

British Association of Sexual Health and HIV national guideline on the management of sexually acquired reactive arthritis 2021

International Journal of STD & AIDS

2021, Vol. 32(11) 986–997

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DOI: 10.1177/09564624211020266

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Abstract

These guidelines update the 2008 UK guideline for the management of sexually acquired reactive arthritis. The guideline is aimed at those over the age of 16 years, presenting to healthcare professionals working in sexual health services. The recommendations are primarily aimed at services offering level 3 care in sexually transmitted infection management within the United Kingdom. However, the principles will apply to those presenting to level 1 and 2 services, and appropriate local referral pathways will need to be developed.

Keywords

Diagnosis, treatment

Date received: 26 April 2021; accepted: 30 April 2021

What is new in the 2021 guideline

1. Changing incidence of sexually acquired reactive arthritis (SARA).
2. Pathogens that are newly recognised as linked to SARA.
3. The emerging importance of enteric pathogens that may be acquired sexually.
4. New treatments for seronegative spondyloarthritis, although their effect on SARA is as yet unknown.
5. Clear graded recommendations using the GRADE system.

Introduction and methodology

Objectives

The aim is to reduce the number of sexually transmitted infections (STIs) and, therefore, their complications. Pertinent to this guideline is to consider STIs in anyone presenting with a suspected reactive arthritis (ReA), particularly if they also have symptoms or signs suggestive of an STI.

This guideline discusses the aetiology and clinical features of SARA and makes recommendations on the diagnostic tests and treatment for effective management with the aim of improving health outcomes for people with SARA. This will include appropriate partner notification and prevention of onward transmission when an STI is identified.

The guideline is aimed at those over the age of 16 years, presenting to healthcare professionals working in sexual health services. The recommendations are primarily aimed

at services offering level 3 care in STI management within the United Kingdom. However, the principles will apply to those presenting to level 1 and 2 services, and appropriate local referral pathways will need to be developed. The guideline will also be of use to rheumatologists assessing and managing patients presenting with possible SARA. In addition, local pathways between rheumatology and sexual health services should be available.

Search strategy

This guideline was produced according to specifications set out in the CEG document ‘framework for guideline development and assessment’ (2015, updated 2019) accessed at <https://www.bashhguidelines.org/media/1229/2015-guidelines-framework-amended-dec-2019.pdf>. It has been updated by reviewing the previous SARA guideline (2008)

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and medical literature since its publication using abstracts and articles in the English language. Where there was a paucity of randomised control trials and high quality evidence, expert judgement was considered.

Search terms: Reactive arthritis, sexually acquired reactive arthritis, SARA, Reiters, Spondyloarthropathy, Spondyloarthritis, Spondyloarthritis, Infectious arthritis.

Sources: OVID, Medline, PubMed, National Institute for Health and Clinical Excellence, Cochrane Library.

Guidelines were produced by IUSTI, British Association for Sexual Health and HIV (BASHH) and CDC.

Equality impact assessment

An assessment of the guideline and its recommendations was undertaken to ensure the principles of equality and diversity were adhered to.

Stakeholder involvement, piloting and feedback

The document was reviewed by the Clinical Effectiveness Group of BASHH, and their comments were incorporated.

The draft guideline was placed on the BASHH website for consultation for a period of two months, and any comments received during the consultation period were reviewed by the authors and acted on appropriately.

The document was also reviewed by a patient representative, target users and the public panel of BASHH, and their feedback was considered by the authors and used to inform the guideline.

Aetiology

Reactive arthritis is one of the seronegative spondyloarthropathies. It is a sterile inflammation of the synovial membranes, fascia and tendons triggered by an infection at a distal site. This can typically be an enteric infection with gastrointestinal pathogens (e.g. *Salmonella*, *Shigella*, and *Campylobacter*), or a STI, when it is termed SARA. Reactive arthritis also encompasses Reiter's syndrome, with its classic triad of arthritis, conjunctivitis and urethritis, with or without cutaneous manifestations such as keratoderma blennorrhagica or circinate balanitis/vulvitis. Today, the majority of patients do not present with the triad and the term Reiter's syndrome is no longer used in clinical practice.

Reactive arthritis is a sterile inflammation of the synovial membranes, fascia and tendons triggered by an infection at a distal site and must be distinguished from septic arthritis, caused by an infection within the joint, and which requires specific management requirements.

