

Is there an unrecognised role for *Campylobacter* infections in (chronic) inflammatory diseases?

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Abstract

Campylobacter species are one of the major causes of global bacterial-related diarrheal disease worldwide. The disease is most frequently associated with the ingestion of contaminated meat, raw milk, pets, contaminated water, and the organism may be frequently cultured from the faeces of chicken and other domesticated farm animals. Of the 17 established *Campylobacter* species, the most important pathogens for humans are *Campylobacter jejuni* (*C. jejuni*), *Campylobacter coli* (*C. coli*) and *Campylobacter fetus* (*C. fetus*), which are all associated with diarrheal disease. Further, *C. jejuni* and *C. coli* are also associated with the neuroparalytic diseases Guillain-Barré syndrome and Miller Fischer syndrome, respectively, whereas *C. fetus* is linked with psoriatic arthritis. The discovery of both "molecular mimicry" and translocation-related virulence in the pathogenesis of *C. jejuni*-induced disease, indicates that *Campylobacter*-related gastrointestinal infections may not only generate localized, acute intestinal infection in the human host, but may also be involved in the establishment of chronic inflammatory diseases. Indeed, pathogenicity studies on several *Campylobacter* species now suggest that molecular mimicry and translocation-related virulence is not only related

to *C. jejuni*, but may play a role in human disease caused by other *Campylobacter* spp. In this review, the authors provide a review based on the current literature describing the potential links between *Campylobacter* spp. and (chronic) inflammatory diseases, and provide their opinions on the likely role of *Campylobacter* in such diseases.

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Key words: *Campylobacter* spp; Infection; Autoimmune diseases; Chronic diseases

Core tip: *Campylobacter* species are able to induce both gastrointestinal and systemic infections in humans and have been linked not only to acute disease, but also to a wide range of (chronic) inflammatory diseases. In this respect, the organism is particularly associated with inflammatory peripheral nerve disease Guillain-Barré syndrome and reactive arthritis. However, the true role of *Campylobacter* in other human inflammatory diseases remains to be determined. This review indicates that the actual role of *Campylobacter* in human inflammatory diseases may be largely underestimated and suggests that further research is necessary in order to accurately determine the importance of *Campylobacter* infection in these diseases.

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INTRODUCTION

Campylobacter species are Gram negative zoonotic hu-

man pathogens that are one of the major causes of global bacterial-related diarrheal disease worldwide, a disease most frequently associated with the ingestion of contaminated animal products such as chicken meat, raw milk, contaminated water, and contaminated farm animals. Currently, of the 17 established *Campylobacter* species the most important associated with human disease is *Campylobacter jejuni* (*C. jejuni*), a leading cause of diarrheal disease worldwide with 400-500 million laboratory confirmed cases each year^[1]. Further, this species can be sub-divided into two separate groups based on the presence or absence of sialic acid components attached to carbohydrate residues present on the bacterial outer surface^[2]. The transfer of these sialic acid components to the carbohydrate outer surface of *C. jejuni* is mediated by the enzymes sialyltransferase Cst-II or Cst-III^[3], with the presence of sialic acid conferring a highly pathogenic phenotype to the bacterium that has the potential to cause severe colitis^[4], as well as paralytic disease. One such paralytic disease is Guillain-Barré syndrome (GBS), a post-infectious life threatening complication often associated with *C. jejuni* infection^[5]. In fact, evidence suggests that GBS is facilitated by bacteria-human cross-reactive antibodies, generated *via* a process called “molecular mimicry”. Essentially, some sialylated carbohydrate lipooligosaccharide (LOS) structures on the *C. jejuni* outer membrane possess epitopes that appear similar to certain ganglioside epitopes present on human peripheral nerves. This similarity may result in the production of auto-antibodies that target not only the bacterium, but also human nerves, inducing complement-mediated nerve destruction^[5]. Further research has also shown that *C. jejuni* strains possessing sialylated LOS structures are significantly more invasive than non-sialylated strains, and are also better able to translocate across the intestinal epithelium^[6-8]. In this respect, the authors have previously suggested that infection with *C. jejuni* and other *Campylobacter* spp. may actually be linked with a significant number of undetected bacteremias^[9], and that the detection of *Campylobacter* species in current blood culture systems might be underrepresented, not least because these systems are not optimized for the special growth requirements of this bacterial genus^[10].

