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Campylobacter Reactive Arthritis: A Systematic Review

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Abstract

Objective—To review the literature on the epidemiology of *Campylobacter* associated ReA.

Methods—A Medline (PubMed) search identified studies from 1966–2006 that investigated the epidemiology of *Campylobacter* associated ReA. Search terms included: “reactive arthritis”, “spondyloarthropathy”, “Reiter’s syndrome”, “gastroenteritis”, “diarrhea”, “epidemiology”, “incidence”, “prevalence”, and “Campylobacter”.

Results—The literature available to date suggests that the incidence of *Campylobacter* reactive arthritis may occur in 1 to 5% of those infected. The annual incidence of ReA after *Campylobacter* or *Shigella* may be 4.3 and 1.3 respectively per 100,000. The duration of acute ReA varies considerably between reports, and the incidence and impact of chronic reactive arthritis from *Campylobacter* infection is virtually unknown.

Conclusions—*Campylobacter* associated ReA incidence and prevalence varies widely from reviews such as: case ascertainment differences, exposure differences, lack of diagnostic criteria for ReA and perhaps genetics and ages of exposed individuals. At the population level it may not be associated with HLA-B27 and inflammatory back involvement is uncommon. Follow up for long-term sequelae is largely unknown. Five percent of *Campylobacter* ReA may be chronic or relapsing (with respect to musculoskeletal symptoms).

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Keywords

Campylobacter jejuni; *Campylobacter coli*; reactive arthritis; incidence; sequelae

Introduction

Campylobacter gastroenteritis is common

In both developed and developing countries, *Campylobacter jejuni* is the most common cause of human bacterial enteritis accounting for 5–14% of all diarrheal diseases worldwide [1]. Most cases are sporadic; however outbreaks do occur. For example *Campylobacter* accounts for 59% of water or food borne cases of diarrhea in Canada and its incidence is increasing [2]. Similarly in the USA, it is estimated that 2.1–2.4 million cases of human campylobacteriosis occur each year [3, 4]. The most common serotype of Campylobacter is *C. jejuni,* which accounts for 90–95% of positive stools. The second most common serotype *C. coli* only accounts for 5–10% of cases [2].

Clinical Presentation of Acute Reactive Arthritis (ReA) after *Campylobacter* and other Enteric Infections

ReA is one of the spondyloarthropathies, a group of diseases with a strong association with HLA-B27, absence of rheumatoid factor (RF), family aggregation and frequent extra-articular symptomatology [5]. Acute ReA is characterized by a sterile joint inflammation. It typically develops within four weeks following an intestinal or urogenital infection with obligate or facultative intracellular bacteria, such as *Salmonella, Shigella, Yersinia* and *Campylobacter*, and to a far lesser extent *E. coli* O157:H7 [6, 7]. The number of infectious agents associated with ReA is gradually increasing (Table 1). A detailed history is critical to establish the diagnosis - the triggering infection is mild and often overlooked as the inciting factor [8]. The symptomatology is predominantly joint and musculoskeletal (MSK) involvement, but skin and mucous membranes, gastrointestinal, ocular [9], and cardiac symptoms have also been described and should be specifically assessed [10, 11]. The joint symptoms vary from mild mono- or oligo-arthralgia to a severely disabling polyarthritis [12–15]. The arthritis has a predilection for joints of the lower extremity, particularly knees and ankles but not necessarily axial involvement. It can also involve small joints (swelling with or without erythematous discolouration of the joint) or it can present as tenosynovitis. ReA should be considered in the differential diagnosis of anyone presenting with a mono- or oligoarthritis of unknown aetiology.

