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# Bacteria-Triggered Reactive Arthritis
## Implications for Antibacterial Treatment

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## Contents



## Abstract

Reactive arthritis (ReA) is definitely caused by an infection. Several observations suggest that the triggering microbe may persist in the tissues of the patient for a prolonged time. The obvious conclusion is to consider antibacterial treatment. In two instances antibacterial agents are of definite value: in the primary and secondary prevention of rheumatic fever and for early eradication of *Borrelia burgdorferi* in order to prevent development of the arthritis associated with Lyme disease. Altogether, clinical and experimental data exist to indicate that if antibacterial treatment of ReA can be started very early during the pathogenetic process, the disease can be prevented or the prognosis improved. In fully developed ReA, the value of antibacterial agents is less certain. All available evidence indicates that short term antibacterial treatment has no effect on the prognosis and final outcome of ReA, and the results with long term administration of antibacterials are also overall poor. In some instances sulfasalazine appears useful, rather as a result of its antirheumatic effect or influence on an underlying inflammatory bowel disease than its action as an antibacterial agent. Tetracyclines have also been found to have an effect on ReA, but again, this is probably due to their anti-inflammatory action rather than any antibacterial effect.

Reactive arthritis (ReA) is an infectious disease. A healthy individual who is genetically predisposed may develop this syndrome after contracting a suitable triggering infection. The prominent role of HLA-B27 in ReA is well established. However, HLA-B27–negative individuals do also develop the disease, and even after a suitable triggering infection some HLA-B27–positive individuals do not. It has been proposed that ReA should be divided into an HLA-B27–associated and a HLA-B27–nonassociated form.[1]

The list of bacteria able to cause ReA is long.[2]

Enteroarthritis, in which the initial infection affects the digestive tract, is most often linked to bacteria such as species of *Salmonella*, *Shigella*, *Yersinia* and *Campylobacter*, and *Clostridium difficile*. Uroarthritis in turn develops after urogenital infection, and the responsible bacteria include most commonly *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Ureaplasma urealyticum*. Although the pathogenetic mechanisms are not yet well understood, important new information has been obtained during the last few years. Components of the triggering microbes can be demonstrated at the site of inflammation, e.g. in the synovium and synovial fluid.[3-5] Bacterial DNA and RNA of *C. trachomatis* has been found by several groups[6-8] and in a few cases even bacterial isolation has been positive.[9,10] However, it is not certain whether and how often *Salmonella* DNA occurs in the synovial fluid cells of patients with ReA.[11,12] On the other hand, the persistence and maturation of antibodies against the triggering bacteria indicate that possibly the bacteria persist somewhere at a distant site in the patient, maintaining an immune response.[13] For enteroarthritis, such persistence might occur in the intestinal epithelium or close to it, and some evidence for this has been presented.[14] In one series of 83 patients with oligoarthritis studied by Weyand and Goronzy,[15] an asymptomatic urogenital infection was detected in 69% of patients. A logical question is whether the eradication of the infection with antibacterial therapy would be the a proper approach.

Several questions remain regarding the treatment of ReA. Although the disease mostly is self-limiting, and the patient recovers within months even in clinically aggressive cases, the long term outcome is problematic. Relapses are common, and up to 60% of the patients experience relapses or various arthralgias and enthesopathies.[16-19] Furthermore, it has become clear that ReA may develop into ankylosing spondylitis and even fatal cases have been described.[20,21] Relapses may be as a result of new triggering infections,[22] but the possibility that a persisting focal infection plays a role in some cases cannot be excluded. Again, antibacterials appear to be a logical choice for therapy.

In Finland, and probably also elsewhere, clinical practitioners have become more aware of ReA and about the role of infection in its aetiology. Consequently patients with symptoms applicable to ReA in outpatient care or in the care of their family practitioner usually receive a short course of antibacterials. However, there is no solid evidence to support this practise and there are few well-designed, prospective, randomised studies on the subject. In this article, the currently available knowledge regarding antibacterial treatment of ReA is reviewed.

## 1. Situations in Which the Value of Antibacterials is Established

In two forms of ReA the use of antibacterial agents is well established. These are rheumatic fever and Lyme disease.

