



Reactive arthritis: newer developments

Diana Flores, MD^a, Javier Marquez, MD^a, Mario Garza, MD^b,
Luis R. Espinoza, MD^{a,*}

^a*Section of Rheumatology, Department of Medicine,*

Louisiana State University Health Sciences Center, New Orleans, LA, USA

^b*Section of Rheumatology, Department of Medicine, Hospital Universitario, Monterrey, Mexico*

Reactive arthritis (ReA) refers to an infection-induced systemic illness and is characterized by an aseptic inflammatory joint involvement occurring in a genetically predisposed patient with a bacterial infection localized in a distant organ/system [5,35,43,60,69,115]. Although ReA is considered a sterile arthritis, accumulated evidence has shown that bacterial degradation products and even bacterial DNA are present in the synovium of patients with this disease. Furthermore, the demonstration of persistent bacterial antigen within the joint has further strengthened the notion for an active role of microorganisms in the pathogenesis of this group of disorders [36,46,58,66,73,75,88]. Nevertheless, based on the strength of the relationship with HLA-B27, ReA is considered a spondyloarthropathy (SpA), and at least one third of patients with undetermined oligoarthritis (UOA) may have a form of ReA that involves asymptomatic primary infection [1,71].

Epidemiology

Lack of agreement in disease definition and of specific criteria for diagnosis may introduce some difficulties in determining the epidemiology of ReA [23,24,90,119,134].

Typically, ReA refers to acute or insidious polyarthritis after enteric or urogenital infections. Incidences of arthritis after infection have varied widely (1% to 20% or more), with this variability being only partially explained by

* Corresponding author. Section of Rheumatology, Department of Medicine, Louisiana State University Health Sciences Center, 1542 Tulane Avenue, New Orleans, LA 70112-2822.

E-mail address: luisrolan@msn.com (L.R. Espinoza).

HLA-B27. In infections with *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia*, the frequency of ReA varies considerably, from 0 to 15%, despite the fact that HLA-B27 can be present in 72% to 84% of cases. Both the genetic background and local environmental factors might contribute to these differences. In a large cohort of German children, the incidence of ReA after a *Salmonella* outbreak in children was very low (<2.1%), which may be related to differences in the immune response between children and adults [106]. While ReA is frequently observed in third-world children, it is rather rare in adults, perhaps because of early exposure to the relevant organisms.

On the other hand, incidences of arthritis after chlamydial infection are less well known. Leirisalo-Repo reported that in Finland, *Chlamydia trachomatis* was the most frequent microbe associated with ReA cases, with an increase from 6655 cases in 1995 to 8806 in 1998 [77]. In this country, the frequency of *Salmonella* infections remained about the same during that period (between 2000 and 3000 cases), while there was a drop in the number of *Yersinia* cases, from 813 to 566. A clear increase in the number of cases of *Campylobacter jejuni* was also observed during that period. It can be assumed that these changes will probably be reflected in a change in the number of cases of ReA due to the different bacteria.

These data clearly demonstrate that there are local differences in the rates of infection with specific bacteria and in the prevalence of ReA, and that even within a given locale, changes in these rates occur.

Pathogenesis

An ineffective immune response seems to contribute to the manifestations and course of ReA [118]. Although arthritis can also occur in its absence, HLA-B27 plays an important role in the pathogenesis of ReA and the other SpA [91]. Current data suggest that B27 probably acts as an antigen-presenting molecule for a still-unknown arthritogenic molecule. However, there has been little study of any possible contribution of HLA class II molecules in reactive arthritis, but one report has described an increased association of HLA-DR β -1c *408 and DQ β -1 *0301 in B27-positive reactive cases.

Comparison of ReA with inflammatory bowel disease-associated arthritis suggests that there might indeed be a common antigen shared by ReA-associated bacteria and bacteria of the gut flora [81].

The immune system undoubtedly plays a crucial role in the pathogenesis of ReA. Th1 cytokines such as interleukin-12 (IL-12), interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF)- α are crucial for the elimination of bacteria. Furthermore, a lack of these cytokines and/or an elevated production of Th2/Th3 cytokines (especially IL-10) inhibit effective clearance of these pathogens. One study reported that levels of TNF- α were significantly lower at the beginning of the ReA disease course than in patients with early rheumatoid arthritis, and a low TNF- α level correlated well with a chronic course of ReA. Thus, there is a relatively low production of Th1 cytokines in ReA, which might partly explain bacterial persistence. Schumacher et al found a high amount of IL-10 (together with

IFN- γ) in the joints of patients with early *Chlamydia*-induced arthritis compared with patients with undifferentiated oligoarthritis [113]. The relative contributions of TNF- α and IL-10 should be explored in more detail in future studies

At the present time, it is not possible to predict whether a cytokine-directed treatment stimulating a Th1 response (such as the application of IFN- γ or IL-12 for the elimination of bacteria) or rather the opposite (eg, an anti-TNF- α therapy) will provide the best approach for treating ReA. It remains to be determined whether the latter treatment can induce an exacerbation of the infection or a suppression of the inflammation without stimulating bacterial growth.

