

Reactive arthritis, diagnosis and treatment

A review

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The diagnosis of reactive arthritis (ReA) is easy in typical cases with a history of an infection within 3 weeks in combination with an asymmetric mono- or oligoarthritis with or without extra-articular manifestations. Subclinical microbial infections, a possible co-existing inflammatory bowel disease and the fact that in 25% of the cases the microbial agent remains unidentified, make the diagnosis more troublesome. The course of disease is usually self-remittent within 6 months but a less good long-term prognosis is

pre-determined by two factors—namely, the presence of HLA-B27 and the recurrence of triggering infections. The finding of microbial fragments in the joint cavity have led to new treatment strategies especially in Chlamydia-triggered ReA. It must, however, be remembered that the antibiotics mostly used (namely, tetracyclines) also possess immunoregulatory and anticollagenolytic potential. In chronic destructive cases, antirheumatic treatment, similar to that used in rheumatoid arthritis, is recommended.

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Definitions and triggering microbes

One of the best definitions of the entity of reactive arthritis (ReA) is the occurrence of a nonpurulent arthritis complicating an infection elsewhere in the body (Ahvonen et al. 1969). This definition brings out the non-septic nature of the arthritis and emphasizes the linkage to a recognized infection elsewhere. The disease is usually triggered by a urogenital or enteral infection; usually the patient recovers well, but later experiences episodes of arthralgia and also extra-articular manifestations (Figure 1). The extra-articular symptoms are shared features among the seronegative spondylarthropathies which, besides reactive arthritis, also include ankylosing spondylitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and juvenile spondylarthropathy (that may develop into ankylosing spondylitis in adulthood). It is calculated that 5–30% of the patients over a time-span of 20 years will present with chronic arthritis, 50% will have peripheral joint symptoms and 30% will present with sacroiliitis (Nordström 1989b). A common immunogenetic peculiarity among the seronegative spondylarthropathies is the occurrence of the HLA-B27 gene, which is seen in about 80 percent of all patients with ReA (Aho et al. 1973).

Several enteral and urogenital tract microbes can trigger ReA after a latency period of usually 1–3 weeks. These penetrant microbial agents include *Campylobacter*, *Clostridium difficile*, *Entamoeba histolytica*, *Giardia lamblia*, *Salmonellae*, *Shigellae*,

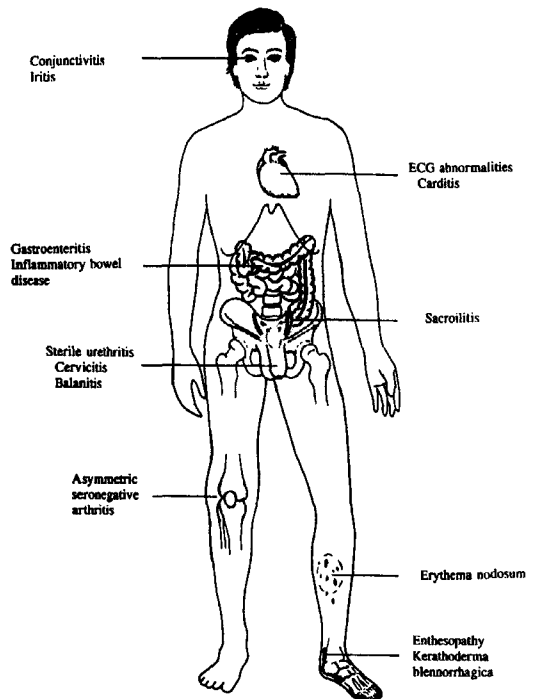


Figure 1. The clinical spectrum of reactive arthritis (ReA). The extra-articular manifestations are shared by all seronegative spondylarthropathies that include ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis/Reiter's syndrome and juvenile spondylarthropathy.

Yersinia and *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, respectively (Nordström 1989b, Nordström and Kontinen 1989, Lauhio et al. 1994, Keat 1995). Furthermore, *Chlamydia psittaci*, *Chlamydia pneumoniae*, streptococcal and staphylococcal infections may trigger ReA (Lauhio et al. 1994a).