### 1.1 Rheumatic Fever

Rheumatic fever develops after a throat infection with the Group A β-haemolytic *Streptococcus pyogenes*. Thus, it can be considered a form of ReA. Since the classical Jones criteria are not always met, some authors have suggested that ReA and rheumatic fever represent different postinfectious complications of a streptococcal throat infection,[23-25] however, this question is not of practical importance when considering the use of antibacterials in the treatment of the disease. In the developing countries, rheumatic fever is still a major problem, but occasional cases are also seen in societies with high hygiene and health standards.[26-28] The disappearance of rheumatic fever from Western countries is often attributed to improved living standards and to vigorous treatment of streptococcal throat infections with penicillin or erythromycin, although factors linked to the pathogenetic potential of the bacteria may also be associated.[29] Regardless, eradication of the triggering streptococci in the early induction phase of rheumatic fever is generally accepted as standard treatment, as is prophylaxis for recurrences with antibacterials, sometimes for several years. It should be noted that the antibacterial agents are used for primary or secondary prevention, not actually for the treatment of

ongoing rheumatic fever. For secondary prevention, intramuscular penicillin every 3 or 4 weeks is recommended in the first instance, but several other agents have also proven effective.[29,30] If poststreptococcal ReA and rheumatic fever are considered separate clinical entities, the possible value of penicillin prophylaxis for ReA needs further prospective investigations before it is accepted as common treatment.[31]

### 1.2 Lyme Disease

Lyme disease is caused by *Borrelia burgdorferi* but this infection can give rise to two different clinical entities. The infectious arthritis with persistence of viable spirochetes in the joints and a wide spectrum of clinical manifestations must be considered a form of sepsis, to be treated with an appropriate antibacterial agent. In addition, antibacterials given immediately after a tick bite or at an early phase of the infection can prevent further development of the disease. Antibacterials are recommended after a tick bite in the absence of any clinical symptoms if ticks in the area often carry spirochetes, i.e. if the risk of borreliosis is high.[32] The agents recommended for use include doxycycline, amoxicillin, cefuroxime and ceftriaxone, but minocycline, azithromycin and penicillin are also valuable.[33]

In addition to the bacterial (spirochetal) arthritis, infections with *B. burgdorferi* can also result in ReA.[2] Conversely, in a series of 51 patients with ReA not associated to dysentery, Weyand and Goronzy[34] found 9 in whom the disease was most probably triggered by *B. burgdorferi*; of them 5 were HLA-B27 positive and 4 HLA-B27 negative.

About 10% of patients with Lyme arthritis develop antibacterial-resistant Lyme arthritis.[35] It is possible that in some instances the explanation is that the spirochete is not eliminated, even if the antibody titres suggest so.[34,36] Apparently, another mechanism is also involved, since a lack of response to antibacterial therapy and the development of chronic arthritis following infection with *B. burgdorferi* is associated with *HLA-DR4* and *HLA-DR2* alleles.[37] Furthermore, a role for cross-reactive autoantigens has been suggested.[35] With such a mechanism playing a role in the pathogenesis it is understandable that any late efforts to treat this chronic condition with antibacterials is not successful.

## 2. Antibacterials in Enteroarthritis or Uroarthritis

The value of antibacterial agents in ReA has been tested using 2 schedules: conventional short term treatment in order to eradicate the triggering infection and long term treatment usually spanning for 3 months, with the aim of eradicating possible persisting bacteria. For clarity, these 2 modalities will be discussed separately in sections 2.1 and 2.2.

### 2.1 Short Term Antibacterial Treatment

Hoogkamp-Korstanje et al.[14] demonstrated persistence of *Yersinia enterocolitica* in the intestinal mucosa and in the lymphoid tissue of the submucosa in patients with prolonged symptoms of the infection. Treatment with cotrimoxazole (trimethoprim-sulfamethoxazole), tetracycline or ciprofloxacin led to recovery or improvement in several patients, 4 of whom apparently had ReA. Later, the same group demonstrated that an antibacterial course of 4 to 6 weeks was effective in eliminating *Y. enterocolitica* from the intestinal mucosa of patients with *Y. enterocolitica*-triggered ReA. The effects on the course of arthritis were not followed.[38] These results are of certain interest but the studies were basically not designed to elucidate the value of antibacterial treatment of ReA.

In a non-blind, prospective study, Frydén et al.[39] consecutively treated 40 patients with enteroarthritis who were randomised to treatment with or without antibacterials. The triggering agents had been *Y. enterocolitica*, *Salmonella* or *Campylobacter*, and the antibacterial agents used included pivampicillin and pivmecillinam, doxycycline, erythromycin, cotrimoxazole or cinoxacin. Several clinical and laboratory parameters were used to evaluate the effect of treatment. No difference was observed concerning duration of arthritis, grade of inflammation or number of joints affected between

those treated and not treated with antibacterials. Furthermore, the laboratory tests (ESR and haptoglobin, IgA and IgG level measurements) did not reveal any significant difference between the 2 groups. The authors conclude that short term antibacterial treatment has no beneficial effect on the clinical outcome of ReA associated with enteric infection.

