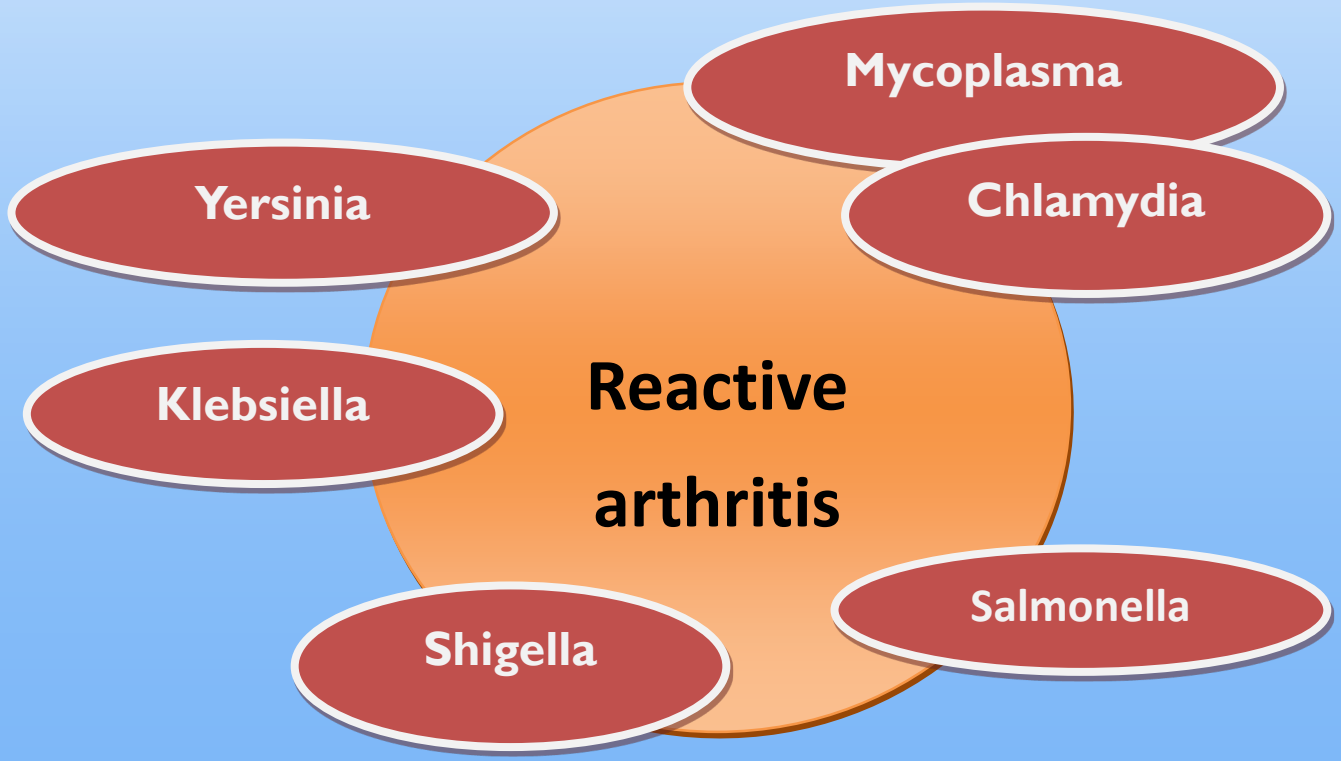
Reactive arthritis

- Reactive arthritis (ReA), also known as Reiter syndrome, is an autoimmune condition that develops in response to an infection.
- In 1916, Hans Reiter described the triad of nongonococcal urethritis, conjunctivitis, and arthritis in a young German officer with bloody dysentery.
- In 1916, Fiessinger and Leroy described 4 patients with what they called oculo-urethro-synovial syndrome and associated the syndrome with an outbreak of *Shigella* dysentery.

- Reactive arthritis has been associated with gastrointestinal infections with *Shigella,Salmonella,* and *Campylobacter* species and other microorganisms, as well as with genitourinary infections (especially with *Chlamydia trachomatis*).



Chlamydia trachomatis, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum,
Salmonella enteritidis, Salmonella typhimurium, Shigella flexneri, Shigella dysenteriae, Campylobacter jejuni,Yersinia enterocolitica, Clostridia difficile

Epidemiology

- Data on the incidence and prevalence of reactive arthritis are scarce, partly because of a lack of a disease definition and diagnosis criteria; these factors complicate differentiation of reactive arthritis from other arthritides.
- The reported annual incidence of reactive arthritis is approximately 30-40 cases per 100,000 adults, with a prevalence of 1%-7%, but this varies greatly among different geographic locations.
- Reports from Latin America, North Africa, India, and Thailand showed low prevalence, with minimal differences between countries.
- As with other spondyloarthropathies, HLA-B27 and reactive arthritis are more common in white people than in black people.
- Reactive arthritis following foodborne enteric infections is equally common in males and females. The male-to-female ratio of disease associated with venereally acquired infections is 9:1.
- Most patients with reactive arthritis are aged 20-40 years.

Pathophysiology

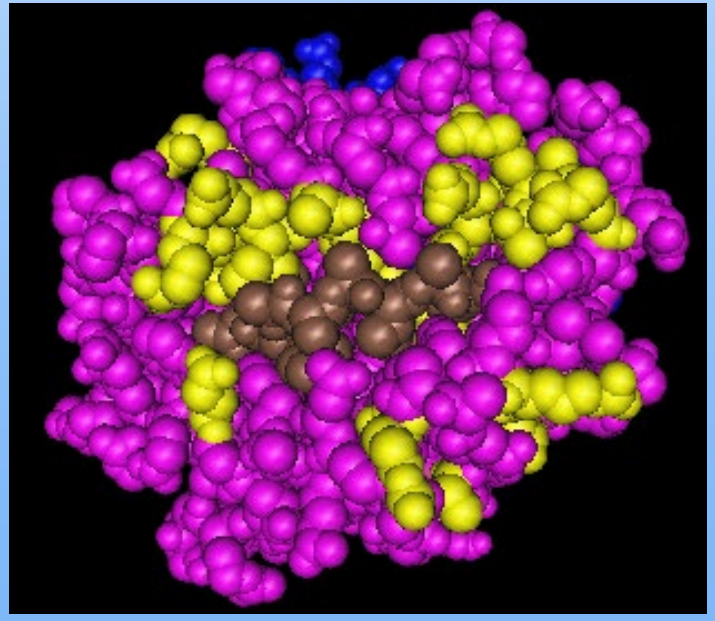
- Reactive arthritis usually develops 2-6 weeks after a genitourinary or gastrointestinal infection.
- Recent evidence indicates that a preceding *Chlamydia* respiratory infection may also trigger reactive arthritis.
- About 10% of patients do not have a preceding symptomatic infection.

