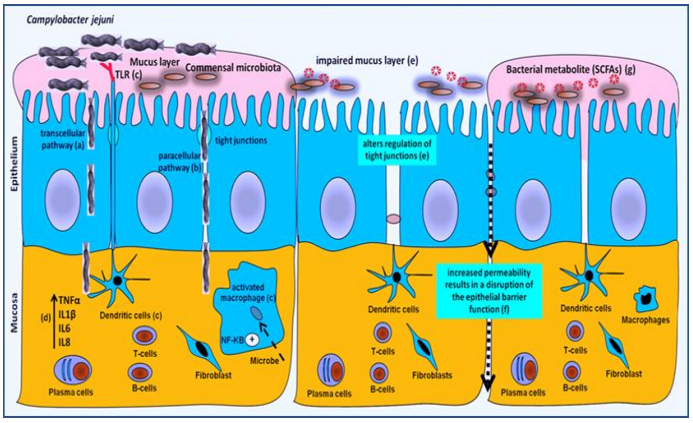

Figure (2): Campylobacter pathogenesis ***(8).***

Virulence factors:

1. Bacterial motility:

With the exception of C. gracilis (which is non-motile) and C. showae (which contains multiple flagella), the Campylobacter species have a single polar unsheathed flagellum at one or both ends of the cell. The colonization of the intestine requires the ability to move into mucus layer covering the intestinal epithelial cells. The helical shape of cell and its amphitrichous flagella are postulated to contribute to the natural high velocity of motility observed in viscous environments. Besides motility, flagella hold a wide set of functions that differ between bacteriae and during the bacterial life cycle. A flagellum can, for example, participate in biofilm formation, protein export, and adhesion***(9).***

2. The chemotaxis system:

As in other motile bacteria, the flagellum of C. jejuni is integrated with a chemotaxis system. Chemotaxis is the ability of a bacteria to move towards favorable environments that contain higher concentrations of nutrients (positive chemotaxis) or lower concentration of toxic chemicals (negative chemotaxis). Chemotaxis has long been implicated in the virulence of many pathogenic bacteria, which relies on this process to invade hosts. Both motility and chemotaxis are essential to C. jejuni colonize the chicken and mammalian gut ***(10).***

3. Polysaccharide capsule and lipooligosaccharide:

The polyssaccharide capsule (CPS) cover the surface of some bacterial cells, and is described in several bacterial species [81], being responsible for various functions related to virulence, such as protection to desiccation, adherence, colonization and resistance to host immune system [81–85]. The CPS of C. jejuni has similarities with class 2 and class 3 E. coli K1 and K5 CPS, being also exported by an ABC transport system [86–88]. The structure of the CPS is variable in C. jejuni strains, and may vary in the sugar composition, and linkage ***(7).***

Pathogenesis:

1. Adhesion of Campylobacter jejuni to the Host's cells:

After entering the host, C. jejuni crosses the mucus layer covering the intestinal epithelial cells and adheres itself to them, and a subpopulation subsequently invades these epithelial cells. The adhesion of C. jejuni to the epithelial cells of the intestine is a multifactorial event in which several binding factors are required to attach to their respective receptors and promote the successful interaction with host cells ***(7).***

Microbial Surface Components Recognizing Adhesive Matrix Molecule(s)(MSCRAMMs), which are synthesized by many pathogenic bacteria, can contribute to pathogenesis. Fibronectin-binding proteins are members of the MSCRAMMs family. A fraction of adhesion proteins of C. jejuni have been proven to be directly interactors with the extracellular matrix component fibronectin, such as Campylobacter adhesion to fibronectin (CadF) and Fibronectin-like protein A (FlpA). The C. jejuniCadF protein is an outer membrane protein (OMP) with molecular mass of 37 KDa that mediates the specific binding of C. jejuni to fibronectin. CadF is comprised of 326 amino acids and it is encoded by the single-copy, highly conserved chromosomal cadFgene***(7).***

