

Reactive arthritis*

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KEY WORDS

infection-related
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ABSTRACT

Reactive arthritis (ReA) is a non-purulent joint inflammation that usually follows bacterial gastrointestinal or urogenital infections. The classic presentation of ReA is characterized by an asymmetric arthritis usually in the lower limbs associated with urethritis, conjunctivitis and occurrence of other articular or extra-articular manifestations. ReA is classified as a type of seronegative spondyloarthropathy. Approximately 65–85% of patients with ReA are HLA-B27 positive. Regardless of the preceding infection, the clinical picture is similar, but management can differ according to the triggering infection. Treatment of Chlamydia-induced ReA should be started with antibiotics because of several mechanisms by which Chlamydia can cause persistent infection. The disease may have an acute or self-limited course, however some patients develop chronic arthritis.

INTRODUCTION In the 4th century B.C. Hippocrates was probably the first who mentioned reactive arthritis (ReA) when he noted that “Young men do not suffer from gout until they initiated sexual activity” (gout was a synonym of acute arthritis at that time).¹ In 1916, 2 independent scientists from France, Fiessinger and Leroy, and Hans Conrad Reiter from Germany described the “oculo-urethro-synovial” syndrome, which was termed Reiter’s syndrome.

Because of ethical controversies around Reiter’s experiments on concentration camp prisoners the term was phased out. The Spondylitic Association of America introduced the term “reactive arthritis” instead of “Reiter’s syndrome”.²

Because of disagreements regarding the classification criteria of ReA, in 1999, at the 4th International Workshop on Reactive Arthritis scientists agreed that the term “reactive arthritis” should be only used in HLA-B27 positive patients with infection-related arthritis, who fulfill the criteria for seronegative spondyloarthropathy. Other types of arthritis triggered by infection, for example Lyme disease and rheumatic fever, are named infection-related arthritis.

Epidemiology The worldwide incidence of ReA is approximately 30 to 200 cases per a 100,000 population, but this varies greatly among different geographic locations.³ ReA usually affects young people aged 20–40 years with almost the same frequency among males and females. Men are 15

times more likely to develop symptoms of Reiter’s disease than women. The frequency of ReA after infection with potentially causative agents is on average 1–4%.

Etiology and pathophysiology Several factors contribute to the development of ReA, including:

- 1 the presence of bacteria or bacterial products in the joint and the local immune response directed against these bacteria
- 2 the effect of the arthritogenic peptides derived from ReA – triggering bacteria (*Salmonella* and *Yersinia*), which epitopes are presented by fagocytes to cytotoxic T lymphocytes in synovial membrane
- 3 recognition of bacterial antigens outside the cells, and forming complexes with class I human leukocyte antigens (HLA) and class II histocompatibility antigen (MHC II) presented on CD4 + and CD8 + T cells in *Chlamydia* infection
- 4 tendency to persistent bacterial infections and imbalance between tumor necrosis factor α (TNF- α), interferon- γ , IL-12, IL-10- activity (increased IL-10 levels in the intestines, urogenital and respiratory system in patients with persistent infections).

Genetic factors also play an important role in the etiology of ReA. The HLA-B27 antigen is found in 65–80% of patients with ReA. The *Shigella* infection HLA-B27 antigen is presented in 80–90% of cases, in 79–80% after *Yersinia* ReA,

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TABLE 1 Clinical manifestations of reactive arthritis and their frequency.

Clinical manifestation	Symptoms (frequency [%])
Peripheral arthritis syndrome	Large, lower limb nondestructive acute asymmetric oligoarthritis Chronic-recurrent arthritis (15–30%) Sausage digit (16%)
Enthesopathic syndrome	Heel pain, Achilles tendonitis, pain at the tibial tubercle (30%)
Pelvic and axial syndrome	Inflammatory low back pain: sacroiliitis (14–49%), spondylitis (12–26%), inflammation of ligamentous or tendinous insertions in the ischial tuberosity (15–30%)
Extramusculoskeletal syndrome	Eye: conjunctivitis (35%), iritis (5%), keratitis, episcleritis Genitourinary: urethritis, prostatitis (80%), hemorrhagic cystitis, cervicitis Gastrointestinal: diarrhea, endoscopic “bowel lesions” (25–70%) Skin: keratoderma blennorrhagica (5–30%), circinate balanitis (4–20%), oral ulcers (5–10%), hyperkeratosis nails (6–12%), erythema nodosum Cardiovascular system: aortic disease, EKG conduction abnormalities (5–14%) Renal: proteinuria, microhematuria, aseptic pyuria

in 40–50% after *Salmonella* and in 40–50% of patients after *Chlamydia* ReA.⁴

The most common causative organisms in ReA are:

1 Gram-negative bacilli members of *Enterobacteriaceae*, i.e. *Salmonella*, *Yersinia*, *Campylobacter*, *Shigella*;

2 *Chlamydiae*:

A *Chlamydia trachomatis* (accounted for 35–70% of cases with Sexually Acquired Reactive Arthritis (SARA);

B *Chlamydia pneumoniae*.⁵

3 Other (less common):

A *Clostridium difficile*;

B *Vibrio parahaemolyticus*;

C *Mycobacterium bovis* – Bacillus Calmette-Guérin vaccine germ;

D Species of *Mycoplasma* (e.g. *Ureoplasma urealyticum*);

E *Mycobacterium tuberculosis* (Poncet’s disease) – considered as ReA by some authors.

The key role in pathogenesis of ReA plays the presence of bacteria and their products in the joints and the local immune response directed against these bacteria.

Clinical manifestations of ReA ReA not only affects the joints, but is also a systemic disease with extra-articular symptoms. The clinical picture is dominated by syndromes of enthesitis (enthesopathies), peripheral arthritis (acute or subacute oligoarthritis mainly of the lower limb joints), pelvic and axial syndromes (spinal involvement with sacroiliitis) and extramusculoskeletal syndromes (TABLE 1).

Articular manifestations Arthritis usually affects large joints of lower limbs (without erosions). In *Chlamydia*-associated arthritis, knees are involved in 70%, ankles in 57%, toes in 35%, and wrists and fingers can be involved in as many as 45% of patients.⁶

The average duration of arthritis is 4 to 5 months, but ⅓ of patients have mild musculoskeletal symptoms that persist for more than 1 year. Recurrent attacks are more common in patients

with *Chlamydia*-induced ReA. Approximately 15–30% of patients develop chronic or recurrent peripheral arthritis, sacroiliitis and/or spondylitis. Most of these patients have a positive family history of spondyloarthropathy or are positive for HLA-B27.⁷ “Sausage-like digit” occurs in 16% of cases, but it has a specificity of 99% to that kind of arthritis.⁸ Inflammation of ligaments and tendons at the sites of their attachments to bones (*enthesitis*) is found in approximately 30% of patients with ReA. The heel pain which is typical of ReA has a specificity of 92%. Affection of the cervical spine may result in atlantoaxial subluxation.⁹ Sacroiliitis or spondylitis occur in 50% of ReA patients and result in inflammatory back pain with characteristic stiffness and buttock pain.

Extra-articular manifestations Conjunctivitis occurs in ⅓ of all patients and in the majority of patients with *Shigella*, *Salmonella* and *Campylobacter* infections. In *Chlamydia*-induced ReA it occurs in 35% of patients and only in 10% of cases with *Yersinia* infections. Conjunctivitis usually appears at the same time as flares of arthritis and has a tendency to recur. Acute anterior uveitis is found in about 5% of patients. Keratitis, corneal ulceration, episcleritis, retrobulbar neuritis, and anterior chamber hemorrhage may be present in chronic disease.^{10,11} Urethritis may also occur in ReA after *Enterobacteriaceae* infections and precedes the symptoms of ReA by 1 to 3 weeks. Genitourinary symptoms occur in 70–80% of patients with *Chlamydia* infections. Prostatitis is common and is found in 80% of cases. In women non-purulent cervicitis may occur and cause cervical bleeding with or without accompanying abdominal pain. Gastrointestinal symptoms occur occasionally in ReA triggered by *Yersinia* and are usually mild, unlike in patients with *Salmonella* and *Campylobacter* infections where symptoms are more severe and of longer duration. The time from *Salmonella* infection to arthritis is generally less than 3 weeks. Diarrhea of longer duration in that kind of infection is more likely to cause ReA. Seventy percent of these

patients have macroscopic or microscopic lesions on colonoscopy that resemble ulcerative colitis or Crohn's disease. Gut inflammation is usually subclinical, but with flares of arthritis the activity in the gut increase. After *Chlamydia*-induced ReA similar findings in the gut are found in 25% of cases.¹²

