Chlamydia-induced reactive arthritis: Hidden in plain sight?

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Reactive arthritis belongs to the group of arthritides known as the spondyloarthritides. There are two main types of reactive arthritis: post-venereal and post-enteric. Chlamydia trachomatis is felt to be the most common cause of reactive arthritis, in general. Until recently, even the terminology for the condition itself was unclear as multiple eponyms and names have been associated with reactive arthritis. In recent years, a great deal has been learnt about the epidemiology, pathophysiology and treatment of reactive arthritis and Chlamydia-induced reactive arthritis, specifically. Prospective epidemiologic data suggest that Chlamydia-induced reactive arthritis is underdiagnosed. Other truths being actively revealed include data suggesting that the pathogen itself (i.e., Chlamydia) might play an equally important role, or perhaps even more important, than the host with disease susceptibility; asymptomatic chlamydial infections might be a common cause of ReA and the two variants of reactive arthritis might respond differently to treatment in spite of the congruent clinical presentation. However, much about this syndrome remains shrouded in mystery. Data covered in this review suggest that Chlamydia-induced reactive arthritis might be a common condition that clinicians fail to recognise. An emphasis is placed on disease awareness since viable treatment options are emerging.

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Reactive arthritis (ReA) belongs to the group of arthritides, collectively referred to as spondyloarthritides (SpA), which are grouped together because they share common clinical features. Although all of the different types of spondyloarthritis (SpA) have been postulated to have a bacterial aetiology [1], the role of bacteria in the genesis of disease is only established in ReA. In general, there are two main types of ReA: post-chlamydial and post-enteric. The major chlamydial species that causes ReA is *Chlamydia trachomatis* (Ct); indeed, this is the most common cause of ReA in general [2]. Data described below also suggest that *C. trachomatis*-induced ReA (CiReA) is underdiagnosed. Although *Chlamydia* (*Chlamydophila*) *pneumoniae* has also been implicated to be aetiologic for ReA, it is a much less common cause than Ct [2]. The known causative triggers of the post-enteric variety of ReA include *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*. Remarkably, the clinical features of post-chlamydial and post-enteric ReA are congruent in spite of their heterogeneous origins. There are also fascinating differences in the pathophysiology underlying the two variants of ReA. These differences in pathophysiology suggest that different treatment approaches might be indicated for post-chlamydial versus post-enteric ReA. On a larger scale, the lessons learnt about the pathophysiology of ReA leads to interesting speculation regarding the aetiology of all forms of SpA, and even perhaps many different types of inflammatory arthritis.

**History of ReA**

Paralleling the controversy regarding the exact role that the bacterial triggers play in disease maintenance of ReA, there has also been confusion over the proper terminology of the disease itself. The literature is replete with multiple terms and eponyms used to describe this condition. Two of the more popular eponyms used in the literature include Reiter syndrome and Feissinger Leroy syndrome. The former was first penned in 1942 when two Harvard researchers (Bauer and Engelmann) recognised the group of symptoms that encompass ReA as one clinical syndrome. Upon their review of the literature, they realised that Hans Reiter had described this same syndrome in 1916 when he published a case of a German soldier who developed the clinical triad of arthritis, non-gonococcal urethritis and conjunctivitis after an episode of bloody diarrhoea [3]. Interestingly, two French physicians (Feissinger and Leroy) described the same syndrome in the same year [4]. Therefore, both eponyms have been used until recently. Waelsch’s syndrome and Ruhr’s syndrome are other more obscure eponyms which have also used to describe ReA.

Apparently, ReA had been rather well described in the literature hundreds of years prior to Reiter’s or Feissinger and Leroy’s publications. Pierre van Forest described a case of “secondary arthritis and urethritis” in 1507 [5], Thomas Sydenham associated arthritis with diarrhoea in 1686 [6]. Stoll documented arthritis following dysentery in 1776 [7] and Yvan described a French captain who developed ‘ophthalmia’ and inflammatory arthritis primarily of the lower extremities 15 days after a venereal infection [8]. In 1897, Launois made the distinction between septic and aseptic arthritis and that patients with the latter occasionally develop cutaneous lesions on the plantar surface of the feet (possibly keratoderma blennorrhagicum) [9]. During this same time period in 1824, Cooper proposed the concept of the relationship between venereal infection and arthritis, particularly of the lower extremities [10].

Perhaps the most compelling description of ReA was by Sir Benjamin Brodie in 1818 when he described five patients with classic ReA in his treatise *Pathological and Surgical Observations on the Diseases of the Joints* [11] Not only did Brodie accurately describe the various clinical symptoms associated with ReA, he recognised that these various symptoms represented one syndrome. Even further, some of his patients developed chronic ReA and he astutely described the relapsing course of this condition and surmised that the recurrent symptoms were all directly related to their initial infection. Brodie’s treatment of choice was *vinum colchici* (wine of the Colchicum seed).

Various descriptive terms exist in the literature to describe ReA. These include conjunctivo–urethro–synovial syndrome and blenorrhoeal idiopathic arthritis. There have also been attempts to create new terminology for the different variants of ReA. One such term used in the literature is sexually acquired reactive arthritis or sexually associated reactive arthritis (SARA). Other names for the individual variants include arthritis urethritis and polyarthritis enterica.
As discussed later in this article, controversy exists regarding the pathophysiology and treatment of ReA. The brief review above highlights the confusion associated even with the terminology of the condition itself. In recent years, the accepted terminology for this syndrome has been ReA. There are several reasons for this strong push to clarify the terminology, most notably outlined earlier. Other reasons include the fact that some previously felt that the ‘classic clinical triad’ described by Reiter and others was a subset of ReA. It is now clear that this is not a distinct subset [2]. Others have relied too heavily on this clinical triad before making the diagnosis of ReA, thereby leading to underdiagnosis, as only a minority of patients with ReA present with the ‘classic triad’. Finally, ReA is a more descriptive term. It is a necessity that the literature uses consistent terminology – ReA – to better define the condition.