2. Colonization:

Campylobacter jejuni contains two systems intended to specifically modify different sets of proteins: an O-linked protein glycosylation system that specifically modifies flagellins forming the extracellular flagellar filament, and an N-linked general protein glycosylation system that modifies many extra-cytoplasmic proteins. In 1999, it became evident that flagellins of C. jejuni are glycosylated [56]. The flagellins of C. jejuni rank among the most heavily glycosylated proteins identified, with the carbohydrate moieties contributing up to ~10% of the total molecular weight. O-linked glycosylation of C. jejuniflagellins (FlaA and FlaB) results in up to 19

serine and threonine residues on a flagellin subunit being modified with pseudaminic acid (Pse) and derivates containing acetyl and acetamidino groups (PseAcOAc or PseAm). Some strains contain additional genes to synthesize related legionaminic acid (Leg) derivates from flagellin glycosylation. Flagellin glycosylation is essential for flagellins to polymerize into the extracellular filament for motility, even though how the modifications contribute to filament polymerization remains unknown. Glycosylation of flagellin with an unusual sugar pseudaminic acid (Pse) plays a crucial role in the biosynthesis of functional flagella, and thereby in bacterial motility and pathogenesis. The Pse synthesis pathway enzymes are considered promising targets for the development of novel therapeutics, since bacterial motility is essential for colonization and development of persistent infection ***(11).***

3. Invasion of target cell:

A major disease-associated feature of *C. jejuni* is its capability to invade host tissues, which is believed to represent a primary mechanism of pathogenesis associated with host tissue damage. A number of molecular players of the bacterium and host cell involved in invasion have been discovered .High-resolution electron microscopy of infected epithelial cells revealed that *C. jejuni* can induce membrane rearrangements upon contact with a host membrane, which eventually leads to cell invasion. According to multiple studies, there are two major strategies utilized by *C. jejuni* to enter cultured cells, either microtubule-dependent or actin-filament-dependent mechanisms, which seem to vary between *C. jejuni* strains ***(12).***

4. Toxin production:

The rate of bacterial invasion does not seem to be the sole responsible for the cytopathic effect associated with C. jejuniinfection, toxins are likely associated to the disease process. The cytolethal distending toxin (CDT) is the best characterized among the toxins produced by C. jejuni. The CDT is produced by a range of Gram-negative pathogenic bacteria, such as the Pasteurelaceae family, the Enterobacteriaceae family, and the Campylobacterales order, including Campylobacter and Helicobacter species ***(13).***

The genotoxin CDT belongs to the AB family toxin, composed by an active subunit (CdtB) and two binding subunits (CdtA and CdtC), which are encoded by an operon comprising cdta, cdtb, and cdtc . All of the mentioned subunits are essential to confer full activity of this holotoxin toxin. CdtA and CdtC subunits are required for CDT binding to target cells and delivery of CdtB into the cell's interior. Once inside the cell, CdtB enters the nucleus and exhibits a DNase I-like activity that results in DNA double-strand breaks (DSB) in the host chromosomes. The eukaryotic cell responds to the DNA double-strand breaks by initiating a regulatory cascade process that results in cell cycle arrest at the G2/M interphase; thereby inducing cellular distention, resulting in senescence or cell death. Due to its DNA-damaging nuclease activity, CDT has been called a genotoxin ***(14).***

Immune response to Campylobacteriosis:

It is believed that the immunological response brought on by C. jejuni is responsible for the disease's unpredictability in course. The intestinal epithelial cells, innate immune cells, and cells of the adaptive immune response all contribute to the pro-inflammatory response brought on by the virulence factors of C. jejuni***(15).***

The functions of several cytokines in controlling immunological reactions against Campylobacter include TNF-, IL-6, and IL-8 that are innate immune cytokines that trigger inflammation. IL-1, IL-12, and IL-23 are cytokines produced by antigen-presenting cells that stimulate inflammation ***(17).***

T cell-produced cytokines (IL-17, IL-22, and IFN-) operate as T cell activators, and anti-inflammatory cytokines (IL-4 and IL-10) act as pro-inflammatory response inhibitors ***(17).***