Mucocutaneous lesions are very specific to ReA. Keratoderma blennorrhagica and pustulosis palmo-plantaris occur in 5–30% of patients. Circinate balanitis is found in 20–40% of cases. Mouth erosions located in the hard and soft palate, gingiva, the tongue and cheeks occur in 5–10% of patients. On the skin, psoriatic-like lesions could often be present. Dystrophic nail lesions are found in 6–12% of patients. Erythema nodosum is characteristic only of *Yersinia* infections and occur in 15% of cases.¹³ Cardiac manifestations are usually asymptomatic and are related with aorta involvement (most commonly the ascending aorta). Electrocardiogram abnormalities are recorded in 5–14% of patients, generally those with long-standing disease, and involve conduction disturbances, mainly the first-degree atrioventricular block.¹⁴ Proteinuria, microhematuria and aseptic pyuria are seen in approximately 50% of patients with SARA syndrome.

Additional investigations Laboratory findings

Laboratory abnormalities are nonspecific and include elevated erythrocyte sedimentation rate, C-reactive protein level with mild normocytic anemia, moderate neutrophilia. Urinalysis can detect aseptic pyuria. Antinuclear antibodies and rheumatoid factor are negative.

Microbiological studies

A Enterobacteriaceae infections Microbiological examination of stool samples for the diagnosis of enteric ReA is indicated only for patients with preceding symptomatic enteritis. *Yersinia* and *Salmonella* are detected in the stool only in 9% of patients who had diarrhea in the preceding 4 weeks.¹⁵ The clinical diagnosis of *Enterobacterial* infection is based on serological testing for serum antibodies to these bacteria using the ELISA method. This method has a specificity of 90% in detecting immunoglobulin (Ig) M, IgG and IgA antibodies in *Yersinia* and *Salmonella* infections. In acute *Yersinia*-induced ReA, IgG and IgA antibodies may be simultaneously detected in almost 100% of patients. The persistence of IgA antibodies for 14 to 16 months after onset of *Yersinia* infection is found in 84% of patients and peak levels of IgA correlate with severity of arthritis. In patients without symptoms of arthritis, these antibodies persist for 5 months. The IgG antibodies to *Yersinia* also persist longer in patients with arthritis than in patients without arthritic symptoms, but not so long as IgA antibodies. The antibodies IgM persist for only 1–3 months after infection onset.¹⁶ It is recommended to test for antibodies of IgM, IgG and IgA classes in patients with acute ReA, and for IgG and IgA

classes in patients with chronic ReA. The sensitivity of the ELISA method to detect *Salmonella* infection is about 92%. In patients with *Salmonella*-triggered ReA these antibodies levels tend to persist longer (9–14 months) than in those with enterocolitis (4 months).¹⁷ The IgA antibodies in patients who develop ReA after *Yersinia* enteritis *Yersinia*-triggered ReA do not tend to persist for a long time after infection. Antibody titers for IgG antibodies of 3 standard deviations (SD) above normal, or titers of 2 SD above normal with accompanying symptoms of enteritis are considered positive. No good serologic test is available for the diagnosis of *Shigella* and *Campylobacter* infections.

B Chlamydia infections The diagnosis of *Chlamydia* infections also relies on serology and detection for *Chlamydia*-specific antibodies in serum of patients. The ELISA test or the more sensitive microimmunofluorescence test are both used for diagnostic purposes. It is recommended to identify all classes of antibodies. *Chlamydia* infection is confirmed when levels of IgG, IgM or IgA antibodies are elevated at the same time. Positive IgG titers should be ≥ 64 , or of 2 standard deviations above normal. Antibodies to *Chlamydia* may be found both in serum and in joint fluid samples. The specificity and sensitivity for determination of IgG antibodies in joints is 80%. The specificity reaches 90% with the determination of synovial fluid IgA antibodies.¹⁸ Molecular biology techniques like the polymerase chain reaction (PCR) and the ligase chain reaction are the most sensitive and specific methods for confirming *Chlamydia* infection. The sensitivity and specificity of these methods is approximately 100%.¹⁹ These techniques can be used for detection of *Chlamydia* DNA in urine samples, synovial fluid samples, synovial membrane biopsy specimens and also in peripheral blood monocytes in patients with persistent infection.²⁰ Chlamydial DNA was detected by the PCR in 30% of patients with other spondyloarthropathies, 21% of patients with rheumatoid arthritis, 35% of patients with osteoarthritis and also in some healthy subjects. The above results limit the use of molecular biology tests alone in the diagnosis of ReA.^{21,22}