At present, there are no clear recommendations for testing to identify the causative bacterium of reactive arthritis in routine practice. For ReA severe enough to prompt the patient to seek medical attention, an acute phase reactants response and neutrophilia is usually seen. RF and antinuclear antibodies are negative. Microscopy along with a culture of synovial fluid should be undertaken to exclude septic arthritis and crystal-induced arthritis. Stool should also be cultured, as *Salmonella, Yersinia* and *Campylobacter* persists for some time after initial infection [16]. Additionally, serological techniques to identify *Campylobacter* exposure can be used; however their sensitivity and specificity appears lower than those for *Salmonella* and *Yersinia* [16]. High titres of IgG to *Campylobacter* are not

necessarily diagnostic of a recent infection as the general population may commonly encounter this organism in food such as chicken and eggs. Rising IgG and/or persistently high IgA are therefore diagnostically preferable [16]. A major drawback in the diagnostic evaluation is that there are no uniform criteria for ReA.

Biological Pathogenesis of Acute ReA After Campylobacter and other Enteric Infections

This risk of developing post-enteric ReA seems to be slightly greater for infection with *Salmonella* and *Yersinia* than for *Campylobacter*, but further work is required to clarify this issue [17, 18]. The pathophysiology is largely unknown; however, it has been hypothesized that an interaction of host HLA-B27 and certain bacteria play a crucial role in the development of ReA. Population prevalence of HLA-B27 ranges from 0 to 50% [19]. In some, but not all studies, HLA-B27 positive individuals tend to have more severe disease with a higher tendency to develop chronic ReA compared to HLA-B27 negative individuals [14, 15, 20]. For example, in a review of reported *Campylobacter*-associated ReA cases in 1994, 56% of 29 subjects were HLA-B27 positive and the presence of the allele was associated with more severe disease [21]. However, a recent population-based study of *Campylobacter*-associated ReA showed no association with HLA-B27 [2]. There may be a referral bias to tertiary care centres in those with more severe or prolonged disease (HLA-B27+ as high as 70% in hospital-based reports) [11, 22–33]. This would select for a higher prevalence of HLA-B27, thus supporting that HLA-B27 is not necessary for ReA development, but it may increase disease severity and chronicity.

ReA occurs after a urogenital or enteric infection, but the organism cannot always be identified [34–36]. In patients with ReA, bacterial antigens derived from the causative organism(s) seem to disseminate in the body, and bacterial antigens have been isolated in the synovial fluid and surrounding tissues, but only in the early stages of arthropathy [37–40]. *Chlamydia* DNA and RNA, and *Yersinia* DNA have been detected in the synovial fluid of joints of ReA patients; however *Chlamydia* nucleic acids were also present in the joints of asymptomatic controls [41–43]. Abnormalities in the production and levels, in addition to polymorphism, of proinflammatory cytokines seem to play an important role in the development and duration of ReA [44–47]. Molecular mimicry is thought to precipitate synovitis in ReA. Molecular mimicry is confusion of self-antigens with infectious antigens. There are many good review articles about lack of tolerance to self/molecular mimicry; however, this is beyond the scope of this review.

Gaston and Lillicrap recently proposed a hypothesis of the pathogenesis of ReA [48], in which bacteria persist in the epithelium, associated lymph nodes, liver and spleen, following invasion of the mucosa. Bacteria and/or their antigens disseminate into the joints, causing an inflammatory response leading to an arthritic process that is driven and probably also supported by CD4+ T-cells. Abnormal T helper responses may favour the bacteria and/or antigen persistence.

Methods

A Medline (PubMed) search was conducted to identify all studies from 1966–2006 that investigated the epidemiology of *Campylobacter* and other bacteria-associated reactive

arthritis. Search terms included: “reactive arthritis”, “spondyloarthropathy”, “Reiter’s syndrome”, “gastroenteritis”, “diarrhea”, “epidemiology”, “incidence”, and “prevalence”, “Campylobacter”, “Shigella”, “E. coli”, “salmonella” and other individual know bacterial triggers of reactive arthritis. Various combinations of the search terms and connectors were used. Studies with relevance to the stated objective were included in this review.