Infective pathogens

The precise mechanisms linking infective pathogens with SARA are not fully understood; nor is it clear why some

individuals develop SARA as a result of an STI and others do not. It is thought that SARA is caused by an immune response to the infective agent, with DNA and/or surface pathogens being identified in the joint material of patients with SARA.¹⁻⁹ *Chlamydia trachomatis* has been shown to exist in an unusual and persistent state in patients with SARA. This aberrant form represses synthesis of the major outer membrane protein and produces heat shock proteins, which contribute to the inflammatory response.¹⁰⁻¹²

• Sexually transmitted infections with a link to SARA include the following:

1. *Chlamydia trachomatis*: This has the strongest association with SARA and has been identified in up to two-thirds of cases. It has been suggested that ocular serovars of *C. trachomatis* (trachoma), rather than genital strains, may be preferentially associated with SARA.¹³ One theory proposes that in a minority of cases, the genital inoculum includes both ocular and genital strains, and that the ocular strains then travel to the joint and are responsible for the development of SARA. However, this is unproven and more work is needed to determine this. There have also been some recent case reports of SARA associated with other chlamydia types, namely, lymphogranuloma venereum.¹⁴ More recently, a decline in the incidence of SARA has been observed despite rising *C. trachomatis* diagnoses. This may reflect detection and treatment of the genital infection at early stage or represent a more complex picture than previously thought.¹⁵
2. *Neisseria gonorrhoeae*: This is associated in up to 16% of cases and distinct from its role in septic arthritis.¹⁶⁻²⁰
3. *Mycoplasma genitalium*: This is a well-recognised cause of urethritis but has only been identified in the joints in a few cases, so its arthritogenic potential is not yet fully known.²¹⁻²³ Similarly, *Ureaplasma urealyticum* has been reported in a few cases of arthritis, but a causal role in the development of SARA has not been established.^{24,25}
4. Sexual transmission of enteric pathogens triggering SARA has been reported,^{26,27} and *Shigella* outbreaks have been identified in men that are independent of travel history, thus raising the likelihood of sexual transmission.²⁸ Therefore, ReA due to *Shigella* could be acquired through the enteric or sexual route. Whether other enteric pathogens may also have this potential is unclear.
5. There is insufficient evidence to suggest a causal role for other genital tract pathogens and commensals.

Risk factors and associations

Sexually acquired reactive arthritis is more commonly seen in men, with a ratio of over 10 to 1, although under

recognition or a different disease phenotype in women may be a possible explanation.^{16,20,29,30} Carriage of the HLA-B27 gene increases susceptibility to SARA and is associated with increased severity of the condition.^{18,30–35} Reports suggest that ReA has increased in incidence in the sub-Saharan HIV-positive population, where almost all cases of HIV-associated ReA are HLA-B27 negative, but similar observations have not been documented in Caucasian populations with HIV.^{36–38}

Reactive arthritis, including SARA, has been considered part of the seronegative spondyloarthritides, a heterogeneous group of related polygenic diseases that affect the axial skeleton. The most representative is axial spondyloarthritis, ranging from the non-radiographic form to the established radiographic subset, known as ankylosing spondylitis. Other related diseases are psoriatic arthritis, inflammatory bowel disease-associated arthritis and synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO).

Clinical features

History

It is important to ask about genital and urinary symptoms, joint and other musculoskeletal symptoms and extra-articular features. There may also be a past or family history of spondyloarthritis, iritis, psoriasis, inflammatory bowel disease or SAPHO.^{16,19,29,33,39}

It is essential to take a thorough sexual history. There is usually a history of sexual intercourse with a new partner within 3 months of the onset of the arthritis symptoms,^{30,32,34} and on average, genital symptoms occur 14 days before the arthritis.^{16,19,29,30,32}

Symptoms and signs

Women are more likely than men to be asymptomatic in terms of genital symptoms. However, they may report altered vaginal discharge, pelvic pain, deep dyspareunia, inter-menstrual or post-coital bleeding. Clinical examination may reveal mucopurulent cervicitis, with or without cervical contact bleeding, and/or tenderness on abdominal or bimanual examination.

