Reactive Arthritis

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Denis Wakefield, Gregory Carr, and Peter McCluskey

Contents

Core Messages

- Reactive arthritis and associated acute anterior uveitis develop in young adults 1–6 weeks after an infection of the gastrointestinal or genitourinary system.
- Always connect acute AU with lower limb red, hot swollen joints inflammatory back pain with reactive arthritis.
- Sixty percent of patients with reactive arthritis and uveitis are HLA-B27 positive.
- Visual prognosis is usually good.

55.1 Definition

Reactive arthritis (ReA) is a relatively common form of arthritis that occurs as a result of an extra-articular microbial infection. Stoll first described the characteristic features of this spondyloarthropathy in 1776, following an outbreak of dysentery. Subsequently the disease has been referred to as Reiter's syndrome, although the latter should be restricted to the classical triad of arthritis, urethritis and conjunctivitis as originally described [1]. The most common sites of infection are the genitourinary and gastrointestinal tracts. Reactive arthritis may occur during epidemics, particularly following gastrointestinal infections, and has a prevalence of 30–40 cases per 100,000. The annual incidence has been

D. Wakefield (✉)
School of Medical Sciences,
University of New South Wales,
Sydney, NSW, Australia
e-mail: D.wakefield@Unsw.edu.au

G. Carr
Organisation Name, 2/8 West promenade,
Manly, NSW 2095, Australia
e-mail: Carrgreg@bigpond.com

P. Mccluskey
Save Sight Institute, Campus of Sydney Eye Hospital,
8 Macquarie Street, Sydney, NSW 2000, Australia
e-mail: peter.mccluskey@sydney.edu.au

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estimated to be 5 cases per 100,000 for gastrointestinal-related reactive arthritis and 4.6 per 100,000 for *Chlamydia*-induced reactive arthritis [1–4]. These estimates probably do not reflect the true incidence of this condition. Given the frequency of genitourinary and gastrointestinal infections by bacteria known to trigger reactive arthritis, it is thought that the prevalence of this disease is much higher than has been previously reported. For example, it has been estimated that between 1 and 3 % of patients with chlamydial urethritis and 6–30 % of patients with severe enterobacterial gastrointestinal infection will go on to develop reactive arthritis [3, 4]. The disease most commonly affects males between 30 and 40 years of age. Reactive arthritis following *C. trachomatis* infection is more common in males, whereas gastrointestinal infection triggers arthritis in both males and females with a similar frequency [2].

55.2 Clinical Manifestations

55.2.1 General Disease

In patients with ReA, usually one or more of three clinical complexes are evident: peripheral oligoarthritis, enthesitis and spinal axial syndrome [2]. Extra-articular manifestations, including urethritis, conjunctivitis and keratoderma blennorrhagicum, circinate balanitis, mouth ulcers and erythema nodosum (associated with *Yersinia*-related ReA), are less common [2]. Not all patients have all manifestations of this symptom complex, and a given patient may have variable clinical features at any point in time or during the natural history of their disease. Reactive arthritis is characterised by an asymmetrical oligoarthritis and enthesitis predominantly affecting the lower limbs [2].

Arthritis, enthesitis and inflammatory back pain may develop between 1 and 6 weeks after an initiating infection which may be asymptomatic. Patients presenting with acute AU and such arthritis should be carefully questioned with regard to recent gastrointestinal or genitourinary symptoms and sexual contacts.

ReA has been repeatedly reported in association with HIV infection and AIDS. Epidemiological evidence indicates that this association is due to sexually acquired infection or enterobacterial infection as opposed to being directly linked to HIV infection. HIV-infected patients who develop ReA have a more severe disease often with disabling arthritis, enthesitis and extra-articular manifestations [5]. The HLA-B27 frequency is similar to that observed in non-HIV-associated ReA and AU [6, 7].

