The consequences of *Campylobacter* infection

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Abstract

Purpose of review

The purpose of this review is to provide an update on the clinical, public health and economic consequences of *Campylobacter* infection.

Recent findings

Campylobacter is a leading bacterial cause of food-related illness. Its importance is enhanced by the chronic sequelae that can result from acute infection. Recent advances include a new clinical classification system for neurological sequelae with the aim of speeding accurate diagnosis and appropriate treatment, a better understanding of the mechanisms underlying post-infectious functional gastrointestinal disorders, the emergence of *C. concisus* and *C. showae* as potential aetiological agents in inflammatory bowel disease, a new mechanism for antimicrobial resistance in campylobacters and a better appreciation of the economic costs.

Summary

Campylobacter infection is very common and can lead to serious chronic sequelae and considerable personal, healthcare and societal costs.

Key Words

Campylobacter, foodborne disease, gastroenteritis, Guillain-Barré syndrome, Miller Fisher syndrome, irritable bowel syndrome, reactive arthritis

Abbreviations

aHR

aRR

Bv.

CI

DALY

ELISA

FGID

GBS

HUS

IBD

IBS

IgA

IgG

IVIg

MFS

MLST

P-OR

QoL

ReA

RT-PCR

Subsp.

Introduction

Since its first identification as a human pathogen in the 1970s *Campylobacter* has emerged as a leading cause of acute gastroenteritis worldwide. Clinically relevant organisms include *Campylobacter jejuni* and *C. coli,* which are the major pathogens, but several species are recognised causes of illness in humans [1•] (Table 1).

Clinical consequences

Acute enteritis

Campylobacter jejuni is among the most frequent causes of bacterial gastroenteritis globally [2-4••]. Using multilocus sequence typing (MLST) more than 8,300 *C. jejuni* sequence types (STs) have been described [5••]. Although generally considered to cause mild and self-limiting acute enteritis, in a recently completed retrospective cohort study in Sweden more than a quarter (27%) of stool culture positive *Campylobacter* cases were admitted to hospital [6•]. The majority (92%) of the laboratory-confirmed cases were admitted because of severe enteritis or colitis. There was a statistically significant 14-fold increase in risk of hospital admission for people with co-morbidities. People infected with *C. jejuni* ST-257 were twice as likely to be admitted to hospital. This study serves as a timely reminder that *C. jejuni* acute enteritis can be severe.

Chronic sequelae

As well as causing very unpleasant acute symptoms, *Campylobacter* infection is also associated with various chronic sequelae although the evidence for an association is stronger for some conditions than others. *Campylobacter* infection has been implicated in the subsequent development of reactive arthritis (ReA), Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS), haemolytic uraemic syndrome (HUS), inflammatory bowel disease (IBD) and functional gastrointestinal disorders (FGID). In a recent systematic review and meta-analysis of 31 observational studies the proportion of *Campylobacter* cases developing chronic sequelae was estimated. The proportion of *Campylobacter*

cases that went on to develop ReA was 2.86% (95% CI 1.40% - 5.61%), IBS was 4.01% (95% CI 1.41% - 10.88%) and GBS was 0.07% (95% CI 0.03%- 0.15%) [7•]. Given the overall incidence of *Campylobacter* infection (see below), these estimates suggest that a considerable number of *Campylobacter* cases can develop chronic sequelae but caution is required when interpreting the results because of high heterogeneity between studies.