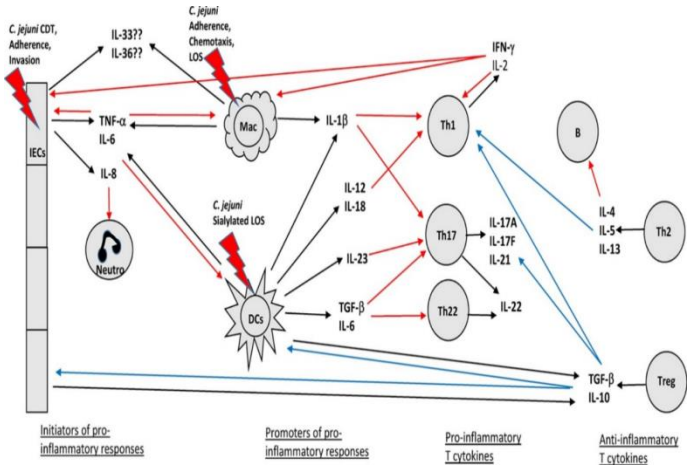

Figure 3: Cytokine responses in campylobacteriosis ***(15).***

Clinical picture and Diagnosis:

Clinical pictureand complication:

One of the most common causes of bacterial diarrhea is known to be campylobacter. The organism is well-known over the world and has been discovered in almost every nation. The signs and symptoms of a Campylobacter spp. infection are not distinguishable enough for a doctor to distinguish it from illnesses brought on by other infections. The clinical sickness brought on by a Campylobacter infection is commonly referred to as "enteritis," which implies that the small intestine is where the infection originated. Vomiting may happen, but it is rarely a noticeable symptom. The patient has weakness and exhaustion after 2 or 3 days of the intense diarrhea. While profuse watery diarrhea is most frequently reported in developing nations, it seems unusual in industrialized regions of the world ***(18)***.

People with *Campylobacter* infection usually have diarrhea (often bloody), fever, and stomach cramps. Nausea and vomiting may accompany the diarrhea. These symptoms usually start 2 to 5 days after the person ingests *Campylobacter* and last about one week ***(19)***

Sometimes Campylobacter infections cause complications, such as irritable bowel syndrome, temporary paralysis, and arthritis. In people with weakened immune systems, such as those with a blood disorder, with AIDS, or receiving chemotherapy, *Campylobacter* occasionally spreads to the bloodstream and causes a life-threatening infection ***(19)***

Although there are no clear-cut case reports, campylobacter has occasionally been linked to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Guillain-Barré syndrome occasionally has a Campylobacter infection as its underlying aetiology. An uncommon side effect of ileal infection is gastrointestinal perforation. Periodontitis has also been linked to campylobacter ***(20).***

Diagnosis

Campylobacters have traditionally been found using culture-dependent procedures, and then the isolates have been identified, confirmed, and typed using biochemical, immunological, and molecular approaches ***(21).***

Testing for Campylobacter is necessary to reduce the risk of foodborne Campylobacter and lower the incidence of foodborne Campoboteriosis, to safeguard people, and to detect whether a person has the infection. Typically, a stool sample or rectum swab taken by a healthcare professional is cultured in the lab to determine the presence of Campylobacter. Preliminary results take between 48 and 72 hours to complete. Additional time is needed for the confirmation test, as well as tests to identify the Campylobacter species or the organism's drug sensitivity ***(6).***

Campylobacter enteritis is often clinically indistinguishable from other viral or bacterial gastroenteridites. Diagnostic testing is not always indicated for children who present with acute diarrheal illnesses, with or without fever or vomiting, because determining the cause often does not change clinical management. However, Infectious Diseases Society of America guidelines suggest testing patients with fever or bloody diarrhea or others in whom treatment may be indicated, including anyone with

immunodeficiencies. In addition, organism-specific diagnosis can be valuable for the management of outbreaks. Blood cultures are recommended in infants younger than 3 months of age, those with signs of sepsis or systemic manifestations, and immunocompromised patients ***(6).***

Stool culture is the gold standard for the identification of Campylobacter species. Most laboratories specifically look for Campylobacter in standard stool cultures, but it can be difficult to isolate. Campylobacter grows best on media containing selective antibiotics and in microaerobic conditions with 5% to 10% oxygen, 1% to 10% carbon dioxide, and some hydrogen. C jejuni and C coli grow best at 107.6°F (42°C). Campylobacter is identified by its characteristic appearance as a comma- or spiral-shaped Gram-negative bacillus as well as oxidase and catalase production. Species level identification is not typically performed, and differentiation of C jejuni from C coli is not usually necessary for management. Speciation and strain typing can be helpful for epidemiologic purposes or when species other than C jejuni or C coli are suspected. This typing is typically performed at reference laboratories. Use of CIDTs, including nucleic acid amplification tests, is increasing. These tests are generally more sensitive and have faster turnaround times than traditional culture based diagnostics. Reverse transcriptase polymerase chain reaction identifies Campylobacter from stool 20% to 40% more frequently than culture-based methods ***(21)***.

