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Campylobacter, from obscurity to celebrity

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ABSTRACT

After its successful isolation from stools in the 1970s, *Campylobacter jejuni* has rapidly become the most commonly recognised cause of bacterial gastroenteritis in man. Reported cases of human campylobacteriosis represent only a small fraction of the actual number. In industrialised countries, the incidence of *C. jejuni/Campylobacter coli* infections peaks during infancy, and again in young adults aged 15–44 years. Acute self-limited gastrointestinal illness, characterised by diarrhoea, fever and abdominal cramps, is the most common presentation of *C. jejuni/C. coli* infection. The introduction of selective media has made the diagnosis of *Campylobacter* enteritis a simple procedure. In general, *Campylobacter* enteritis is a self-limiting disease which seldom requires antimicrobial therapy, although one in 1000 infections may lead to the Guillain–Barré syndrome. In industrialised countries, most infections are acquired through the handling and consumption of poultry meat. In developing countries, where the disease is confined to young children, inadequately treated water and contact with farm animals are the most important risk factors. Many infections are acquired during travel. Fluoroquinolone resistance has been reported in *C. jejuni* since the late 1980s in Europe and Asia, and since 1995 in the USA. The use of fluoroquinolones to treat animals used for food has accelerated this trend of resistance. In Australia, where fluoroquinolones have not been licensed for use in food production animals, *C. jejuni* remains susceptible to fluoroquinolones. The public health burden of *Campylobacter* spp. other than *C. jejuni/C. coli* remains unmeasured. Better diagnostic methods may reveal the true health burden of these organisms.

Keywords Animals, *Campylobacter* spp., food infections, gastroenteritis, review

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INTRODUCTION

Campylobacter spp. have been the focus of growing attention for the past 30 years because of the increasing frequency with which they have been isolated from man, animals, food and water. Although several *Campylobacter* spp. (*C. jejuni*, *C. coli*, *C. upsaliensis*, *C. lari*, *C. concisus*, *C. fetus* subsp. *fetus*, *C. jejuni* subsp. *doylei*, *C. hyointestinalis*) and *Arcobacter butzleri* have been shown to cause diarrhoea, *C. jejuni* is by far the most frequent species isolated from man. *C. jejuni* is a frequent cause of morbidity, in both industrialised and developing countries, and represents a considerable drain on economic and public health resources. In the 1970s, collaboration between medical doctors and their veterinary colleagues led to the discovery of *Campylobacter* enteritis. This review focuses on the historical perspectives and the clinical, diagnostic and epidemiological aspects of human campylobacteriosis.

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HISTORICAL PERSPECTIVES

The beginnings

Although campylobacters were not recognised as human pathogens until the 1970s, they have probably caused illness in man for centuries. In 1886, Escherich published a series of articles in the *Münchener Medizinische Wochenschrift* [1] in which he described spiral bacteria in the colons of children who had died of what he called 'cholera infantum'. Attempted culture on solid medium was unsuccessful. Furthermore, he observed spiral organisms microscopically in stool specimens

from 35 of 72 infants suffering from enteric disease but, despite the increased frequency, thought the spiral bacteria played no aetiological role [1]. Unfortunately, these articles, published in German, remained unrecognised for many decades until Kist [2] reported Escherich's findings at the Third International *Campylobacter* Workshop held in Ottawa in 1985.

The veterinary era

Found frequently in animals, particularly in bovines and ovines, *Campylobacter* has been known for more than 40 years as a cause of veterinary disease. In 1909, two veterinary surgeons, McFadyean and Stockman [3], surveyed epizootic abortion in ewes and reported an unknown bacterium that was frequently isolated from aborted foetuses and which resembled a vibrio. In 1919, Smith investigated infectious abortions of bovines in the USA and isolated (in addition to the 'Bacillus of Bang') a bacterium that was described as a spirillum [4]. Finishing the study, Smith became acquainted with the work of McFadyean and Stockman, and assumed that they had been studying the same bacteria. He confirmed this, together with Taylor, and proposed the name '*Vibrio fetus*' [5]. In 1949, Stegenga and Terpstra demonstrated the pathogenic role of *V. fetus venerealis* in enzootic sterility in cows [6]. In 1959, Florent was able to distinguish two types of *V. fetus* by their biochemical and pathogenic characteristics, namely *V. fetus venerealis* and *V. fetus intestinalis* [7]. In 1931, Jones *et al.* [8] attributed winter dysentery in calves to infection with a 'vibrio' that they called *Vibrio jejuni*, and Doyle described a similar organism associated with swine dysentery in 1944 [9].