Results

Epidemiology of Acute ReA after *Campylobacter* and *E. coli*

The prevalence of acute ReA has been estimated between 1–7%, where variability in the estimates may have been due to the criteria used for diagnosis and the setting in which the study was undertaken (hospital series vs. single-source outbreaks vs. community-based series) [9, 49–54]. The annual incidence of ReA after bowel or urogenital infection is 30–40/100,000 [55–59]; however, the true incidence is difficult to assess because of the varied clinical severity and milder cases that are frequently unreported.

Hannu et al. reported the annual incidence of ReA in Finland due to *Campylobacter* to be 4.3/100.000 [2], which is higher than the recently reported 1.3/100.00 incidence of *Shigella*-induced ReA [60]. As *Campylobacter* has become the most common cause of gastroenteritis in the western world, it can be predicted that the number of *Campylobacter*-induced ReA will increase [7, 9, 61].

The most commonly affected age group is young adults with males and females being equally affected. ReA seems to be a rare complication of *Campylobacter* infection in children [24, 28, 62, 63], this is similar to the findings for ReA due to *Salmonella* [18] and *Yersinia* [14] infections. Sporadic cases of ReA have been described following *Campylobacter* infection [11, 22–33, 51, 62–66]. Only a few outbreaks have been followed from a rheumatologic perspective, and all were limited to short follow-up (Table 3). Following infection with *Campylobacter* species symptoms of probable chronic ReA, which include arthralgias to overt arthritis have been described in 0.7 and 24% of cases [2, 51, 59, 65, 67]. Similarly, symptoms of chronic ReA have developed in 6% of cases following an infection with *E. coli* [67] (Table 4). Hannu et al described a 7% incidence of ReA in a cohort of 870 post-*Campylobacter* enteritis patients, with the majority of cases (82%) associated with *C. jejuni* infection [2]. One study suggested that half of affected individuals had ReA symptoms lasting longer than one year [67]. Figure 1 summarizes the incidence of acute ReA following Campylobacter gastroenteritis reported from various studies since the late 1970s.

At the time of arthritis, the symptoms of triggering infection have usually subsided and the stool cultures are usually negative. If cultures are negative, the causative agent has to be confirmed by serological methods, which may very between facilities. Table 3 summarizes the incidence data on the acute ReA due to *Campylobacter* infection.

Discussion

The Possibility of Chronic Arthritis and other Long-term Musculoskeletal Symptoms after *Campylobacter* or *E. coli* Infection

Data are lacking on the proportion of patients that develop chronic ReA. The duration of arthritis for more than 6 months has been arbitrarily regarded as a sign of chronic pathology. Very few cohort studies have investigated the incidence and chronicity of ReA after infection with *Campylobacter* species and/or enterotoxigenic *Escherichia coli* (ETEC) [2, 51, 65, 67, 68]. It was only in the late 1970's that ReA was noted to be triggered by an infection with *Campylobacter* [64]. *E. coli* urinary infection or diarrhea has also been associated with ReA [40, 67, 69]. The typical duration of symptoms is less than 6 months; however, some individuals exhibit chronic symptoms for a longer period [40]. It has been reported that ReA recurred 7 years after the initial exposure in a HLA-B27 positive woman[65]. Acute gastroenteritis may lead to a chronic inflammatory state with elevated CRP and ESR [55]. The signs and intensity of ReA in relation to the initial gastrointestinal infection has not been completely determined. Locht *et al* observed that *Campylobacter* patients who reported joint pain had more severe gastrointestinal symptoms and a longer duration of diarrhea compared to those who did not report joint pain [67].

In contrast, Bremell *et al* found minimal association between acute gastroenteritis severity and the chronicity of ReA - 20% of patients with acute intestinal infection developed a self-limited ReA of less than one months duration, while 13% of patients with positive *Campylobacter* serology but no symptoms of gastroenteritis reported long-term rheumatic problems months following infection [67]. Table 4 summarizes data regarding the chronic sequelae of *Campylobacter* and *E. coli* ReA.