Another interesting study was carried out when a total of 126 participants at a radiology symposium held in Sweden contracted a *S. enteritidis* infection, and 108 had enterocolitis. The high rate of enterocolitis was, according to the authors, probably attributable to a heavy bacterial contamination of the food. 17 patients developed ReA. 58% of the 126 patients received antibacterials for the intestinal infection. The treatment lasted for an average of 9.1 days, and included ciprofloxacin, norfloxacin, doxycycline, cotrimoxazole or pivmecillinam-pivampicillin. Ten of 65 patients treated with antibacterials and 7 of 48 untreated patients reported of joint symptoms. The authors conclude that although the treatment was initiated only a few days after the first symptoms of diarrhoea, it was not sufficient to prevent the development of arthritis, suggesting that the pathological event leading to ReA must take place at a very early stage during the infection.[40] A similar negative experience was reported after a large single-source *Salmonella* outbreak caused by a rare serovar Bovismorbificans. Altogether, 210 people who had a positive stool culture were later contacted and the 66 who reported articular symptoms were either examined clinically or contacted by telephone. 94 patients (49%) had received antibacterials for their enteritis. 14 of the patients with ReA had taken fluoroquinolones before the joint or tendon symptoms manifested.[41]

Reports on the effects of antibacterials in uroarthritis are somewhat controversial. In an early study involving 82 patients with Reiter's syndrome who were divided in 2 groups, those designated to the treatment group received oxytetracycline for 5 days combined with prostatic massage daily for 14 days. Compared with an untreated control group, no influence on the course of the disease was seen in the treatment group.[42] This result has later been questioned, since the duration of antibacterial treatment was too short to eradicate *C. trachomatis*.[43]

A study by Bardin et al.[44] demonstrated the effect of prompt and proper antibacterial treatment in preventing recurrences of postvenereal ReA. They carried out a retrospective evaluation of the medical charts of Inuit patients in Greenland. The setup was favourable, since the healthcare is highly centralised and the population relatively stable. A group of 109 patients with postvenereal Reiter's syndrome was identified and their medical information was collected for a 36-month period. A total of 224 episodes of genitourinary tract infections occurred in 60 out of the 109 patients studied. In 59 episodes no treatment was given, 97 were treated with penicillin only, and 68 received either erythromycin or tetracycline for at least 10 days. Thus, the antibacterial agent was given before the arthritis had developed. The results were quite clear: 37% of the patients who were not treated or were treated with penicillin developed ReA, compared with 10% of those treated with erythromycin or tetracycline.

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

### 2.2 Long Term Antibacterial Treatment

The obvious question derived from the results discussed in section 2.1 is whether intensive antibacterial treatment over an extended period of time would, possibly by also eliminating 'inactive' bacteria hiding in the tissues, break the immunological mechanism that maintains the ReA. Several studies are on-going and some results have already been published.

In 1989, the favourable effect of a 3-month course of tetracyclines (minocycline) on ReA was reported. This nonblind study included 10 patients with *C. trachomatis*–induced uroarthritis. An im-

provement was observed in the clinical parameters used.[45] The main parameters examined were a visual analogue scale for pain and for well-being, duration of early morning stiffness, number of inflamed joints, overall spinal movement, Schober index and ESR. There are 2 points to be considered in regard to these results. First, there is a tendency to a spontaneous recovery in ReA, at least in short term. Therefore, as the authors point out, a proper control group would be essential for any further conclusions. Secondly, minocycline may have immunosuppressive properties.

Later a double-blind, placebo-controlled, randomised study of a 3-month course of lymecycline in ReA was carried out by Lauhio et al.[46] A total of 40 patients were included: 21 of whom had *Chlamydial*-triggered disease and 2 a preceding uroarthritis of unknown aetiology; and 17 of whom had enteroarthritis, triggerd by *Yersinia* in 8 patients, by *Campylobacter* in 3 and in 6 by an unidentified gastroenteritis. 21 patients were randomly assigned to lymecycline and 19 to placebo. The adverse effects associated with lymecycline were mild and few. The time point at which 50% of the patients had recovered was 26.5 weeks in the treatment group and 29.0 weeks in the placebo group. This difference was not statistically significant. A statistically significant effect of lymecycline could be detected only when the patients with *Chlamydial*-triggered disease receiving lymecycline (n = 12) were compared with those receiving placebo (n = 9). There were, however, only 12 such patients in the treatment and 9 in the placebo group. Taken together, clinical and laboratory parameters suggested that the 3-month course of lymecycline had a favourable effect in *Chlamydial*-triggered ReA but not in other groups of patients. In a later article the same group suggests that the effect may at least partially be due to other, non-antibacterial features of lymecycline, such as suppression of neutrophil function and an anticollagenolytic potential.[47]