HLA-B27 testing Overall, routine HLA-B27 testing is not clinically useful, because it is not present in 100% of patients with ReA and other seronegative spondyloarthropathies. In epidemiological studies the frequency of HLA-B27 in *Salmonella*-, *Campylobacter*-, and *Chlamydia*-triggered ReA is not higher than 50%, and 80% in patients with *Shigella*-induced ReA. The antigen HLA-B27 is a useful prognostic marker of ReA. Patients with positive HLA-B27 antigens are more likely to develop chronic or recurrent arthritis, uveitis, aortitis, sacroilitis, and spondylitis.²³

Joint aspiration and synovial tissue examination

Joint fluid (when possible) should always be examined to exclude alternative diagnoses like septic

TABLE 2 Modified ACR criteria for reactive arthritis

Arthritis for longer than 1 month with uveitis or cervicitis
Arthritis for longer than 1 month and other urethritis or cervicitis or bilateral conjunctivitis
Episode of arthritis and conjunctivitis
Episode of arthritis of more than 1 month, urethritis, and conjunctivitis

TABLE 3 Third International Workshop diagnostic criteria for reactive arthritis – 1996

Peripheral arthritis
Predominantly lower limb, asymmetric oligoarthritis
plus
Evidence of preceding infection
Diarrhea or urethritis in the prior 4 weeks
No evidence of infection
Exclusion
Other causes of monoarthritis or oligoarthritis excluded

arthritis, and to find possible causative pathogens of ReA. Synovial fluid analysis is not helpful in diagnosis of ReA. In the early course of the disease synovial fluid cell count is increased, with predominant neutrophils. The presence of so-called Reiter's cells is not specific of ReA. Crystals are not detected. Synovial cultures are always negative. Synovial biopsy shows nonspecific inflammatory changes.

Imaging

A Radiographic findings In the early stage of the disease radiographs are usually unhelpful, because they may be entirely normal. Radiographic changes are found in 70% of patients with long-standing disease (chronic ReA). Erosive joint damage affects especially small joints of the feet and are found in 12% of patients. Radiographic changes of sacroiliac joints, usually unilateral, are found in one-third of patients with chronic ReA.²⁴ In the spine, the disease usually affects thoracic and lumbar parts of vertebral column. Asymmetric paravertebral ossification and syndesmophyte formation of the anterior surface of vertebral bodies is characteristic.

B Other imaging modalities Scintigraphy with ^{99m}Tc is a sensible diagnostic tool for use in screening for enthesopathy in the early stage of the disease. Magnetic resonance imaging is very helpful to assess enthesitis and involvement of sacroiliac joints, when radiographs may be negative. Ultrasonography is a reliable technique to demonstrate soft tissue lesions (e.g. enthesitis, synovitis)

Diagnosis The diagnosis of ReA still remains a problem, because the preceding bacterial infection is often asymptomatic, and identification of the triggering bacterium is difficult at the time when arthritis occurs. No good criteria for the diagnosis of ReA are available. Two sets of diagnostic criteria are currently used, the first established by the American College of Rheumatology (ACR) in 2004 (TABLE 2), and the second

developed at the Third International Workshop on Reactive Arthritis in 1996 (so-called European criteria) (TABLE 3). According to the ACR criteria for the definite diagnosis of ReA, the evidence of peripheral arthritis with urethritis or cervicitis need to be confirmed, but laboratory confirmation is not necessary. According to the European criteria a typical pattern of clinical presentation of spondyloarthropathies plus the evidence of gastrointestinal or urogenital infection in the preceding 4 weeks must be found.^{25,26} These criteria are not precise and need to be revised. The best diagnostic results are focused on both laboratory and clinical settings. The diagnostic approach to *Chlamydia trachomatis*-, *Yersinia*-, and *Salmonella*-induced ReA has also been worked out (FIGURE 1, FIGURE 2).²⁷

Differential diagnosis The following conditions should be considered in the differential diagnosis of ReA:

- 1 other seronegative spondyloarthropathies
- 2 septic arthritis
- 3 infection-related arthritis, e.g. Lyme disease, poststreptococcal arthritis, arthritis due to *Bruce*lla infection, viral arthritis, parasitic arthritis, sexually acquired arthritis (gonococcal, HIV)
- 4 sarcoid arthritis
- 5 Behçet's disease.