Pathophysiology

- Inflammation of joints, entheses, axial skeleton, skin, mucous membranes, gastrointestinal tract, and eyes may occur.
- Results for HLA-B27 are positive in 65%-96% of patients (average, 75%) with reactive arthritis.
- The likelihood of developing reactive arthritis is increased 50-fold in patients who are HLA-B27–positive, but this syndrome can also occur in patients who are HLA-B27 negative.

Pathophysiology

HLA-B27

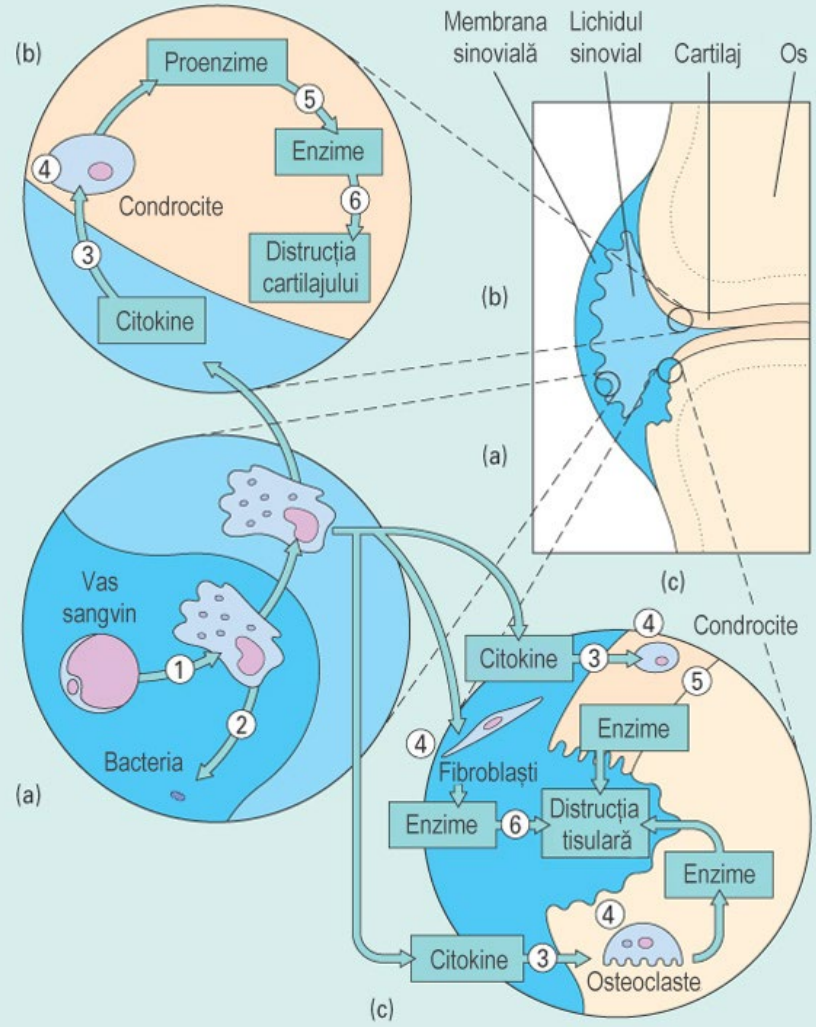


- Patients with HLA-B27, as well as those with a strong family clustering of the disease, tend to develop more severe and long-term disease.
- The frequency of reactive arthritis after enteric infection averages 1%-4% but varies greatly, even among outbreaks of the same organism.

Pathophysiology

- The mechanism of the interaction of the inciting organism with the host (often HLA-B27–positive) leading to the development of reactive arthritis is not known.
- It is unclear if microbial antigens cross-react with self-proteins, stimulating (molecular mimicry) and perpetuating a Th2-cell–mediated autoimmune response.
- Chronicity and joint damage have been associated with a Th2 cytokine profile that leads to decreased bacterial clearance.
- **Synovial fluid cultures are negative** for enteric organisms or *Chlamydia* species. However, a systemic and intrasynovial immune response to the organisms has been found with intra-articular antibody and bacterial reactive T cells. Furthermore, bacterial antigen has been found in the joints. Thus, the elements for an immune-mediated synovitis are present.

Pathophysiology



- Molecular evidence of bacterial DNA (by polymerase chain reaction [PCR]) in synovial fluids has been found only in *Chlamydia* -related reactive arthritis.
- This suggests that persistent infection may play a role, at least in some cases of chlamydial reactive arthritis.
- The role of HLA-B27 in this scenario remains to be defined but, as discussed elsewhere (Ankylosing Spondylitis and Undifferentiated Spondyloarthropathies), molecular mimicry, presentation of pathogenic peptides, and an altered host response to the bacteria are all possible.

Pathophysiology

- Reactive arthritis, including classic Reiter syndrome, can occur in patients infected with HIV or who have AIDS.
- This is likely because both conditions can be sexually acquired rather than being triggered by HIV.
- The course of reactive arthritis in these patients tends to be severe, with a generalized rash that resembles psoriasis, profound arthritis, and frank AIDS.
- The frequency of HLA-B27 is the same of that associated with non–AIDS-related reactive arthritis in a similar demographic group.
- This association points out the likely importance of CD8+ cytotoxic T cells compared to CD4+ helper T cells in the pathogenesis of reactive arthritis.