Epidemiology

In keeping with previous controversy regarding proper terminology, the true incidence and prevalence of ReA is enigmatic. The Office of Rare Diseases of the National Institutes of Health lists ReA as a ‘rare disease’. This means that ReA affects less than 200,000 people in the United States. Orphanet, who are a consortium of European partners for rare diseases and orphan drugs, also lists ReA as a ‘rare disease’, meaning that it affects less than 1 person in 2000. Two previous surveys have attempted to define the incidence of ReA. A US survey suggested the age-adjusted incidence rate for males under the age of 50 years was 3.5 cases per 100,000 men [12]. Similarly, a survey in Norway estimated a minimum incidence rate of approximately five cases per 100,000 [13]. However, the true incidence of ReA continues to be debated because of the protean nature of its symptoms, as well as a lack of consensus in defining the syndrome. Further, the true number of post-chlamydial ReA cases is equally difficult to document because the triggering infection can be asymptomatic or never definitively diagnosed.

Prospective data assessing the attack rate of ReA in patients after an acute C. trachomatis infection suggest a much higher incidence. A US study in 1996 that followed patients after a venereal infection demonstrated that 4.1% of the patients developed ReA after a C. trachomatis infection, specifically [14]. Importantly, the majority of these patients with post-chlamydial ReA developed their condition after an asymptomatic infection. Further, this study was performed on an urban population with a rather high African-American study population. African-Americans are known to have a lower prevalence of the human leucocyte antigen (HLA)-B27. Therefore, this could represent an underestimate of the true attack rate. We have recently completed a similar study of 368 subjects and found a ReA attack rate of 8.1% in patients after a C. trachomatis infection (unpublished data).

The Centers for Disease Control in the US estimates the annual incidence of C. trachomatis infections to be 3 million in persons of the ages 15–44 years [15]. By using the attack rate of 4.1% in 3 million people, 123,000 new cases of post-chlamydial ReA should be estimated in the US every year. This estimate is likely low for reasons cited earlier; further, it does not include cases of ReA secondary to Cpn. For comparison, the estimated annual incidence of rheumatoid arthritis (RA) in the US is 44.6/100,000 [16], translating into a very similar number, that is, about 125,000 new cases of RA per year. Indeed, a 2002 study in Sweden found the annual incidence of ReA to be higher than that of RA [17]. In spite of this, a range of clinical evidence tells us that RA is diagnosed far more often than ReA.

A variety of explanations exist for the apparent underdiagnosis of CiReA. The most obvious explanation is that CiReA will spontaneously remit in 50–70% of cases; therefore, the condition could resolve before the patient is diagnosed. Another compelling explanation relates to the fact that asymptomatic Ct infections could account for as many as 78–88% of cases of CiReA [14,18]. An over-reliance on the classic triad of symptoms and/or HLA-B27 positivity, the more subtle clinical presentation in women and the lack of specific diagnostic criteria [2,19] are other factors that likely contribute to underdiagnosis. Finally, a recent survey by our group suggests that a large percentage of patients with ReA could be misdiagnosed with psoriatic arthritis sine psoriasis, palmpoplantar–pustular psoriasis with arthritis or even seronegative rheumatoid arthritis [20].

Chlamydiae

All chlamydial species are obligate intracellular bacterial parasites of eukaryotic cells. For the most part, chlamydiae are incapable of generating their own energy; therefore, they rely on the host cell’s
adenosine triphosphate (ATP) for energy. There are several different chlamydial species, but our focus will be on *C. trachomatis* and *C. pneumoniae*, as these are the only chlamydial species known to cause CiReA.

The term *Chlamydia* first appeared in the literature in 1945. It is derived from the ancient Greek word ‘chlamys’ that means cloak. The name was given to these intracellular pathogens which were believed to cloak the nucleus of the infected cell. They were once felt to be viruses due to this dependence on the host cell. Older names for these organisms include ‘Bedsonia’, ‘Miyagawanella’ and ‘Halprowia’. Important animal data from the 1960s and early 1970s demonstrated that *Bedsonia* recovered from patients with ReA caused arthritis 100% of the time when injected into rabbits; in addition, intra-articular injection of these same organisms often caused ocular involvement [21,22]. These important findings demonstrated that not only were these organisms arthritogenic, but they were also able to disseminate causing clinical disease in distant organs.

Chlamydial infections are initiated at mucosal surfaces. For *C. trachomatis*, the sites of primary infection are the epithelial surfaces of the urogenital system or the ocular conjunctivae [23,24] and *C. pneumoniae*, a respiratory pathogen, is acquired through the nasal and pulmonary mucosae [25,26]. At their sites of primary infection, each organism can cause acute disease or be asymptomatic. The pathology engendered by each chlamydial species is a function of their particular biology and of the immune response they elicit. The chlamydial developmental life cycle is biphasic [27,28]; interestingly, the names used to describe the developmental stages of *Chlamydia* were coined when it was still felt to be a viral pathogen. In the first phase, the elementary body (a term borrowed from virologists), the infectious extracellular form of the organism, attaches to the appropriate host cell and is brought in a membrane-bound vesicle into the host cell cytoplasm. It is within this inclusion that the elementary body reorganises into the non-infectious form, the reticulate body; the contents of each reticulate body were “reticulated” or homogeneous. The reticulate body undergoes several rounds of division reorganising back into elementary bodies, which are then released from the host cell to cause further infection. This developmental cycle takes around 48 h to complete. Chlamydiae in the normal developmental life cycle are rather easily detected with traditional culture techniques.

The traditional description of CiReA is that of a sterile or aseptic arthritis that occurs after exposure to the organism. It was termed a ‘sterile arthritis’ because early studies performed in the 1970s and 1980s using traditional culture techniques failed to demonstrate live chlamydial organisms in the synovial fluid [29,30]. However, electron microscope (EM) studies performed during that same time period did show what appeared to be intact chlamydiae along with elementary bodies and/or reticulate bodies from synovial samples of patients with a prior infection of that same organism [31,32].