First human infections

In 1947, Vinzent *et al.* [10] isolated *V. fetus* from the blood of three pregnant women admitted to hospital because of fever of unknown origin. The illness lasted about 4 weeks, and two of the three women aborted. On examination, large necrotic and inflammatory areas were found on the placenta. However, even before this report, an event took place in Illinois in May 1938 that is now regarded as the first well-documented instance of human *Campylobacter* infection [11]. This involved a milk-borne outbreak of diarrhoea that affected 355 inmates of two adjacent state institutions. Faecal cultures from 73 victims tested were negative, although microscopy was positive in 31 cases, but organisms resembling '*V. jejuni*' were grown in broth cultures of the blood of 13 victims.

In 1957, King [12,13] described a vibrio with several features in common with the agents described by Vinzent, but with different biochemical and antigenic characteristics. King termed this organism 'related vibrio' but, until 1972, only 12 cases of 'related vibrio' infections were reported in the literature, involving seven infants, two children and three adults [12,14–17]. The reason for this paucity of reports was that the selective culture techniques necessary for the isolation of this organism, later renamed by Sebald and Véron [18] as *Campylobacter*, from faeces had not been developed at that time. Consequently, the infection could be diagnosed only from the blood of bacteraemic patients. However, King believed that the infection was not as rare as these few reports suggested, and emphasised the need to devise a method for culturing the organisms from faeces. Unfortunately, such a method was not developed in her lifetime, but her vision and diligence paved the way.

The breakthrough

The crucial step—the isolation of *Campylobacter* from faeces—was accomplished in 1968 by Dekeyser at the National Institute for Veterinary Research, Brussels Belgium, in conjunction with Butzler and his team at the St Peter University Hospital, and was published in 1972 [19]. A 20-year-old female was admitted on 18 July 1968 to the St Peter University Hospital in Brussels with severe diarrhoea and fever (40°C). There was no underlying pathology. A 'related vibrio' (*C. jejuni*) was isolated from blood and, after use of a special filtration technique, from the faeces. This technique consisted of differential filtration of faecal suspensions through 0.65-μm filters, which allowed *Campylobacter* organisms to pass through. The filtrate was then inoculated on to a selective medium. No other enteric pathogens were isolated from the stools of this patient. This first faecal culture demonstrated intestinal infection as the origin of the bacteraemia. This clinical case was the starting point of a collaboration

between Butzler and Dekeyser, which included a search for campylobacters in the stools of healthy individuals and patients with diarrhoea, a search for specific serum antibodies in these groups, the collection of clinical data, and the elaboration of a therapeutic scheme. *C. jejuni/C. coli* were isolated from 5.3% of 3800 children with diarrhoea, but from only 1.6% of 7200 individuals without diarrhoea [20]. Specific complement-fixing antibodies to the strain of *C. jejuni* isolated from stools were demonstrated in children with diarrhoea [21]. Of most importance was the finding of a high susceptibility of *C. jejuni* to erythromycin [21,22]. Once the sensitivity of *C. jejuni* to erythromycin was known, this antibiotic was used as a therapeutic test [21]. The cessation of diarrhoea in combination with the disappearance of *C. jejuni* from stools was an argument in favour of *C. jejuni* being the cause, since erythromycin had no effect on ordinary intestinal pathogens. In all treated cases, erythromycin caused the symptoms to disappear rapidly.

Subsequently, the invasive ability of *C. jejuni* was demonstrated in poultry [21]. Antigenic typing of the *C. jejuni* isolates was performed by agglutination and complement fixation tests with antisera raised from reference strains of *C. jejuni* and *C. coli.* A close antigenic relationship, and even identity, was shown between isolates from man and those from poultry, sheep and pigs [21]. In 1973, Butzler [23] reported the first cases of *Campylobacter* enteritis in the tropics (in Zaire, now the Democratic Republic of Congo). In 1977, Skirrow [24] confirmed the findings of the Belgian team and described a simpler technique for culturing *C. jejuni* and *C. coli* from stool specimens, which allowed widespread isolation of these organisms. The later development of selective media, obviating the need to filter suspensions, brought the isolation of *Campylobacter* into the realm of routine microbiology [24–30]. Reports from industrialised countries, including European countries [19–21,24,30–33], Canada [34] and the USA [35], and from developing countries, including Zaire [23] and Rwanda [36], have shown that *Campylobacter* enteritis occurs worldwide. In 1979, the first full account of *Campylobacter* enteritis in man was published [37], and in the 1980s Penner and Hennessy [38] and Lior *et al.* [39] described serotyping techniques that, aided by biotyping, phage typing and genotyping, still form the basis of strain typing. It was not until the mid-1980s that *C. jejuni* was recognised as the most frequent cause of bacterial enterocolitis in man.