Classification

- Reactive arthritis belongs to seronegative spondiloarthritis, with two major forms:
  - uro-genital form;
  - entero-colitis form.
- After onset of illness:
  - Acute <6 months;
  - Trenant (dragged on) 6-12 months,
  - Chronic> 12 months;

Clinical manifestations

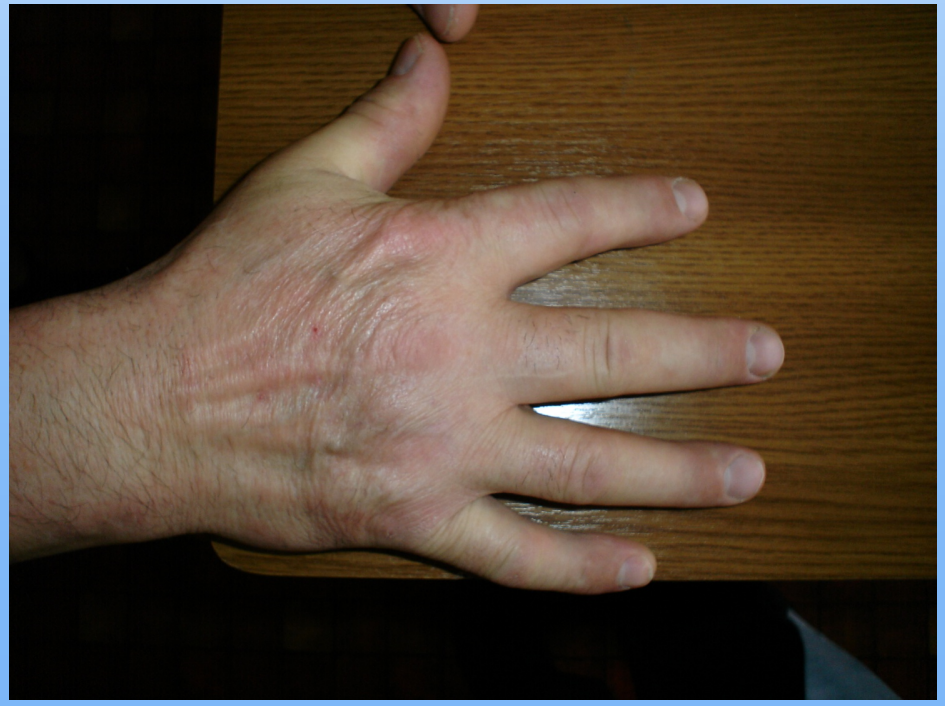
- Reactive arthritis usually develops 2-4 weeks after a genitourinary or gastrointestinal infection.
- About 10% of patients do not have a preceding symptomatic infection.
- Both postvenereal and postenteric forms of reactive arthritis may manifest initially as nongonococcal urethritis.
- Mild dysuria, mucopurulent discharge, prostatitis and epididymitis in men, and vaginal discharge and/or cervicitis in women are other possible manifestations.

Clinical manifestations

- The onset of reactive arthritis is usually acute and characterized by malaise, fatigue, and fever.
- An asymmetrical, predominately lower-extremity, oligoarthritis is the major presenting symptom.
- Low-back pain occurs in 50% of patients.
- Heel pain is common because of enthesopathies at the Achilles or plantar aponeurosis insertion on the calcaneus.
- The complete Reiter triad of urethritis, conjunctivitis, and arthritis may occur.

Clinical manifestations

- Joints, axial skeleton, entheses
  - Peripheral joint involvement associated with reactive arthritis is typically asymmetric and usually affects the weight-bearing joints (ie, knees, ankles, hips), but the shoulders, wrists, and elbows may also be affected.
  - In more chronic and severe cases, the small joints of the hands and feet may also be involved. As in other spondyloarthropathies, dactylitis (ie, sausage digits) may develop.