Male genital symptoms include urethral discharge, dysuria and/or testicular pain or swelling. On examination, there may be visible urethral discharge, testicular pain and/or swelling.^{19,20,30,34,40}

Depending on the sexual history, STIs at extra-genital sites may produce rectal discharge, bleeding, discomfort and tenesmus. However, rectal infection may be asymptomatic, and pharyngeal infections frequently are. Rectal discharge, bleeding and/or inflammation may be visible on proctoscopy examination in the presence of a rectal STI.

The arthritis is inflammatory in nature, with joint pain, often at night, possible swelling and early morning stiffness.

Peripheral joint involvement typically occurs as an asymmetrical arthritis, typically an oligoarthritis, primarily involving the lower limbs – knees, ankles and feet.^{19,29–31,33,41}

Other musculoskeletal symptoms include pain or difficulty on walking due to Achilles enthesitis and/or plantar fasciitis (20–40%),^{16,18,20,29,30,41} painful movements due to tenosynovitis (30%), fusiform swelling of a finger or toe with dactylitis (16%),^{29,30,41} and lower back pain and stiffness if sacroiliitis is present in an acute episode (10%).^{16,18–20,30,31,41–43}

Examination of the articular system may reveal multiple swollen joints, with pain on active or passive movement. Specific entheses to examine are the Achilles tendon and plantar fascial attachments to the calcaneum.^{16,18,20,29,30,33} In the presence of enthesopathy, there may be tenderness with or without swelling. Tenosynovitis may produce crepitus on movement over tendon sheaths,^{29,30} with associated tenderness and or swelling. Tenderness on direct sacral pressure may indicate sacroiliitis,^{16,18,20,29,30} though can also be present with lumbosacral disc disease and other pathologies.

Irritable and red eyes with photophobia may occur with conjunctivitis (20–50%) or iritis (2–11%) and less commonly disturbance of visual acuity and ocular pain with uveitis. Any individual with eye symptoms should undergo formal slit lamp examination to identify iritis, corneal ulceration, keratitis, intra-ocular haemorrhage, optic neuritis and posterior uveitis. These are all rare but reported manifestations.^{16,18–20,29,30,33,43}

Circinate balanitis or vulvitis is present in 14–40% of patients.^{16,18,20,29,30,35,43} Extra-genital mucocutaneous features include psoriasiform eruptions (12%),¹⁹ keratoderma blennorrhagica (5–33%)^{16,18–20,29,30,33,35,43} and nail dystrophy (6–12%).^{19,43} Inspection of the oral cavity may reveal oral ulceration or geographical tongue which are both reported in a minority of cases.⁴³

- Other rare extra-articular features which may have few or no symptoms or signs are as follows:
 1. Cardiovascular: tachycardia, left ventricular dilatation, aortic valve disease and cardiac conduction delays.^{18–20,29,35,44}
 2. Renal: proteinuria, microscopic haematuria, aseptic pyuria and glomerulonephritis.^{31,45}
 3. Others: cranial nerve palsies, meningoencephalitis, thrombophlebitis of the lower limbs and subcutaneous nodules.^{16,19,20,29}

Non-specific systemic symptoms of malaise, fatigue, weight loss and fever are seen in some patients.^{30,41,42}

Diagnosis

The diagnosis of SARA is based on clinical findings, namely, typical features of spondyloarthritis with a sexually transmitted genital infection. There are no specific diagnostic criteria.

All patients should be offered screening for STIs (Grade 1A), as per BASHH guidelines⁴⁶ and as follows:

- Male genital samples:
 1. Urine NAAT for *C. trachomatis* and *N. gonorrhoeae*.
 2. Urethral gram stained smear (if urethral symptoms).
 3. Urethral culture and sensitivity testing for *N. gonorrhoeae*.
- Female genital samples:
 1. Vulvovaginal NAAT for *C. trachomatis* and *N. gonorrhoeae*.
 2. Endocervical culture and sensitivity testing for *N. gonorrhoeae* (if microscopy or NAAT positive).
- Genital samples in trans people:
 1. Urine NAAT for *C. trachomatis* and *N. gonorrhoeae* in all patients.
 2. If the patient has a vagina (including post-genital reconstruction surgery) and is using it for sex, vulvovaginal NAAT for *C. trachomatis* and *N. gonorrhoeae*.
 3. Urethral and/or endocervical gram stained smear and culture for *N. gonorrhoeae* as appropriate (depending on symptoms, genital configuration and any reconstructive surgery).
 4. More details on STI screening in trans people are available from the BASHH standards document at <https://www.bashh.org/media/4400/bashh-recommendations-for-integrated-sexual-health-services-for-trans-including-non-binary-people-2019pdf.pdf>.
- Samples in both men and women:
 1. Pharyngeal and rectal NAAT samples for *C. trachomatis* and *N. gonorrhoeae* where indicated by the sexual history.
 2. Screening for HIV and syphilis.
 3. Screening for hepatitis B and C based on risk factors in the sexual history.
 4. Consider *M. genitalium* NAAT (urine in men/ vulvovaginal sample in women).
- The following are also useful initial investigations:
 1. Acute phase response: erythrocyte sedimentation rate, C-reactive protein or plasma viscosity.
 2. Full blood count.
 3. Urinalysis.