From investigations of TNF- α microsatellites, an association of ReA with a TNF-a6 allele has been described. This allele, which has previously been associated with low TNF- α secretion, was also associated with HLA-B27, and the association of TNF-a6 with ReA was thought to be secondary to B27. Thus, there is some evidence that TNF- α genotypes that seem to be associated with low TNF- α production are present in a higher percentage in ReA.

T cells and macrophages seem to play an important role in ReA. Also, in ReA, T cells have been implicated in the pathogenesis of the arthritis, but which of the different subsets is involved is still debated. One study has shown that both CD4+ and CD8+ T cell populations demonstrate evidence of recent activation in the joint. Whether these cells are involved in either inducing or regulating inflammation, or have become active as a result of migration through the endothelium, remains to be determined by functional studies.

An important step in clarifying the pathogenesis of ReA would be to identify the target for the synovial T cell response. In ReA, both antigen-specific CD4 and CD8 T cells have been detected in the synovial fluid and synovial membrane [18]. In *Chlamydia*-induced arthritis, the chlamydial heat shock protein 60 (hsp60) and the Hc1 protein (a histone) have already been identified and an OMP (Omp2) has also been recognized by CD4+ T cells. The T cells specific for hsp60 did not cross-react with hsp60 from enterobacteria or from humans. There were several T cell clones, however, that did not respond to any of the tested chlamydial proteins, although whole *Chlamydia* elicited an immune response, suggesting that there are other relevant chlamydial antigens. Kingsley et al have also investigated *Chlamydia*-specific T cell clones from synovial fluid that were specific for the chlamydial hsp60 but did not recognize the human counterpart, suggesting that autoimmunity did not play a relevant role in this patient with chronic arthritis. Moreover, one study reported that humoral immune response to *C trachomatis* in patients with ReA is against multiple serovars (D to K), whereas in patients with urethritis alone, the response is usually to one serovar. The stimulatory epitopes identified were homologous to those from a number of common bacteria, suggesting a role for cross-triggering in disease. This would also provide evidence for a role in reinfection as well as persistence for *Chlamydia* in the pathogenesis of ReA [15–17].

In *Yersinia*-induced arthritis, the strongest CD4 response is found against the β -subunit of urease (the 19-kilodalton protein) and hsp60. Most interestingly, IL-10 secretion after antigen peptide-specific stimulation showed a wide

variation among the T cell clones, suggesting that both high and low IL-10 secretion can occur in vivo after specific stimulation with *Yersinia* antigens. As far as the CD8 response is concerned, only peptides derived from hsp60, but not from any other *Yersinia* proteins, were recognized by synovial fluid T cell lines [130,131]. By further mapping the epitopes for the CD4 and CD8 response, two nearly identical epitopes were identified: amino acid sequence 322 to 333 from the hsp60 for CD4 T cells and amino acid sequence 321 to 329 from the hsp60 for CD8 T cells.

In summary, T cell responses (both CD4+ and CD8+) directed against bacterial hsp60 seem to be relevant in ReA. However, because there is no or only a small amount of cross-reactivity among different bacteria and between bacterial and self-hsp60, there does not seem to be a single relevant hsp60 epitope on which to focus a unifying pathogenetic hypothesis. There is to date no known cross-reactive T cell response to bacterial or autologous hsp60 in ReA. The lack of such a response might partly explain the ongoing inflammation, and whether an anti-human hsp60 T cell response can be detected in ReA during or shortly before remission remains to be investigated.

Causative organisms

Characteristically, and in contrast to classical infectious arthritis, the agents cannot be cultured and, therefore, may not be “viable” once having reached the joints. The fact that such a variety of bacteria can induce arthritis, yet some bacterial subtypes (such as *Yersinia* O:8 or *Shigella sonnei*) in a single species do not provide evidence that antigenicity alone does not determine induction of arthritis. While *Chlamydia* seem to hide inside the joint, other areas such as gut mucosa or lymph nodes seem to be more likely places for *Salmonella* and *Yersinia*.

In addition, components of triggering microbes can be demonstrated at the site of inflammation (eg, in the synovium and synovial fluid). Several groups have found bacterial DNA and RNA of *C trachomatis*. In a few cases even bacterial isolation has been positive using sensitive detection methods such as immunohistology, electron microscopy, and polymerase chain reaction (PCR).

The classical microbes associated with ReA are enterobacterias and *Chlamydia*, but more recent studies have shown that other bacterial species such as *Pseudomonas migulae*, *Pseudomonas fluorescens*, and *Pseudomonas putida* can be found in synovial tissue; *Clostridium* sp, *Lactobacillus*, *Neisseria meningitidis* serogroup B, and *Bacillus cereus* can be found in synovial fluid. These investigators found one class of bacterial DNA in four out of eight samples, and *C trachomatis* and *Pseudomonas* sp were the most common bacterial DNA identified in this group. In four out of eight (50%) of the PCR-positive samples, two to three different classes of bacterial DNA were identified (*P fluorescens*, *P putida*, and *P migulae*). *B cereus*, *Clostridium* sp, and *Lactobacillus* sp were present in two cases. The bacterial DNA products identified appeared to be derived from several bacterial species, although all of them can be found in the

human intestinal, urogenital and respiratory tracts. Furthermore, PCR products were found with similar frequency in synovial fluid and synovial tissue samples, although not often simultaneously detected in all of them. It is remarkable that *Pseudomona* spp and certain species of *Salmonella* spp have not been thought to be pathogens to humans. Box 1 shows the agents related to ReA [117].