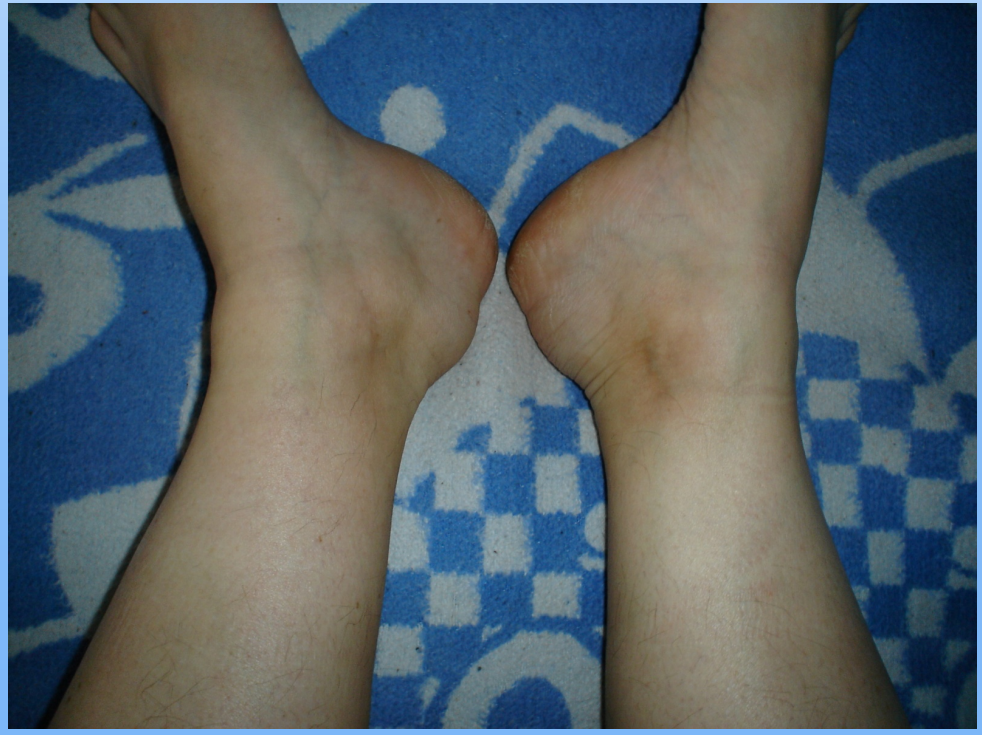


Clinical manifestations

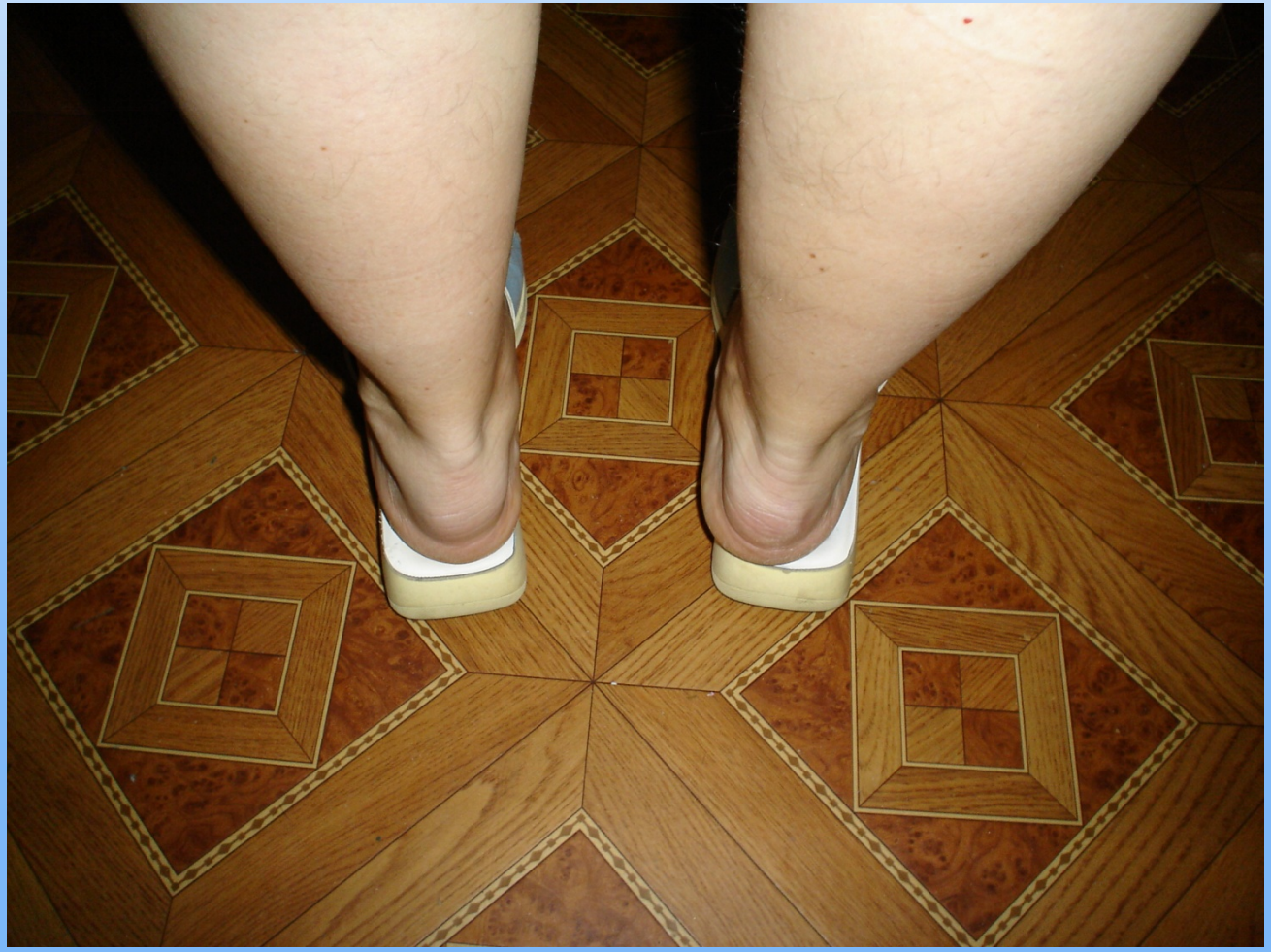
- Joints, axial skeleton, entheses
  - While 50% of patients with reactive arthritis may develop low-back pain, most physical examination findings in patients with acute disease are minimal except for decreased lumbar flexion.
  - Patients with more chronic and severe axial disease may develop physical findings similar to ankylosing spondylitis.

Clinical manifestations

- Joints, axial skeleton, entheses
  - As with other spondyloarthropathies, the enthesopathy of reactive arthritis may be associated with findings of inflammation (ie, pain, tenderness, swelling) at the Achilles insertion. Other sites include the plantar fascial insertion on the calcaneus, ischial tuberosities, iliac crests, tibial tuberosities, and ribs.