After an acute infection with *C. trachomatis* and *C. pneumoniae*, these organisms have the ability to disseminate from their site of primary infection and establish long-term residence at distant anatomic locations [33]. It is at these sites that the organism enters into an unusual biological state referred to as “persistence” [28,33]. In the persistent state, a block in gene expression impedes completion of the developmental life cycle and the organisms exhibit aberrant morphological and transcriptional factors. The means by which persistent chlamydiae might cause pathology is poorly understood, but they do elicit an immunopathogenetic response [34]. Importantly, these persistent chlamydiae cannot be detected with traditional culture techniques, but are readily detectable by EM or polymerase chain reaction (PCR).

The pattern of gene expression associated with persistent chlamydiae is significantly different than that seen during normal acute infections. For example, during persistence, expression of the major outer membrane protein (*omp1*) gene and several genes required for the cell division process are severely down-regulated; this is coupled with an up-regulation of heat shock proteins (HSPs). HSPs, in general, are paramount to the persistent state of both Ct and Cpn, as they provide many functions involved with cell survival. Under stressful conditions, HSPs allow cells to survive lethal assaults by preventing protein denaturation [35,36]. The HSP-60 molecule, specifically, has many functions that appear to be important to the pathophysiology of CiReA. HSP-60 has been shown to be pivotal in the maintenance of the persistent state. These molecules prevent chlamydial-infected cells to undergo apoptosis [37], play a role in antibiotic resistance [35] and are potentially immunogenic [38].

There appears to be differences even between chlamydial species in terms of chlamydial persistence and CiReA. In the persistent state, there are different HSP-60 paralog genes seen in *C. trachomatis*,...
whereas there are no similar paralog genes in the case of *C. pneumoniae* [39]. There have also been differences in cytokine and chemokine messenger RNA (mRNA) profiles demonstrated in human synovial tissue chronically infected with *C. trachomatis* versus *C. pneumoniae* [40]. Perhaps these differences explain the apparent arthritogenic virulence difference between these two chlamydial species.

Very recent data dictate that the arthritogenic potential of *C. trachomatis* might exist at an even more basic level. It is important to remember that there are different serovars of *C. trachomatis*. Serovars A through C are ocular serovars and the genital serovars include serovars D through K. As their name implies, serovars A through C cause ocular disease and genital infections are caused by serovars D through K. Because CiReA results after genital infections, it was natural to assume that all or some of the D through K serovars would be responsible. Remarkably, a recent study analysing the chlamydial serovars of 36 subjects with known Ct-induced ReA demonstrated that all 36 synovial tissue samples were positive for the ocular serovars, not for the genital serovars [41]. Interestingly, the ocular strains are rarely passed with genital infections, sometimes as part of a monoclonal infection [42,43]. This might explain, at least in part, the conundrum of why only a small percentage of patients with acute genital chlamydial infections develops CiReA. That the ocular strains are arthritogenic might also account for the fact that many patients with ReA develop eye disease (conjunctivitis and/or iritis/uveitis). Finally, these data suggest that the ocular strains might be much more likely to disseminate compared with the genital strains, perhaps vacating the initial site of the inoculum entirely.

The true meaning of synovial-based chlamydiae has been questioned. The mere presence of persistent chlamydial organisms in synovial tissue is not diagnostic of CiReA, as these same organisms have been detected in the synovial tissue of patients with other types of arthritis, namely osteoarthritis (OA), rheumatoid arthritis and even normal controls [44–46]. PCR or real-time-PCR (RT-PCR) detection of synovial-based chlamydiae in these non-ReA patients, although limited, has ranged from 5% to as high as 20% of samples. However, the prevalence of chlamydiae in the synovial tissue of patients with other conditions is significantly less compared with synovial tissue of patients with CiReA [18,47]. A recent study that directly compared the PCR positivity rate for synovial-based chlamydiae in patients with suspected ReA versus OA resulted in 62% versus 12% positivity, respectively (*p* < 0.0001) [18]. It appears clear that patients with suspected ReA, or CiReA specifically, are much more likely to harbour these persistent organisms in their synovial tissue, but it is not pathognomonic for the condition. The fact that a small percentage of patients with OA and even a smaller percentage of normal controls harbours these same synovial-based organisms highlights the important potential differences in host genetics/tolerance and possibly specific factors about the organism itself that determines arthritogenic virulence, such as the specific serovar. None of these studies have specifically examined the *C. trachomatis* serovar type in the synovial samples from patients with these other conditions.

**Host response in CiReA**

CiReA represents the classic interplay between host and environment in which both parties play a role in disease susceptibility. The exact role that each plays is still not clearly defined. Although the causative bacteria of ReA have been known for many years, the traditional focus in determining disease susceptibility has been on the host. HLA-B27 is a class I surface antigen, encoded in the major histocompatibility complex (MHC) on the short arm of chromosome 6 and presents antigenic peptides to T cells. B27 as an HLA allele was discovered in 1969 and shortly thereafter was demonstrated to show a very strong association with ankylosing spondylitis, but it is not pathognomonic for the condition. Later, it was linked to all subsets of SpA, although the strength of this association varies with the type of SpA and the population studied. HLA-B27 shows remarkable polymorphism and there are over 70 known alleles and 62 subtypes. Not all of the subtypes are associated with disease and, quite remarkably, some of the subtypes that are not associated with disease differ by a single amino acid from those that are [48,49]. The presence of HLA-B27 in ankylosing spondylitis has also been shown to influence the clinical manifestations of the disease; HLA-B27-positive patients have earlier disease onset, higher prevalence of eye involvement and more hip arthritis [50,51].

