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Intestinal Infections of *Campylobacter*: A Review

Aicha El Baaboua[1,2*], Mohamed El Maadoudi[2], Abdelhakim Bouyahya[1,3] and Jamal Abrini[1]

[1]Biotechnology and Applied Microbiology Team, Laboratory of Biology and Health, Department of Biology, Faculty of Science, Abdelmalek-Essaadi University, Tetouan, Morocco.
[2]Regional Laboratory for Analysis and Research, National Office for Food Safety, Tangier, Morocco.
[3]Laboratory of Biochemistry-Immunology, Department of Biology, Faculty of Science, Mohammed V University, Rabat, Morocco.

Authors' contributions

This work was carried out in collaboration between all authors. Author Aicha El Baaboua designed and wrote the first draft of this review. Authors MM and JA revised the manuscript critically for important intellectual content. Author Abdelhakim Bouyahya read and approved the manuscript.

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Review Article

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ABSTRACT

Campylobacter are Gram negative bacteria, ubiquitous, found in the gastrointestinal tract of warm blooded animals, including poultry and also in their nature. The most dominant species is *Campylobacter jejuni*, followed by *Campylobacter coli*. For a long time, these bacteria have been known as a pathogen of foodborne infections in the worldwide. The most cases of campylobacteriosis, which have been observed in many countries, are sporadic with a seasonal peak during the summer. Usually, the disease is benign and self-limited, manifested by fever, abdominal pain and diarrhea. Often accompanied by blood in the stools, which requires antimicrobial therapy for children, elderly and immunocompromised, but rarely for adults.
This review aims to give an overview of the historical approaches, properties, sources and different ways of transmissions of *Campylobacter* spp. also clarifying its pathogenesis, its treatment and the prevention against these bacteria.

**Corresponding author: E-mail: elbaabou.aicha@gmail.com;*

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1. INTRODUCTION

Each year, more than 14 pathogens kill humans around the world, where foodborne diseases account for a significant proportion. Campylobacteriosis affects more than 2.4 million people worldwide each year [1]. The genus *Campylobacter* is in the first class of infectious agents of food poisoning in the European Union (EU) [2] and the third in the United States after *Salmonella* and *Escherichia coli* O157 [3].

Campylobacteriosis is one of the most commonly reported zoonotic diseases over the world, transmitted directly or indirectly to humans, whose *C. jejuni* and *C. coli* are the most dominated species. Those bacteria are commensals in ceca of healthy animals especially cats, dogs, birds, poultry, etc… that cause the major clinical detected in human's feaces suffering from diarrhea [4].

In 2012, European Food Safety Authority and European centre for Disease Prevention and Control reported 214,268 of confirmed cases with an incidence rate of 64.8 per 100,000 inhabitants [5]. Indeed, the EU loses more than €2.4 billion per year because of *Campylobacter*, which presents an extensive challenge related to food security and economy as well [6]. In this context, the present work aims to give an overview of the historical approaches of *Campylobacter*, its properties, its sources and its various modes of transmission, also showing its pathogenicity, its treatment and prevention.

2. HISTORY OF TAXONOMY

For many years *Campylobacter* has been recognized, its first observation has been made by a pediatrician Theodor Escherich in German children suffering from diarrhea and suspected of having infantile cholera [7].

In 1906, John McFadyean and Stewart Stockman succeeded in isolating bacteria resembling those isolated by Theodor from the fetal mucus of aborted sheep [8]. Seven years later, the two scientists had cultivated these microorganisms for the first time. Because of their spiral shape, Smith added these microorganisms in 1918 to *Vibrio* group and identified these bacteria as *Vibrio fetus* which is known today as *C. fetus* [9].

In 1957, Elizabeth King's work on the growth and metabolic profile of these bacteria led to differentiating them from the *Vibrio* genus and called "Related *Vibrio*" [10]. As early as, in 1963, the "Related *Vibrio*" was definitively separated from the *Vibrio* genus and took a new genus named *Campylobacter* (curved bacillus), since the composition of Guanine-Cytosine is different from that of *Vibrio* and because that *Campylobacter* do not assimilate sugars [11].

The year 1972, in Belgium, marks the success of the microbiology team who isolated *Campylobacter* from a child's stool using the filtration method. In 1977, Skirrow described a simple technique for the direct isolation of *Campylobacter* on a selective blood agar and incubated at 43℃ in a microaerophilic atmosphere [12].

Following the great success of *Campylobacter* isolation methods, several studies have focused on the development of selective culture media for *Campylobacter* spp. [13]. Since the 1970s, both *C. jejuni* and *C. coli* have been the most frequently observed in millions of cases of human's campylobacteriosis [8].