Depending on the infectious agent and follow-up time 18% of patients may suffer from chronic arthritis, up to 49% and 26% from sacroiliitis and ankylosing spondylitis, respectively [70]. The long-term prognosis for post-*Campylobacter* ReA is not defined in the current literature (Table 4). A 5-year follow-up of patients with acute ReA following *Campylobacter* enteritis reported chronic or relapsing rheumatic symptoms in 5% of the exposed population [65], but the numbers in the outbreak were small.

Campylobacter and to a lesser extent *E. coli* infection play a role in the development of acute ReA; however it is uncertain to what extent they induce chronic MSK symptomatology. Future studies are required to look at the health and economic impact of ReA, especially its chronic forms.

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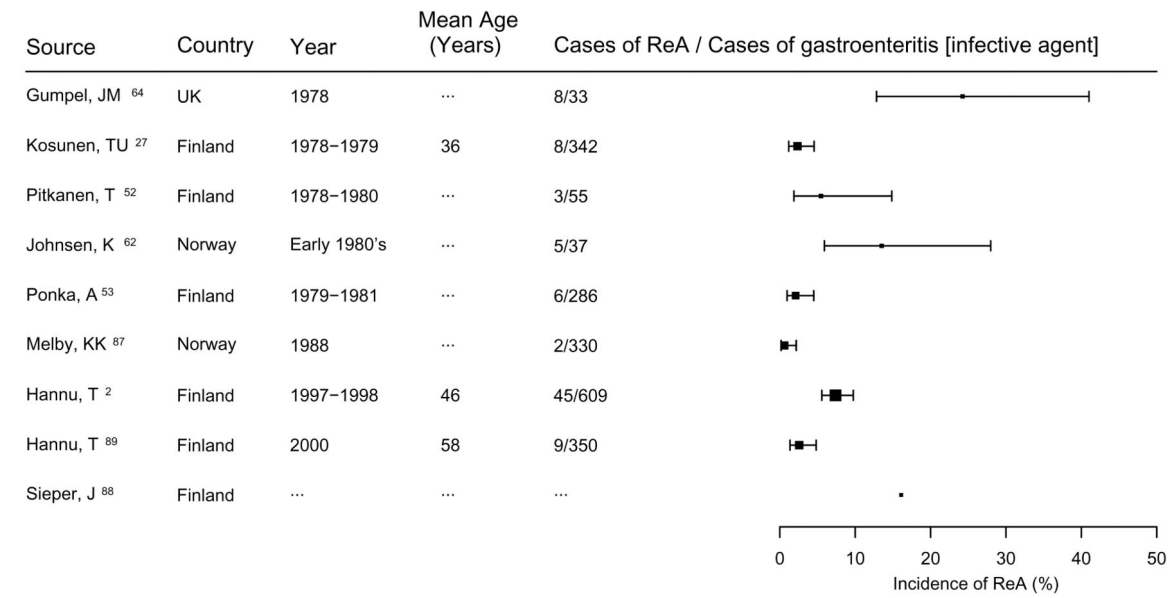

Results were not mathematically pooled because of statistical heterogeneity between studies (Chi^2 79.4, $p<0.01$, I^2≈91%).

Ellipses (...) indicate not reported. The size of each square is proportional to the size of the study.

Figure 1.
Incidence of acute ReA following Camplobacter gastroenteritis

Table 1

Infectious agents associated with the development of reactive arthritis (Modified from [71])

Enteric bacteria
• Salmonella * (various serovars; especially S. Typhimurium and S. Enteritidis) [72]
• Shigella * (S. flexneri, dysenteriae, sonnei)
• Yersinia * (Y. enterocolitica, Y. pseudotuberculosis)
• Campylobacter * (C jejuni, C. coli, C. lari [66], possibly C. fetus φ [73])
• Clostridium difficile [74]
• Giardia lamblia [75–77]
• Tropheryma whipplei [78]
Urinary bacteria
• Chlamydia trachomatis *
• Mycoplasma genitalium φ [79]
• Ureaplasma urealyticum φ[79]
• Possibly E. coli [67, 69, 80]
Respiratory bacteria
• β-haemolytic Streptococcus φ [81, 82]
• Campylobacter pneumoniae [83, 84]