Course and prognostic factors A 20-year follow-up of ReA patients showed that the following factors influence the course of the disease: nature of the triggering infection, presence of HLA-B27, gender of patients, presence of recurrent arthritis.²⁸ After 6 years after onset of the disease mild activity of the disease was reported in 83% of patients, 34% of patients had symptoms of chronic ReA, 11% of patients developed long-term disability. The antigen HLA-B27 is much more likely to be detected in patients with persistent arthropathy. Also, the heel pain at the beginning of the disease is an adverse prognostic factor.²⁹

Treatment Treatment of extra-articular manifestations

A Cutaneous and mucosal involvement Carcinat balanitis and psoriatic-like lesions should be treated with topical steroids and keratolytic agents. More severe skin lesions respond well to methotrexate or retinoids.

Carcinate balanitis should be treated for one week with weak steroid in cream, e.g. hydrocortisone. Oral lesions resolve spontaneously and require no treatment.

B Eye involvement Eye lesions, especially uveitis, should be managed with ophthalmologic advise. It is recommended to use topical or intravitreal steroids with mydriatics. In patients who are unresponsive to topical therapy systemic corticosteroids should be administrated.

Treatment of arthritis

A Nonfarmacological treatment and physiotherapy Exercises may help improve joint functions, but

FIGURE 1 Diagnostic algorithm to *Chlamydia*-induced reactive arthritis. The post-test in the case of a positive result (+) is given in parentheses. diagnostic approach to *Chlamydia*-induced reactive arthritis

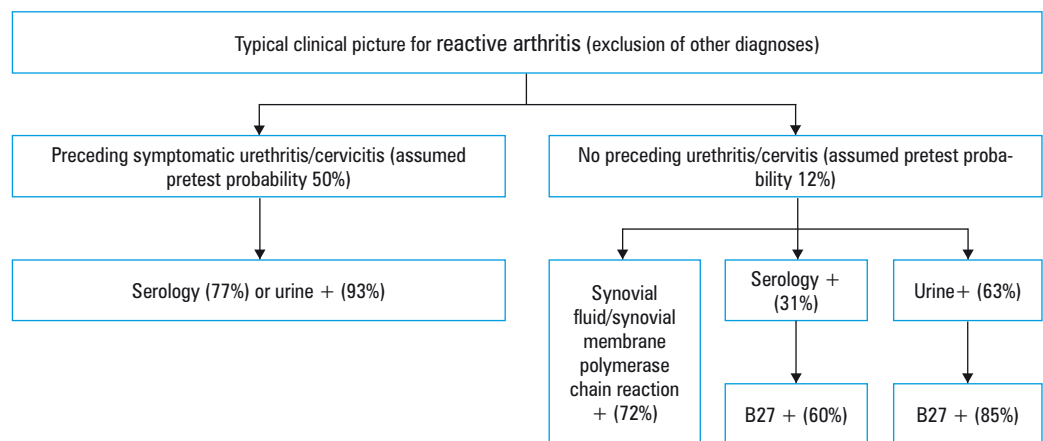
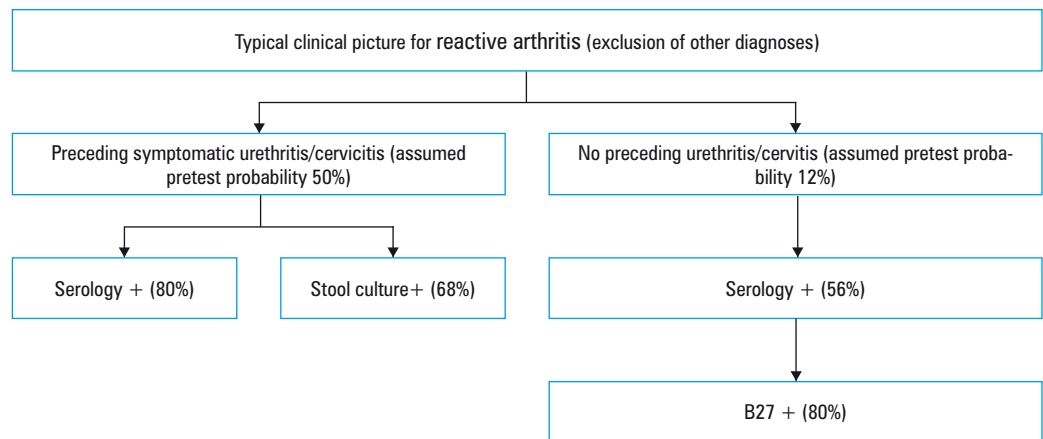