A double-blind, placebo-controlled study included 32 patients with *Chlamydial*-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 treated for 4 months, and 3 of 17 who received the drug for 2 weeks went into remission. The authors conclude that long term treatment is not superior to short term treatment.[48] 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.[49]

More recently, another double-blind, placebo-controlled study on the effects of a 3-month course of ciprofloxacin on ReA has been reported.[50] Altogether 116 patients were included, most of them with uroarthritis. No difference in the outcome between ciprofloxacin and placebo treatment in the whole group or in any other separately analysed subgroups was found. The authors conclude that even long term ciprofloxacin is not effective in ReA or undifferentiated oligoarthritis. In patients with *Chlamydial*-triggered ReA, ciprofloxacin seemed to be better than placebo. However, the difference was not statistically significant probably because of the small sample size.[50]

Our group has also tried to evaluate the effect of long term ciprofloxacin treatment on ReA. Ciprofloxacin was chosen because it is effective against many of the bacteria linked to the pathogenesis of ReA, is well tolerated, penetrates the tissues well and has a bactericidal effect *in vitro*. In the first phase, 36 patients with prolonged or chronic ReA were included. 32 patients had enteroarthritis, and 4 had *Chlamydial*-triggered disease. Using a double-blind study design, they were randomised to receive ciprofloxacin or placebo for 3 months, and a number of laboratory and clinical parameters were followed for a total of 9 months. The group with active treatment showed significant improvement according to many of the parameters used, but so also did those receiving placebo and no definite advantage of ciprofloxacin could be demonstrated.[51]

A prospective, randomised, placebo-controlled study on the effect of a 3-month course of ciprofloxacin in acute ReA was recently completed. Al-

together 71 patients participated and after the 1-year follow-up period, 30 patients in the ciprofloxacin and 32 in the placebo group could be included in the efficacy and safety analysis. 30 patients in the ciprofloxacin group and 30 in the placebo group had enteroarthritis, 6 in the former and 5 in the latter group had uroarthritis, thus, the majority had enteroarthritis. The treatment-associated adverse effects were mild and few. Both groups showed improvement during the follow-up period. In such clinical parameters as number of swollen joints, patient global assessment using a visual analogue scale, or complete recovery as well as the laboratory parameters, no statistically significant differences between the 2 groups could be detected. Further, no difference was seen when the enteroarthritis and uroarthritis groups were analysed separately.[52] In a double-blind randomised, placebo-controlled trial ciprofloxacin was given to patients with ReA and anterior uveitis for a year; the antibacterial had no significant effect.[53]

Taken together, the evidence would indicate that long term antibacterial treatment of ReA does not have a definite effect on the course or prognosis of the disease. However, some suggestive evidence of improvement due to antibacterial therapy has been obtained for uroarthritis. The possibility that sexually acquired *Chlamydia* persisting intracellularly in the urogenital tract can be eradicated by antibacterials in some patients, resulting in a favourable result in ReA, cannot be excluded.[54] Obviously, more research is needed, and in fact, a large multinational collaborative study with azithromycin is currently organised under the auspices of the European League Against Rheumatism (EULAR). It is probable that a good number of patients with uroarthritis are included, and the results are eagerly awaited.

### 2.3 Sulfasalazine

Sulfasalazine has antibacterial potential and is a well recognised antirheumatic agent. Considering the role of inflammatory bowel diseases in both ReA and ankylosing spondylitis, it appears theoretically useful in both of these diseases.[20,55] In an early nonblind study, 15 young HLA-B27–positive patients with ReA who did not improve on conventional treatment with nonsteroidal anti-inflammatory drugs were given sulfasalazine. Inflammatory bowel disease was suspected to be the background factor in the arthritis and it was verified by ileocolonoscopy in 7 patients. A long-lasting remission was obtained after 3 to 12 months of treatment in 11 patients and a significant improvement was seen in the remaining 4. No significant adverse reactions were reported.[56] In a later study by the same group, 48 patients with ReA or ankylosing spondylitis were treated with sulfasalazine when conventional therapy proved unsuccessful. 33 of the 37 patients who underwent ileocolonoscopy had signs of inflammation of the ileum or ileocecal valve. 32 patients had asymmetrical pauciarticular arthritis, compatible with the diagnosis of ReA. After 3 to 12 months treatment, 42 patients improved and 50% of the 42 went into remission. No separate analysis of the 2 patient groups, i.e. those with and without GI inflammation, was carried out. Adverse reactions were rare and did not necessitate interruption of treatment.[57] Encouraging results were also obtained by Trnavský et al.[58] who treated 18 patients with severe ReA not improving with nonsteroidal anti-inflammatory agents or corticosteroids. 15 patients showed definite improvement and were able to discontinue the other drugs. The suppression of disease activity persisted even after sulfasalazine treatment was stopped after 9 months. Three patients had haematological adverse effects and 2 had mild GI disturbances. A case report of successful treatment of HIV-associated Reiter's disease with sulfasalazine has been published more recently.[59] All these positive reports were nonblind studies and the influence of spontaneous recovery could not be excluded.