Interestingly, Houlston *et al.*^[11] established that *Campylobacter* spp. are able to synthesize a much broader range of human mimicking glycolipid/glycoprotein structures in their lipopolysaccharides (LPS) and LOS than previously thought, *i.e.*, *Campylobacter* species are equipped with a set of LPS/LOS genes that allow adaptation to their host, possibly allowing the organism to “hide” from recognition by the host immune system. In this hypothesis, LPS or LOS epitopes that mimic host antigens are expressed on the surface of *Campylobacter* bacteria in order to provide protection against the host immune response (*Campylobacter* antigens being recognized as self-antigens and therefore being less likely to be recognized by the host). However, this type of *Campylobacter* LPS and LOS molecular mimicry could potentially be a trigger for the

development of as yet unrecognised inflammatory disease states in susceptible hosts. For example, there already exists many publications describing the role of *C. jejuni* in the aetiology of inflammatory diseases such as GBS and Miller Fischer syndrome (MFS), and the reader is referred to^[5] for a recent review on this subject.

Worryingly, there are indications that healthy people may actually be (chronic) carriers of *Campylobacter* bacteria, again suggesting that this bacterium is able to adapt itself to the human host and escape immune recognition^[12,13]. To confirm these observations, well designed surveillance programs are required in order to identify whether apparently healthy humans can be carriers of *Campylobacter* bacteria^[14]. Although the carrier state of *Campylobacter* is not completely clear for humans, it has already been established that various animal species can act as carriers of *Campylobacter* spp. without displaying symptoms^[15-19], and animal carriers have been linked to the induction of Campylobacteriosis in humans^[20-22]. Acute infections with *Campylobacter* species *via* food products, water or animals may also lead to chronic infections in humans^[23,24], specifically when patients are suffering from an immunodeficiency^[25-28].

In this review, the authors describe and comment on the current literature regarding the potential role of *Campylobacter* spp. in human (chronic) inflammatory diseases. The authors concentrate first on those immunologically-related diseases where a strong association between *Campylobacter* infection and disease has been shown, and then highlight those diseases where an association with *Campylobacter* infection is weaker, but where further research may be warranted. The authors conclude that there is indeed a potential role for *Campylobacter* spp. in the induction of many different types of (chronic) inflammatory diseases, and that this is most likely related to the link between *Campylobacter* infection, inflammation and molecular mimicry.

GBS AND MF SYNDROME

GBS and MF syndromes are (sub)acute inflammatory polyradiculoneuropathies affecting the peripheral nerves of affected patients^[5]. GBS and MF patients experience degeneration and demyelination of specific neuronal axons after an episode of gastrointestinal or respiratory infection, with demyelination being triggered by an auto-immune-like response^[5]. In GBS patients the muscles in the body become paralysed, whereas in MF patients, only the facial muscles are affected^[5].

GBS is also called the Landry-Guillain-Barré-Strohl syndrome and is named after the four scientists that originally discovered and reported on this disease^[29]. In 1859 Landry de Thézillat was the first to describe an ascending paralyzing disease in great detail^[30], although earlier publications mimicking the disorder of Landry were reported by Auguste François Chomel (1788-1858) in 1828^[31] and James Wardrop (1782-1869) in 1834^[32]. In 1916 Guillain *et al.*^[33] reported on an examination of

two soldiers that were suffering from muscular weakness, paresthesias, and muscular pain. In 1927, Draganesco *et al*^[34] defined the nomenclature “Guillain-Barré syndrome” to describe this paralyzing disease. In 1982, Rhodes *et al*^[35] reported for the first time that the GBS syndrome was associated with *Campylobacter* infection, which was later confirmed by Constant *et al*^[36] and Speed *et al*^[37]. In all of these studies, it was recognized that diarrhoea often preceded the appearance of Guillain-Barré syndrome, with later bacterial culture and serum diagnostic tests revealing that *C. jejuni* was often the causative agent of the intestinal infection that preceded the onset of the GBS syndrome^[38-45].