55.2.2 Ocular Disease

Acute AU associated with ReA usually follows the onset of joint disease and the mucocutaneous manifestations of the disease. An acute bilateral conjunctivitis may precede the AU. The uveitis is usually of sudden onset and is quite symptomatic, similar to that seen in other forms of HLA-B27-associated AU (see Chap. 87). Patients may also develop episcleritis, scleritis and rarely posterior uveitis [6, 7]. ReA may occasionally be associated with vitreous cells and features of retinal vasculitis.

55.3 Etiology and Pathogenesis

There are two major factors implicated in the pathogenesis of reactive arthritis, microbial infection and genetic factors, especially HLA-B27.

55.3.1 Microbial Infection

This form of spondyloarthropathy usually follows a mucosal infection by Gram-negative bacteria (GNB) or *Chlamydia trachomatis* genital infection, and individuals who have the HLA-B27 antigen are more likely to develop ReA after such infections [1, 3].

The characteristic feature of reactive arthritis is that microorganisms like *Chlamydia trachomatis* and GNB cannot be cultured from the synovial fluid in patients with this disease. However

Table 55.1 Microbial causes of reactive arthritis

Sight of infection	Syndrome	Microorganism	HLA-B27
Urogenital tract	Urethritis, cystitis Cervicitis	*Chlamydia trachomatis*	Yes
	Cervicitis	*Ureaplasma urealyticum*	No
	Prostatitis, epididymitis	*Mycoplasma hominis*	No
	Salpingitis, endometritis	*Neisseria gonorrhoeae*	No
Gastrointestinal tract	Diarrhoea	*Yersinia enterocolitica*	Yes
	Gastroenteritis	*Salmonella*	Yes
	Enterocolitis	*Shigella flexneri*	Yes
	Mild infections	*Campylobacter jejuni/coli*	Yes

Table 55.2 Evidence of microbial infection in synovial fluid of patients with ReA

	Antigen	DNA	RNA	Vitality	Electron microscopy
Chlamydia trachomatis	+	+	+	+	Viable organisms
Yersinia species	+	–/+	+	ND	Presence of antigens
Campylobacter	ND	+	ND	ND	ND
Salmonella	+	+	ND	ND	ND

ND not detected

Chlamydia trachomatis and GNB DNA have been detected in the joints of patients with reactive arthritis (Table 55.1). In such patients with anterior uveitis, the triggering pathogens have been found to be similar, although uveitis has not been extensively studied to ascertain whether or not there is evidence of microbial infection in the aqueous humour of inflamed eyes [6].

There is compelling evidence implicating *Chlamydia* in the pathogenesis of ReA, where the presence of *Chlamydia* in the genitourinary tract and joints of patients with ReA has been reported. The involvement of *Chlamydia* in ReA has been further supported by: (1) the observation of chlamydial inclusions in synovial cells, analysed by both electron microscopy (EM) [8] and immunoelectron microscopy (IEM) [2, 8, 9], (2) immunohistological detection of chlamydial antigens in affected joints [9] and (3) demonstration of chlamydial nucleic acids by polymerase chain reaction (PCR) and ribosomal RNA hybridisation techniques [3, 9–12] (Table 55.2). Studies of *C. trachomatis*-associated ReA indicate that synovial cells are one of the main sites of residence for this organism in the joint [13]. Such findings have not been replicated in ocular tissues of patients with AU, with or without associated ReA. Additionally, *Chlamydia* has been cultured ex vivo in synovial-derived cells and their cellular effects elucidated. Such studies have not been performed in human ocular cells, despite the obvious relevance to understanding the role of these triggering microbes in the pathogenesis of AU. In addition, it is not known if *Chlamydia* can infect uveal cells and persist in the intraocular environment.

55.3.2 Role of HLA-B27 (See Also Chaps. 54 and 87)

Using recent advances in molecular biology (PCR and transgenic animals) and immunology (MHC tetramers and MHC-binding peptides), it has been shown that "uveogenic" peptides from *C. trachomatis* may generate a CD8 T cell response in which there is cross-reactivity with epitopes on the HLA-B27 molecule leading to a possible autoimmune response in the eye [14].