Chlamydia

C trachomatis is a common pathogen and can be found in about 50% of patients with a preceding symptomatic infection of the urogenital tract who developed ReA [102]. Positivity for *Chlamydia* can be found by PCR in 65% of patients with ReA and 42% of patients with other reactive arthritides, as well as in 21% of patients with rheumatoid arthritis (RA) and 14% of patients with osteoarthritis (OA). Of special interest is the increasing evidence that *Chlamydia*

Box 1. Etiologic organisms in reactive arthritis

Frequent association

Chlamydia trachomatis
Ureaplasma urealyticum
Salmonella enteritidis
Salmonella typhimurium
Shigella flexneri
Shigella dysenteriae
Campylobacter jejuni
Yersinia enterocolitica
Streptococcus sp

Less common association

Chlamydia pneumoniae
Neisseria meningitidis serogroup B
Bacillus cereus
Pseudomona
Clostridium difficile
Borrelia burgdorferi
Escherichia coli
Helicobacter pilory
Lactobacillus
Brucella abortus
Hafnia alvei
Trophyma whippelii
Propionibacterium acnes
Bacille Calmette-Guérin
Intestinal parasites

may be viable although difficult to culture. With *C trachomatis*, initial observations were based on demonstration of *Chlamydia* antigen and preferential lymphocyte transformation by joint cells along with electron microscopic identification of organisms, but since the early 1990s, there has been a fairly convincing stream of reports from several groups about molecular demonstration of the agent in the synovium and synovial fluid [115]. Studies in Philadelphia and Bethesda National Institute of Arthritis and Musculoskeletal and Skin Disorders (NIAMS) have identified structures that look like whole *Chlamydia* by electron microscopy, chlamydial RNA, which strongly suggests at least recent viability (because RNAases should destroy old RNA), and now even a series of primary transcripts using reverse transcriptase PCR. Schumacher et al also reported on the investigation of synovial biopsy specimens from 30 healthy volunteers, two of who were positive for *C trachomatis* by PCR. *Chlamydia* reaches the joint and remains alive, and monocytes seem to be likely candidates for transportation to the joint. In humans, *Chlamydia* does persist in the joint, and one intriguing possibility is that the presence of any bacterial DNA may act as an immunostimulant and contribute to disease pathogenesis. In fact, an intra-articular immunoglobulin G (IgG) production and a possible role for some *Chlamydia* antigens such as OMP2 in the pathogenesis of *C trachomatis* ReA have been reported. Not only chlamydial DNA but also chlamydial RNA of *Chlamydia pneumoniae* was also detected in joint material, though less frequently than *C trachomatis* (13% versus 53% in patients with ReA and 21% versus 68% in patients with Reiter's). DNA of *C pneumoniae* is present in synovial specimens from some arthritis patients. The prevalence of this organism in the joints was lower than that of *C trachomatis*, and synovial presence of the organism was not associated with any distinct clinical syndrome. Widely disseminated nucleic acids such as those of *C pneumoniae* might have some role in the pathogenesis of several arthritides because the organism was not found in the synovial tissue from normal control individuals. *C pneumoniae* also has been found in patients with ReA [114,124].

Shigella

The first bacterial infection to be causally related to reactive arthritis was *Shigella*, which was described in an outbreak among Finnish troops in 1944 [97]. Of the four species of *Shigella* (*Shigella sonnei*, *Shigella boydii*, *Shigella flexneri*, and *Shigella dysenteriae*), *S flexneri* has been most commonly implicated in cases of reactive arthritis, both sporadic and epidemic. *S dysenteriae* has also been commonly associated with post-*Shigella* reactive arthritis, but *S sonnei*, though responsible for the majority of cases of shigellosis in the United States, has been implicated only rarely [14,29].

Autoantibodies to HLA-B27 cross-react with *Shigella* proteins to form circulating antigen-antibody complexes, although the pathogenic significance of this finding is not known. HLA-B27 positivity approaches 80%, and there is a high incidence of genital inflammation (70%), balanitis (24%), and chronicity of symptoms (18%) associated with post-*Shigella* ReA.

Shigella has been identified as the causative agent of ReA in patients with a history of diarrhea episodes but with negative stool cultures, by means of synovial lymphocyte proliferation to bacterial antigens, raising the possibility that the incidence of *Shigella*-associated ReA may be underappreciated. *Shigella* is hampered by the lack of an animal model because humans are the only host. Epithelial cells are the major targets of *Shigella* infections, and transportation by monocytes is highly unlikely because *Shigella* rapidly kills monocytes through apoptosis. *Shigella* DNA has not been convincingly demonstrated in the joints of ReA patients, making it more likely that only pieces of bacteria are transported to the joint. Only the *Shigella* containing the pHS-2 plasmid are arthritogenic. *Shigella* are transported in monocytes or persist somewhere in vivo. Instead, bacterial fragments seem to be sufficient for the induction and maintenance of inflammation in ReA.