FIGURE 2 Diagnostic algorithm to *Yersinia*- or *Salmonella*-induced reactive arthritis. The post-test in the case of a positive result (+) is given in parentheses. diagnostic approach to *Chlamydia*-induced reactive arthritis



patients should avoid too much exercises, especially of the infected joints. Physiotherapy and kinesiotherapy are an essential component of the treatment.

B Drug treatment **Non-steroidal anti-inflammatory drugs** (NSAIDs) usually provide effective relief of pain (particularly at nights) and morning stiffness. They should be used early, at full doses. The individual response to the different NSAIDs varies, and no individual NSAIDs is recommended.³⁰

Corticosteroids. The systemic use of corticosteroids is not indicated, except for short courses (no more than 2–4 months) in case of severe unresponsive peripheral joint symptoms or progressive atrioventricular conduction abnormalities.³¹

In many cases the use of intra-articular steroid injections (septic arthritis must be excluded before) gives prompt relief, but it should be limited to one joint at every one visit.

Disease modifying antirheumatic drugs (DMARDs). Only 25% of patients respond to NSAIDs therapy. Second-line therapy with DMARDs should be considered for those patients who demonstrate persistent symptoms (more than 3 months), and who have not responded completely to NSAIDs. Sulfasalazine therapy (2 g/day) is effective in treating ReA even for patients with 10 years of disease duration.³² Sulfasalazine is effective mainly in peripheral disease and has little or no effect on spinal disease. Methotrexate can be used with good effects, also

in patients with spinal involvement. It may prevent radiological progression of peripheral-, and spinal-joint destruction.³³ Azathioprine is effective in treating peripheral arthritis when given at a dose of 1 to 2 mg/kg. The efficacy of other DMARDs has not been confirmed in controlled clinical trials.³⁴

Anti-TNF α therapy in ReA remains controversial, and clinical practice is based on a small series of cases. In persistent infection there is also a concern about reactivation of the triggering infection in patients with ReA.³⁵

Antibiotics Antibiotic treatment is indicated only if the infection is well established, and mainly for those with *Chlamydia* infection. However, some studies of small group of patients showed the benefit of using ciprofloxacin in ReA triggered by different kinds of bacteria. A double-blind study with ciprofloxacin (500 mg twice a day for 3 months) in chronic ReA showed a favorable effect on the duration of the arthritis and decreasing morning stiffness during a 6-month follow-up.³⁶ Also another double-blind study with a 3-month course of ciprofloxacin in acute ReA showed improvement in clinical symptoms after the 4- and 7-year follows-up.³⁷ The clinical study of long-term antibiotic therapy (3 months) with ciprofloxacin in *Yersinia*-induced ReA showed a beneficial effect on the outcome of ReA and a decrease in joint pain.³⁸ Clinical trials assessing the efficacy of ciprofloxacin in ReA vs. placebo

have not so far been conducted in large patient populations. Evidence demonstrated that antibiotics should be given to patients with ReA triggered by *Chlamydia*. Azithromycin taken 1 g weekly for 3 months turned out to be effective only in that kind of ReA.³⁹ The clinical study of the effect of the 9-month course of doxycycline at the dose 100 mg twice a day vs doxycycline at the dose 200 mg twice a day plus rifampicin 600 mg/day demonstrated the efficacy of combined therapy regarding the duration of morning stiffness, the visual analog scale, and a number of affected joints.⁴⁰ In another study, performed however in a small group of patients, beneficial effects of the treatment with lymecycline on the outcome of ReA were demonstrated only after *Chlamydia* infection.⁴¹ Evidence also showed that levofloxacin used in patients with *Chlamydia* infection suppressed the production of inflammatory cytokine IL-6 in human fibroblast-like synovial cells. Doxycycline was less effective in that study. These findings indicate that antibiotic therapy in *Chlamydia* infection will not be only effective in treating infections, but might also have a beneficial effect on the outcome of ReA, and is an effective therapeutic option.⁴²

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