In 1990, it was suggested for the first time that *C. jejuni* might stimulate the production of antibodies against the myelin sheath of the peripheral nerves of GBS patients^[45]. In this same year, Yuki *et al*^[46], demonstrated that 2 GBS patients possessed high serum IgG titres against GM1 ganglioside following *C. jejuni* enteritis, a significant finding as these results greatly accelerated the research on *C. jejuni*-induced GBS. Subsequently, multiple research groups confirmed the work by Yuki *et al*^[46], linking anti-ganglioside antibodies with *C. jejuni*-induced GBS^[47-50]. Eventually, other research groups established that certain *C. jejuni* serotypes (Penner O:4, O:19 and O:41) were more frequently isolated from GBS patients than from enteritis patients, and that anti-GQ1 antibodies were linked to the onset of Miller Fisher syndrome^[51-59]. The results of these findings lead to the hypothesis that there exists a form of “molecular mimicry” between *C. jejuni* cell envelope structures and ganglioside structures present on the peripheral nerves of affected patients, suggesting that an immunopathogenic mechanism might be causing damage to the nerves in GBS and MFS disease^[60,61]. Indeed, Goodyear *et al*^[62], not only showed that monoclonal antibodies raised against the LOS isolated from GBS-inducing *C. jejuni* strains reacted with ganglioside structures on the peripheral nerves, but that they possess the potential to block muscle-nerve interactions. The subsequent finding that *C. jejuni* possesses genes that enable the sialylation of its outer membrane LOS further increased the suspicion that molecular mimicry might form the basis for *C. jejuni*-induced GBS^[63-65]. Though mainly associated with *C. jejuni*, research has indicated that molecular mimicry may play roles in human infections associated with several other *Campylobacter* species, particularly with *C. coli*^[38,41,66,67].

Based on these findings, there is the potential for an as yet undescribed *Campylobacter*-human autoimmune interactions at the level of molecular mimicry. Further, these interactions could provide the basis for a range of, as yet undefined, chronic and acute inflammatory *Campylobacter*-associated diseases in humans.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a term used for a group of chronic inflammatory disorders of the gut that

includes two major diseases. These are Crohn’s disease (CD) and ulcerative colitis (diseases associated with alteration of the ileum, colon and rectum leading to cramps, fever and bloody diarrhoea). Currently, the association between *C. jejuni* infection and chronic IBDs such as CD is controversial^[25,68]. During a four-year study in 1982 in Belgium, 45 patients were found to exhibit signs of an acute infective colitis. Twenty percent of these patients were found to be positive for *C. jejuni*, the bacterium found to be associated with focal colitis, necessitating a differential diagnosis from Crohn’s colitis^[69]. During the same period, 12 patients were also admitted with an acute attack of IBD due to an intercurrent infection with bacterial pathogens including *C. jejuni*^[69]. These data indicate that, in the presence of an acute attack of colitis, an infective etiologic agent should always be sought, and that an attack of chronic idiopathic IBD may be caused by an intercurrent infection. van Spreuwel *et al*^[70] compared 22 patients with *C. jejuni*-induced colitis against 10 healthy controls, 10 ulcerative colitis patients and 10 CD patients, and concluded from immunological analyses that *C. jejuni* colitis can be distinguished from ulcerative colitis and CD patients by IgG containing plasma cells. Also, around the same time, Simson *et al*^[71] found that *C. jejuni* was associated with acute relapse and abscess formation in CD. In a Bulgarian study, Boyanova *et al*^[24] analyzed the frequency of *Campylobacter* species isolation from patients with acute enterocolitis, IBD, and other chronic intestinal diseases. The authors screened 682 Bulgarian patients and established that *Campylobacter* species were detected in patients with acute enterocolitis (7.8%), chronic enterocolitis (6.2%), CD (6.2%), ulcerative colitis (3.7%), and irritable bowel syndrome (8.3%)^[24]. Further, hippurate-positive *C. jejuni* isolates accounted for 62.2% of *Campylobacter* strains. The authors concluded that *Campylobacter* could be one of the causes of chronic intestinal diseases in Bulgaria^[24]. Interestingly, Berberian *et al*^[72] (1994), showed that the expression of a novel autoantibody defined by the VH3-15 gene could be detected in both IBD and *C. jejuni* enterocolitis patients. These authors screened 101 individuals with ulcerative colitis, CD or other acute or chronic colitis symptoms. Compared with normal subjects, BK2⁺ anti-erythrocyte Abs were elevated in most sera from patients with CD and ulcerative colitis (including post-colectomy)^[72]. However, BK2⁺ anti-erythrocyte antibodies were also elevated in 10 of 38 non-IBD patients, all of whom had *C. jejuni* enterocolitis^[72]. The findings by Berberian *et al*^[72] tended to suggest that a common immunopathogenetic factor, manifested by VH3-15 B cell activation, may be shared between ulcerative colitis, CD, and *C. jejuni* enterocolitis. An indirect effect of *C. jejuni* in the aetiology of IBD was suggested by several different studies of Kalischuk *et al*^[73], who established that transcytosis of *C. jejuni* across gut epithelia allowed other commensal gut flora to also cross the intestinal epithelial barrier^[68,73,74]. Apparently, the translocation of commensal flora may result in an inflammatory immune response against the commensal gut flora (luminal antigen translocation hypothesis),