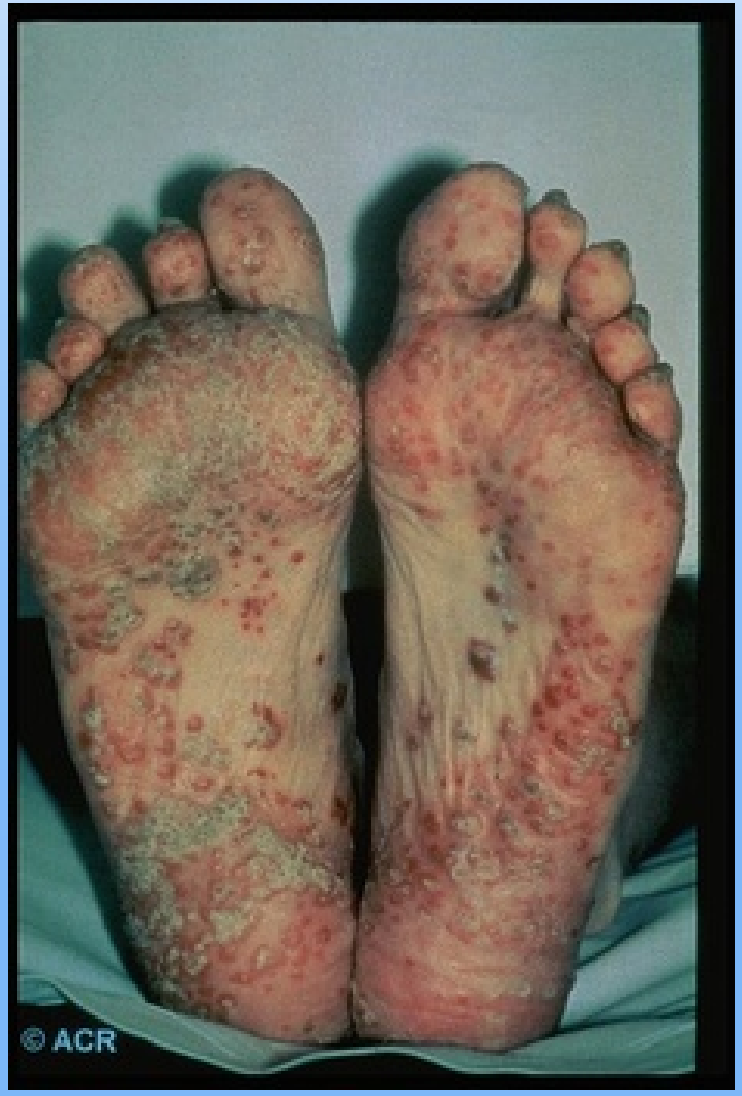


Clinical manifestations



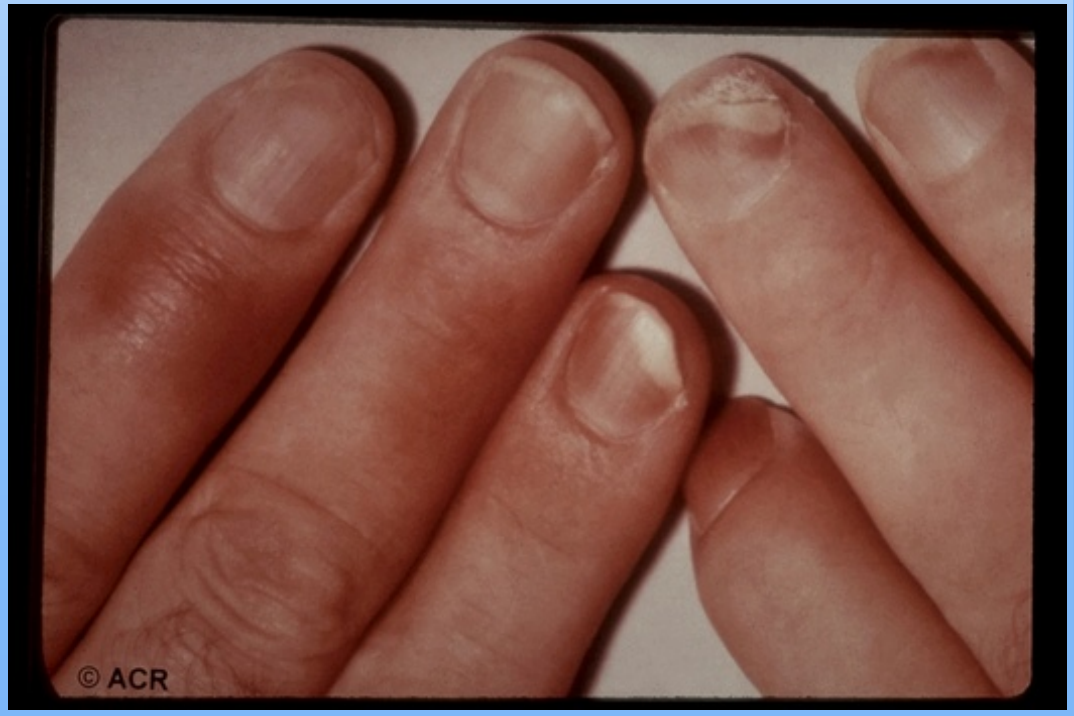
Clinical manifestations

- Skin and nails
  - Keratoderma blennorrhagica on the palms and soles is indistinguishable from pustular psoriasis and is highly suggestive of chronic reactive arthritis.



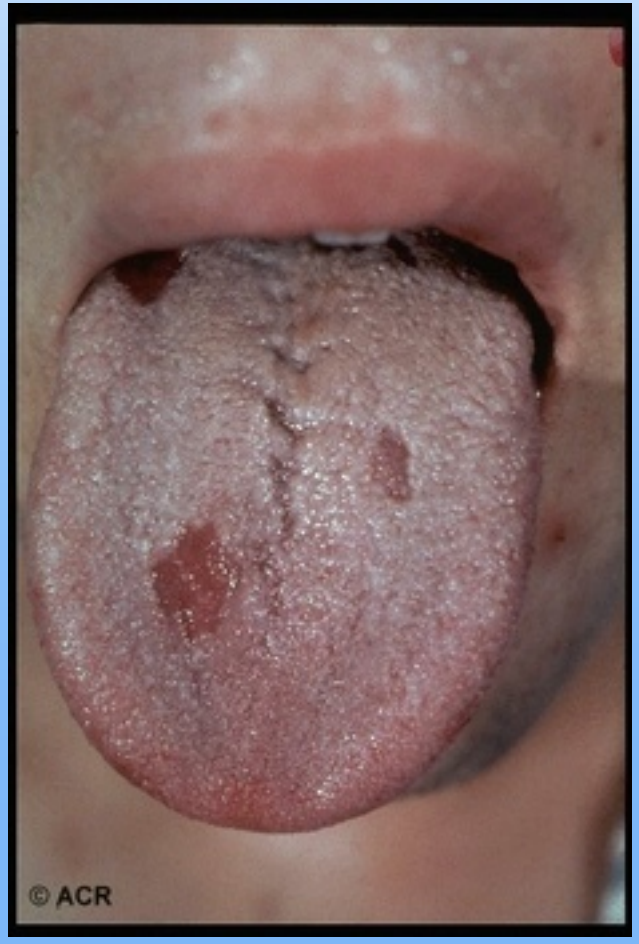
Clinical manifestations

- Skin and nails
  - Erythema nodosum may develop but is uncommon.
  - Nails can become thickened and crumble, resembling mycotic infection or psoriatic onychodystrophy, but nail pitting is not observed.
  - Circinate balanitis may also develop.