Could current concepts regarding HLA-B27 in ankylosing spondylitis represent lessons learned for CiReA? This appears to be the case. Older literature placed a heavy emphasis on the potential role of
HLA-B27 in the pathogenesis of ReA. Attempts to link infection with disease included the demonstration of sequence homology between B27 and these arthritogenic pathogens, so called molecular mimicry. An in vitro model suggested that Chlamydia could break self-tolerance of B27 [52]; however, definitive proof of molecular mimicry or autoreactivity as the underlying mechanism of ReA has never been established. It was previously felt that as many as 70–80% of patients with ReA were HLA-B27 positive [53,54]. However, more recent large epidemiological studies indicate that, in reality, about 30–50% of ReA patients are positive for this antigen [55–59]. Some studies report no association with HLA-B27 and ReA [60–62]. However, these data are primarily derived from epidemiologic data after large food-borne illness outbreaks; therefore, the true background prevalence of the HLA-B27 antigen in patients with CiReA is less well defined.

Rather than truly increasing disease susceptibility, HLA-B27 might portend a different prognosis. Several large studies are in agreement that HLA-B27-positive patients have more severe symptoms, thereby making the condition more clinically apparent [63,64]. HLA-B27-positive patients with ReA also appear to be more likely to develop the complete triad of symptoms [65]. Therefore, HLA-B27 could actually function as a surrogate marker of severity of disease rather than a true genetic susceptibility locus. This might further explain the apparent underdiagnosis of CiReA previously discussed.

The first line of host defence is innate immunity. Whether the causative organism disseminates from the initial site of infection as a viable and intact pathogen, as is the case with chlamydiae, or fragments of the pathogen, as appears to be the case with the enteric triggers of ReA, the innate immune system likely plays a key role in the early events underlying ReA. Toll-like receptors (TLRs) function as an integral part of innate immunity. There are significant polymorphisms in the TLR families and recent studies with ReA have demonstrated that single nucleotide polymorphisms (SNPs) in TLR2 increase disease susceptibility to ReA [66]. However, these studies were performed in patients with post-enteric ReA. Whether these same SNPs in TLR2 play a role in CiReA is unknown, but animal models do indicate that TLR2 plays a critical role in acute genital infections of C. trachomatis, leading to downstream inflammatory activation [67]. Other data indicate that the pro-inflammatory cytokine response generated by C. trachomatis involves the TLR2/TLR1/TLR6 pathways, but not TLR4 [68]. The latter is somewhat surprising since lipopolysaccharide, which is abundant on the cell wall of chlamydiae, directly stimulates TLR4. The C. trachomatis-generated inflammatory response via these various TLRs is thought to be mediated, at least in part, by macrophage inhibitory potentiator (Mip); Mip has recently been demonstrated to be a ‘classic bacterial peptide’. Conversely, data suggest that TLR4 is associated with chlamydial infections via the HSP-60 pathway. It has been shown that HSP-60 from both C. trachomatis and C. pneumoniae activates TLR4 through the MyD88 pathway [69,70]. Regardless of the exact role of TLRs, it is possible that certain bacterial peptides, referred to as pathogen-associated molecular patterns (PAMPs), might be important in disease generation, and the specific peptides expressed could help determine the resulting clinical syndrome.

Downstream from the TLRs, cytokines and chemokines play a key role in disease expression. In vitro data suggest that background cytokine and chemokine levels in the host are important in promoting or maintaining persistent chlamydial infections. It has been well documented in several different laboratories that decreased expression of tumour necrosis factor (TNF)-alpha and/or interferon (IFN)-gamma promotes the persistent state, and as levels of these two cytokines decrease, chlamydial replication increases [71–75]. A Chlamydia-induced animal model demonstrated that susceptible rats mounted a lesser initial TNF-alpha, IFN-gamma and interleukin–4 (IL–4) response to an acute infection with C. trachomatis compared with non-susceptible rats [76]. Along these same lines, treatment of established CiReA in a murine model resulted in induction of cytokines IFN-gamma, IL-4 and IL-10 with suppression of chemokines macrophage inflammatory protein (MIP)-2 and IFN-gamma inducible protein (IP)-10 [77]. These cytokine and chemokine changes were coupled with a decreased synovial chlamydial load. It has also been shown that TNF receptor p55 knockout mice develop more severe arthritis with concomitant impaired bacterial clearance in the joints, spleen and mesenteric lymph nodes along with excessive mRNA expression of pro-inflammatory cytokines compared with their wild-type counterparts; however, these data were in a post-enteric ReA model [78].

Interesting correlates with these in vitro results can be made with emerging in vivo data. Recently, a study analysing both peripheral blood and synovial fluid mononuclear cells from patients with ReA
demonstrated that IL-17-positive CD4+ T-cells were increased in the latter and this was coupled with attenuated IFN-γ expression [79]. In parallel, cervical washes from women with acute C. trachomatis infections have been compared with normal controls demonstrating up-regulation of IL-17 with a lesser response of IFN-γ in the infected samples [80]. Another recent study analysed the gene-expression profile from three patients with ReA revealing a remarkably high proportion of IP-10 along with ENA-78 and IL-8 [81]. Our group completed a clinical trial assessing combination antibiotics as a treatment for CiReA that will be described later in this review. A cytokine analysis follow-up to this clinical trial was recently completed, demonstrating a significant treatment effect on IL-12p70 [82]. Interestingly, IL-12p70 is required for optimal IFN-gamma response against intracellular pathogens and endocervical IL-12 expression has been shown to decrease with clearance of C. trachomatis [83]. Taken together, these in vitro and in vivo data suggest that low initial expression of pro-inflammatory cytokines, such as IFN-γ and TNF-α, with acute chlamydial infections might promote the development of CiReA. This mirrors epidemiological data suggesting that asymptomatic infections appear to be a common cause of CiReA. If the triggering infection is often occult in nature, it renders the correct diagnosis of CiReA nearly impossible, further strengthening the supposition that CiReA is under-diagnosed. These same cytokine and chemokine changes also appear to promote the proper environment for establishment of the persistent chlamydial state and recent data are hopeful that successful treatment is accompanied with alterations of this abnormal cytokine signature.