CLINICAL MANIFESTATIONS

In the industrialised world, acute self-limited gastrointestinal illness, characterised by diarrhoea, fever and abdominal cramps, is the most common presentation of *C. jejuni* infection, but symptoms and signs are not so distinctive that the physician can differentiate this infection from illness caused by other organisms [21,24,31–35,40]. The incubation period is commonly 2–5 days, but estimates have extended up to 10 days. In *c.* 50% of patients, diarrhoea is preceded by a febrile period with malaise, myalgia, abdominal pain and fever of *c.* 40°C; fresh blood may appear in the stools by the third day. Faecal samples show an inflammatory exudate with leukocytes on microscopic examination; moreover, it is usually possible to recognise numerous *Campylobacter* organisms from their characteristic morphology. Vomiting is rare. The diarrhoea continues for *c.* 2–3 days, but abdominal pain and discomfort may persist after the diarrhoea has stopped. In a significant proportion of patients, the stools contain fresh blood, pus or mucus, which suggests that colorectal inflammation is not uncommon in *Campylobacter* infection. Sigmoidoscopy usually reveals abnormalities ranging from mucosal oedema and hyperaemia, either with or without petechial haemorrhage, to mucosal friability. Severe abdominal pain may mimic acute peritonitis. Occasionally, these patients, especially teenagers or young adults, develop peritonitis from acute appendicitis, but in most patients there is inflammation of some part of the ileum and jejunum with mesenteric adenitis [37,40–42]. Local complications such as cholecystitis, pancreatitis and peritonitis occur rarely [42]. Recently, immunoproliferative small intestinal disease has been associated with *C. jejuni* [43]. Bacteraemia is detected in $<1\%$ of patients with *Campylobacter* enteritis, and occurs most often in patients whose immune system is severely compromised [40–42,44]. Some patients develop erythema nodosum or reactive arthritis. Extraintestinal infections, including meningitis [45], osteomyelitis [46] and neonatal sepsis, are rare.

It has been recognised that the paralytic condition, Guillain–Barré syndrome (GBS), is the most serious complication of *Campylobacter* infection [47–52], with an incidence of 1/1000 infections [41,42,47–52]. *C. jejuni* is the most frequently observed antecedent infection in cases of GBS. In general, one in three GBS patients has suffered from a preceding infection with *C. jejuni*. Symptoms of GBS usually occur 1–3 weeks after the onset of *Campylobacter* enteritis. GBS cases associated with *Campylobacter* infection are usually more severe and can require intensive hospital treatment, with possible long-term disability. Molecular mimicry has been proposed as an attractive concept to explain the pathogenesis of GBS [49–52]. Starting with food-borne *Campylobacter* diarrhoea, antibodies and/or T-cells are induced by the infection and are directed initially against *Campylobacter*, leading to eradication of the organism. However, because of the strong resemblance between the microbial antigens and the self-antigens, in this example the peripheral nerve cells, the tissue is destroyed, leading to GBS [49–52].

MICROBIOLOGY

Campylobacter and *Arcobacter* are now included in the family Campylobacteriaceae [53–56]. When the diagnosis of infection is based exclusively upon culture on selective media, it appears that >95% of *Campylobacter* infections are caused by *C. jejuni* or *C. coli*. However, with refinements in isolation and identification methods, other related species, such as *C. upsaliensis* [57,58], *C. lari* [59], *C. fetus* subsp. *fetus* [60,61], *C. jejuni* subsp. *doylei* [61], *C. concisus* [61,62], *A. butzleri* [63–68] and *Arcobacter skirrowii* [69], have been isolated from human patients with diarrhoea.

Campylobacter spp. are small, curved or spiral-shaped Gram-negative bacilli that exhibit rapid darting and spinning motions. In a clinical context, the main role of the laboratory is to detect campylobacters in the faeces of patients with diarrhoea. For same-day deliveries to the laboratory, faeces can be transported in conventional containers, but if delay is anticipated, faeces should be put in transport medium, such as Cary–Blair medium, and kept cool [37,40–42,60,61,70]. Transport medium should also be used for rectal swabs. Modern blood culture systems are efficient at detecting *Campylobacter* bacteraemia, and blood cultures should be taken if the clinical features and immunocompetence of the patient indicate campylobacteriosis [70].