Salmonella

Salmonella infection may be a cause of ReA, osteomyelitis, and septic arthritis [37,47,82–85,106]. *Salmonella typhimurium* and *Salmonella enteritidis* have most commonly been identified as pathogens, but other *Salmonella* species have been implicated as well. The exact incidence of reactive arthritis after *Salmonella* infection has been reported to be between 1% and 15%, and up to 84% of patients with *Salmonella*-related ReA are HLA-B27 positive but genital inflammation is uncommon. Also, Ekman et al suggested that HLA-B27 did not confer strong susceptibility to *Salmonella* infection [42,107]. It has been suggested that lymph nodes or the intestinal mucosa are also likely sites for persistent *Salmonella*. In patients with early-stage *Salmonella* infections, this microbe can be identified in peripheral blood monocytes, suggesting that *Salmonella* is probably transported by monocytes to the joints and other tissues. Whether the *Salmonella* that reach the joint are alive for only a short time, if at all, remains to be established. Reports by Ford and Schulzer have also noted preferential synovial lymphocyte transformation in response to enteric and other pathogens as further support for antigen presence in the joint [46].

After an outbreak with *Salmonella* in Finland, arthritis involving mainly the wrists, knees, and ankles developed in 6.9% of subjects [86]. Most of the patients (63%) had oligoarthritis (fewer than six joints involved), and in 31% the symptoms persisted longer than 5 months. In another outbreak in Syracuse, New York, frequency of joint symptoms correlated with duration of diarrhea, and overall severity correlated with HLA-B27 positivity. In approximately 10% of cases of *Salmonella* infection, bacteremia may develop, with or without gastrointestinal involvement. Once the organism invades the bloodstream, almost any organ can become involved, and localized infections, including septic arthritis and osteomyelitis, occur in approximately 5% of patients. It is also been shown that the occurrence of ReA after an outbreak of *S typhimurium* was at the same level as in outbreaks caused by other salmonella serotypes

reported previously, indicating that the frequency of ReA after various outbreaks is approximately 10% [57,65,125,127].

Yersinia

While infection with *Yersinia enterocolitica* is uncommon in the United States, a large body of data regarding *Yersinia*-associated ReA has been obtained in Europe, where infection is reported more frequently [79]. Reactive polyarthritides occurs in between 2% and 20% of patients with yersiniosis [3,4]. Similar to other reactive arthritides, *Yersinia*-associated ReA has a high prevalence of HLA-B27 positivity (75%), and about 13% of afflicted patients may have genital inflammation, and 10% may develop a clinical picture of ReA. A feature unique to *Yersinia* is the small percentage (5%) of patients, usually HLA-B27 negative, who develop erythema nodosum. In comparison with individuals who fail to develop ReA after infection with *Yersinia*, patients with *Yersinia*-associated ReA show far fewer gastrointestinal symptoms attributable to the infection, a smaller initial IgM response, stronger and more persistent IgA and IgG responses, higher levels of IgA anti-*Yersinia* antibodies with a secretory component, and reduced T-cell proliferative responses to *Yersinia* antigens. These findings suggest an unusual persistence of the immune response to the infecting organism in those individuals in whom ReA develops. In addition, *Yersinia* antigens can be detected for years in peripheral blood cells from patients with *Yersinia*-induced ReA [48,52]. This finding suggests that *Yersinia* persist within the body for a long time, possibly in lymph nodes or mucosa. In humans, however, it is difficult to detect *Yersinia* in the joint by PCR, with only a single positive patient found in one study, and the presence of *Yersinia* 16S rRNA indicates that viable organisms were also able to reach the joint [55]. Although bacterial antigen is transported to the joint, live *Yersinia*, and hence *Yersinia* DNA, is present for only a short period. *Yersinia* lipopolysaccharide (LPS), or Yad A, seems to be essential because after deletion of these proteins from *Yersinia* it was not possible to induce arthritis in these rats.

Campylobacter

The most important *Campylobacter* species in humans is *Campylobacter jejuni*, estimated to cause 4% to 11% of all diarrhea cases in the United States [38]. ReA occurs in approximately 1% to 3% of patients with *Campylobacter* enteritis, and a smaller percentage of patients develop chronic symptoms. HLA-B27 positivity has been reported in 72% of afflicted individuals. A case series reported the knee as the most commonly involved site, with an average of about three joints involved, and HLA-B27 status correlated with frequency of involvement [53,56,80,99].

Intestinal parasites

A number of intestinal parasites, including *Strongyloides stercoralis*, *Taenia saginata*, *Giardia lamblia*, *Ascaris lumbricoides*, *Filariasis*, and *Cryptospori-*

dium, have been linked to reactive arthritis [6,21,25,31,98,128,136]. The presentations have been variable, although many patients have demonstrated a seronegative, polyarticular inflammatory arthritis resistant to nonsteroidal anti-inflammatory drugs (NSAIDs). Some people think that this is not a real ReA because in some cases patients required treatment with medications directed against the parasites to effect resolution of their symptoms. Another objection could be made to the so-called parasitic ReA because the articular manifestations are cured by specific treatment of the parasite and for the so-called *Brucella* ReA.