**C. trachomatis versus C. (Chlamydia) pneumoniae ReA**

Whereas both *C. trachomatis* and *C. pneumoniae* are known triggers of ReA, *C. trachomatis* is a much more common cause. Although both are very common causes of bacterial infections worldwide, it is widely accepted that *C. pneumoniae* is more prevalent. However, it is difficult to know the true incidence and prevalence of *C. pneumoniae* infections worldwide. Further, these rates could vary depending on the year or country studied.

Acute infections with *C. pneumoniae* cause bronchitis or pneumonia; however, the majority of the time it is felt to be asymptotically acquired with some data suggesting this is true as frequently as 90% of the time [84]. Approximately 50% of young adults and 75% of older individuals have seroepidemiology evidence of previous infection and the pathogen is estimated to cause 10–20% of community-acquired pneumonia cases among adults [85]. When symptomatic, the incubation period is approximately 3–4 weeks. The onset is usually gradual and may be biphatic.

Much of the difficulty in defining the true incidence and prevalence of *C. pneumoniae* has to do with the lack of a simple and definitive diagnostic test. A prospective study in the US demonstrated that seroconversion for *C. pneumoniae*, as demonstrated by a rise in specific immunoglobulin G (IgG) titres, occurred at an annual rate of 9.2% in those between the ages of 5 and 10 years and dropped to 1.5% in those over the age of 20 years [86]. However, the true importance of seroconversion with *C. pneumoniae* specific titres is unknown, as this is not always coupled with a clinical infection. Perhaps this is indicative of asymptomatic acquisition of the organism, but this, too, is poorly understood. Debate exists regarding the importance of IgG- versus IgA-specific antibodies, but the majority of the studies suggest that IgA antibodies do not add additional diagnostic value [86]. Finally, studies have shown that *C. pneumoniae* can be isolated from the nasopharynx of up to 4.7% of subjectively healthy subjects, but the pathophysiologic importance of this finding is not entirely clear [87].

In spite of the diagnostic difficulties associated with *C. pneumoniae*, the organism is known to be a very common pathogen that exists throughout the world. Although this pathogen is frequently encountered, it is equally clear that it is a trigger of CiReA less often than is *C. trachomatis*. The explanation for this disconnect is unknown. In spite of the fact that both organisms are from the same genus, there are some important interspecies differences. A study analysing the synovial tissue of patients CiReA sought to determine differences in cytokine or chemokine expression in those infected with *C. trachomatis* versus *C. pneumoniae*. In *C. trachomatis*-infected synovial tissue samples, high levels of IL-10 mRNA were present, with less mRNA for IL-8, IL-15, IFN-γ and TNF-α. Synovial tissues from patients with synovial *C. pneumoniae* only showed significant levels of mRNA for IL-8 and IL-1β [40]. As previously stated, persistent *C. trachomatis* organisms demonstrate differential expression of three separate HSP-60 paralog genes (Ct110, Ct604 and Ct755), whereas these same paralog genes do not
exist with persistent *C. pneumoniae* [39]. The different chlamydial species could also have an additive or synergistic effect in determining ReA attack rate or incidence. Previous exposure to Cpn could have an effect on a subsequent response to a Ct infection. Reports have demonstrated that prior Cpn infection primes a Th1T-cell response to Ct antigens [88]. Perhaps these differences explain the apparent discordant arthritogenic virulence of each organism. Finally, the common, yet cryptic, acquisition of *C. pneumoniae* might help further explain the apparent underdiagnosis of CiReA, in general.

**Phenotypic convergence**

Although the focus of this review is CiReA, it should be noted that the two main types of ReA, that is, post-venereal and post-enteric, share clinical features. Clearly, post-chlamydial and post-enteric ReA are triggered by different organisms, yet the phenotypic expression of the resulting clinical disease is congruent. The clinical features of ReA are well described. They include inflammation not only in the synovium (articular and tendon), but also the eye, mucosal membranes, skin and possibly other organ systems. It is unclear how different bacterial triggers culminate into single clinical entity. Even more cryptic is the fact that the same bacterial trigger (e.g., *C. trachomatis*) can cause the 'classic triad' of symptoms in one individual, an incomplete form in another, with spontaneous resolution in some and chronic disease in others.

The pathophysiology of CiReA is described above. This differs in many important aspects from post-enteric ReA. Although PCR technology has demonstrated the presence of chromosomal DNA from the known enteric triggers in the synovial tissue of patients with the post-dysentery form of ReA [89,90], unlike chlamydiae, these organisms do not exist in a persistently viable state, with the possible exception of *Yersinia* [91]. This divergence in pathophysiology further highlights the complex role the triggering organisms play and the importance of host response in determining clinical disease expression.

Although the resulting clinical syndrome is felt to be relatively uniform regardless of the original triggering bacteria, few comparative studies have been performed to see if this is true. One study, indeed, suggested that CiReA caused by *C. trachomatis* compared with *C. pneumoniae* resulted in no significant differences in terms of clinical features; however, Cpn-induced ReA patients had slightly worse physician global scores compared with Ct-induced ReA subjects [92]. The vast amount of epidemiologic data detailing patients with post-enteric ReA also seems to confirm this same phenotypic convergence regardless of the triggering organism.

Much has been learned about the genesis and perpetuation of ReA in recent years. The fact that these various bacterial starting points can culminate into a similar set of clinical features suggests that we need to broaden the paradigm regarding the role that environmental triggers play in the initiation, and possibly maintenance, of chronic arthritis. To this end, there is a great deal of data implicating various bacteria as aetologic triggers for all of the different types of SpA [1]; however, these data are far more speculative for SpA subsets other than ReA. A review of these data is beyond the scope of this article, but the gap between infection and arthritis appears to be narrowing, at least with the SpA, and ReA is leading this transformation.