A systematic collaborative study of 6-months duration using a double-blind, placebo-controlled design was published in 1997. The treatment group included 37 patients and the placebo group 42 patients, and the parameters measured included the number of swollen joints, the patient's estimate of

pain using a visual analogue scale, duration of sick leave, and complete recovery, in addition to laboratory parameters. Although the sulfasalazine treatment was started slowly, there were severe adverse effects and 9 patients in the sulfasalazine group withdrew because of them. Both groups showed definite improvement with time and there were no significant differences between them after 6 months. Of those patients who had completed the trial according to the protocol, persistent complete remission had occurred within 2 months in 5 of the actively-treated but in none of the placebo-treated patients.[60] A reanalysis of a large multicentre study which included 619 patients with seronegative spondylathropathy, 134 of them with ReA, was recently carried out to evaluate the benefit of sulfasalazine. In patients with persistently active peripheral arthritis the drug appeared to be well tolerated and effective.[61]

Thus, experience with sulfasalazine in ReA is controversial. Possible beneficial effect can, according to the reports presented here, be expected only after a at least 2 months and adverse reactions may necessitate interruption of the treatment in a considerable number of patients. Sulfasalazine should be tried in patients with ReA resistant to conventional treatment and in those with inflammatory bowel disease as a background factor. The observations of Mielants and Veys[20] that intestinal lesions are common in ReA and other spondyloarthropathies also suggest that an ileocolonoscopic search for bowel lesions should be carried out more frequently than is the case at present.

## 3. Lessons from Experimental Work

A beneficial effect of antibacterials is not necessarily due to their antibacterial effect, as has been pointed out regarding minocycline[45] and lymecycline.[47] The same may be true also for ciprofloxacin, which has been found to have a protective effect against type II collagen induced arthritis in rats. The authors suggest that this may be due to its capacity to inhibit the production of interleukin-1β and tumour necrosis factor-α.[62] This does not imply any drawback for the drug in the treatment of arthritic disease with an autoimmune background, rather the contrary.

Studies on ReA were for a long time hampered by a lack of a suitable experimental model, however, when a rat model using *Y. enterocolitica* O:8 became available,[63,64] we applied it to study the effect of ciprofloxacin treatment on arthritis.[65,66] Arthritis develops in about 70% of the rats, starting usually on days 6 to 7 after administration of the bacteria. It subsides in approximately 40 days but exacerbations occur in some animals. In the first phase ciprofloxacin was administered for 7 days in 2 dosages, 20 mg/kg/day or 100 mg/kg/day. Four different schedules in relation to the injection of the bacteria were used: starting on day 3, 5, 10 or 13. The animals were monitored daily and the follow-up was for 60 days. A 7-day course of ciprofloxacin with 100 mg/kg/day, started on day 3 after bacterial inoculation before any signs of arthritis had appeared, completely prevented the development of arthritis and eliminated *Y. enterocolitica* as assessed by faecal culture. If a dosage of 20 mg/kg/day was used, development of arthritis was prevented but some animals had positive faecal cultures at the end of the experiment. If ciprofloxacin was started on day 5, a preventive effect was still observed but it was less pronounced. If the treatment was started at the peak of the arthritis, no treatment effect could be detected.[65]

A second set of experiments with a similar design but giving the ciprofloxacin for 3 weeks in a dose of 20 mg/kg/day was then carried out. This dosage was chosen as it is approximately equal to that used in human medicine. The results were again quite straightforward. If ciprofloxacin was started on day 3, before any signs of joint inflammation had developed, arthritis could be completely prevented and no late exacerbations occurred in this group. If the drug was started on day 10 or 13, i.e. at the time of well developed arthritis, no beneficial effect could be seen; rather, increased faecal excretion of *Y. enterocolitica* followed.[66] The observation that unsuccessful antibacterial therapy led to prolonged faecal excretion of the causative bacteria is alarming. It is general clinical

knowledge that failed antibacterial therapy of *Salmonella* enteritis may also lead to a carrier state.