Streptococcus

Poststreptococcal reactive arthritis (PSReA) is a recognized inflammatory articular syndrome that follows group A streptococcal infection in persons not fulfilling the Jones criteria for the diagnosis of acute rheumatic fever. One study done in The Netherlands, a prosperous western European country with State Welfare, showed that arthritis secondary to β -hemolytic A *Streptococcus* infection is not accompanied by carditis, contrary to literature on classical acute rheumatic fever (ARF) [20,67].

Characteristic features include nonmigratory arthritis, lack of response to aspirin or nonsteroidal anti-inflammatory agents, and the presence of extra-articular manifestations, including vasculitis and glomerulonephritis. Cardiac involvement did not occur in this group of patients with PSReA. Prolonged prophylactic antibiotic therapy may not be required for adult patients presenting with PSReA, which is characterized by a shorter latency period between the inciting streptococcal infection and the onset of arthritis, a higher frequency of involvement of the small joints and axial skeleton, poor response to aspirin and other NSAIDs, a protracted course of arthritis, a low incidence of carditis, and absence of other major manifestations of acute rheumatic fever. Recent studies have demonstrated an increased frequency of DRB1*01 in patients with PSReA, which contrasts with the increased frequency of DRB1*16 in rheumatic fever [2]. Because 6% of patients with PSReA have been reported to have late-onset carditis, it is judicious to recommend that patients with PSReA receive prophylactic antimicrobials for at least 5 years or until the age of 21 years, whichever is longer. PSReA should be included in the differential diagnosis of all adult patients presenting with arthritis. Treatment strategies include aspirin, other NSAIDs, and corticosteroids [12,13,64].

Other micro-organisms

Other less common infectious causes of ReA exist. In rare cases, reactive arthropathy can complicate infections of *Clostridium difficile* and the pathogenesis appears to be similar to other reactive arthropathies [22,89,101,122]. The arthritis may involve either large or small joints, is self-limited, and usually resolves within a few months. A single case report exists of a man with *Hafnia alvei*, which is known to be a cause of gastroenteritis, who developed acute

arthritis that resolved with treatment after 10 weeks [93]. *Klebsiella* has been linked to a possible association with ankylosing spondylitis (AS) [39,45,49, 54,62,116]. *Escherichia coli* followed by either urinary infection or diarrhea has been associated with ReA. A case report showed that infection with *Helicobacter pylori* or its eradication can trigger ReA; for this reason, *H pylori* should be included in the list of possible arthritis-triggering microbes.

As mentioned above, commensal microbes such as *P migulae*, *P fluorescens*, *P putida*, *Clostridium* sp, *Lactobacillus*, *Neisseria meningitidis* serogroup B, and *B cereus* can be detected in patients with ReA, either in an isolated way or two or more bacterias at the same time [34].

Whipple's disease, an uncommon systemic disease caused by *Tropheryma whippelii*, a small rod-shaped, Gram-positive bacillus, has both gastrointestinal and rheumatic manifestations [28]. Arthritis is among the most common of extraintestinal symptoms and may precede the development of gastrointestinal complaints by many years. The arthritis is seronegative and may manifest itself as an acute or subacute process. Typically the pattern of presentation is a migratory polyarthritis, a synovial reaction that waxes and wanes, commonly involving the ankles, knees, shoulders, elbows, and fingers. Axial arthritis also occurs but AS, although reported, is rare. Joint symptoms include tenderness, redness, swelling, and warmth. Permanent joint deformity is rare in Whipple's disease and many patients have arthralgias only. Treatment involves prolonged administration of antibiotics, which leads to prompt, dramatic improvement of the joint and intestinal manifestations.

Enthesopathic pains and ReA are rarely described in Lyme disease; in these cases, treatment with high doses of penicillin alone (or in combination with other antibiotics) does not seem to be helpful [123].

Clinical features

Clinical differences have long been recognized between postenteric and postgenital infection ReA, but the clinical features of ReA are generally similar [7,11,19,70,72,74,108,129,132]. Box 2 shows the clinical manifestations, of which patients can have one or more.

Postenteric ReA is described equally in men and women, whereas postchlamydial disease is reported much more often in men [68,135].

In the setting of postenteric ReA, patients who go on to develop arthritis frequently have more prolonged episodes of diarrhea, higher antibody levels of the IgA type, and persistent titer elevations [126]. Acute diarrhea may precede the musculoskeletal symptoms by 2 to 3 weeks and dysenteric symptoms are sometimes very mild in these patients, even milder than in nonarthritic patients and, moreover, antecedent symptoms may be absent in a sizable minority. The typical duration of symptoms is less than 6 months, but in some cases of relapse, antecedent of diarrhea can be absent. Some patients may exhibit joint symptoms for longer than 6 months.

Box 2. Clinical manifestations of reactive arthritis

Arthritic skin

- Asymmetric
- Oligoarticular
- Lower extremity predilection
- Enthesitis
- Sacroiliitis
- Genitourinary
- Nonspecific urethritis
- Cervicitis
- Cystitis
- Hematuria
- Hydronephrosis

Skin

- Keratoderma blenorrhagica
- Balanitis circinata
- Ulceration on tongue

Ocular

- Conjunctivitis
- Acute anterior uveitis

Cardiac

- Aortitis
- Aortic insufficiency
- Heart block

The provocative agent may have disappeared from the gut when the joint symptoms arise. During an epidemic it is identified in diarrheic but not in arthritic patients. Isolation of a triggering agent from the stool of an arthritic patient is a rare event, except for *Salmonella*.