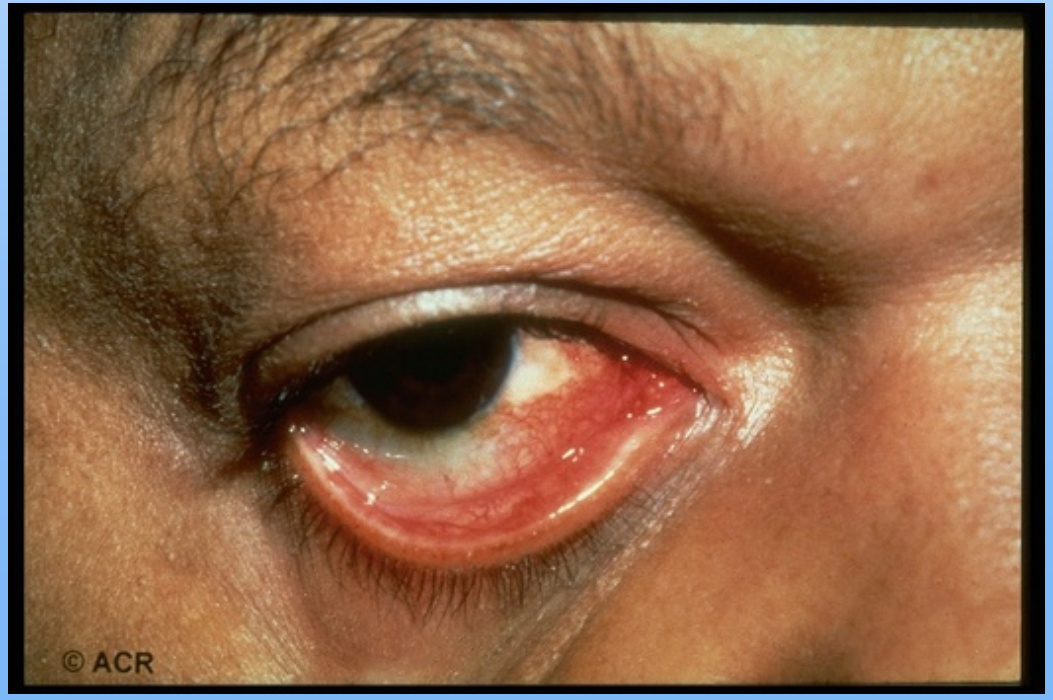
Clinical manifestations

- Other mucosal signs and symptoms: Painless shiny patches in the palate, tongue, and mucosa of the cheeks and lips have been described.



Clinical manifestations

- Ocular findings
  - Conjunctivitis is part of the classic triad of Reiter syndrome and can occur before or at the onset of arthritis.
  - Other ocular lesions include acute uveitis (20% of patients), episcleritis, keratitis, and corneal ulcerations. The lesions tend to recur.



Clinical manifestations

- Enteric infections
  - Enteric infections may trigger reactive arthritis.
  - Pathogens include *Salmonella, Shigella, Yersinia,* and *Campylobacter* species.
  - The frequency of reactive arthritis after these enteric infections is about 1%-4%.
  - Other enteric bacteria that have been associated with reactive arthritis include *Clostridium difficile*, *Escherichia coli,* and *Helicobacter pylori.*
  - Some patients with reactive arthritis continue with intermittent bouts of diarrhea and abdominal pain. Lesions resembling ulcerative colitis or Crohn disease have been described when ileocolonoscopy is performed in patients with established reactive arthritis.

Clinical manifestations

- Other manifestations
  - Other manifestations of reactive arthritis include mild renal pathology with proteinuria and microhematuria.
  - In severe chronic cases, amyloid deposits and immunoglobulin A (IgA) nephropathy have been reported.
  - Cardiac conduction abnormalities may develop, and aortitis with aortic regurgitation occurs in 1%-2% of reactive arthritis cases.

Laboratory Studies

- The values of acute-phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually elevated markedly but later return to the reference range when the inflammation subsides.
- Other laboratory findings include a normocytic normochromic anemia along with mild leukocytosis and thrombocytosis during the acute phase.
- IgA antibodies to specific bacterial antigens have been reported.
- Urinalysis may reveal aseptic pyuria.

Laboratory Studies

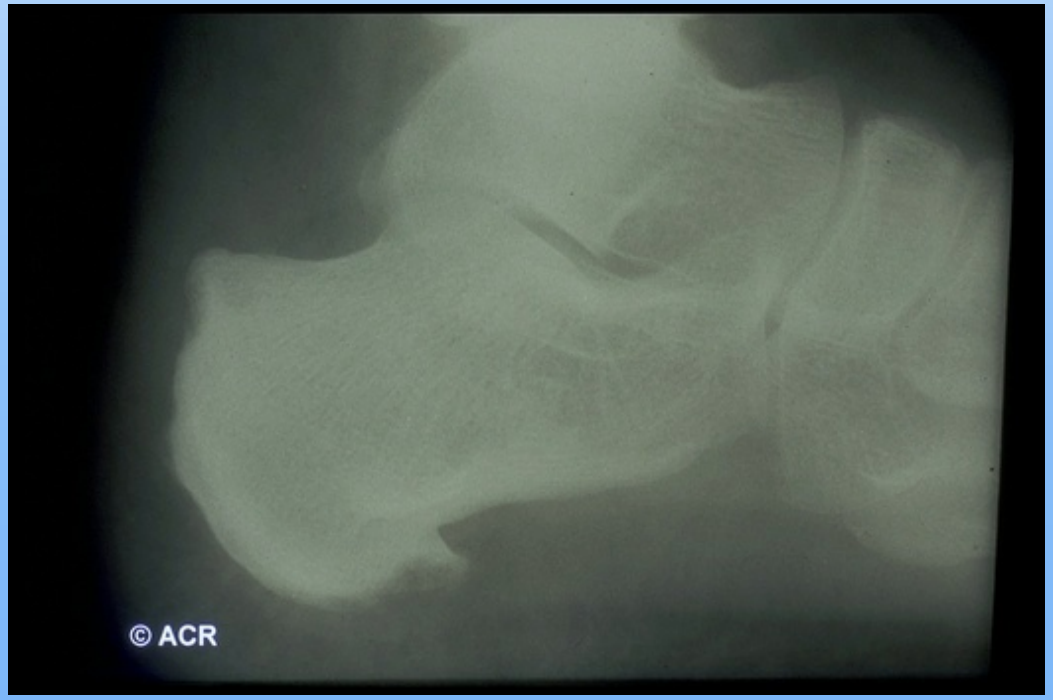
- Synovial fluid analysis reveals a high WBC count, most often with elevated polymorphonuclear leukocytes acutely.
- Gram stain and culture results are negative and are necessary to exclude septic arthritis.
- Microbial components and antigens have been identified in joint fluid using sophisticated laboratory techniques.