However, because these tests identify the presence of nucleic acid rather than viable organisms, the clinical significance is not always clear. The identification of multiple pathogens is not uncommon and can be difficult to interpret. In addition, CIDTs cannot be used to identify antibiotic susceptibility patterns. Unlike organisms such as Shigella and Salmonella, cultures of Campylobacter often are not performed automatically when the organism is detected by CIDT. Antibiotic resistance to quinolones and tetracyclines is common in Campylobacter isolates, so if treatment is warranted and there is concern for resistance, cultures can still be beneficial after identification by CIDT ***(6).***

Serologic testing can be used to detect recent Campylobacter infection in patients with reactive arthritis or GBS who have negative stool studies. Serologic studies are not helpful in the diagnosis of acute Campylobacter infection. If Campylobacter infection is suspected or confirmed, it is important to attempt to identify the source of infection, mostly to prevent others from becoming infected. Families should be asked about exposures, including consumption of raw milk or contaminated drinking water, undercooked meats or poultry, contaminated fruits or vegetables, and contact with animals (wild and domesticated fowl, puppies, kittens) or their feces. Travel exposure may also be relevant, although most infections are acquired domestically ***(6).***

The most reliable method for determining if a sample contains living bacteria is cultural isolation. For the detection of Campylobacter species in various sources, molecular and immunological techniques, mainly PCR, and more recently whole genome sequencing technologies, have also been utilized***(21)***.

Management and Treatment of Campylobacteriosis:

Strong evidence supports the claim that antibiotic treatment of Campylobacter infections shortens infection time by a day and shortens shedding time. According to consensus, however, treatment is not advised for uncomplicated infections in immunocompetent hosts due to the infection's mildness, little benefit, and risk of antibiotic resistance development. For severe infections or infections in immunocompromised hosts, erythromycin or azithromycin treatment is advised ***(6).***It was shown that those infected with resistant *C. jejuni* experience illness that is prolonged and more severe than those with sensitive strains. However, the magnitude of this effect is not as yet sufficiently great to require a move away from erythromycin and fluoroquinolones for the treatment of *C. jejuni* enteritis ***(22).***

Patients with GBS may need ventilatory assistance and plasmapheresis. Intravenous immunoglobulins may also be needed and can significantly reduce the duration of illness ***(23).***

According to a wealth of research, it is crucial to properly prepare poultry, prevent the cross-contamination of poultry with other foods, chlorinate water, pasteurise milk, and follow hand hygiene guidelines after coming into touch with animals or their faeces ***(6).***

Bacteriophage:

It is challenging to pinpoint the earliest reports of Campylobacter bacteriophages because of the complex Campylobacter taxonomy that has developed over the years. In the 1960s, researchers discovered bacteriophages specific to the species now known as C. coli and C. foetus (formerly known as Vibrio coli and V. foetus), and campylobacter bacteriophage therapy is now an active field of study in the era of bacterial drug resistance***(20).***

Prevention of Campylobacter:

Even in industrialised countries, C. jejuni infections are on the rise despite increased awareness of good sanitation and hygiene habits, including food safety precautions, and there is presently no vaccination for humans. The lack of a comprehensive understanding of the immunological correlates of host protection and the genetic diversity of C. jejuni strains continue to be the key obstacles to the creation of a potent C. jejuni vaccine ***(24)***.

Few candidates for C. jejuni vaccines are currently being developed, despite the fact that several Campylobacter antigens have been explored for vaccines. In a number of preclinical studies, a prototype monovalent capsular polysaccharide (CPS) conjugate vaccine using CRM197 as the protein carrier was assessed. It was found to be highly immunogenic in mice and to be effective against diarrheal disease in the new world owl monkey species Aotusnancymaae. Recently, a Phase 1 first-in-human trial proving the safety and immunogenicity of the vaccine candidate was finished ***(25)***.