On the other hand, nonspecific urethritis is generally limited to a mild, painless, and nonpurulent discharge in patients with postchlamydial disease and sometimes goes unnoticed by the patients.

Another clinical feature is conjunctivitis, and is observed very early, before or at the onset of arthritis. The discharge is sterile and subsides in 1 to 4 weeks. Uveitis is less frequent in early disease but occurs in 15% of patients with recurring disease, often as an incident separated from arthritis.

The clinical manifestations of ReA range from an isolated, transient monoarthritis to a more severe multisystem disease.

Like other spondyloarthropathies, it combines four syndromes:

1. Peripheral arthritis syndrome. The onset of reactive arthritis is sometimes acute, with fever as high as 102.2°F (39°C), severe weight loss, and asymmetric peripheral arthritis syndrome, that within a few days involves

- two to four large joints (oligoarthritis), most commonly of the lower extremities. Mono- and polyarthritis may be observed. The sensitivity of asymmetric oligoarthritis distribution is 44.3% and the specificity is 95%. Diffuse swelling of an entire finger(s) or toe(s), commonly described as sausage digit, had a low sensitivity of 26.6% but a very high specificity of 99%. In most cases when synovitis is limited to a few joints, however, low-grade fever or no fever at all is the rule [103,104].
2. Enthesopathic syndrome. Enthesitis is present in 42% of patients. Heel pain is the most frequently recognized enthesopathic pain. The sensitivity of heel pain is 51.6% and the specificity is 92.2%.
 3. Pelvic and axial syndrome. Highly distinctive features of this syndrome are inflammatory dorsal or lower back pain or buttock pain. Sensitivity is 71.4%, and specificity is 77.3%.
 4. Extramusculoskeletal syndrome. Dermatological lesions like balanitis circinata and keratoderma blennorrhagica are diagnostically very suggestive, as are hyperkeratosis and parakeratosis of the nails [92].

Visceral involvement, very similar to that observed in other spondyloarthropathies, is infrequent (1%).

Diagnosis

The diagnostic criteria of what has now been termed ReA are still under debate and there is no single diagnostic test for it. There is no agreement on how to classify and diagnose ReA, and it is also unclear what kind of specific clinical and laboratory investigations are appropriate [41,61,63]. Classification criteria require high specificity because they are designed for studies in which the diagnosis is likely to ensure a homogeneous and identifiable study group. With the use of such criteria, sensitivity will obviously be lost. In contrast, diagnostic criteria will have high sensitivity (necessarily with reduced specificity) because the diagnosis should not be missed in an individual patient. There are nearly no diagnostic criteria, and most of the classification criteria are misused as diagnostic criteria. There is agreement on the nomenclature and recommendation to use the term “reactive arthritis” only if the clinical picture and the microbes involved are HLA-B27 and spondyloarthropathy (SpA) associated, whereas the term “infection-related arthritis” is used for all other arthritides related to or associated with infections.

A differentiation between acute and chronic ReA with a cutoff of 6 months is recommended. The history of a preceding symptomatic infection is thought to be most relevant for a diagnosis of ReA. The minimal interval between preceding symptoms and arthritis is proposed to be 1 to 7 days, maximally 4 weeks. The joint pattern in ReA is asymmetrical, with predominance of the lower limbs. SpA-related symptoms might contribute to the diagnosis. A search for *Chlamydia* in urine/urethra/cervix is recommended, while in the case of diarrhea enterobacteria should be searched for in stool and antibodies against them in serum. There are also the

following areas of disagreement: Is arthritis essential for the diagnosis of ReA? Is it oligoarthritis or any arthritis? What are the roles and values of polymerase chain reaction investigation? What is the role and value of serology? Is the diagnostic sensitivity of microbiological tests for ReA increased by HLA-B27 determination? Criteria for ReA of the French Society of Rheumatology (FSR) showed a sensitivity of 80% and a specificity of 90% with a positive predictive value of 0.55 and a negative predictive value of 0.97. Pacheco et al propose three categories of disease for patients entering clinical and basic studies on ReA: probable ReA (two subgroups), definite ReA triggered by bacteria (two subgroups), and bacteria-associated undifferentiated oligoarthritis or spondyloarthropathy [96].

The isolation of the microorganisms is sometimes difficult and, moreover, a positive serology is hard to interpret as a recent infection. In 52 patients with ReA, Feldner et al showed that a causative pathogen was identified in 29/52 (56%) of all patients ReA. In 17 (52%) of the patients with enteric ReA one of the enteric bacteria was identified: *Salmonella* in 11 of 33 (33%) and *Yersinia* in 6 of 33 (18%). *C trachomatis* was the causative pathogen in 12 of 19 patients (63%) with urogenic ReA. In patients with the clinical picture of UOA, a specific triggering bacterium was also identified in 35 of 74 patients (47%): *Yersinia* in 14 of 74 (19%), *Salmonella* in 9 of 74 (12%), and *C trachomatis* in 12 of 74 (16%) [44,50].