Campylobacter enteritis can be diagnosed readily by direct microscopic examination of fresh liquid faeces, either with Gram's stain (counterstain with carbol fuchsin) or a phase-contrast optical system. *Campylobacter* spp. can be seen and distinguished from other organisms by virtue of their spiral morphology and extremely rapid darting and spinning motions. Commercial kits are available for the direct detection of *C. jejuni* and *C. coli* antigens in faeces, e.g., by latex agglutination [71,72]. PCR-based identification methods can detect several *Campylobacter* spp., including some uncommon species that are difficult to culture [73]. An advantage of PCR methods over culture is the ability to achieve same-day detection and speciation of the organism, but these methods are expensive, are labour-intensive, and do not provide an isolate for typing or sensitivity testing.

C. jejuni and *C. coli* can be isolated easily from faeces by primary plating on selective media and incubation for 48–72 h at 42°C in a microaerobic atmosphere. A variety of selective media (blood-based, blood-free charcoal-based) are available [24–30]. These contain antibiotics that suppress the normal bacterial enteric flora. However, the antibiotic-containing *Campylobacter* selective media and the elevated incubation temperature (42°C) may also inhibit the growth of some of the *Campylobacter* spp. encountered less commonly. If a *Campylobacter* sp. other than *C. jejuni* is suspected, stool filtration and culture on a non-selective medium, with incubation at 37°C and 42°C, should also be used [61–70].

The minimal standards for identifying *Campylobacter* spp. after primary isolation are colony morphology, Gram's stain, motility and an oxidase test. The hippurate hydrolysis test differentiates most *C. jejuni* strains from other *Campylobacter* spp. [37,70]. For organisms other than *C. jejuni* and *C. coli*, including atypical *C. jejuni* strains, additional biochemical tests are required. Several typing methods, namely serotyping [38,39,74,75], phage-typing [76], pulsed-field gel electrophoresis [77] and genotyping [78], can be used to characterise the strains further. Serology is indicated for certain culture-negative cases of suspected *C. jejuni* infection involving reactive arthritis, erythema nodosum and GBS [79,80].

TREATMENT

In general, *Campylobacter* enteritis has a very good prognosis, and the isolation of these organisms from stools does not warrant chemotherapy [21,24,35,37]. In the absence of chemotherapy, faeces remain positive for *c.* 2–7 weeks after the illness. Antibiotic therapy is indicated for patients with *Campylobacter* infection who are acutely ill with enteritis, have persistent fever, bloody diarrhoea, have more than eight bowel movements/day or significant volume loss, or have a >7-day history of diarrhoea. HIV-positive or immunocompromised individuals should receive antibiotic treatment [40–42]. When antimicrobial therapy is indicated, erythromycin is the drug of choice, given its efficacy, low toxicity and low cost [21,24,35,37,40–42,81,82].

Fluoroquinolones such as ciprofloxacin have been used commonly for the treatment of infections caused by *Campylobacter*. However, since the late 1980s, fluoroquinolone resistance has been reported from Europe [83,84], Asia [85], and Latin America [86]; since 1995, it has also been reported from the USA [87–90]. The prevalence of fluoroquinolone-resistant *C. jejuni* in the USA was 0% in 1990, increasing to 13% in 1997, and to 18% in 1999, following the approval of fluoroquinolones for use in poultry farming in 1995 [87–90].

In contrast, in Australia, where fluoroquinolones are not used in poultry farming, human *Campylobacter* isolates remain susceptible to fluoroquinolones [91]. In the USA, eating poultry outside the home and foreign travel have both been identified as risk factors for infections with fluoroquinolone-resistant *Campylobacter* spp. [87–90,92–94]. In industrialised countries, dehydration caused by *C. jejuni* is infrequent, but fluid and electrolyte replacement are sometimes necessary for infected infants. However, the best treatment for *C. jejuni* infections in developing countries could well prove to be different. Factors such as low socio-economic status and malnutrition may determine the severity of infection with *C. jejuni* and its great prevalence in very young children. Vomiting and watery diarrhoea are frequent, and oral rehydration is sometimes required in children. Antibiotics should be reserved for severe cases. It is certain that education and better hygiene have far greater roles in reducing infections than do antibiotics [82].

EPIDEMIOLOGY

Campylobacter enteritis is the most frequent form of acute bacterial diarrhoea in industrialised countries, where it affects people of all ages but with a distinctive bimodal distribution, affecting particularly children aged <4 years and young adults aged 15–44 years [95]. Individuals with AIDS are at higher risk of acquiring *Campylobacter* spp. and have a greater risk of invasive disease. The infection is seasonal in temperate climates. About twice as many infections occur in summer as in winter.