**Treatment of CiReA**

As is the case with CiReA in general, the treatment of CiReA is equally complex, continuing to evolve and currently unresolved. In keeping with the apparent underdiagnosis of the condition itself, prospective trials analysing various therapeutic agents are few compared with the other types of SpA. Paralleling the opposing schools of thought regarding the true role of persistent chlamydiae in the pathophysiology of CiReA, both traditional disease-modifying anti-rheumatic drugs (DMARDs) and antibiotics have been assessed as potential therapeutic options. However, there are far more data for antibiotics. Because of the phenotypic convergence between CiReA and post-enteric ReA, almost all of the previous therapeutic trials in ReA have lumped together patients with both CiReA and post-enteric ReA. A second look at some of these previous trials might provide insight that mirrors recent findings.

Until recently, ReA in general, and CiReA specifically, was felt to be a ‘sterile arthritis’ that was triggered by these various bacterial pathogens. Although the underlying mechanism was not
completely understood, and still remains fundamentally a mystery, the paradigm held that these bacterial triggers culminated in an autoreactive process that was sustained in some patients. In those with chronic disease, ReA can lead to joint damage that is often quite similar to that of psoriatic arthritis. For these reasons, a DMARD, sulphasalazine (SSZ) specifically, was assessed as a therapeutic agent for those with both acute and chronic disease. The first was a US Department of Veterans Affairs Cooperative Study prospective, placebo-controlled trial assessing SSZ at a dose of 2000 mg day\(^{-1}\) in 134 subjects (69 subjects on SSZ and 65 on placebo) with chronic ReA [93]. All subjects had previously failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs) and were followed up in the study for 36 weeks. The subjects' mean duration of disease was approximately 10 years and the definition of response was based on joint tenderness and swelling as well as patient and physician global assessments. Using the last-observation-carried-forward technique, the response rates were 62.3% in the SSZ group and 47.7% in the placebo group (\(p = 0.089\)). SSZ was analysed in another double-blind, placebo-controlled study of 6-months' duration in 79 subjects (37 on SSZ and 42 on placebo) with acute ReA (mean disease duration of approximately 4 months) [94]. The dose studied ranged from 2 to 3 g day\(^{-1}\). Intention-to-treat analysis revealed no significant difference between the two groups in terms of pain, number of swollen joints and erythrocyte sedimentation rate (ESR). Surprisingly, there are no other prospective trials assessing any other traditional DMARD, including methotrexate, in patients with ReA in general or CiReA in particular.

It could be argued that SSZ is a more appropriate choice for patients with post-enteric ReA rather than CiReA. SSZ has been employed for years as a treatment for inflammatory bowel disease and a study involving bowel biopsies in 55 patients with ReA demonstrated that 67% had histologic evidence consistent with inflammatory bowel disease [95]. Of these ReA subjects, it was felt that 46 (84%) had the post-enteric variety. In spite of these interesting findings, there was no effort to determine the triggering pathogen in the previous SSZ trial of patients with chronic disease; in the study of those with acute ReA, attempts to determine the initial trigger were minimal.

Despite the abundance of their use in clinical practice, the data evaluating the efficacy of NSAIDs in ReA are even more scant. There are two small prospective trials analysing three different NSAIDs in patients with ReA; these trials also included patients with other types of SpA. The first was a double-blind crossover study comparing azapropazole to indomethacin in patients with both psoriatic arthritis and ReA [96]. This study only included 16 patients with ReA and it suggested that indomethacin might be a more effective treatment for ReA. The second study to analyse the efficacy of NSAIDs in ReA compared ketoprofen with indomethacin in 50 subjects with ReA [97]. In this study, both ketoprofen and indomethacin were efficacious at treating articular symptoms of ReA without a significant difference between the two.

Although a wealth of clinical experience demonstrates that corticosteroids are efficacious at treating many of the symptoms of ReA, they have never formally been studied. It has been suggested that systemic corticosteroids are more effective at relieving peripheral arthritis of ReA compared with the axial symptoms [98]. Because ReA often presents as an oligoarthritis involving the large proximal joints, intra-articular corticosteroid injections can be a useful treatment. Topical corticosteroids also help alleviate many of the extra-articular features including iritis/uveitis, keratoderma blenorrhagicum and circinate balanitis. However, theoretical concerns exist with the use of corticosteroids in CiReA, specifically. Because of the documented chlamydial persistence in patients with CiReA and emerging data suggesting that these persistently viable organisms might perpetuate disease, the effect that corticosteroids might have on maintaining or promoting chlamydial persistence is unknown. Further, the fact that in vitro data demonstrate that low initial cytokine levels during acute chlamydial infections provide the proper milieu for chlamydial persistence adds to the concerns associated with their use in patients with CiReA, particularly early in the disease course. However, there are no longitudinal data in acute CiReA to assess if the use of corticosteroids might predispose to chronic disease.

The TNF antagonists have proved to be remarkably efficacious in the treatment of various types of chronic arthritis including other types of SpA, namely ankylosing spondylitis and psoriatic arthritis. However, the concerns outlined above with the use of corticosteroids in CiReA are magnified with these drugs. In vitro data have demonstrated that persistent chlamydial levels are inversely proportional to TNF-alpha levels [74,75]. Therefore, anti-TNF therapy could, in theory, increase chlamydial replication or persistence when these agents are given to a patient with an established chlamydial
infection. Further, persistently viable chlamydiae share many features with persistent/latent Mycobacterium tuberculosis (Mtb). It has been demonstrated that 67 C. trachomatis genes in the persistent state are orthologous to Mtb persistence-related genes [99]. The fact that anti-TNF therapy can unmask latent Mtb is well known.