Several recent observations have significantly improved our understanding of the link between infection with *C. trachomatis* and the fundamental biological role of HLA molecules in antigen presentation. Class I HLA molecules, such as

HLA-B27, generally present antigen to CD8 cytotoxic T cells. Kuon and colleagues [15] searched the proteome of *C. trachomatis* for HLA-B27-binding peptides that were stimulatory for $CD8^+$ T cells using a murine model of HLA-B27 disease and in patients with ReA. Combining two biomathematical computer programs, they detected several relevant peptides. Eleven peptides were found to be stimulatory for patient-derived $CD8^+$ T cells, of which eight overlapped those found in transgenic mice. Additionally, investigators used HLA tetramers to show that a HLA-B27-chlamydial peptide complex (containing one of the chlamydial peptides) stained $CD8^+$ T cells in patients with *Chlamydia*-induced ReA [15]. This comprehensive approach offers the possibility of clarifying the pathogenesis of HLA-B27 AU by examining a similar range of peptides and CD8 T cell responses to *C. trachomatis* in patients with uveitis.

Persistent *Chlamydiae*, present in the joints of patients with ReA and eyes of patients with AU, might be a source of chronic antigenic stimulation. Thus, *Chlamydia*-derived proteins might be continuously available to provide peptides, such as that homologous to HLA-B27(309–320) and those described by Kuon et al. [16], for presentation to T cells in HLA-B27-positive patients with *C. trachomatis*-triggered ReA and AU. If so, chronic stimulation of chlamydia-specific CTL in these individuals could lead to autoimmunity directed against the HLA-B27-derived peptide.

55.3.3 The Role of Toll-Like Receptors

Toll-like receptors (TLRs) are a family of pattern-recognition receptors (PRRs) of the innate immune system that recognise unique pathogen-associated molecular patterns (PAMPs). The expression of TLR4 and its associated lipopolysaccharide (LPS) receptor complex by synovial and uveal resident APCs has recently been demonstrated [17]. Such APCs are strategically located in the perivascular and subepithelial locations in the synovial and uveal stroma, possibly to survey blood-borne synovial or intraocular LPS [17]. Given the role of GNB in triggering uveitis, it was postulated that this represents a novel mechanism by which the LPS of GNB may initiate ocular inflammation by activating TLR4 expressed on uveal APCs. This concept is supported by the fact that mice that have a naturally defective TLR4 gene (C3H/HeJ) do not develop endotoxin-induced uveitis (EIU), whilst the C3H/HeN mice (which have functional TLR4) develop uveitis. TLRs may provide the critical pathogenic link between the experimental and clinical observations of microbial triggers to the development of ReA and associated uveitis.

TLR single nucleotide polymorphisms (SNPs) have been associated with several inflammatory diseases such as rheumatoid arthritis and susceptibility to bacterial infections. The Asp299Gly mutation of TLR4 has been shown to be associated with hyporesponsive to endotoxin in humans; however, no such association has been found between such SNPs and ReA and AU [17, 18].

55.4 Diagnosis

ReA is a clinical diagnosis based on typical clinical features (ocular and joint inflammation following a gastrointestinal or genitourinary infection), exclusion of active joint infection and supporting laboratory tests [2].

Radiological signs are often non-specific and only helpful in the diagnosis of chronic arthritis, enthesitis and spondylitis. Plain X-ray of involved joints, including the sacroiliac joints, is a sensitive indicator of disease in patients with long-standing disease. CT scans may give added information in patients with chronic arthritis, enthesitis and sacroiliitis. Recently MRI, with its capacity to detect active inflammation, has been shown to be of value in the diagnosis of early disease. Thus MRI is useful for the early detection of enthesitis and synovitis in both axial and peripheral joints [2].