Probiotics in food (biological preservatives):

Foods enriched with probiotic cultures of the genera Lactobacillus and Bifidobacterium contributes to health (***26).*** For the fermentation of dairy products, one of the most well-known species is Lactobacillus acidophilus. Lactobacillus convert sugars into lactic acid and serve in the preparation of fermented products. Lactobacillus have the ability to synthesize bacteriocins that damage pathogens. The effect is still being investigated, and nisin is used. Bacteriocins are used today as biological food preservatives, and canning of dairy products is also recommended. Lactobacillus salivarius and Lactobacillus plantarum can inhibit the growth of Campylobacter spp. From food ***(27).***

Strategies of Campylobacter vaccines:

Three strategies exploiting highly conserved antigens have been investigated as potential Campylobacter vaccine candidates. Flagellin, the immunodominant antigen detected during Campylobacter infection, is one of them. Development of disease resistance is correlated with flagellin-specific antibodies ***(28)***.

Preclinical development is underway for the final two strategies. One is based on the similarity between the 53 KDaPorA of Campylobacter and the cholera toxin B component (CTB), a key outer membrane protein. Adult mice exposed to C. jejuni had less colonisation after receiving the CTB vaccine ***(29)***.

The other method involves immunising patients using a conserved N-glycan heptasaccharide of Campylobacter. To immunise hens, this antigen was shown on E. coli, which resulted in a 10-log decrease in C. jejuni colonisation after challenge. A heptasaccharide conjugated to the synthetic N-glycan carrier protein GlycoTag that was administered parenterally to hens likewise had this effect ***(30).***

References*:*

1. **Fitzgerald, C. (2015).** Campylobacter. Clinics in Laboratory Medicine, 35(2), 289-298.
2. **Vandamme, P., Dewhirst, F. E., Paster, B. J., & On, S. L. (2015).** Campylobacter. Bergey's Manual of Systematics of Archaea and Bacteria, 1-27.
3. **Peterson, M. C. (1994).** Clinical aspects of Campylobacter jejuni infections in adults. Western Journal of Medicine, 161(2), 148.
4. **Facciola, A., Riso, R., Avventuroso, E., Visalli, G., Delia, S. A., & Laganà, P. (2017).**Campylobacter: from microbiology to prevention. Journal of preventive medicine and hygiene, 58(2), E79.
5. **Ammar, A. M., El-Aziz, N. K. A., Elgdawy, A. A., Emara, M. S., & Hamdy, M. M. (2019).** Genotyping and antimicrobial resistance of campylobacter Jejuni: A review. *Adv. Anim. Vet. Sci*, *7*(s2), 129-136.
6. **Same, R. G., &Tamma, P. D. (2018).** Campylobacter infections in children. Pediatrics in review, 39(11), 533-541.
7. **Lopes, G. V., Ramires, T., Kleinubing, N. R., Scheik, L. K., Fiorentini, Â. M., & da Silva, W. P. (2021).** Virulence factors of foodborne pathogen Campylobacter jejuni. *Microbial pathogenesis*, *161*, 105265.
8. **Awad, W. A., Hess, C., & Hess, M. (2017).** Enteric pathogens and their toxin-induced disruption of the intestinal barrier through alteration of tight junctions in chickens. Toxins, 9(2), 60.
9. **Li, J., Gulbronson, C. J., Bogacz, M., Hendrixson, D. R., & Thompson, S. A. (2018).**FliW controls growth-phase expression of Campylobacter jejuniflagellar and non-flagellar proteins via the post-transcriptional regulator CsrA.*Microbiology*,*164*(10), 1308.
10. **Chandrashekhar, K., Srivastava, V., Hwang, S., Jeon, B., Ryu, S., &Rajashekara, G. (2018).** Transducer-like protein in Campylobacter jejuni with a role in mediating chemotaxis to iron and phosphate. *Frontiers in microbiology*, *9*, 2674.
11. **Burnham, P. M., &Hendrixson, D. R. (2018).** Campylobacter jejuni: collective components promoting a successful enteric lifestyle. *Nature Reviews Microbiology*, *16*(9), 551-565.
12. **Tegtmeyer, N., Sharafutdinov, I., Harrer, A., SoltanEsmaeili, D., Linz, B., &Backert, S. (2021).** Campylobacter Virulence Factors and Molecular Host–Pathogen Interactions. *Fighting Campylobacter Infections*, 169-202.
13. **Faïs, T., Delmas, J., Serres, A., Bonnet, R., & Dalmasso, G. (2016).** Impact of CDT toxin on human diseases. *Toxins*, *8*(7), 220.
14. **DiRienzo, J. M. (2014).** Uptake and processing of the cytolethal distending toxin by mammalian cells. *Toxins*, *6*(11), 3098-3116.
15. **Al-Banna, N. A., Cyprian, F., & Albert, M. J. (2018).** Cytokine responses in campylobacteriosis: Linking pathogenesis to immunity. *Cytokine & growth factor reviews*, *41*, 75-87.
16. **Zilbauer, M., Dorrell, N., Elmi, A., Lindley, K. J., Schüller, S., Jones, H. E., ...& Bajaj-Elliott, M. (2007).** A major role for intestinal epithelial nucleotide oligomerization domain 1 (NOD1) in eliciting host bactericidal immune responses to Campylobacter jejuni. *Cellular microbiology*, *9*(10), 2404-2416.
17. **Abbas, A. K., Lichtman, A. H., & Pillai, S. (2014).** Cellular and molecular immunology E-book. Elsevier Health Sciences.
18. **Karmali, M. A., & Skirrow, M. B. (2018).**Taxonomy of the genus Campylobacter. In *Campylobacter infection in man and animals* (pp. 1-20). CRC Press.
19. https://www.cdc.gov/campylobacter/faq.html. Accessed at 12novamber 2022.
20. **Bolton, D. J. (2015).** Campylobacter virulence and survival factors. Food microbiology, 48, 99-108.
21. **Huang, H., & Garcia, M. M. (2022).** Isolation and Identification of Campylobacter species from