Unfortunately, there are no randomised trials in CiReA or ReA to accurately assess the efficacy and safety of anti-TNF therapy. Several case reports and a small open-label study suggest clinical benefit with these drugs in the treatment of ReA, but many of these data are in patients with post-enteric ReA [100–104]. Of the case reports, there are only two in which the suspected trigger of the ReA was Chlamydia (S and W). The largest amount of data is available from the small open-label study assessing etanercept in 16 patients with undifferentiated arthritis or reactive arthritis [100]. Only 10 of the 16 patients completed the 6-month study and nine of the 16 were considered responders. Interestingly, this study did include synovial biopsies to assess for chlamydiae by PCR before and after treatment with etanercept in some patients. There were three patients who were PCR positive for chlamydiae in the synovium before biologic treatment. Of these three, two became PCR negative on therapy and one remained PCR positive. However, two patients with negative PCR results at baseline became PCR positive for chlamydiae while on etanercept. In another preliminary experiment, the relative bacterial load in paired synovial tissue samples from a patient with C. trachomatis-induced ReA was assessed before and after several months of treatment with etanercept. RT-PCR analyses demonstrated that the second biopsy sample contained a bacterial load that was several-fold higher than that of the initial, pre-treatment sample (personal communication with Alan P. Hudson, PhD., November 2008).

Perhaps the most curious aspect involving TNF antagonists, in general, relates to some of their side effects. As noted, these agents are remarkably efficacious in treating psoriatic arthritis and they are also very effective treatments for psoriasis. Paradoxically, these same drugs have been associated with de novo cases of psoriasis. How could these drugs both treat and cause the same condition? The answer to this medical conundrum remains an open debate, but perhaps the answer lies only skin deep. Of the reported cases of de novo psoriasis caused by TNF antagonists, which number in the hundreds, well over 50% are palmoplantar pustular psoriasis (PPPP). However, PPPP accounts for only 1.7% of idiopathic cases of psoriasis [105]. Interestingly, PPPP and keratoderma blenorrhagica, a rash associated with CiReA, are both clinically and histologically indistinct. Could this ‘paradoxical’ side effect actually be cases of keratoderma blenorrhagica rather than PPPP and, in fact, represent an unmasking of latent/persistent chlamydiae? A case series of three patients with rheumatoid arthritis who developed a new palmoplantar–pustular rash while on anti-TNF therapy found all to be PCR positive for C. trachomatis on skin biopsies of the affected areas [106]. Adding to this problematic issue, these same anti-TNF agents are felt to be efficacious treatments for anterior uveitis. Recently, these same drugs have also been demonstrated to rarely cause anterior uveitis, another symptom associated with CiReA [107]. Is this yet another medical paradox? Do we have one more conundrum? Or could this, too, represent the unmasking of a latent chlamydial infection? Recent data demonstrating the role of the ocular serovars of C. trachomatis in CiReA and their apparent propensity to disseminate from the initial site of infection add another possible clue to this puzzle.

This leads us to the role of antibiotics in the treatment of CiReA. If persistent chlamydiae are present in the synovium and possibly other affected organs in patients with CiReA, and these chlamydiae are viable, surely antibiotics are the treatment of choice. Unfortunately, the data are not straightforward. The first prospective trial assessing antibiotics as a therapeutic option for ReA and CiReA was positive [108]. This study analysed patients with both acute post-chlamydial and acute post-enteric ReA. Subjects were treated with either lymecycline or placebo in a double-blind fashion for 3 months. Lymecycline significantly decreased the duration of illness in those subjects with post-chlamydial ReA, but not those with the post-enteric variety. Critics cited data demonstrating that tetracycline antibiotics possess anti-inflammatory properties, thereby lending a potential explanation for the benefit [109]. However, if the explanation for the improvement observed in this trial was truly the anti-inflammatory effect of the drug, then both post-chlamydial and post-enteric subjects should have fared equally, but this was not the case.

The ‘phenotypic convergence’ that is characteristic of ReA is a possible explanation for the apparent negative data that followed upon subsequent antibiotic trials [59,110–113]. The notion that post-chlamydial ReA patients might respond differently to treatment than those with post-enteric ReA was
lost in these follow-up studies. The study populations were expanded to include patients with chronic ReA of any type. Further, one of these studies included patients with anterior uveitis as their only disease manifestation. These somewhat more ambitious studies assessing ciprofloxacin, azithromycin and doxycycline produced negative results. The hope provided by the earlier study was dashed and the consensus was that prolonged antibiotics had no effect on the disease manifestations of ReA.

The fact that the post-enteric pathogens responsible for ReA have been demonstrated in the synovial tissue of these patients parallels the findings with chlamydiae. However, the post-enteric organisms are no longer viable once they reach the synovial tissue; only bacterial fragments have been documented. Perhaps the antigenic stimulus from these bacterial fragments is enough to produce the same phenotypic clinical syndrome; however, if these bacteria are no longer viable, there is no reason to expect benefit from antibiotics. Perhaps CiReA is uniquely susceptible to antibiotic therapy? Could the very first antibiotic trial by Lauhio et al. have provided some of this insight? However, even if these persistent chlamydiae are susceptible to antibiotics, standard treatment techniques, that is, those associated with acute chlamydial infections, might not apply. The minimum inhibitory concentration of a given antibiotic is well known in the treatment of acute chlamydial infections. However, individuals with CiReA harbour persistent organisms with an attenuated life cycle, thus equivocating the validity of the standard means of testing for drug efficacy. In vitro data have also demonstrated that standard concentrations of many different antibiotics, including ciprofloxacin, induce the persistent state rather than clear the infection [114]. These same in vitro studies have further demonstrated that when a combination of azithromycin and rifampin are used as a treatment for persistent chlamydiae, the persistent chlamydial infection is eradicated [115].

Because persistent chlamydiae have an attenuated life cycle, an effective antimicrobial treatment approach would likely require a prolonged course. As is the case with other latent/persistent infections, such as Mtb or Helicobacter pylori, a combined antimicrobial approach might prove most efficacious. We recently completed a double-blind, placebo-controlled trial assessing a 6-month course of two different antibiotic combinations in patients with CiReA [116]. Enrolment criteria were strict in that study subjects had to fulfill the clinical criteria of ReA, they had to have chronic disease (i.e., their disease was very unlikely to remit spontaneously) and they had to be PCR positive for C. trachomatis or C. pneumoniae in their synovial tissue or peripheral blood at screening. In this study, a 6-month course of combination antibiotics resulted in a significantly higher response rate in subjects with chronic CiReA compared with placebo. Coupled with this clinical improvement, significantly more subjects became PCR negative for chlamydiae at month 6 in the active therapy group compared with those on placebo. Finally, 22% of these subjects with chronic CiReA who were treated with combination antibiotics (average disease duration of approximately 10 years) went into complete remission, whereas no placebo-treated patient achieved this same end point.