There are no diagnostic laboratory tests for ReA. The most important consideration is the exclusion of active infection in the joint and urinary or gastrointestinal tract. Patients may have a raised serum IgA level and antibody evidence of recent chlamydial or enterobacterial infection. Patients with chronic disease often have a normochromic, normocytic anaemia and neutrophil leucocytosis. Acute phase reactants, including ESR

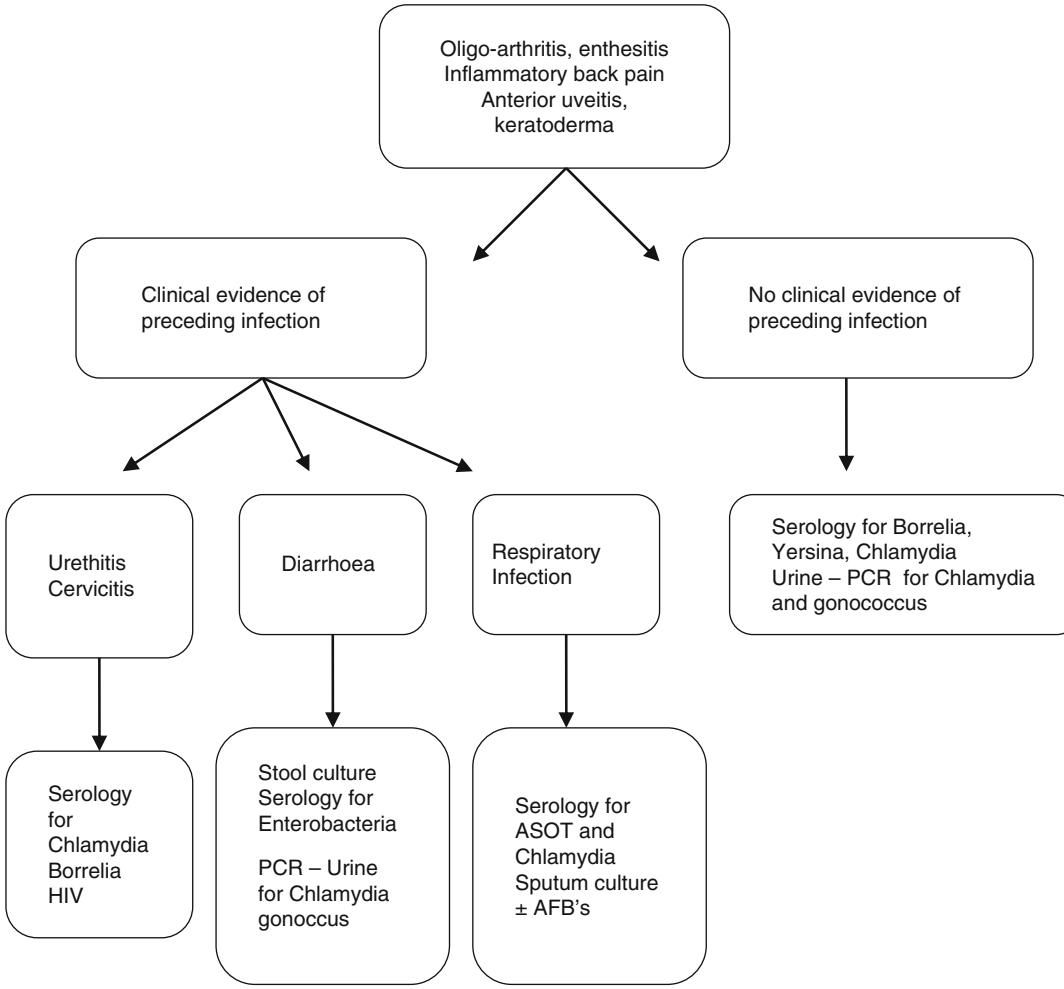

Fig. 55.1 Investigations for infections in patients with anterior uveitis and suspected reactive arthritis. *ASOT* anti-streptolysin-O titre, *AFB* acid-fast bacilli

and CRP, are usually normal as are serum rheumatoid factor and other autoantibodies. HLA-B27 is an important factor for diagnosis of spondyloarthritis and associated AU. The performance of the HLA-B27 test depends on the population prevalence of HLA-B27, which varies for different races. In Caucasians the frequency of HLA-B27 in patients with ReA is 50–75 % [2].