Reactive Arthritis

Reactive arthritis (ReA), formerly known as Reiter's Syndrome, is a post-infectious spondylo-arthropathy, which occurs around two to four weeks after gastrointestinal or genitourinary infections. The pain associated with ReA occurs most often in the knees, ankles and feet. In a systematic review using stringent criteria to define diarrhoea-associated ReA the weighted mean incidence of reactive arthritis following *Campylobacter* infection was 9 per 1,000 cases [8]. Further evidence for the contribution of *Campylobacter* infection to subsequent ReA comes from sero-prevalence data. Using an optimised ELISA assay for diagnosing a previous *Campylobacter* infection around 53% (44-62%) of ReA cases demonstrated *Campylobacter* sero-positivity (OMP18 and P39 for IgA and in the P39-antigen for IgG) [9]. Polymorphisms in the interleukin-18 and interferon-gamma genes appear to be associated with the development of *Campylobacter*-associated ReA [10]. Symptoms of ReA usually disappear completely within six months. However, in 10–20% of people the symptoms persist beyond six months although it is said that only a few people develop an ongoing arthritis beyond 12 months requiring longer-term treatment. Finally, antibiotic treatment does not appear to improve the outcome in ReA [11].

Guillain-Barré Syndrome

The most severe late consequence of *Campylobacter* infection is Guillain-Barré syndrome (GBS), which is the most frequent cause of acute flaccid symmetrical weakness of the limbs and absence of deep tendon reflexes [12]. The incidence of post-*Campylobacter* GBS is estimated to be between 1 in

1,000 and 1 in 5,000 cases. It is characterised initially by tingling in the toes, feet and legs, and the fingers, hands and arms. This is followed by ascending muscle weakness and paralysis (not to be confused with the descending paralysis of botulism). Symptoms of GBS can progress very rapidly. The majority of people reach the stage of greatest weakness within the first 2 weeks after symptoms first appear, and by the third week 90% of patients are at their weakest. Approximately 30% of patients with GBS have persisting weakness after 3 years. Around 3% can experience a relapse of muscle weakness and tingling sensations many years after the original episode.

The heterogeneity of presenting symptoms presents a considerable challenge in the initial clinical diagnosis of GBS. In a retrospective review of 69 GBS patients presenting to emergency rooms in Texas atypical clinical signs and symptoms led to delayed diagnosis [13]. In that study, neuropathic pain and the presence of intact deep tendon reflexes were significantly associated with delayed GBS diagnosis. Patients who were assessed by a neurologist during the initial visit experienced significantly better clinical outcomes. However, patients in whom GBS was not suspected during the initial neurology assessment were significantly more likely to need intubation and to have residual weakness at the time of discharge from hospital [13].

The mechanism of neural damage involves molecular mimicry between *C. jejuni* and human peripheral nerve proteins [14]. It is known that sialylated lipo-oligosaccharides (LOS) of *C. jejuni* are crucial virulence factors for the development of GBS. However, there is now a suggestion that the polysaccharide capsule of *C. jejuni* is also an important virulence factor [15]. In two geographically distinct GBS-associated *C. jejuni* strain collections researchers concluded that capsular types HS1/44c, HS2, HS4c, HS19, HS23/36c and HS41 were markers for GBS compared with controls with uncomplicated enteritis [15]. Using MLST they found restricted genetic diversity for strain populations with HS2, HS19 and HS41 capsular types. Thus these capsules may also confer susceptibility to GBS.

Management of GBS involves plasmapheresis and high-dose immunoglobulin therapy plus supportive treatment e.g. mechanical ventilation, prevention of complications such as pneumonia or bed sores and physiotherapy as muscle strength returns. In a Cochrane systematic review of six randomised controlled trials plasmapheresis was found to help speed recovery from GBS without causing significant harm [16]. The authors concluded that there was moderate-quality evidence showing significantly greater improvement with plasmapheresis than supportive care alone in adults with Guillain-Barré syndrome without a significant increase in serious adverse events. They found a small but significant increase in the risk of relapse during the first six to 12 months after onset in patients treated with plasmapheresis exchange compared with patients not undergoing this treatment. Nevertheless, after 12 months, patients who had undergone plasmapheresis were significantly more likely to recover fully and were less likely to suffer severe residual weakness [16]. More recently in a Cochrane review of 12 trials there was moderate quality evidence that, in severe disease, starting intravenous immunoglobulin (IVIg) started two weeks from onset hastened recovery as much as plasmapheresis [17]. There was also moderate quality evidence that administering IVIg after plasmapheresis did not afford significant additional advantage [17]. Finally, often overlooked features of GBS are fatigue, pain and psychological distress, which can have a considerable impact on health-related quality of life (QoL) [18•].