At the beginning of the 20th century, in 2001, the first sequencing of *C. jejuni* strain NCTC 11168 revealed several mysteries of *Campylobacter* [14]. This is why the taxonomy of *Campylobacter* and related organisms has been amended on molecular databases.

Nowadays, the genus *Campylobacter* belongs to the class of *Epsilonproteobacteria*, order *Campylobacterales*. This bacterial genus with *Arcobacter* and *Sulfospirillum* forms the *Campylobacteriace* family, with 25 species and 8 subspecies of the genus *Campylobacter* [15,16].

3. PROPERTIES OF *Campylobacter*

Campylobacter in young culture are typically Gram-negative, non-sporulating, comma-shaped, or helical bacilli when clustered in long chain. These bacteria have a diameter of 0.2 to 0.5 µm in width and 0.5 to 5 µm in length with one or more flagella at the ends. In fact, flagella are two to three times longer than the cell. This morphological character gives them a special motility, described as corkscrew shape except *C. gracilis* [17]. After several days of culture, the

bacillus transforms to spherical or coccoid shape of 0.5 micrometer [18].

3.1 Genome

Sequencing of the microbial genomes of *Campylobacter* spp. shows the existence of a small circular chromosome of 1.641.481 base pairs of which 30.6% is composed of guanine and cytosine [G + C] containing several well-known regulatory systems [19]. Admittedly, *C. jejuni* comprises at least one circular plasmid, which contains genes of resistance to antibiotics and the size of each one differs from species to another. In addition, *Campylobacter* plasmids share homologous sequences [20].

Several studies have shown that the genome of *C. jejuni* exhibits a high degree of plasticity and genetic rearrangements [21]. Indeed, the analysis of the genetic profiles of the homologous sequences of *C. jejuni* isolated from humans and those isolated from animals, showed the conservation of some proteins while others are absent [22]. This instability is explained by the absence of DNA repair.

3.2 Origin and Habitat

Several studies have shown the presence of *Campylobacter* spp. in human and animals in multiple organs [8,16]. The first strains isolated were linked to a disease observed in humans and cattle. Moreover, these bacteria have a particular tropism for the digestive tract of animals, some strain colonize the intestines of homeothermic animals including poultry as a main reservoir [21]. These species are mainly *C. jejuni* and *C. coli* which are related to gastroenteritis in humans and isolated from their stool. While, *C. fetus* is also considered pathogenic, responsible for abortions in cattle and isolated from human blood [23].

Other reservoirs have been described such as cattle, pigs, small ruminants, but also pets (cats, dogs and hamsters). Because of the asymptomatic aspect of these microorganisms in digestive tract of warm-blooded animals, excreta can contaminate soils and rivers [24]. Because of contaminated surface water by animal feces, *Campylobacter* can survive in these untreated waters by binding to an intermediate hosts such as protozoa [25].

The strain adaption in the environment is preferential, which reveal a unique survival conditions through hypervariable sequences [19]. For example, hypervariable regions PR1 contain important genes used as alternative electron acceptors for respiration and may confer to strains a selective advantage in restricted oxygen environments. However, PR2, 3 and 7 contain abundantly outer membrane proteins and hypothetical proteins of unknown function, some of which may be related to phenotypic variation and adaptation to different ecological niches [21].

3.3 Biochemical Characteristics

Biochemically, these microorganisms have positive oxidase, catalase and nitrate reductase. In contrast to the Voges-Proskauer reaction, methyl red, urease and indole production which are negative, as well as the absence of production of dihydrogen sulfide on "Triple Sugar Iron ". In addition, *Campylobacter* are unable to utilize glucose in Hugh and Leifson's medium either by the fermentative or by the oxidative pathway, due to the absence of the phosphofructokinase [26].

Instead, bacteria draw energy through the use of the Embden-Meyerhof-Parnas pathway and by catabolizing amino acids such as L-aspartate, L-glutamate, L-serine and L-proline or by tricarboxylic acids cycle [27].

Campylobacter is microaerophilic by reason of requirement of an atmosphere enriched with CO_2. Generally, the gaseous mixture suitable for cultivation *in vitro* is 5% dioxygen (O_2); 10% carbon dioxide (CO_2) and 85% molecular nitrogen (N_2). Nevertheless, some species may tolerate aerobic conditions although others tend towards anaerobiosis [28].

The blood is added in culture media in order to detoxify potentially harmful compounds due to the presence of catalase and superoxide dismutase [29]. In fact, these microorganisms are extremely sensitive to the free radicals formed during the respiratory chain (nitrite, nitric oxide and sulfite). Thus, the addition of blood, charcoal, ferrous sulphate, sodium metabisulphite and sodium pyruvate to culture media will improve the aerotolerance [16].