In the case of *Chlamydia* serology, for example, it is helpful just in patients with clinical features of ReA, and the presence of IgG alone does not reflect a recent infection because it can be elevated for months after an infection. Therefore, determination of IgG antibodies should be combined with a test for IgM and IgA antibodies, the latter two indicating an acute or persistent infection.

C trachomatis in the joint can also be detected by PCR. *C trachomatis*, *Yersinia*, or *Salmonella* can be identified as the causative pathogen in about 50% of patients with probable or possible ReA if the appropriate tests are used. Antigens of the enteric pathogens, *Y enterocolitica*, *S enteritidis*, and *S typhimurium*, have been identified in joints using immunohistochemistry on synovial tissue or synovial fluid [87,94,95,133].

The exact use of a single test, however, which has to consider the specificity and the sensitivity of the test and the prevalence of ReA in a given setting, needs to be evaluated in future studies.

Laboratory features and other complementary examinations

The inflammatory nature of the disease is biologically confirmed by an elevated erythrocyte sedimentation rate (ESR) and an increased concentration of C-reactive protein; however, a normal ESR is not incompatible with the diagnosis. Synovial fluid analysis always shows more than 2000 cells/ml, with a majority of polymorphonuclear leukocytes. Synovial biopsy shows inflammatory changes, including vascular congestion and perivascular cell infiltration, mainly neutrophils. Synovial tissue or synovial fluid cultures are negative. The synovial

complement concentration is normal. One study demonstrated positive IgG-ANCA in 31 (56%) patients with ReA, 23 (42%) patients had antilactoferrin antibodies, 9 (16%) had anti-myeloperoxidase (MPO), and 8 (15%) had anti- α -antigen antibodies, none of which reacted with PR3. Only 6 (14%) AS or sacroiliac joint arthritis patients had anti-neutrophil cytoplasmic antibody (ANCA) ($P < 0.001$) [112].

Radiographs of affected joints are usually normal, and except for a low percentage (4%) of sacroiliitis pain as described by the patients, they more sensitive and more specific than any of these techniques.

Treatment

Therapy of ReA is currently under debate. Although the symptoms also commonly resolve spontaneously after weeks to months, chronic courses with deformities or radiographic evidence of erosion or sacroiliitis can occur and often necessitate therapy with disease-modifying antirheumatic drugs (DMARDs) such as sulphasalazine or methotrexate [8,27,30,40,77]. There is recent evidence suggesting that biological agents such as remicade and enbrel may be helpful in ReA patients with refractory arthritis—peripheral and central.

For joint inflammation, NSAIDs are effective in ReA but they sometimes take a few weeks for a maximal effect to be achieved. Steroids have only limited value for axial symptoms and are mostly effective for peripheral arthritis. Local injection of steroids into peripheral joints and the sacroiliac joint, as well as for heel pain, is helpful.

Several observations suggest that the triggering microbe may persist in the tissues of the patient for a prolonged time and in this case therapy with antibiotics could reduce the duration of the disease and prevent chronic arthritis. Some patients with ReA may have clinical improvement resulting from either antibacterial effect or immunomodulatory effects of these drugs.

At the present time, however, there is no role for antibiotics in the treatment of fully developed enteric ReA. Treatment with either ciprofloxacin or tetracycline has no effect on enteric ReA and there is no benefit in treating patients who have acute *Salmonella enteritis* because treatment does not prevent the occurrence of arthritis. Regardless, according to an experimental animal model, the early use of antimicrobial drugs in the prevention of enteric ReA is not unreasonable and an early course of ciprofloxacin before the appearance of any signs of arthritis might prevent ReA [120,121,137–139].

The situation is less clear for Chlamydia-induced arthritis because a small effect has been observed in some studies, but the numbers of patients studied to date have been too small to allow clear conclusions to be drawn. The value of antibacterial agents in ReA has been tested using two schedules: conventional short-term treatment to eradicate the triggering infection and long-term treatment, usually spanning 3 months, with the aim of eradicating possible persisting bacteria.

Long-term treatment

An early 1989 study reported favorable effects of tetracyclines in 10 patients with *C trachomatis*-induced uroarthritis. Another double-blind, placebo-controlled study included 32 patients with *Chlamydia*-triggered ReA that had lasted for at least 6 months. They were treated with doxycycline either for 2 weeks or 4 months. Four of 15 patients who received the drug for 2 weeks went into remission. This seems to show that long-term therapy is not necessary for ReA. In another study, two patients with chronic ReA who had received intensive and prolonged antibacterial treatment were shown to still have chlamydial RNA and DNA in their joint tissue, demonstrating how difficult its eradication from the joints may be.

More recently, several studies have reported that long-term treatment of ReA with ciprofloxacin is not effective; however, it might be useful in the subgroup of patients who have *Chlamydia*-induced arthritis [59]. This has to be proven in a larger study focusing on patients with *Chlamydia*-induced arthritis.