Miller Fisher Syndrome

Miller Fisher syndrome (MFS) is a rare late consequence of *Campylobacter* infection. Essentially, it is a non-paralytic variant of GBS in which patients present with ophthalmoplegia, ataxia and areflexia. Recently a new, simple, clinical classification system has been proposed for GBS, MFS and their sub-types to help to facilitate early clinical diagnosis with a view to starting appropriate immunotherapy as rapidly as possible [19••].

Haemolytic Uraemic Syndrome

Antecedent *Campylobacter* infection has been associated with diarrhoea-related HUS. It is believed to be a rare cause of pulmonary-renal syndrome leading to life-threatening pulmonary haemorrhage [20].

Inflammatory Bowel Disease

There has been considerable debate over the years about a role for *Campylobacter* infection in the aetiology of inflammatory bowel disease (IBD). It has been postulated that in genetically predisposed people gut microbes, in association with a disrupted gastrointestinal epithelium, can fuel and then drive a dysregulated immune response that results in chronic inflammation in the intestine [21,22•]. In a recent systematic review and meta-analysis the association between IBD and a variety of *Campylobacter* spp. was investigated [23••]. In total the sample comprised 519 patients with IBD and 1,133 non-IBD controls. Overall there was an almost three-fold increase in risk of IBD following infection with *Campylobacter* spp. (pooled odds ratio (P-OR) = 2.97 (95% confidence interval (CI) 1.33 - 6.63, p =0.008). In that review *Campylobacter* spp. were confirmed in 39% of patients with IBD compared with 13% of non-IBD controls. On stratification by *Campylobacter* spp. the analyses showed that the organisms chiefly responsible for the observed association with increased risk of IBD were *C. concisus* (P-OR: 3.76, 95% CI 1.46 to 9.70, p value=0.006) and *C. showae* (P-OR: 2.39, 95% CI 1.11 - 5.18, p =0.027) [23••].

Functional Gastrointestinal Disorders

The link between acute gastroenteritis and subsequent post-infectious irritable bowel syndrome (IBS) has been established for some time but there are few studies which have quantified pathogen-specific risk. In a retrospective cohort study of FGID amongst the US military there were statistically significant associations between antecedent *Campylobacter* infection and the risk of developing post-infectious IBS (Adjusted relative risk (aRR) = 2.8 (95% CI 1.9 - 4.1), functional dyspepsia (aRR =

2.0 (95% CI 1.3 - 3.0), functional constipation (aRR = 1.8 (95% CI 1.3 - 2.5) and gastro-oesophageal reflux disease (aRR = 1.7 (95% CI = 1.4 - 2.1) [24••]. In a prospective study risk factors for new-onset irritable bowel syndrome (IBS) among active personnel enrolled in the US military's Millennium Cohort Study significant risk factors included preceding acute gastroenteritis (adjusted hazard ratio (aHR) = 2.05 (95% CI = 1.53 – 2.75), female sex (aHR = 1.96 (95% CI = 1.53 –2.52) and anxiety syndrome (aHR = 1.74 (95% CI = 1.17 – 2.58)). There was also a dose-response relationship with number of life stressors (1 stressor: aHR = 1.82 (95% CI = 1.37–2.41); 2 stressors: (aHR = 2.86 (95% CI = 2.01 –4.06); 3 or more stressors: (aHR = 6.69 (95% CI = 4.59 – 9.77. Pre-existing anxiety or depression and acute gastroenteritis interacted with increased IBS risk compared with acute gastreonteritis alone [25••]. The complex interplay between intestinal microbiota and the autonomous nervous system (the so-called "gut-brain axis") in conjunction with the immune system suggest that the gut-brain axis has a central function in perpetuating irritable bowel syndrome and that the intestinal microbiota play a critical part [26••].