Recent studies have questioned the definition of ReA which stipulates that the joint is sterile; microbial components of *Yersinia* (Granfors et al. 1989), *Salmonella* (Granfors et al. 1990) as well as *Chlamydia trachomatis* (Keat et al. 1987, Schumacher et al. 1988) have been detected in the joint. However, no viable microbes have, with certainty, been identified in the joints (Wordsworth et al. 1990, Taylor-Robinson et al. 1992) and the time-interval before the arthritic complication speaks in favor of an immunologic reaction (Nordström et al. 1989). On the other hand, if indeed causative microbes hide within the body (in the joints or elsewhere), maintaining the disease process, the obvious treatment of choice would be antibiotics. A few controlled studies show beneficial results, see below.

Pathogenesis

Despite the fact that the HLA-B27 gene association with ReA and other seronegative spondylarthropathies has been known for more than 20 years, the mechanisms responsible for morbidity are still not fully understood. The most popular recent theory is the "arthritogenic peptide theory" in which HLA-B27 serves as a restricting element for a cytotoxic T-cell response induced by an arthritogenic peptide derived from the triggering microbe and perpetuated by persistent local bacterial antigens or by a cross-reactive joint-specific auto-antigen in the form of T-cell molecular mimicry, thus explaining the tissue-specificity of disease (Kingsley 1993). This theory relies on the migration of bacteria or its products to the joint triggering the local synovial immune response; we know that the microbe fragments are there (Keat et al. 1987, Schumacher et al. 1988, Granfors et al. 1989, 1990, Taylor-Robinson et al. 1992). Moreover, the bacteria most strongly implicated in triggering ReA all quite easily penetrate mucosal barriers and have at least some capacity for surviving intracellularly (Nordström 1989b). We also know that there exists an exaggerated antibody production especially of type IgA towards yersinial peptide fragments, which indicates a delayed elimination of antigenic material from within the joint cavity (Lahesmaa-Rantala et al. 1987). This pathogenetic pathway also needs the demonstra-

tion of an MHC class I restricted synovial T-cell response in ReA which seems to be present (Nordström 1989a, Sieper et al. 1991).

Diagnostic and clinical aspects

The typical patient is an HLA-B27 positive young adult who develops an asymmetric oligoarthritis probably in the lower extremities of the weight-bearing larger joints; the disease is very rare in children. Monoarticular manifestations are seen in 5–20% of the cases. The clinical features of arthritides associated with genital or enteral infections are similar and cannot be distinguished (Nordström 1989b). Arthritis typically appears within 1–3 weeks of the inciting urethritis or diarrhea. It should be noted that symptoms of urethritis can also be found in ReA patients in whom the triggering microbe is enteral. The classical Reiter's triad of arthritis, conjunctivitis, and urethritis is likewise seen in both enterally- and genitally-triggered ReA. Postenteric arthritis affects both sexes equally, but genital arthritis predominantly occurs in men, perhaps because of different sexual behaviour including a variety of partners. Constitutional symptoms are usually mild and fever, if present, is low-grade. A distinctive arthropathic symptom in ReA patients, as in all spondylarthropathic cases, includes a local enthesopathy that may even be the only arthropathic manifestation. The main target of inflammation is located at the tendinous insertion into bone rather than to the synovium. This sausage-like appearance (sausage digit) contrasts with rheumatoid arthritis, where the inflammation is primarily confined to the synovium. Achilles tendinitis as well as plantar fasciitis are common features in ReA patients. Other extra-articular manifestations (Figure 1) give valuable diagnostic clues. In a study by Lauhio et al. (1991) of 40 ReA patients, 5 presented with eye inflammation, 13 with urethritis, 14 with enthesopathy and 5 with mucocutaneous lesions. Of the mucocutaneous lesions, erythema nodosum occurs in 10% of the patients with *Yersinia* arthritis (Lauhio et al. 1994). The frequent colonoscopic finding (30–50%) of an asymptomatic Morbus Crohn in the terminal ileum or colon of ReA patients is interesting and raises questions of possibly shared pathogenetic mechanisms in these two disease entities, involving mucosal penetrant antigenic microbes and a possibly compromised immune defense (Mielants et al 1993).