Joint aspiration of acutely involved joints reveals an exudate with neutrophil leucocytosis and no evidence of infection or crystals. Figure 55.1 outlines the diagnostic approach in patients with suspected ReA. Although conjunctivitis is a common component of the syndrome of ReA, the conjunctiva is sterile, and usually there is no evidence of chlamydial infection.

The diagnosis of the associated uveitis is described in detail in Chap. 87, and AS-associated uveitis in Chap. 54.

55.5 Differential Diagnosis

ReA should be carefully differentiated from the other spondyloarthropathies as well as from infectious diseases involving the spine and large joints of the lower limbs. Septic arthritis associated with the so-called gonococcal arthritis-dermatitis syndrome should be carefully excluded, by urethral, blood and synovial culture, in patients presenting with post-urethritis arthritis and rash [2]. A large number of diseases may be

associated with HLA-B27 and uveitis, outlined in Chap. 87, and with arthritis and uveitis, outlined in Chap. 40.

As in the case of patients with ankylosing spondylitis (AS), there are a large number of causes of lower back pain, which are discussed in Chap. 54.

Sacroiliitis may be associated with a number of diseases including ankylosing spondylitis (Table 87.1 in Chap. 87). Important differential diagnoses of ReA include infection (including bacterial especially gonococcal and tuberculosis), Behçet's disease, SAPHO syndrome and as a complication of intestinal bypass surgery [2].

55.6 Treatment

55.6.1 Arthritis

The treatment of patients with reactive arthritis and the other spondyloarthropathies is best managed within a multidisciplinary team approach. The aims of therapy are fourfold: education of patients and their family, relief of pain and stiffness, maintenance of mobility, prevention of disability and early diagnosis and management of extra-articular complications of ReA, particularly AU. The PREP process (pretreatment, review, education, prevention), as outlined in Chap. 54, is a good way to approach therapy.

The main clinical features important in assessing the functional status of patients with ReA are similar to those of patients with AS, namely: pain, stiffness, peripheral arthritis, global assessment, acute phase reactants, fatigue and radiological changes.

The quality of the evidence for treating patients with ReA, and in fact most seronegative arthropathies, is often subjective or based upon small case series. There are a number of well-controlled randomised double-masked trials comparing different antibiotic treatment regimens in the treatment of ReA and associated inflammatory disorders (Table 55.3).

Recommendations for the management of patients with ReA have not been as well defined as for patients with AS, although the same treatment principles apply [19, 20]. Treatment should be tailored according to the manifestations of the disease at presentation, the severity of symptoms and the wishes and expectations of the patient [20].

Monitoring of patients should include clinical history and signs, laboratory tests and imaging. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and drug therapy. Treatment usually involves a combination of non-pharmacological and pharmacological treatments, including education and physical therapy [20]. The standard symptomatic treatment for patients with ReA has consisted of NSAIDs, exercise and physical therapy. Corticosteroid joint injection of inflamed knee and ankle joints, following joint aspiration and synovial fluid culture, is often helpful in relieving severe arthritis as is a short course of oral corticosteroid therapy for patient not responding to NSAIDs.