Laboratory Studies

- Throat, stool, or urogenital tract cultures can be performed in an attempt to isolate the causative organism.
- Other serologic techniques for the detection of *Chlamydia* species, including PCR, may be considered.
- Test results for rheumatoid factor and antinuclear antibodies are negative.

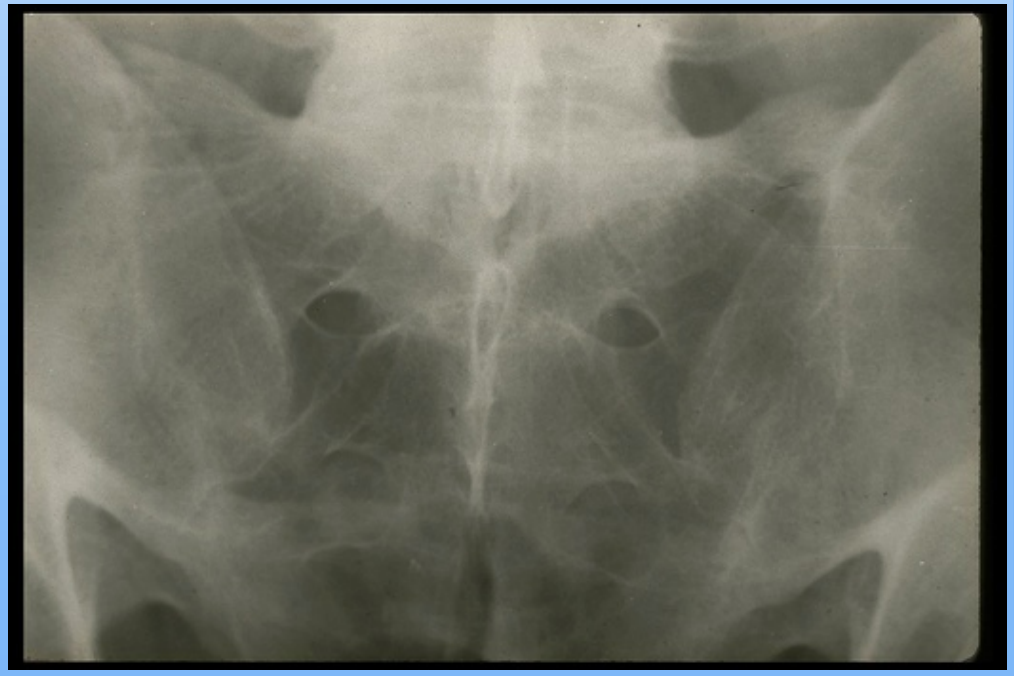
Imaging Studies

- Radiography
  - Early in the disease process, radiography reveals no abnormalities.
  - In more advanced or long-term reactive arthritis, periosteal reaction and proliferation at sites of tendon insertion are visible.
  - Exuberant plantar spurs are a common sign in long-term reactive arthritis.



Imaging Studies

- Radiography
  - In the hands and feet, marginal erosions with adjacent bone proliferation occur.
  - Spinal radiographic findings include sacroiliitis and syndesmophytes. Sacroiliitis occurs in less than 10% of acute cases but develops in half of patients with chronic severe disease.
  - Syndesmophytes are usually asymmetrical and are found most commonly in the thoracolumbar region.
  - Severe ankylosing spondylitis occurs in less than 5% of cases.



Imaging Studies

- MRI: MRI of the sacroiliac joints may reveal disease earlier than conventional radiography.

Other Tests

- ECG should be performed in patients with a prolonged course of reactive arthritis to evaluate for conduction disturbances.
- HLA-B27 testing results are positive in 65%-96% of cases. HLA-B27 testing is not necessary in classic Reiter syndrome but may be helpful to support the diagnosis of reactive arthritis in patients with joint-restricted symptoms.
- Needle aspiration of a joint may be necessary to rule out septic or crystal-induced arthritis.

Criteria of Amor et al for Spondylarthropathy

- Amor et al developed a scoring system for the diagnosis of spondylarthropathy based on clinical, radiologic, genetic and therapeutic criteria. The authors are from Paris, France.
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- Parameters (12 items):
- (1) clinical symptoms, current or past history of: 9 items
- (2) radiological findings: 1 item
- (3) genetic background: 1 item
- (4) response to treatment: 1 item

Criteria of Amor et al for Spondylarthropathy

Parameter	Finding	Points
lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal pain	present	1
	absent	0
asymmetrical oligoarthritis	present	2
	absent	0
buttock pain	none	0
	present	1
	alternating between left and right sides	2
sausage-like toe or digit	present	2
	absent	0
heel pain or other well-defined enthesiopathic pain	present	2
	absent	0
iritis	present	2
	absent	0

Criteria of Amor et al for Spondylarthropathy

Parameter	Finding	Points
non-gonococcal urethritis or cervicitis within 1 month before the onset of arthritis	present	1
	absent	0
history of acute diarrhea within 1 month before the onset of arthritis	present	1
	absent	0
psoriasis, balanitis, or inflammatory bowel disease (ulcerative colitis or Crohn's disease)	present	2
	absent	0
sacroiliitis	bilateral >= 2	2
	unilateral >= 3	2
	other	0

Criteria of Amor et al for Spondylarthropathy

Parameter	Finding	Points
genetic background	HLA-B27	2
	family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis or inflammatory bowel disease	2
	neither	0
response to NSAID intake	clear-cut improvement within 48 hours	2
	rapid relapse on discontinuation	2
	neither	0

score = SUM(points for all 12 parameters)

Interpretation: minimum score: 0 maximum score: 21
A score >= 6 indicates that the patient has a spondylarthropathy.