a process that is commonly observed in patients suffering from IBD^[75,76]. With respect to population studies, Gradel *et al*^[77] (2009) compared 13148 people from 2 Danish counties who had been exposed to *Salmonella* and *Campylobacter* gastroenteritis, with 26216 unexposed individuals. After an average follow-up of 7.5 years, the hazard ratio of first-time IBD diagnosis was 2.9 (exposed to unexposed), and was raised for both CD and ulcerative colitis^[77]. In those exposed to *Campylobacter* and *Salmonella* only 1.2% of the studied subjects developed IBD. Thus, while the study identified bacterial exposure as a statistically significant factor in IBD the role of *Campylobacter* seems to be only of relative importance. Following the Danish population, but in a different study (1992-2008), Jess *et al*^[78] showed that infection with *Campylobacter* species, confirmed by *Campylobacter* isolation from stool samples, significantly increased the risk of developing IBD. However, contradicting this observation, was the finding that culture negative stool samples were also significantly associated with an increased risk for the development of IBD^[78]. The final conclusion of the authors was that the increased risk of IBD after infections with intestinal pathogens might be a result of a detection bias, due to increased testing for such pathogens in this patient group^[78]. Subsequently, Riddle *et al*^[79] further discussed this conclusion stating that due to study limitations and diagnostic bias there could in fact be several different explanations for finding an association between culture positivity or culture negativity in IBD patients.

A more direct link between a *Campylobacter* species (not *jejuni*), CD and IBD was observed more recently. In 2009-2011, Zhang *et al*^[80] were able to link the presence of *Campylobacter concisus* (*C. concisus*) to pediatric CD using the techniques of polymerase chain reaction (PCR) bacterial detection and the presence of specific IgG antibody, an observation that has also been associated with adults presenting with IBD^[80-82]. Further, in 2011, Kovach *et al*^[83] identified actual *C. concisus* proteins that were immunoreactive within patients with CD.

However, not all studies have been successful in linking *C. jejuni* (or any other *Campylobacter* species) with IBDs. In 1984, Blaser *et al*^[84] studied 72 CD patients using culture, serology and immunohistochemistry, and concluded that *C. jejuni* was not likely to be an etiological agent of CD or chronic ulcerative colitis. In a Scandinavian study using 95 patients with *Campylobacteriosis*, it was observed that 77%-86% patients harbored a raised antibody titre against an antigen mixture comprising seven *C. jejuni/coli* strains including a PEN 0:6, 7 isolate, which represented the most common serotype in Scandinavia^[85]. In this same study, the authors also analyzed the sera of 56 IBD patients and found that none reacted with this *C. jejuni/coli* antigen mixture and concluded that *Campylobacteriosis* was not associated with these chronic diseases^[85]. In 1992, a prospective study began by analyzing 64 IBD patients 15 of whom were diagnosed with ulcerative colitis. Stool samples were screened for enteric pathogens, but only a low number of these samples were confirmed to be culture positive. The conclusion of this

study was that enteric microorganisms including *C. jejuni* only play a minor or indeed a negligible role in the exacerbation of IBD^[86]. Therefore, the link between *C. jejuni* and IBD seems to be weak, but based on current literature, *C. concisus* might by *Campylobacter* species harboring more potential to be a causative agent of IBD.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) differs from IBD in the fact that IBS is a collection of gut-related disease signs and symptoms with no known aetiological cause. Though they have several symptoms in common, treatments for IBS and IBD vary greatly. Only a minority of IBS reported disease is associated with a post-infection process (PI-IBS)^[87], though one of the commonest causes of PI-IBS appears to be *C. jejuni* infection^[88]. The main mechanism for inducing *C. jejuni*-related IBS appearing to be the production of cytolethal distending toxin (CDT) by *C. jejuni*^[89]. However, experiments in a rat model have indicated that histopathological changes in the gut during *C. jejuni* infection may be caused by both CDT-producing and non-producing isolates^[90]. Therefore the role of *C. jejuni* CDT in IBS remains a point of discussion. One other mechanism involved in the aetiology of IBS is the promotion of inflammation of the gut tissue *via* the generation of a “low grade” immune response (involving autoendocrine cells, CD3, CD4 and CD8 lymphocytes) and gut permeability^[91].