The first episode of arthritis usually resolves within 6 months, the recurrence rate, however, being 15–50%. 5–30% of the cases become chronic (Kontinen et al. 1988, Nordström 1989b, Keat 1995). In our

Table 1. Clinical features of reactive arthritis in comparison with rheumatoid arthritis and bacterial arthritis

Feature	Reactive arthritis	Rheumatoid arthritis	Bacterial arthritis
Mono/oligo/polyarticular disease	mono/oligo	poly	mono
Age of patients (years)	20–35	50–60	50–60
Previous joint condition	normal	normal	disease
Knee involvement (%)	75	40	50
Synovial fluid cell count ($\times 10^6/L$)	<50,000	5,000–50,000	20–150,000
Microbe in joint	microbe fragments, no viable microbes	no	yes
HLA-association	HLA-B27	HLA-DR4-subgroups	?

study of the occurrence of various triggering infections (Konttinen et al. 1988), we found that ReA in total remission could be triggered and reactivated by a different microbial antigen causing fulminant relapsing ReA and even leading to chronic arthritis. It therefore seems that ReA is more dependent on the genetic constitution of the host (HLA-B27) than on the type of triggering infection. The spine is markedly affected in those patients with severe, chronic, or recurrent disease. Moreover, ankylosing spondylitis has been noted in 20–50% of ReA patients with relapsing symptoms (Nordström 1989b, Nordström and Konttinen 1989).

One of the main concerns among orthopedic surgeons and rheumatologists alike is to distinguish ReA from other arthritides (Table 1). Features generally considered to be pathognomonic for bacterial arthritis are also present in ReA (highly cellular synovial fluid with a predominance of polymorphonuclear cells, fever, elevated sedimentation rate), although the pathogenesis differs. Bacterial arthritis always implies viable bacteria, which multiply within the joint and may destroy cartilage, whereas ReA develops because of the antigenic properties of the invading microbes in certain genetically prone individuals (Konttinen et al. 1988, Nordström 1989b, discussed below). The clinical presentation may be similar in both diseases. However, anamnestic data, differences in age and the common existence of an articular comorbidity (arthrosis) in bacterial arthritis often reveal the diagnosis, as also does a positive synovial fluid culture (Kortekangas 1994). Other differential diagnoses are psoriatic arthritis, gout, and pseudogout (Kortekangas 1994).

Management

The course of ReA is usually self-remittent within 6 months. The prognosis is determined by two factors, namely HLA-B27 and the recurrence of triggering infections (Konttinen et al. 1988, Nordström and Kont-

tinen 1989). HLA-B27-negative patients have a milder course of disease than do patients with only one ensuing microbial incident. Due to the usually benign course following the initial episode, treatment consists of NSAIDs, physical therapy and intra-articular corticosteroids. Furthermore, it is very important to advise the patients against reexposure to triggering infections. ReA may cause great discomfort and invalidity and therefore, modern management also involves antimicrobial treatment which starts with the treatment of the triggering infection, continues with the treatment of acute ReA and ends with the treatment of prolonged or chronic ReA. In chronic destructive arthritis, antirheumatic therapy seems warranted as well and will be discussed in some detail.

Treatment of the triggering infection

The treatment of the triggering infection is considered especially important in uroarthritis (*Chlamydia* or *Gonococcus*), in which case the partner also has to be treated to avoid re-infections. Even though we have as yet little scientific evidence about early treatment of enteroarthritis, a 2-week course of quinolone treatment is recommended for HLA-B27-positive ReA patients with diarrhea or microbe-positive stools (Konttinen et al. 1988, Leirisalo-Repo 1992).

Treatment of acute ReA with long-term antibiotics

Recent studies in which *Chlamydial* particles, *Yersinia* and antigen from *Salmonella* have been found (Keat et al. 1987, Schumacher et al. 1988, Granfors et al. 1989, Granfors et al. 1990, Taylor-Robinson et al. 1992) have raised the question that antimicrobial therapy may modify the course and prognosis of ReA. The treatment of acute ReA with short-term antimicrobial therapy has had no effect (Fryden et al. 1990). Promising results have been reported by Pott et al.