The species of *Campylobacter* have a slow growth compared to the enteric flora, their optimum pH is 6.5-7.5. The temperature of growth is a limiting factor that influences the survival of these species whose optimum is 37℃, but never at 25℃ with the exception of *C. fetus* [30].

3.4 Viable but Non-cultivable Colony

The concept of a viable but non-culturable colony (VBNC) is described as an adaptive form to degeneration and resistance when conditions of survival become unfavorable [31].

C. jejuni is fragile and sensitive to many environmental factors, including atmospheric oxygen, drying, nutrient deficiency, disinfectants, extreme pH, freezing and heating [32]. During exposure to these stress conditions, the cells become damaged and slow down its metabolic activities until they gradually become coccoid [18]. For now, the process of reviving cell to its infectious form is not clear yet [33].

4. TRANSMISSION

Campylobacter are commensal microorganisms in the intestines of healthy animals, especially poultry that are heavily involved [30]. In reality, healthy birds often excrete *Campylobacter* species in stools including *C. jejuni*. The origin of the first infection of *Campylobacter* reservoirs is probably related to the environment, soil and contaminated surface water [24].

Moreover, due to the redundancy of these bacteria in the chicken ceaca (between 10^6 and 10^8 colony forming units per gram) and the asymptomatic aspect [34], the contamination of their surroundings occurs very fast, even if the researchers suppose that some organisms of *C. jejuni* cause colonization in 80% of birds [35]. However, birds are infected with *C. jejuni* only from the second or third week of life; this is possibly related to specific maternal antibodies present at first period [36].

Two main modes of transmission of *Campylobacter* are suggested in humans. First, direct contact with reservoirs which causes a relatively rare infection among farmers, health workers, nurseries and slaughterhouse workers. [37] In fact, contact with livestock, surfaces and handling materials of animals at risk or with infected patients cannot be negligible [38]. Second, indirect transmission is frequently due to a food vector. Carcass contamination occurs during evisceration when there is ceaca rupture or contact with excreta, resulting cross-contamination through slaughterhouses and food industries [39].

In developed countries, the consumption of raw or half-cooked chickens are the most involved sources in the transmission of these zoonotic microorganisms in humans [8]. In addition to food sources, transmission in developing countries is supplemented by untreated surface water, direct contact with animals of company and environment.

5. PATHOGENICITY

The chemotaxis of epithelial cells, adherence and invasion of mucus are the crucial stages in an intestinal bacterial infection. In fact, the authors agree that the presence of lipopolysaccharides and lipooligosaccharides on bacterial membranes provides a wide variety of structural and functional roles in host-pathogen interactions and surface adhesion to translocation of factors of virulence.

In the stomach, *C. jejuni* and *C. coli* survive due to the presence of the capsule. However, the motility is facilitated by the presence of flagella, matter how these bacteria move to the small intestine to the target organs; colon, ileum and jejunum. After successful colonization of the intestinal mucosa, *C. jejuni* adheres to the enterocytes. Indeed, adhesion is a multifactorial process in which multiple binding factors are necessary to bind to protein receptors during efficient interaction with host cells (BPE1, FLPA, CADF, JlpA and CapA) [39].

The pathogenicity of certain strains is related to the secretion of a thermolabile enterotoxin inducing direct cytotoxicity, in particular by *C. jejuni*, *C. lari*, *C. coli*, *C. fetus* and *C. upsaliensis* [40]. Moreover, the cytolethal distending toxin (CDT) is formed by CdtABC complex, made up of three subunits: CdtA, CdtB and CdtC. In the intestines, *Campylobacter* spp. produces the toxin and causes destruction of the endothelial cells via the heat produced by this endotoxin. The CdtA and CdtC subunits are responsible for binding connection with target cell, while the CdtB subunit and with the interaction of the other two subunits (CdtA and CdtC) induces the activation of enzymatic complex which attacks the target cell, DNA of the intestinal cells and recruits proteins kinases in order to stop the cell cycle [40,41]. As a result, cells of the intestinal mucosa die through the apoptosis process and the infected patient manifests as watery or often bloody diarrhea.

6. CAMPYLOBACTERIOSIS

The majority of *Campylobacter* infections are caused by two species of *C. jejuni* and *C. coli*.

Between 500-800 colonies forming units of *C. jejuni* can cause disease in children, the elderly or immunocompromised [42].