Recently, it has been suggested that blockage of the PI3K- γ signalling pathway in *Campylobacter* infection may be a means of reducing severe inflammation facilitated by the innate immune system^[92]. Indeed, treatment of *C. jejuni* infection with the antibiotic rifamixin in a rat model of IBS infection stopped the development of long-term altered stool function and form (a phenomenon linked to the overgrowth of the small intestine with *C. jejuni* bacteria, and a characteristic IBS-associated phenotype)^[93].

REACTIVE ARTHRITIS (REITER'S SYNDROME)

Reactive arthritis is an inflammation of the joints which develops whilst suffering/recovering from a recent infection. Though other symptoms also usually develop in addition to arthritis, joint inflammation is the main characteristic of this disease. Any site of infection may be associated with reactive arthritis, including the intestine (the site of infection for *C. jejuni*)^[94], with symptoms commonly lasting 3-12 mo, though in some cases, the arthritis may persist long-term^[94]. Reiter's syndrome a variant of reactive arthritis is established when the following symptoms occur simultaneously; urethritis, arthritis and conjunctivitis^[94].

In 1979, a case report was published that linked a *C. jejuni* infection with the induction of reactive arthritis for the first time^[95]. In this case report, reactive arthritis de-

veloped two weeks after the subject experienced watery diarrhoea containing blood, and was experiencing anorexia, and severe weight loss^[95]. The causative agent of the infection was found to be *C. jejuni*^[95]. In a later study, it was established that reactive arthritis was more likely to occur in *C. jejuni* enteritis patients that were positive for histocompatibility antigen HLA-B27^[96], and around the same time period different groups more or less confirmed this finding^[97,99]. Importantly, HLA-B27-negative arthritis-related *C. jejuni* enteritis cases are nevertheless sporadically reported^[97,100-105]. Interestingly, patients presenting with ankylosing spondylitis (a chronic inflammatory disease) overwhelmingly possess HLA-B27 and molecular mimicry with the gut bacterium *Klebsiella pneumoniae* is thought to play a key role in disease development^[106,107]. However, research has indicated that there are no signs of *C. jejuni*/*C. coli*-related antibodies in patients with active ankylosing spondylitis^[108]. More recently, Mortensen *et al*^[4] was able to link a potential virulence factor, namely class A sialylated lipooligosaccharide structures, to a more severe gastro-enteritis phenotype and reactive arthritis, suggesting that sialylated LOS structures, structures that mimic human gangliosides, are also a risk factor in the development of reactive arthritis. Interestingly, the possession/expression of reactive arthritis-related sialylated LOS structures does not appear to be related to any particular *C. jejuni* genotype^[109]. For further information, the reader is referred to a systematic review by Pope *et al*^[110], which summarizes the link between *Campylobacter* spp. and reactive arthritis.

Up to this point, there has been strong evidence for an association between *Campylobacter* infection and a range of (chronic) inflammatory diseases, GBS, MF, IBD and IBS. However, in the following section, the authors discuss diseases where the link between *Campylobacter* infection and (chronic) inflammatory disease is much weaker. In this respect, the authors would like to see more research in this area, in order to finally confirm or deny any unrecognised association between *Campylobacter* infection and the following diseases.

SYSTEMIC LUPUS ERYTHMATOSUS

Systemic lupus erythematosus, often abbreviated to SLE or lupus, is a systemic autoimmune disease that can affect any part of the body^[111]. As with other autoimmune diseases, the immune system attacks its own cells and tissues, resulting in inflammation and tissue damage^[111]. Lupus most often affects the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system^[111]. The course of the disease is unpredictable, with periods of illness (flares) alternating with remissions. The disease occurs nine times more often in women than in men, mainly in women in the child-bearing years of 15 to 35, and is also more common in those of non-European descent^[111]. Currently, over a 100 articles linking SLE with the GBS have been published, one of the main causative agents of GBS being *C. jejuni*^[5]. As early as