Criteria of Sieper and Braun for Reactive Arthritis

Features of reactive arthritis - all of the following:

- (1) asymmetrical arthritis
- (2) predominantly of the lower limbs
- (3) evidence of a preceding infection - one or more of the following:
  - (3a) diarrhea within the 4 weeks preceding onset
  - (3b) urethritis within the 4 weeks preceding onset
  - (3c) stool culture positive for Salmonella, Shigella, Yersinia
  - (3d) detection of Chlamydia trachomatis
  - (3e) serologic evidence of Salmonella or Shigella infection (antibodies to lipopolysaccharide or specific antigen)
  - (3f) antibodies to Chlamydia trachomatis
  - (3g) detection of chlamydial DNA in a joint by PCR
- (4) exclusion of other rheumatic diseases

Treatment

- The goals of pharmacotherapy are
  - to reduce morbidity,
  - to prevent joint damage, and
  - to alleviate extra-articular disease.

Treatment

- **Antibiotics**
  - The current concepts on the pathogenesis of reactive arthritis indicate that an infectious agent is the trigger of the disease, but antibiotic treatment does not change the course of the disease, even when a microorganism is isolated.
  - In these cases, antibiotics are used to treat the underlying infection, but specific treatment guidelines for reactive arthritis are lacking.
  - However, in chlamydia-induced reactive arthritis, studies have suggested that the appropriate treatment of the acute urogenital infection can prevent reactive arthritis and that treatment of acute reactive arthritis with a 3-month course of tetracycline reduces the duration of illness.

Treatment

- **Tetracycline group**
  - Doxycycline - 200 mg / day
- **Macrolide group:**
  - Clarithromycin - 1 g / day
  - Azithromycin - 500 mg - first day, after THEN 250 mg / day - 6 days
  - Roxithromycin - 300 mg / day
- **Quinolones:**
  - Ciprofloxacin – I g/ day
  - Ofloxacin – 400 mg/ day
  - Lomefloxacin – 400 mg/ day
  - Perfloxacin – 800 mg/ day

Treatment

- **Nonsteroidal anti-inflammatory drugs**
  - NSAIDs are the foundation of therapy. These agents should be used regularly to achieve a good anti-inflammatory effect.
  - The choice of a specific agent depends on the individual response to treatment.
- Diclofenac (75-150 mg) or
- Meloxicam (7,5-15 mg) or
- Nimesulid (100-200 mg) or
- Ibuprofen (800 – 1600 mg) or
- Flurbiprofen (100 – 200 mg)

Treatment

- **Corticosteroids**
  - These agents can be used as either intra-articular injection or systemic therapy.
  - Joint injections can produce long-lasting symptomatic improvement and help avoid the use of other systemic therapy. Sacroiliac joints can be injected, usually under fluoroscopic guidance.
  - Systemic corticosteroids can be used, particularly in patients in whom NSAIDs elicit a poor response or in those who develop adverse effects related to their use.
  - The starting dose is guided by a patient's symptoms and objective evidence of inflammation.
  - Prednisone 0.5-1 mg/kg/d can be used initially and tapered according to response.

Treatment

- **Disease-modifying antirheumatic drugs**
  - In patients with chronic symptoms or in patients with persistent inflammation despite the use of the agents mentioned above, other second-line drugs may be used.
  - Clinical experience with these so-called disease-modifying antirheumatic drugs (DMARDs) has been mostly in rheumatoid arthritis and in psoriatic arthritis.
  - DMARDs have also been used in reactive arthritis, although their disease-modifying effects in the reactive arthritis setting are uncertain.

Treatment

- **Disease-modifying antirheumatic drugs**
  - Sulfasalazine may be beneficial in some patients.
  - The use of this drug in reactive arthritis is of interest because of the finding of clinical or subclinical inflammation of the bowel in many patients.
  - Sulfasalazine (2-3 gr per day) is widely used in all seronegative spondylitis.

Treatment

- **Disease-modifying antirheumatic drugs**
  - Methotrexate (7.5 – 15.0 mg per week) can be used in patients who present with rheumatoidlike disease.
  - Several reports have shown good response. Reports also describe the use of azathioprine.
  - Patients with reactive arthritis and HIV/AIDS should not receive methotrexate or other immunosuppressive agents.

Treatment

- **Disease-modifying antirheumatic drugs**
  - Although biologic agents such as TNF-blockers have been demonstrated to be beneficial and formally approved for the treatment of psoriatic arthritis and ankylosing spondylitis, double-blind, randomized trials have not been performed to prove clinical benefit in reactive arthritis or in undifferentiated spondyloarthropathy.
  - Case reports using the chimeric monoclonal antibody infliximab have shown potential efficacy in symptom relief in patients in whom other therapies failed.

Treatment

- Physical therapy may be instituted to avoid muscle wasting and to reduce pain.
- Activities should otherwise be as tolerated by the patient.

Prognosis

- Reactive arthritis typically follows a self-limited course, with resolution of symptoms by 3-12 months, even in patients who are acutely incapacitated.
- However, reactive arthritis has a high tendency to recur, particularly with ocular and urogenital inflammation.
- Individuals who are HLA-B27–positive are at a higher risk of recurrence.
- A new infection or other stress factor could cause reactivation of the disease.

Prognosis

- About 15% of patients with reactive arthritis develop a long-term, sometimes destructive, arthritis or enthesitis or spondylitis. In a study by Amor et al (1994), 7 factors were analyzed as predictors of long-term outcome in spondyloarthropathies.
- The number of patients with reactive arthritis in this study was low, and a valid subgroup analysis was impossible.
- The presence of hip-joint involvement, an erythrocyte sedimentation rate (ESR) higher than 30, and unresponsiveness to nonsteroidal anti-inflammatory drugs (NSAIDs) probably portend a severe outcome or chronicity in reactive arthritis.