According to the clinical picture, the human infections are sporadic and rarely reportable. In adults, abdominal pain, fever and headaches are the clinical signs that precede diarrhea for several hours and occasionally these diarrhea are accompanied by nausea and vomiting [43]. These symptoms occur between 2 and 5 days after infection, but may persist for up to 10 days. The endothelial cells vacuolate *C. jejuni*. However, this microorganism sometimes resists to lysosomal degradation via the production of catalase. Subsequently, *C. jejuni* is found on the basolateral surface of endothelial cells and undergoes exocytosis. *C. jejuni* causes extra-intestinal infections and therefore leads to long-term complications, including septicemia, meningitis, pancreatitis, abortion of pregnant women, reactive arthritis, Guillain-Barré syndrome, Miller Fisher syndrome [43] etc…

Guilain-Barré syndrome (GBS) and Miller Fisher syndrome (SMF) are acute autoimmune diseases of the most declarable peripheral systems worldwide [44], which result from the secondary localization of *Campylobacter* in the systemic circulation. Because of the structural similarity between the lipo-oligosaccharides of *C. jejuni* and the glycoforms of human brain gangliosides, *C. jejuni* exhibits molecular mimicry with gangliosides since the synthesis of anti-lipo-oligosaccharide and anti-gangliosides antibodies attacks the self-antigen and bacterial cells, so the patient suffers from weakness or paralysis after several weeks of the initial disease [45].

Except *C. fetus* which causes abortions in cattle and humans [9], the most of *Campylobacter* are rarely pathogenic to their animal reservoirs [30].

7. TREATMENT

The gastroenteritis induced by *C. jejuni* is self-limiting for one week or less and does not require antimicrobial treatment. In order to treat a patient, it is essential to replace water and electrolytes lost by liquids. In general, oral rehydration is sufficient, but intravenous rehydration may be necessary in cases of severe dehydration, especially in children, elderly patients and pregnant women with severe electrolyte abnormalities or severe anemia and blood during diarrhea.

The use of antibiotics to treat campylobacteriosis is appropriate in cases involving high fever, bloody diarrhea or in immunocompromised patients. Indeed, the use of erythromycin or other molecules of the class of quinolones and fluoroquinolones reduces the duration of the symptoms when they are administered in early stage of the disease [11]. On the other hand, several researchers confirm that *Campylobacter* spp. have an antibiotic resistance rate over the past 20 years, particularly quinolones, fluoroquinolones and macrolides over the world [46]. It is important to monitor this resistance to avoid controversies over their use in human medicine as well as in veterinary medicine since this resistance limits the therapeutic possibilities not only in diarrhea where the antibiotics of choice would have the advantage to be active on most other intestinal pathogenic bacteria, but also in systemic infections where an antibiotic with good tissue diffusion is sometimes necessary.

Campylobacteriosis cannot be easily distinguished from other diarrheal diseases, so medication with antidiarrhoeal agents theoretically increases the risk of systemic bacterial invasion when used alone. In addition, travel abroad is a risk factor for infection and spread of resistant *Campylobacter* [47].

Treatment of Guilain-Barré syndrome requires intensive follow-up. Patients with this syndrome are treated with immunomodulators such as intravenous immunoglobulin or plasmapheresis [48].

8. PREVENTION

In recent years, various researches have contributed to the development of effective approaches of control of *Campylobacter* in poultry meat. These approaches are based on two main objectives, the first prevent the risk of colonization of *Campylobacter* in poultry ceaca on the farm, i.e to reduce the probability risk of birds to be colonized by *Campylobacter*. The second aims to minimize the intestinal burden of *Campylobacter* present in the cecal content of poultry colonized before slaughter and after evisceration thereby reducing surface contamination of carcasses by physical or chemical means [49].

In this regard, numerous studies have been carried out to take place of many effectiveness measures such as biosecurity measures and

personal hygiene practices, to avoid poultry contamination and transmission between batches. The use of various substances is also recommended to control *Campylobacter* such as essential oils, prebiotics, probiotics, bacteriocins, bacteriophages and immunization measures [50].

9. CONCLUSION

Several countries are now adopting multiple interventions to control these microorganisms. In short, these programs are very beneficial to public health because of their impact throughout the food production chain. However, the preventive approach seems to be the best strategy in itself. It represents a real challenge because of the commensal behavior of this bacterium in the intestines of broiler chickens, at a time when the control of colonization of poultry at farm minimizes the transmission of *Campylobacter* in broiler farms.

Campylobacter spp. have become highly resistant to antibiotics belonging to the class of macrolides, quinolones and fluoroquinolones which are widely used in human and veterinary medicine. Clinical therapy with these antibiotics of cases of gastroenteritis represents limits, hence the need for openness to new routes such as herbal medicine through the use of natural substances.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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