1984, Johnson *et al*^[112] described a persistent *C. jejuni* infection in a patient with lupus and a deficiency in serum IgA and IgM. The authors showed that the serum of this patient was not able to kill the *C. jejuni* bacterium. In 1998, Gatterbauer *et al*^[113] used an ELISA assay to determine the antibody types [IgM, IgG, IgA, and IgG subclass anti-GM1, anti-GQ1b, and anti-asialo-GM1 (anti-GA1)] that were present in patients presenting with neurological or other complicated neurological diseases. Increased anti-GM1 and/or anti-GA1 was found to be more frequent in lupus patients with central nervous system involvement than without^[113]. Additionally, in 1999, a case report was published that found antibodies against ganglioside GM1 (indistinguishable from GBS) in the serum of a patient with SLE and a “drop foot”, though no antibodies against *C. jejuni* were observed^[114]. It has also been reported that an SLE like disease may be triggered in a Balb/c mouse animal model, after immunization of mice with formaldehyde-treated *C. jejuni* and Freud’s complete adjuvant^[115,116]. However, although *Campylobacter* species may be isolated from lupus patients, it is currently debatable whether *C. jejuni* is the causative agent of lupus disease *per se*, or is simply able to maintain itself in lupus patients due to the immunosuppressive treatment they receive. Particularly interesting are the two articles in which the authors show that they were able to induce an SLE like illness in Balb/c mice using formaldehyde fixed *C. jejuni*^[115,116].

CELIAC DISEASE

Celiac disease is an autoimmune disease in which individuals possess antibodies against gluten protein, a protein found in wheat, barley and rye. Sufferers from celiac disease should avoid eating gluten-containing foodstuffs and therefore are subject to dietary restrictions. At least one report has indicated a role for *C. jejuni* in the aetiology of celiac’s disease^[117]. Additionally, a case report was published in 2010 of a girl suffering from celiac disease that was associated with recurrent Guillain-Barré syndrome (*C. jejuni* being one of the main microorganisms proven to be associated with Guillain-Barré syndrome)^[118]. Alaedini *et al*^[119] showed increased levels of ganglioside antibodies in celiac disease patients, and suggested that a pre-disposition of celiac patients to bacteria possessing cross-reactive lipopolysaccharides (LPS) such as *C. jejuni* (and *Haemophilus influenzae*), may predispose to the development of anti-ganglioside antibodies (similar to the aetiology of Guillain-Barré syndrome). A similar hypothesis involving tissue atrophy and degeneration of mucosa was also proposed by Sabayan *et al*^[120] in 2007.

CARDIOMYOPATHY/MYOCARDITIS

Cardiomyopathy is a measurable deterioration of the function of the heart muscle, usually leading to heart failure. Common symptoms include breathlessness and peripheral oedema (*e.g.*, swelling of the legs). People

with cardiomyopathy are often at risk of dangerous forms of irregular heart beat and sudden cardiac death. The most common form of cardiomyopathy is dilated cardiomyopathy. Myocarditis is an inflammation of the myocardium (heart muscle) and is synonymous with the term inflammatory cardiomyopathy. Interestingly, *C. jejuni* has been linked to cardiac disease in several case reports^[121-136]. Also, more severe cases of *C. jejuni* infection may result in heart failure of the patient^[123,128,131]. In 2007, Becker *et al.*^[137] investigated whether the incidence of perimyocarditis is increased following *C. jejuni* infection. Their conclusion after screening 6204 patients for perimyocarditis, and after the patients had experienced a *C. jejuni* infection, was that the incidence rate of myocarditis was 16.1 (95%CI: 2.3-114.4) per 100000 person-year in the *Campylobacter* population compared to 1.6 (95%CI: 0.2-11.4) per 100000 person-year in the control cohort^[137]. Although this observation was not found to be statistically significant, the authors did conclude that, based on the rarity of this condition and case reports in the literature linking *Campylobacter* cases with perimyocarditis, it could not be ruled out that a potential association between *Campylobacter* and perimyocarditis might exist^[137]. Additional research, indicates that there seems to be a tendency for males to be overrepresented in cardiomyopathy patient groups following *C. jejuni* gastroenteritis symptoms^[121-126,138-140], which warrants further investigation. Alzand *et al.*^[125], suggested that the mechanism by which *Campylobacter* causes myo(pericarditis) could be attributed to direct bacterial invasion of cardiac tissue, bacterial toxins, circulating immune complexes, or cytotoxic T-cells. However, at the moment, the mechanisms leading to cardiac disease after *C. jejuni* infection remain unknown, but support the idea that *C. jejuni* is able to cause systemic infections^[9,10].