## 4. Conclusions

Although the role of infection in the pathogenesis of ReA is indisputable, the value of antibacterial therapy is not clear. In 2 forms of ReA their use is generally accepted: in eradication of streptococcal infections for primary or secondary prevention of rheumatic fever, and in borreliosis or Lyme disease. Some encouraging experiences with sulfasalazine have been published in ReA associated with inflammatory bowel disease. However, experience in other forms of ReA are rather negative.

The pathogenesis of ReA can be divided into 4 stages: an incubation time after contracting the infection, the more or less clear clinical manifestation of the infection, an asymptomatic interval period and then the ReA. Most reports cited in this review indicate that antibacterial therapy is only effective when given early enough during this pathogenetic chain of events. This creates a dilemma as patients mostly seek medical help at the time when arthritis has developed and, according to current knowledge, this is too late. Antibacterial agents could – and should – be given if there are signs of active infection at this time, in accordance with normal clinical practise, but this should not be confused with an effort to treat the ReA.

## Acknowledgements

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## References

1. Toivanen P, Toivanen A. Two forms of reactive arthritis? Ann Rheum Dis 1999; 58: 737-41
2. Toivanen A, Toivanen P. Aetiopathogenesis of reactive arthritis. Rheumatol Europe 1995; 24: 5-8
3. Lahesmaa-Rantala R, Granfors K, Isomäki H, et al. Yersinia-specific immune complexes in the synovial fluid of patients with Yersinia-triggered reactive arthritis. Ann Rheum Dis 1987; 46: 510-4
4. Merilahti-Palo R, Söderström K-O, Lahesmaa-Rantala R, et al. Bacterial antigens in synovial biopsy specimens in yersinia-triggered reactive arthritis. Ann Rheum Dis 1991; 50: 87-90
5. Granfors K, Jalkanen S, von Essen R, et al. Yersinia antigens in synovial-fluid cells from patients with reactive arthritis. N Engl J Med 1989; 320: 216-21
6. Gérard HC, Branigan PJ, Schumacher Jr HR, et al. Synovial Chlamydia trachomatis in patients with reactive arthritis/Reiter's syndrome are viable but show aberrant gene expression. J Rheumatol 1998; 25: 734-42
7. Hughes RA, Keat AC. Reiters syndrome and reactive arthritis: a current view. Semin Arthritis Rheum 1994; 24: 190-210
8. Hammer M, Nettelnbreker E, Hopf S, et al. Chlamydial rRNA in the joints of patients with chlamydia-induced arthritis and undifferentiated arthritis. Clin Exp Rheumatol 1992; 10: 63-6
9. Vilppula AH, Yli-Kerttula UI, Ahlroos AK, et al. Chlamydial isolations and serology in Reiter's syndrome. Scand J Rheumatol 1981; 10: 181-5
10. Schachter J, Barnes MG, Jones JP, et al. Isolation of bedsoniae from the joints of patients with Reiters syndrome. Proc Soc Exp Biol Med 1996; 122: 283-5
11. Nikkari S, Rantakokko K, Ekman P, et al. Salmonella-triggered reactive arthritis: use of polymerase chain reaction, immunocytochemical staining, and gas chromatography-mass spectrometry in the detection of bacterial components from synovial fluid. Arthritis Rheum 1999; 42: 84-9
12. Ekman P, Nikkari S, Putto-Laurila A, et al. Detection of Salmonella infantis in synovial fluid cells of a patient with reactive arthritis. J Rheumatol 1999; 26: 2485-8
13. Toivanen A, Granfors K, Lahesmaa-Rantala R, et al. Pathogenesis of Yersinia-triggered reactive arthritis: immunological, microbiological and clinical aspects. Immunol Rev 1985; 86: 47-70
14. Hoogkamp-Korstanje JAA, de Koning J, Heesemann J. Persistence of *Yersinia enterocolitica* in man. Infection 1988; 16: 81-5
15. Weyand CM, Goronzy JJ. Clinically silent infections in patients with oligoarthritis: results of a prospective study. Ann Rheum Dis 1992; 51: 253-8
16. Sairanen E, Paronen I, Mähönen H. Reiter's syndrome: a follow-up study. Acta Med Scand 1969; 185: 57-63
17. Kvien TK, Glennås A, Melby K, et al. The natural history of reactive arthritis. Rheumatol Europe 1995; 24: 15-9
18. Leirisalo-Repo M, Suoranta H. Ten-year follow-up study of patients with *Yersinia* arthritis. Arthritis Rheum 1988; 31: 533-7
19. Leirisalo-Repo M, Helenius P, Hannu T, et al. Long term prognosis of reactive salmonella arthritis. Ann Rheum Dis 1997; 56: 516-20
20. Mielants H, Veys EM. The gut and reactive arthritis. Rheumatol Europe 1995; 24: 9-11
21. Yli-Kerttula T, Möttönen T, Toivanen A. Different course of reactive arthritis in two HLA-B27 positive brothers with fatal outcome in one. J Rheumatol 1997; 24: 2047-50
22. Konttinen YT, Nordström DC, Bergroth V, et al. Occurrence of different ensuing triggering infections preceding reactive arthritis: a follow up study. BMJ 1988; 296: 1644-5
23. Jansen TL, Janssen M, van Riel PLCM. Acute rheumatic fever or post-streptococcal reactive arthritis: a clinical problem revisited. Br J Rheumatol 1998; 37: 335-40
24. Jansen TL, Janssen M, Traksel R, et al. A clinical and serological comparison of group A versus non-group A streptococcal reactive arthritis and throat culture negative cases of post-streptococcal reactive arthritis. Ann Rheum Dis 1999; 58: 410-4
25. Ahmed S, Ayoub EM, Scornik JC, et al. Poststreptococcal reactive arthritis: clinical characteristics and association with HLA-DR alleles. Arthritis Rheum 1998; 41: 1096-102
26. Mason T, Fisher M, Kujala G. Acute rheumatic fever in West Virginia: not just a disease of children. Arch Intern Med 1991; 151: 133-6
27. Amigo M-C, Martínez-Lavín M, Reyes PA. Acute rheumatic fever. Rheum Dis Clin North Am 1993; 19: 333-50