Antibiotic Therapy

The use of antibiotics in the treatment of ReA remains controversial. It is assumed that the treat-

Table 55.3 Studies of antibiotic therapy in patients with reactive arthritis (ReA)

Study/year	Number of patients	Antibiotic therapy	Duration of therapy (weeks)	Result: P-value
Lauhio et al. (1991) [27]	40	Lymecycline 300 mg/day	12	NS Decrease in CRP, ESR and arthralgia
Toivanen et al. (1993) [24]	36	Ciprofloxacin 2 × 500 mg/day	12	NS
Sieper et al. (1999) [25]	55	Ciprofloxacin 2 × 500 mg/day	12	NS
Wakefield et al. (1999) [22]	52	Ciprofloxacin × 750 mg/day	52	NS? decrease in AU
Yli-Kerttula et al. (2000) [36]	71	Ciprofloxacin 2 × 500 mg/day	12	NS
Kvien et al. (2004) [28]	152	Azithromycin 1 g/week	12	NS

NS non significant

ment of acute *C. trachomatis* infection will decrease the prevalence of subsequent reactive arthritis. It is thus reasonable to treat *C. trachomatis* urethritis in both the patients and in their sexual contacts. Azithromycin (1 g orally) or doxycycline (100 mg twice a day for 7 days) is usually effective. A significant number of control trials have used a variety of antibiotics in the treatment of reactive arthritis [21–28]. These are summarised in Table 55.3. A recent meta-analysis of antibiotic treatment in patients with reactive arthritis concluded that such treatment resulted in heterogeneous results that may be related to differences in study design and that the efficacy of antibiotics is uncertain [29].

The lack of efficacy of antibiotic therapy in patients with reactive arthritis may be related to the altered metabolic state of the microorganisms that trigger ReA. For example, in the case of *C. trachomatis*, an in vitro model of the disease has shown that antibiotics help to eradicate the organism from host cells. However, a combination of two antibiotics (azithromycin and rifampicin) had a beneficial effect [28]. Recent studies have indicated that combination therapy in the case of post-urethritis-induced ReA may have been more effective than single drug therapy [30]. Long-term follow-up studies of patients with ReA and AU treated with antibiotics indicate a beneficial effect in the case of ciprofloxacin therapy. However, lymecycline had no effect in a 10-year follow-up study [27, 31]. In contrast, in patients with post-enteritic reactive arthritis, there was a lack of evidence of the efficacy of antibiotic therapy.

Anti-TNF Therapy

Anti-TNF therapy has been very effective in the treatment of spondyloarthritis, particularly in patients with ankylosing spondylitis and psoriatic arthritis [32]. Recent studies indicate that this form of therapy is also effective in patients with ReA and uveitis [32, 33]. Several anti-TNF agents are now available including: infliximab, which is given intravenously in a dose of 3–5 mg per kg every 6–8 weeks, the fully humanised monoclonal adalimumab (subcutaneously injection of 40 mg fortnightly) and etanercept (75 kD TNF receptor fusion protein) [33–35]. An ongoing issue with regard to this therapy is that it is usually contraindicated in patients with active infection and what will be the long-term effect of treating patients with this potential infectious disease with a suppressive form of biological therapy.

55.6.2 Uveitis

AU in patients with ReA usually responds to topical therapy with mydriatics and steroids. The treatment is extensively described in Chap. 87. The conjunctivitis associated with ReA is usually self-limiting and responds to topical steroids.

55.7 Prognosis

The natural history of reactive arthritis and associated AU is variable [2]. Whereas most patients will recover within a six-month period, between 20 and 70 % of patients will have ongoing joint symptoms. It has been estimated that between 10 and 20 % of patients have persistent disease lasting for up to 2 years. Duration of disease also seems to vary with the triggering infection. Depending on the nature of the initiating infection, long-term follow-up studies indicate that arthritis will develop in between 2 and 18 % of patients, sacroiliitis in between 15 and 50 % and ankylosing spondylitis in 12–26 % of patients [2]. The prognosis of ReA-associated acute anterior uveitis is favourable and is similar to that of other HLA-B27 diseases (see Chap. 87).

Take-Home Pearls

- Connect AU and acute arthritis with preceding gastrointestinal and genitourinary infections.
- Reactive arthritis is particularly severe in subjects with HIV infection.
- Despite the close association with preceding infection, the arthritis and AU do not respond to antibiotic therapy.
- Recent studies indicate that anti-TNF therapy is an effective treatment.

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