At this point in the review, the authors present evidence for an association between infection with *Campylobacter* spp. and (chronic) inflammatory diseases, which is based mainly on case reports in the scientific literature.

ACUTE TRANSVERSE MYELITIS

Acute transverse myelitis is a neurological disorder that affects the spinal cord through inflammation, generating for example complications such as axonal demyelination. The disease is associated with an infection or vaccination^[141]. In two relatively recent case reports, from 2007 and 2012, acute transverse myelitis was associated with *C. jejuni*-induced gastroenteritis^[141,142]. Patients were found to harbor cross-reactive antibodies against the sialylated LOS structures of *C. jejuni*, specifically high titres of anti-GM1 were observed.

GLOMERULONEPHRITIS

Glomerulonephritis is a renal disease that is characterized by inflammation of the glomeruli, or small blood vessels in the kidney^[143,144]. It may present with isolated

hematuria and/or proteinuria (blood or protein in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute renal failure, or chronic renal failure^[144]. Diagnosing the pattern of glomerulonephritis is important because the outcome and treatment differs in different types of glomerular disease^[144]. The primary causes of glomerular disease are intrinsic to the kidney^[144], but secondary causes of disease may be associated with; certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis), or diabetes^[143]. Several case reports have shown a potential link between *C. jejuni* infection and glomerular disease^[145-150]. In some reports a *C. jejuni* antigen was identified in the glomeruli suggesting a causal role for this bacterium in the disease process^[145,148].

VASCULITIS

Vasculitis is a group of autoimmune diseases in which blood vessels are attacked by the immune system and where inflammation is present^[151]. *C. fetus* subsp. *intestinalis* was one the first *Campylobacter* species linked to vasculitis and is seen most often in older, debilitated, or chronically ill men^[152]. In case reports, *C. jejuni* has been linked to patients experiencing various forms of vasculitis^[114,146,153-158], though whether an actual causal relationship exists between disease and infection is as yet is unknown.

PSORIATIC ARTHRITIS

Psoriatic arthritis is a form of inflammatory arthritis that will develop in up to 30% of people who have the chronic skin condition psoriasis^[159]. Psoriatic arthritis is said to be a seronegative spondyloarthropathy and therefore occurs more commonly in patients with tissue type HLA-B27^[159]. A strong link between anti-*Campylobacter fetus* antibodies in psoriatic arthritis patients (rheumatoid arthritis, non-arthritic-psoriasis and psoriatic arthritis patients) was observed in the study of Lapadula *et al.*^[160]. Currently, no further studies on this subject have been reported, and it should be noted that the patient group used in the Lapadula study was small.

CANCER

C. jejuni is phylogenetically closely related to *Helicobacter pylori*, a bacterium established to be a causative agent of gastric cancer^[161]. Further, the cytolethal distending toxin of *C. jejuni* may possess DNase activity and could induce the breakage of double stranded DNA^[162], one of the possible steps on the development of cancer. Currently, there is some evidence indicating that *C. jejuni* may possibly be linked to the development of mucosa-associated lymphoid tissue (MALT) lymphoma^[163-165]. MALT is a cancer type that originates from B cells in the marginal zone of the MALT, and is also called extra-nodal marginal zone B cell lymphoma. However, a large

cohort study of Scandinavian patients who had tested positive for *C. jejuni*, and were followed over time (≥ 10 years) showed no increased risk of developing malignancies following an infection by *C. jejuni*^{1166]}. Interestingly, the authors did find a decrease in respiratory cancers following an infection by *C. jejuni*.

CONCLUSION

Campylobacter species are able to induce both gastrointestinal and systemic infections in humans and have been linked not only to acute disease, but also to a wide range of (chronic) inflammatory diseases. In this respect, the organism is particularly associated with the development of neurological diseases such as GBS, MFS, and with reactive arthritis, diseases that are facilitated by the development of cross-reactive antibodies to *Campylobacter* sialylated LOS carbohydrate structures. However, the true role of *Campylobacter*-induced molecular mimicry in other human inflammatory diseases remains to be determined, though this review indicates that the actual role of *Campylobacter* infections in human disease may be largely underestimated. Therefore, further research is required in order to accurately determine the importance of *Campylobacter* infection in a wide range of (chronic) inflammatory diseases of humans.

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