Campylobacteriosis is a zoonosis [21,24,37,40–42,60,96]. The reservoir of infection comprises wild and domestic animals, particularly birds. Chickens constitute by far the largest potential source of human infection. Campylobacteriosis is mainly a food-borne infection in which foods of animal origin, particularly poultry, play an important role [96–100]. Any raw meat bred for consumption may be contaminated with *Campylobacter* organisms. Almost all parts of poultry carcasses, whether fresh, chilled or frozen, are frequently contaminated with *C. jejuni*. Raw or undercooked beef, hamburgers, sausages and clams have also been implicated in outbreaks of *Campylobacter* enteritis, but, generally, food-borne outbreaks, as opposed to sporadic food-borne infections, are uncommon. Epidemiological investigations have demonstrated a significant correlation between the handling and consumption of poultry meat and the occurrence of *Campylobacter* enteritis.

In June 1999, the dioxin crisis, caused by dioxin-contaminated food components, resulted in the withdrawal of chicken and eggs from the market in Belgium. Through the sentinel surveillance system, a corresponding decrease in *Campylobacter* infections during June 1999 was noticed [101]. Barbecues and similar activities appear to present special hazards for infection, as they permit easy transfer of bacteria from raw meat to hands and other foods, and from these to the mouth. Raw or inadequately heat-treated milk and inadequately treated water have been incriminated as sources of massive outbreaks of infection [102].

Direct transmission is mainly occupational (farmers, butchers, abattoir workers, poultry processors), but pets can bring infection into ordinary homes. Inter-human transmission has been

described infrequently in young children. Perinatal transmission, from a patient who is not necessarily symptomatic, may occur following exposure *in utero*, during passage through the birth canal, or during the first days of life. Many cases of campylobacteriosis are associated with foreign travel, accounting for 3–50% or more of all cases, and usually result from the consumption of contaminated food or water in the countries visited. In developing countries where campylobacters are hyper-endemic, the disease is confined to young children who, through repeated exposure to infection, develop immunity early in life [103–105]. In these countries, *Campylobacter* plays an important role, and its effects are particularly acute during weaning. Consequently, campylobacteriosis contributes significantly to malnutrition in infants, who represent an at-risk group. In developing countries, exposure in the household to the faeces of live chickens infected with *C. jejuni* is the predominant risk factor for childhood diarrhoea. Exposure to inadequately treated water is also assumed to be an important risk factor.

A lack of national surveillance data prevents the public health impact and the burden of *Campylobacter* infections in developing countries from being assessed. The recent incorporation of *Campylobacter* in the WHO *Salmonella* surveillance network (WHO SalmSurvNet) may allow the development of a more accurate picture regarding the public health impact and the burden of campylobacteriosis in developing countries. The public health burden of *Campylobacter* spp. other than *C. jejuni/C. coli* remains unknown in both industrialised and developing countries.

PREVENTION

As the major source of human campylobacteriosis in the industrialised world is poultry, prevention should aim at reducing infection at all stages of poultry production. It is difficult to control *Campylobacter* during poultry processing because of the high incidence of this pathogen in poultry flocks and the high levels in chicken intestines. The strategies that have been successful for controlling *Salmonella* infection in poultry are generally ineffective against campylobacters [106]. More information is needed about the effectiveness of biosecurity measures for poultry farms, and about the impact of these measures on human campylobacteriosis. *Campylobacter* is relatively sensitive to low-dose radiation treatment and could be eliminated readily from poultry meat products by this means, but there is still considerable resistance among consumers to this method of disinfection. Appropriate precautions in the handling and preparation of foods of animal origin will reduce cross-contamination. Raw meat and poultry should be cooked adequately. Hands should be washed thoroughly with soap after handling raw foods of animal origin and before touching anything else. Chopping boards used for raw meats should not be used for preparing other foods. Chopping boards and utensils should be cleaned with soap and hot water after preparation of raw food of animal origin [107,108].

Campylobacter is an important cause of travellers' diarrhoea. A World Health Organization fact sheet on avoiding travellers' diarrhoea is available. The Copenhagen consultation [109] recommends that the World Health Organization should educate travellers on the risks involved in travelling, give advice on the avoidance of *Campylobacter* infections, and publish relevant data concerning antibiotic resistance in different countries. Prevention depends also on the purification of water supplies and the heat treatment of milk sold for consumption. In developing countries, the keeping of chickens outside the home and the prevention of contact with their faeces reduces transmission of *C. jejuni* substantially [110]. Breast-fed infants are less likely to develop *Campylobacter*-associated diarrhoea than their non-breast-fed counterparts [111]. *Campylobacter* vaccines have shown promise in animal models [112,113]. The recent determination of the genome sequence of *C. jejuni* [114] will facilitate the development of a safe and effective *Campylobacter* vaccine for possible application in the prevention of travellers' diarrhoea.

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