In another study, 18 patients with *Yersinia*-triggered ReA were double blind randomly allocated to receive treatment with ciprofloxacin 500 mg twice daily orally or placebo during 3 months. The diagnosis was made by serology [specific IgA and IgG antibodies to *Yersinia* outer membrane proteins (yops)], positive culture, and/or demonstration of *Y enterocolitica* antigen in colon biopsy specimens. Patients were evaluated monthly during and after treatment for up to 12 months. There was a tendency towards faster remission and pain relief in those receiving ciprofloxacin. Patients receiving placebo had more and prolonged circulating IgA antibodies against yops than patients treated with ciprofloxacin [120].

In conclusion, at the present time, the addition of prolonged courses of antibiotics to eradicate microbial organisms from the joint cannot be recommended generally for ReA. It remains to be established whether long-term treatment has a definite effect on the course or prognosis of the disease. However, some evidence suggests benefit from antibacterial therapy has been obtained for uroarthritis. It is obvious that more studies are needed to clarify this point.

Short-term treatment

No difference has been observed in short-term treatment with antibiotics in patients with enteric ReA. Basically, treatment after enteric infection is usually with NSAIDs and occasional intra-articular injections of depot corticosteroids.

There is one report that showed some benefit from a 3-month course of lymecycline in *Chlamydia*-associated ReA but no response to the same regimen in patients with enteric infection. Three months of treatment with doxycycline did not improve pain or functional status in patients with chronic reactive or seronegative arthritis. Of 60 patients randomly allocated to receive doxycycline or placebo, results from 37 were evaluable at 3 months. Doxycycline had no detectable effect at three months on pain change scores (mean difference 1.5; 95% CI -1.2 to 4.2, $P = 0.25$) or composite functional change scores (mean

difference 0.8; 95% CI -5.6 to 7.1 , $P = 0.81$). One study suggested that treating patients with *Chlamydia*-associated ReA with a 3-month course of lincycline reduced disease severity and significantly shortened disease duration [76].

In summary, a short conventional course of antibacterials may eradicate the triggering infection in the majority of patients and it appears to be effective in preventing the development of ReA, if given early enough. In an established arthritis, no definite effect has been proven.

In conclusion, antibiotic treatment may not be effective, probably because the triggering bacteria are already dead or in a partly latent state at the time the arthritis occurs. Based on this knowledge and on new technologies, it should be possible to develop more appropriate therapeutic interventions in future years.

Prognosis

In some studies, 10% to 20% of patients with Reiter's syndrome (RS) and ReA were found to have persistent disease 2 years after the onset of symptoms [32,33,51,78]. Chronic disease occurs in a small minority of patients with community-acquired disease but in as many as 52% in hospital practice. For improved follow-up of ReA patients, proposed an index score for disease activity has been proposed [113]. It included number of swollen joints, number of tender joints, patient's pain and global assessments, and C-reactive protein (CRP) (mg/dl). This index could be helpful in making a therapeutic decision for some patients.

Prognosis is generally better after enteric infections than after sexually acquired disease. The possibility has been raised that re-infection is more common in the latter. Despite the initial complete resolution noted in at least 80% of post-enteric cases, some post-*Salmonella* arthritis may become chronic or recurrent.

Despite being a more chronic arthritis than many had initially expected, some patients get no joint destruction. Joint-space narrowing and erosions do occur and may be seen more easily in the small joints and in the sacroiliac joints than in the knees.

The first oligoarticular episode subsides in 3 to 6 months, during which time symptomatic therapy is generally required. Seventy-five percent of the patients are in complete remission at the end of the second year after onset. One percent of ReA patients, particularly those with keratoderma blennorrhagica lesions, may have a very severe and even fatal outcome.

At long-term, relapses begin 3 to 4 years after the first episode and can consist of recurrence of peripheral arthritis or enthesopathic pain of pelvi-axial symptoms, or of iritis or other extra-articular symptoms. These symptoms can be isolated or associated. Radiographic changes may now be observed. Narrowing of joint spaces and erosions are very uncommon except when arthritis is associated with psoriatic lesions. The frequency of sacroilitis increases with time. It is observed in 37% of patients followed for 15 years or more and is associated with axial lesions of ankylosing spondylitis in 15% of the cases. When the sum of these factors (hip

arthritis, erythrocyte sedimentation rate (ESR) > 30, poor efficacy of NSAIDs, limitation of lumbar axis, sausage-like finger or toe, oligoarthritis, onset \leq 16 years) at entry is three or less, a benign outcome could be predicted with a sensitivity of 92% and a specificity of 78%. Hip joint involvement, a permanently increased ESR (>30 mm/hr), and unresponsiveness to NSAIDs, however, are risk factors for bad prognosis [9,10].

One might wonder, in view of the high prevalence of *Borrelia burgdorferi* infections in Central Europe, whether or not this spirochete rheumatism was one of the first reports of Lyme arthritis [100,111,123]. Identical observations have been made in other situations quite closely related to ReA. *Propionibacterium acnes*, a microbe implicated in inflammatory outbreaks of acne, was recently identified in articular samples from SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis) patients, suggesting an infectious origin of this syndrome often regarded as a form of spondyloarthropathy [109]. *Mycobacterium bovis*, used in BCG (Bacille Calmette-Guérin) treatment, is known to cause presumably aseptic oligoarthritis and polyarthritis [26,105] and bacterial DNA has also been detected in synovial fluid from patients with arthropathy triggered by intravesical injection of BCG (Schaefferbeke et al 1999) [110].

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