(1988) and Panayi and Clark (1989) in two uncontrolled studies with prolonged antimicrobial therapy. In a recent double-blind, placebo-controlled, randomized study in patients with Chlamydia trachomatis-triggered ReA, Lauhio et al. (1991) showed that a 3-month treatment with lymecycline (tetracycline-L-methylenelysine, 300 mg twice daily) significantly reduced the duration of illness, duration of arthralgia and the mean duration of joint swelling compared to placebo. Enteroarthritis patients did not react favorably to lymecycline which may be due to different pathogenesis or to different antimicrobial responses. Ziedler (1992) have confirmed these findings, showing that long-term doxycycline therapy is beneficial in the treatment of Chlamydia arthritis. Independently of the antimicrobial properties, tetracycline derivatives may also decrease inflammation and tissue destruction by their ability to inhibit interstitial collagenases (Kontinen et al. 1991, Lauhio et al. 1994b). Furthermore, tetracyclines depress inflammation-mediated tissue destruction by suppressing neutrophil function (Gabler and Creamer 1991) and by inhibiting reactive oxygen species (Wasil et al. 1981). In keeping with this, we have recently shown that therapeutic levels of lymecycline do not directly inhibit the activity of human neutrophil interstitial collagenase, but can prevent the oxidative activation of latent human neutrophil collagenase (Lauhio et al. 1992), thus, supposedly preventing tissue destruction of the joint.

Treatment of chronic ReA with antibiotics

It is still debated whether chronic symptoms of chronic ReA/sacroiliitis/ankylosing spondylitis can be altered with antimicrobial therapy. Ziedler (1992) has suggested that prolonged treatment is superior to NSAIDs concerning both the short-term and long-term courses of Chlamydia arthritis. A double-blind study by Toivanen et al. (1993) showed somewhat confusing results when treating 36 chronic enteroarthritis patients with quinolone ciprofloxacin for three months (500 mg twice daily): arthralgia, morning stiffness and pain on movement decreased significantly, whereas joint score index and erythrocyte sedimentation rate showed a significant decrease in the placebo group. On the contrary, in Lyme arthritis where, in some patients, the arthritis is reactive in character, antibiotic treatment is recommended (ceftriaxone, 2g/day intravenously for 2 weeks; Caperton et al. 1990).

Treatment of chronic ReA with anti-rheumatic drugs

Chronic ReA is not usually associated with systemic malaise, fatigue and disability, as seen in rheumatoid arthritis (RA). Hence, antirheumatic drugs have been administered less commonly. Recently, it has become quite clear that a more aggressive line of treatment familiar from the treatment of RA is needed in prolonged cases to prevent severe joint destruction. Among antirheumatic drugs, the largest documentation is available about sulfasalazine. Most of the earlier open, uncontrolled studies show beneficial effects on both peripheral and axial disease; a group of 15 HLA-B27-positive ReA patients was treated for an average of 13 months. After 3–6 months, all patients showed significant improvement in objective and subjective variables (Mielants et al. 1985). Better improvement was seen in another uncontrolled study of 16 patients with ReA than in a series of ankylosing spondylitis patients studied simultaneously (Zwillich et al. 1988). Two placebo-controlled studies (Tmavnsky et al. 1988, Egsmose et al. 1993) have shown beneficial effects on joint pain, joint score index, erythrocyte sedimentation rate and C-reactive protein, compared to placebo. No placebo-controlled studies with oral or intramuscular gold or d-penicillamine in ReA are available; however, clear-cut benefits have been documented in ankylosing spondylitis patients. Only open studies are also available concerning ReA patients treated with methotrexate. Responses of mucocutaneous lesions to methotrexate are good, or even dramatic, whereas arthritis seems less responsive (Farber et al. 1967, Lally and Ho 1985). A 4-month placebo-controlled crossover study has been performed, using azathioprine in 8 patients with Reiter's syndrome. Joint score was reduced during treatment, but it increased again during the placebo period (Calin 1986). Two fatal cases of Reiter's syndrome treated with azathioprine have been reported; the causes of death were amyloidosis and infection, respectively (Paulus et al. 1972, Chee and Chan 1977). Alkylating agents such as cyclophosphamide have also been used in fulminant cases of ReA with some benefits (Miehlke and Kafarnik 1972). Concerning antirheumatic drugs, we may conclude that sulfasalazine seems to be sufficiently established in the treatment of chronic ReA, for both peripheral and axial symptoms, and especially in those patients who also suffer from inflammatory bowel disease. Among the other disease-modifying antirheumatic drugs, gold compounds and azathioprine may be used in active and destructive cases, preferably for peripheral manifestations. Methotrexate is worth trying in

chronic ReA patients, especially with mucocutaneous involvement.

Acknowledgements

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