28. Feuer J, Spiera H. Acute rheumatic fever in adults: a resurgence in the Hasidic Jewish community. J Rheumatol 1997; 24: 337-40
29. Bisno AL. Group a streptococcal infections and acute rheumatic fever. N Engl J Med 1991; 325: 783-93
30. Lue HC, Wu MH, Wang JK, et al. Long-term outcome of patients with rheumatic fever receiving benzathine penicillin G prophylaxis every three weeks versus every four weeks. J Pediatr 1994; 125 : 812-6
31. Jansen TL, Janssen M, de Jong AJ, et al. Post-streptococcal reactive arthritis: a clinical and serological description, revealing its distinction from acute rheumatic fever. J Intern Med 1999; 245: 261-7
32. Magid D, Schwartz B, Graft J, et al. Prevention of Lyme disease after tick bites. N Engl J Med 1992; 327: 534-41
33. Weber K, Pfister H-W. Clinical management of Lyme borreliosis. Lancet 1994; 343: 1017-20
34. Weyand CM, Goronzy JJ. Immune responses to *Borrelia burgdorferi* in patients with reactive arthritis. Arthritis Rheum 1989; 32 : 1057-64
35. Gross DM, Forsthuber T, Tary-Lehman M, et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science 1998; 281: 703-6
36. Preac-Mursic V, Weber K, Pfister HW, et al. Survival of *Borrelia burgdorferi* in antibiotically treated patients with Lyme borreliosis. Infection 1989; 17: 355-9
37. Steere AC, Dwyer E, Winchester R. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. N Engl J Med 1990; 323: 219-23
38. Hoogkamp-Korstanje JAA, de Koning J, Heesemann J, et al. Influence of antibiotics on IgA and IgG response and persistence of *Yersinia enterocolitica* in patients with Yersinia-associated spondylarthropathy. Infection 1992; 20: 53-7
39. Frydén A, Bengtsson A, Foberg U, et al. Early antibiotic treatment of reactive arthritis associated with enteric infections: clinical and serological study. BMJ 1990; 301: 1299-302
40. Locht H, Kihlström E, Lindström FD. Reactive arthritis after Salmonella among medical doctors: study of an outbreak. J Rheumatol 1993; 20: 845-8
41. Mattila L, Leirisalo-Repo M, Pelkonen P, et al. Reactive arthritis following an outbreak of Salmonella bovismorbificans infection. J Infection 1998; 36: 289-95
42. Popert AJ, Gill AJ, Laird SM. A prospective study of Reiter's syndrome: an interim report on the first 82 cases. Br J Vener Dis 1964; 40: 160-5
43. Bardin T, Schumacher HR. Should we treat postvenereal Reiters syndrome by antibiotics? J Rheumatol 1991; 18: 1780-2
44. Bardin T, Enel C, Cornelis F, et al. Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. Arthritis Rheum 1992; 35: 190-4
45. Panayi GS, Clark B. Minocycline in the treatment of patients with Reiter's syndrome. Clin Exp Rheumatol 1989; 7: 100-1
46. Lauhio A, Leirisalo-Repo M, Lähdevirta J, et al. Double-blind, placebo-controlled study of three-month treatment with lymecycline in reactive arthritis, with special reference to Chlamydia arthritis. Arthritis Rheum 1991; 34: 6-14
47. Lauhio A, Sorsa T, Lindy O, et al. The anticollagenolytic potential of lymecycline in the long-term treatment of reactive arthritis. Arthritis Rheum 1992; 35: 195-8