* most common pathogens

φ Hypothesized causal agents

Table 2

Reactive Arthritis Classification Criteria

Proposed Diagnostic Criteria for Reactive Arthritis [85]		
	Exclusion criteria	
• Typical peripheral arthritis (predominantly lower limb, asymmetric oligoarthritis, +/− enthesopathy, +/− sacroiliitis)	Other known causes of mono/oligoarthritis, such as:	
Plus	• Other spondyloarthropathies	
• Evidence of preceding infection	• Septic arthritis	
	• Crystal arthritis	
	• Lyme disease	
	• Post-streptococcal arthritis	
Proposal for classification of reactive arthritis for patients entering clinical and experimental studies [86]		
Probable reactive arthritis	• MSK symptoms (arthritis, oligoarthritis, polyarthritis or arthropathy) and • Extra-articular disease (signs of Reiter's syndrome: mucositis, conjunctivitis, urethritis, cervicitis or keratoderma blennorrhagica, circinate balanitis)	
Definite reactive arthritis triggered by bacteria	• Bacterial identification preceding the above mentioned MSK symptoms • Bacterial identification in a recent onset (4–6 weeks) episode of MSK symptoms	
Bacteria associated undifferentiated oligoarthritis or spondyloarthropathy	Classification which may be used in the absence of the above stated criteria	

Table 3

Incidence of acute reactive arthritis (ReA) following *Campylobacter* gastroenteritis

Source/Year of infection	Cases of ReA/Cases of gastroenteritis [infective agent]	Mean age (yrs)	Comments
Gumpel, JM [64] UK 1978	8/33 (24%) [serotypes not reported]	NR	• retrospective chart/data review of hospitalized pts • 6 of 8 developed mild rheumatic symptoms • 2 of 8 referred to rheumatology • symptom duration max 1 month
Kosunen, TU [27] Finland 1978–1979	8/342 (2.3%) [C. jejuni]	36	• retrospective chart review/hospital data/clinical exams • time between onset of diarrhea and arthritis 7–28 days • ReA symptomatic for 7–17 weeks • arthralgia persisted for at least 21 months in 4 patients, 1 had a transient hydrops of the knee 6 months after arthritis disappeared
Pitkanen, T [52] Finland 1978–1980	3/55 (1.7%) [C. jejuni]	NR	• hospital chart review/Q to patients with enteritis • 2 of 3 developed Re monoarthritis (HLA-B27 −) • 1 of 3 developed Re polyarthritis (HLA-B27 unknown) • symptom duration max 2 months
Johnsen, K [62] Norway ≠ Early 1980's	5/37 (13.5%) [C. jejuni]	NR	• 2 adults with classical Reiter's syndrome • 3 children • 0% of HLA-B27+
Pönkä, A [53] Finland 1979–1981	6/283 (2.1%) [C. jejuni]	NR	• Q to lab confirmed outpatients • N=524 (283 provided information about arthritis) • arthralgia reported in 54/282 (19%) • no further details about ReA
Pitkänen, T [56] Finland 1978 – 1981	9/188 (5%) [C. jejuni]	NR	• 188 patients hospitalized for *Campylobacter jejuni* • Symptoms of sequlae determined by chart review and Q • 5% (n = 9) had arthritis; n = 6 (3%) of patients sought hospital care because of arthritis • Monoarthritis or polyarthritis occurred 1 to 3 wks after gastroenteritis; usually resolved within 6 mos