Food and Food-Related Environment. *Campylobacter*, 43.

22. **Moore, J.E. and Madden, R.H. (2003):** Comparison of eight phenotypic methods for subspecies characterization of thermophilic Campylobacter spp. Isolated from pig liver. J. Food Prot. 66(6):1079-1084.
23. **Crushell, E.; Harty, S.; Sharif, F. and Bourke, B. (2004):** Enteric Campylobacter: purging its secrets? Pediatr. Res. 55(1):3-12.
24. **Singh, A., Khan, A., Ghosh, T., Mondal, S., & Mallick, A. I. (2020).** Naturally secreted bacterial outer membrane vesicles: potential platform for a vaccine against Campylobacter jejuni. *bioRxiv*.
25. **Poly, F., Noll, A. J., Riddle, M. S., & Porter, C. K. (2019).** Update on Campylobacter vaccine development. *Human vaccines &immunotherapeutics*, *15*(6), 1389-1400.
26. **Toma, M. M., &Pokrotnieks, J. (2006).** Probiotics as functional food: microbiological and medical aspects. ActaUniversitatisLatviensis, 710, 117-129.
27. **HRUSTEMOVIĆ, E., ČAKLOVICA, F., & ĐEĐIBEGOVIĆ, J. (2022).** Food pathogen of chicken meat Campylobacter spp.: a review. *Scientific Journal*, 80.
28. **Lee, L. H., Burg III, E., Baqar, S., Bourgeois, A. L., Burr, D. H., Ewing, C. P., ...&Guerry, P. (1999).** Evaluation of a truncated recombinant flagellin subunit vaccine against Campylobacter jejuni. *Infection and immunity*, *67*(11), 5799-5805.
29. **Albert, M. J., Mustafa, A. S., Islam, A., & Haridas, S. (2013).** Oral immunization with cholera toxin provides protection against Campylobacter jejuni in an adult mouse intestinal colonization model. *MBio*, *4*(3), e00246-13.
30. **Nothaft, H., Davis, B., Lock, Y. Y., Perez-Munoz, M. E., Vinogradov, E., Walter, J., ...& Szymanski, C. M. (2016).** Engineering the Campylobacter jejuni N-glycan to create an effective chicken vaccine. *Scientific reports*, *6*(1), 1-12.