Links between acute gastroenteritis (including *Campylobacter* infection) and FGID other than IBS are also gaining recognition. For example, there is a statistically significant association between functional dyspepsia and preceding acute gastroenteritis (summary odds ratio for post-infectious functional dyspepsia = 2.54 (95% CI = 1.76–3.65) [27•].

Public Health Consequences

Illness burden

The population burden of illness associated with *Campylobacter* infection is very high. On a global scale *Campylobacter* spp. are estimated to cause some 96 million (95% uncertainty interval (UI) 52 - 177 million) cases of foodborne illness [4••]. In the UK there are some 280,000 cases of *Campylobacter* foodborne illness [28] whilst in Canada the estimate is around 145,000 cases [29].

An increasingly common metric for describing the burden of disease associated with foodborne pathogens is the disability-adjusted life year (DALY), which is a useful method for combining loss of life and health due to illness compared with a "perfect" state of health, using time as the common measure. In the US *Campylobacter* infection is estimated to cause about 22 500 DALYs annually [30], whilst in the Netherlands Campylobacter spp. are responsible for around 3,600 DALYs per year [31].

Outbreaks

The association between eating undercooked poultry and developing *Campylobacter* infection is well known. However, consuming lightly cooked chicken livers, chicken liver pâté and chicken liver parfait has emerged as important risk factors [32-34]. Recognising this emerging trend in the UK, the Food Standards Agency commissioned research to develop a recipe for manufacturing commercial quantities of chicken liver pâté that reliably kills campylobacters [35•]. Further evidence that cooking practices are responsible for *Campylobacter* cases and outbreaks associated with lightly cooked chicken livers comes from an interdisciplinary study in the UK [36•]. In an online survey most chefs who took part could correctly identify safely cooked chicken livers. However they tended to overestimate consumers' preference for "pinkness" and so chefs tended to serve chicken livers more lightly cooked than the public would have preferred. Moreover it was estimated that 19%-52% of livers served commercially in the UK do not reach the recommended cooking temperature of 70°C and that predicted *Campylobacter* survival rates in those undercooked livers were between 48% and 98% [36•]. More esoteric causes of recent outbreaks have included contact with wildlife [37], and consumption of raw milk (either intentionally or through failure of pasteurisation) continues to pose risks for Campylobacter infection [38,39•].

Sporadic infection

The majority of *Campylobacter* cases are unrelated to outbreaks. Newly identified risk factors for sporadic in recently published case-control studies include contact with garden soil for *C. jejuni* and *C. coli*, and consuming beef (C. coli only) [40], and eating cantaloupe and queso fresco (Mexican

cheese) [41]. However, consumption of contaminated poultry continues to feature prominently in the epidemiology of sporadic cases [42,43]. This is not necessarily surprising given the continued high prevalence of contamination of poultry on retail sale [44].

Antimicrobial resistance

Fluoroquinolone and macrolide resistance are well established in campylobacters. Recently a new mechanism for enhanced multidrug resistance in campylobacters has been discovered, which confers remarkably high-level resistance to fluoroquinolones [45••]. This involves the emergence of so-called "super" efflux pump variants that enhance resistance to multiple antimicrobials. This is a resistance-enhancing variant (so-called RE-CmeABC) of the predominant *Campylobacter* efflux pump CmeABC. It also seems that RE-CmeABC can be transferred horizontally [45••].

Economic consequences

Various researchers have monetised the cost of *Campylobacter* infection (Table 2). The estimates of cost vary quite widely reflecting differences in, for example, study design, costing elements included and type of healthcare system. Some researchers included in their cost estimates the impact of long term sequelae whilst others did not. Despite the differences in study design the broad message is the same – namely that *Campylobacter* is a costly infection.