Source/Year of infection	Cases of ReA/Cases of gastroenteritis [infective agent]	Mean age (yrs)	Comments
Melby, KK [87] Norway 1988	2/330 (0.6%) [serotypes not reported for ReA cases]	NR	• O utbreak/Q to N=3085, responded N=520, GI symptomatic N=330 • Responders: – Joint swelling in 21% – Arthralgia in 9%
Hannu, T [2] Finland ≠ 1997–1998	45/609 (7%) [C. jejuni N=37 C. coli N=8]	46	• Large, population-based study of Campylobacter + stools/Q/+ evaluation by a rheumatologist • N=7 not clinically evaluated, described symptoms of ReA in the Q (ReA occurrence N=52 (9%) without clinical evaluation) • ReA: – 14% HLA-B27+ (similar to the Finnish general population) – 80% affected small joints – majority cases were poly-articular, mild and transient • 8/609 developed ReTEB – Report of enthesopathy associated with Campylobacter infection • GI symptomatology longer in pts with MSK symptomatology (vs those without) • No ReA in matched controls
Hannu, T [9] Finland 2000	9/350 (2.6%) [C. jejuni]	58	• outbreak, 350 exposed subjects contacted the Health Centre/all acute MSK symptomatic pts referred to a rheumatologist within 3 months of outbreak • N=11, acute MSK symptomatology – N=9 ReA (all mild cases; oligo- N=6, poly-articular N=3; + 1 patient had also sacroiliitis; 33% HLA-B27 +) – N=2 reactive arthralgia – N=3 exacerbation of RA – N=1 exacerbation of fibromyalgia
Sieper, J for Leirisalo-Repo [88] Finland	Overall ReA frequency 16.1%	NR	• Community based study/Q/those with rheumatic symptoms evaluated further • Overall ReA frequency 16.1% – True arthritis 6.7% – Re sacroiliitis 2.3% – Re enthesitis 1.1% – Re “arthralgia/lumbalgia” 5.9%

NR, not reported; RA, rheumatoid arthritis; Re, reactive; ReTEB, reactive tendonitis, enthesopathy or bursitis; Q, questionnaire

‡[67] At the population level, the frequency of ReA seems to be higher vs. post-outbreak *Campylobacter* ReA, have low association with HLA-B27 and arthritis seems to affect small joints.

Table 4

Chronic Sequelae of *Campylobacter* and *E. coli* gastroenteritis

Source/Year of infection	Cases of ReA/ Cases of gastroenteritis	Mean age (yrs)	Chronic ReA	Comments
Eastmond [51] United Kingdom 1979	1/130 (0.8%) [*C. jejuni*]	34	• Minimal symptoms at 2 years • Patient HLA-B27 +	• Hospital study type • N=347 (outbreak), 167 had enteritis, 88 culture + • study included 88 culture +, and 42 culture +, but GI asymptomatic pts. • acute symptoms for 2 weeks
Bremell, [65] Sweden 1981	5/86 (5.8%) [*C. jejuni*]	27	**Group A 1/35** **1** patient HLA-B27+, relapsed 7 yrs post-infection after an episode of gastroenteritis **Group B 4/31** Symptoms started 3–8 months after outbreak: **1** Arthralgia/enthesopathy (recurrent) **2** Enthesopathy **3** Sacroiliitis **4** Recurrent synovitis (probable SLE) **Group C 0/20** • No ReA	• cohort study • N=106 (outbreak) – Group A: n=35, enteritis, culture+ – Group B: n=31, no GI symptoms, culture+ – Group C: n=20, no GI symptoms, culture • N=86 (81%) had 2-year FUP Q • N=15 MSK complaints from Group B had 5 year FU telephone interview
Locht, [67] Denmark 1997–1999	27/173 (16%) ReA spectrum [*C. jejuni, C. coli*] 10/177 (6%) [*ETEC*]	36 (median) 43 (median)	5 pts symptomatic for > 1 year	• Q on MSK symptoms in pts with culture + *Campylobacter* infection (*ETEC* was a control group) • ReA spectrum: reactive arthralgia to overt arthritis • Median duration of joint symptoms – *Campylobacter* group 60 days – *E. coli* group 165 days

Source/Year of infection	Cases of ReA/ Cases of gastroenteritis	Mean age (yrs)	Chronic ReA	Comments
				• Antibiotics did not prevent reactive symptoms

Q = questionnaire