Lack of a diagnostic test

The role that Chlamydia plays in the genesis of CiReA has been known for years. The mystery of how this same organism might function in terms of disease perpetuation is beginning to be solved. Along with this, the treatment of CiReA is becoming more defined. In spite of these advances, underdiagnosis of CiReA remains a significant problem. The lack of a universally available diagnostic test for CiReA and persistent chlamydial infections, in general, represents a roadblock to accurate disease recognition. This, in turn, leads to less efficacious treatment, particularly if an adequate therapy exists but the condition goes largely undiagnosed. As previously stated, it appears that we can no longer rely on a recent history of an acute C. trachomatis infection to diagnose patients with CiReA, as it appears that asymptomatic infections are also a common cause. Such a truth renders obsolete the current disease definition, that is, an inflammatory arthritis that occurs 1–6 weeks after an acute chlamydial infection. The concept describing CiReA as a ‘sterile’ arthritis is becoming antiquated. Could the same be true for the disease definition? In spite of these limitations, the condition itself proceeds in an apparent stealthy fashion. As clinicians and scientists, we must maintain our vigilance aimed at disease recognition.

Currently, our most accurate diagnostic testing for ReA is PCR analyses of affected synovial tissue [18]. However, this involves an invasive procedure that is very difficult to apply to everyday practice. Further, PCR interpretation is a learned science and few laboratories are equipped to accurately analyse
synovial tissue in such a manner. Some advocate similar PCR testing on urine or genital samples in patients with suspected CiReA. However, the diagnostic utility of such testing has never formally been evaluated in the setting of CiReA. Further, the pathogen is known to disseminate from the initial site of infection once it enters the persistent state. Does this then mean that PCR analysis of such samples is futile?

It is vitally important that a sensitive and specific diagnostic test for these persistent infections be established. Ideally, this test should be non-invasive, inexpensive and easily interpreted. Once this goal is attained, CiReA will undoubtedly become a more common diagnosis and the condition will emerge from the shadows of our current diagnostic paradigm employed for patients with undifferentiated chronic inflammatory arthritis. Unfortunately, such a test does not currently exist.

CiReA: hidden in plain sight?

Have we come full circle? As stated, rather clear descriptions of CiReA exist in the literature as far back as the early 1500s. It is even possible that a description of CiReA dates back to circa 460 B.C. when Hippocrates wrote: “A youth does not suffer from gout until sexual intercourse” [117]. Could this be the earliest description of CiReA? C. trachomatis has been a known trigger of ReA for approximately 50 years. Mirroring this clinical knowledge were EM studies in the 1970s and 80s that showed what appeared to be intact chlamydiae along with elementary bodies and/or reticulate bodies from synovial samples of patients with a prior infection of that same organism. The earliest study assessing the role of long-term antibiotics was performed 20 years ago and it suggested that CiReA might be uniquely susceptible to this treatment strategy. Yet, the phenotypic convergence of CiReA and post-enteric ReA clouded the picture, so that improved understanding of the underlying pathophysiology of the condition, along with the proper treatment, became more elusive.

Does CiReA represent one of the earliest described types of inflammatory arthritis, and yet continues to be one of the most underdiagnosed? Is CiReA really a “rare” disease, or does the medical community fail to recognise it? Epidemiologic data suggest the latter to be the case. Although an asymptomatic trigger can pose a great hurdle to our diagnostic capabilities, it might be time to revise the very definition of the condition. Such a change would further highlight the need for a sensitive and specific diagnostic test.

Could the most efficacious treatment vary even within the same phenotypic clinical syndrome? Recent data suggest that CiReA might be most effectively treated with a prolonged combination antimicrobial approach, though we have no such data suggesting this is true for post-enteric ReA. One of our most fertile areas of knowledge with CiReA does involve various treatment strategies. In this era of evidence-based medicine, should clinicians be comfortable with using a traditional DMARD, such as methotrexate, for patients with chronic CiReA when it has never been systematically studied as a treatment for this condition? What barriers exist to the application of new therapies, such as combination antibiotics, that have demonstrated efficacy in patients with CiReA specifically, but in which the data are more equivocal in other trials with patients with both variants of ReA using antibiotic monotherapy?

Does our intimate knowledge of the pathophysiology of CiReA and persistent chlamydiae narrow the gap between infection and arthritis on a more global scale? Could the pathophysiology of CiReA serve as a model for other types of inflammatory arthritis, especially the other types of SpA? The notion that bacteria could be aetiology for chronic diseases was in vogue many years ago, yet was felt to be archaic more recently. However, these most recent data with CiReA reopen this debate. Future studies should answer these important questions.

In almost ironic fashion, the term Chlamydia, derived from the ancient Greek word “chlamys,” means cloak. Have many truths about CiReA actually been known for some time but were cloaked by confounding elements? Have many of the apparent mysteries associated with CiReA actually been hiding in plain sight? Clinical research is poised to bring CiReA out of the shrouds of mystery as investigators start focusing on the considerable evidence available for this condition. With the realisation that the condition is more common than has been previously recognised, more studies can be performed to answer the remaining questions that surround this fascinating, and still challenging, syndrome.
References


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Inman RD, Chiu B. Early cytokine response to Chlamydia trachomatis elementary bodies in human macrophages is partly mediated by a lipoprotein, the macrophage infectivity potentiator, through TLR2/TLR1/TLR6 and CD14. Journal of Immunology 2008;180(2):1158–68.


Inman RD, Chiu B, Hudson AP, Carter JD. IL-12p70 alteration in antibiotic treatment of Chlamydia-induced reactive arthritis (ReA). Arthritis & Rheumatism 2010;62(10 Suppl.):S290(696) [abstract].