The likely costs of prevention can be hard to estimate but point to the fact that whilst the savings from prevention would accrue mainly to cases and health services the costs would lie elsewhere in government and in industry. Nevertheless in New Zealand, where there has been a considerable effort to reduce *Campylobacter* contamination of poultry flocks the benefit:cost ratio was extremely high [50••]. The beneficial effect of reduced campylobacteriosis to the New Zealand economy was around NZD 57 million per year. So investing in food safety compliance measures at primary production was very worthwhile [50••]. In the absence of such measures in other countries

preventing *Campylobacter* infection still relies on the so-called “4Cs”- thorough cooking and cleaning (including hands and work surfaces), proper chilling and avoiding cross-contamination.

Conclusions

Campylobacter causes considerable morbidity worldwide. Post-infectious sequelae mainly affect the gastrointestinal tract (FGID, IBD), the musculoskeletal system (ReA) and the peripheral nervous system (GBS, MFS) and these sequelae can lead to lifelong disability and reduction in health-related quality of life. The economic costs of *Campylobacter* infection are very high for cases, the healthcare system and for society in general. However, in general, prevention still depends on tried and tested methods i.e. good food (and personal) hygiene.

Key points

- *Campylobacter* is one of the leading bacterial foodborne pathogens worldwide.
- Chronic sequelae post *Campylobacter* infection can be very serious, causing considerable lifelong morbidity.
- There is growing evidence of the importance of the interaction of the gut-brain axis, microbiota and immune system in the pathogenesis of irritable bowel syndrome.
- *C. concisus* and *C. showae* are emerging as potentially important triggers of inflammatory bowel disease.
- Preventing *Campylobacter* infection still relies on the so-called “4Cs”- thorough cooking and cleaning (including hands and work surfaces), proper chilling and avoiding cross-contamination.

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Disclaimer

The views expressed are those of the author and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

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Table 1: Summary of clinically relevant *Campylobacter* species [1]

***Campylobacter* species**	**Clinical Features/Associations**	**Reservoir(s)**
C. coli	Gastroenteritis, septicaemia	Dogs, cattle, pigs
C. concisus	Gastroenteritis, periodontal disease, septicaemia; associated with inflammatory bowel disease, Barrett's oesophagus	Humans, dogs, cats
C. curvus	Abscess, gastroenteritis	Humans
C. fetus subspecies (subsp.) *fetus*	Meningitis, septicaemia, foetal loss, vascular infection	Cattle, dogs, sheep, turtles
C. fetus subsp. *venerealis*	Septicaemia	Cattle
C. gracilis	Abscess	Dogs, humans
C. hyointestinalis subsp. *hyointestinalis*	Gastroenteritis, septicaemia	Cattle, hamsters, pigs
C. insulaenigrae	Gastroenteritis, septicaemia	Porpoises, seals
C. jejuni subsp. *jejuni*	Gastroenteritis, septicaemia, foetal loss, mesenteric adenitis, colitis, myocarditis, reactive arthritis, Guillain-Barré syndrome, Miller Fisher syndrome	Cattle, dogs, poultry, sheep, wild birds
C. jejuni subsp. *doylei*	Gastroenteritis, septicaemia	Humans, dogs
C. lari subsp. *lari*	Gastroenteritis, septicaemia	Cats, dogs, chickens, seals

C. rectus	Abscess	Humans
C. showae	Septicaemia, cholangitis; associated with inflammatory bowel disease	Humans, dogs
C. sputorum biovar (bv.) *sputorum*	Abscess	Humans, cattle, pigs, sheep
C. upsaliensis	Enteritis, septicemia, abortion, abscesses	Cats, dogs, ducks, monkeys
C. ureolyticus	Associated with ulcerative colitis	Cattle

Table 2: Summary of recently published studies estimating the monetary costs of *Campylobacter* infection

Country	Year	Estimated Annual Cost	Estimated cost per case
UK [46]	2008-9	GBP 50 million	GBP 85
Netherlands [47]	2011	EUR 76 million	EUR 706
Switzerland [48]	2012-14	EUR 29–45 million	EUR 63–95
US [49]	2013	USD 1.9 billion	USD 2,283