48. Wollenhaupt J, Hammer M, Pott HG, et al. A double-blind, placebo-controlled comparison of 2 weeks versus 4 months treatment with doxycycline in Chlamydia-induced reactive arthritis. Arthritis Rheum 1997; 40: S143
49. Beutler AM, Hudson AP, Whittum-Hudson JA, et al. *Chlamydia trachomatis* can persist in joint tissue after antibiotic treatment in chronic Reiters syndrome/reactive arthritis. J Clin Rheumatol 1997; 3: 125-30
50. Sieper J, Fendler C, Laitko S, et al. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis. Arthritis Rheum 1999; 42: 1386-96
51. Toivanen A, Yli-Kerttula T, Luukkainen R, et al. Effect of antimicrobial treatment on chronic reactive arthritis. Clin Exp Rheumatol 1993; 11: 301-7
52. Yli-Kerttula T, Luukkainen R, Yli-Kerttula U, et al. Effect of a three-month course of ciprofloxacin on the outcome of reactive arthritis. Ann Rheum Dis 2000; 59: 565-70
53. Wakefield D, McCluskey P, Verma M, et al. Ciprofloxacin treatment does not influence course or relapse rate of reactive arthritis and anterior uveitis. Arthritis Rheum 1999; 42: 1894-7
54. Sieper J, Braun J. Treatment of reactive arthritis with antibiotics. Br J Rheumatol 1998; 37: 717-20
55. Toivanen A, Möttönen T. Ankylosing spondylitis: current approaches to treatment. BioDrugs 1998; 10: 193-200
56. Mielants H, Veys EM. HLA-B27 related arthritis and bowel inflammation. Part 1. Sulphasalazine (Salazopyrin) in HLA-B27 related reactive arthritis. J Rheumatol 1985; 12: 287-93
57. Mielants H, Veys EM, Joos R. Sulphasalazine (Salazopyrin) in the treatment of enterogenic reactive synovitis and ankylosing spondylitis with peripheral arthritis. Clin Rheumatol 1986; 5: 80-3
58. Trnavský K, Pelišková Z, Vácha J. Sulphasalazine in the treatment of reactive arthritis. Scand J Rheumatol 1988; 67: 76-9
59. Youssef PP, Bertouch JV, Jones PD. Successful treatment of human immunodeficiency virus-associated Reiters syndrome with sulfasalazine. Arthritis Rheum 1992; 35: 723-4
60. Egsmose C, Hansen TM, Andersen LS, et al. Limited effect of sulphasalazine treatment in reactive arthritis: a randomised double-blind placebo-controlled trial. Ann Rheum Dis 1997; 56: 32-6
61. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulphasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. Arthritis Rheum 1999; 42: 2325-9
62. Breban M, Fournier C, Gougerot-Pocidalo M-A et al. Protective effects of ciprofloxacin against type II collagen induced arthritis in rats. J Rheumatol 1992; 19: 216-22
63. Toivanen A, Merilahti-Palo R, Gripenberg C, et al. Yersinia-associated arthritis in the rat: experimental model for human reactive arthritis? Acta Pathol Microbiol Immunol Scand (C) 1986; 94 : 261-9
64. Merilahti-Palo R, Gripenberg-Lerche C, Söderström K-O, et al. Long term follow up of SHR rats with experimental yersinia-associated arthritis. Ann Rheum Dis 1992; 51: 91-6
65. Zhang Y, Gripenberg-Lerche C, Söderström K-O, et al. Antibiotic prophylaxis and treatment of reactive arthritis. Lessons from an animal model. Arthritis Rheum 1996; 39: 1238-43
66. Zhang Y, Toivanen A, Toivanen P. Experimental Yersinia-triggered reactive arthritis; effect of a 3-week course with ciprofloxacin. Br J Rheumatol 1997; 36: 541-6

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