Further investigations

The following tests may be useful in some situations but are not necessarily always required. Close liaison with relevant pathology departments is advisable to ensure that the correct samples are obtained.

- Biochemistry:
 1. Liver and kidney function tests.
- Microbiology:
 1. Blood cultures.
 2. Stool culture.

3. Synovial fluid aspirate for cell count, gram stain, crystals and culture (to exclude septic arthritis and gout).
- Radiology:
 1. X-rays of affected joints.
 2. Ultrasonography of affected joints or entheses.
 3. Magnetic resonance imaging of sacroiliac joints and spine.
 - Others:
 1. HLA-B27.
 2. Electrocardiograph.
 3. Echocardiogram.
 4. Synovial biopsy.
 5. Exclusion tests for other rheumatological diseases.
 - a. Anti-cyclic citrullinated peptide (rheumatoid arthritis).
 - b. Autoantibodies (systemic lupus erythematosus).
 - c. Plasma urate (gout).
 - d. Chest x-ray and serum angiotensin-converting enzyme level (sarcoidosis).

Management

General advice

In the majority of cases, SARA may be self-limiting, and the principles of management reflect this. However, this is not always the case. Patients should receive a detailed explanation of their condition and the likely prognosis. This should be supported by appropriate written information and online resources. Patient information leaflets are available via the BASHH website.

As with all STIs, patients should be advised to abstain from all sexual contact until they and their partner(s) have completed treatment and follow-up.

Patients should be advised to avoid potentially 'triggering infections' in the future, either urogenital or enteric, to avoid a new flare of SARA. Therefore, safer sexual practice should be discussed and the importance of food hygiene stressed.³¹

Close liaison between relevant specialists, depending on the clinical features, is advised. This may include GUM physicians, rheumatologists, dermatologists, ophthalmologists and microbiologists.

Treatment

Therapy is directed at the distinct elements of the condition with specialist advice being obtained depending on the individual's symptoms and signs.

All patients with eye symptoms should be urgently referred for specialist ophthalmological advice.

In those cases where significant peripheral joint or spinal joint symptoms are present, prompt liaison with the rheumatologists and/or a referral to an Early Arthritis Clinic is recommended.

Recommended and alternative regimens

Antibiotics

- Antimicrobial therapy for any genital infection identified is essential and should be as in uncomplicated infection, as directed by relevant infection guidelines.^{47–49}
- Whether short course antibiotic treatment for the acute genital infection influences the non-genital aspects of SARA is controversial. It may reduce the risk of recurrent arthritis developing in individuals with a history of ReA but is unlikely to affect the arthritis once it is manifest^{30,41,43,50,51} (Grade IB).
- Longer course antibiotic therapy for joint symptoms has been considered as some have anti-collagenolytic properties.⁵² Many studies had small numbers of individuals with SARA, and mostly, the antibiotic therapy had been commenced after the arthritis had become established. Conflicting results have been obtained, with various antibiotic regimens including combination antibiotic therapy.^{53–64} Similarly, the effect of antibiotic therapy on the late prognosis of arthritis has not been confirmed.^{65,66} The role of longer term antimicrobial therapy in SARA has not been proven and is therefore not recommended^{33,41,53–60,62–70} (Grade 1C).

Physical therapy

- Rest is helpful for constitutional symptoms, enthesitis and arthritis, particularly in weight-bearing joints and tendons where restriction of activity is part of first-line treatment.
- Physiotherapy should be used, as necessary, to prevent muscle wasting and, when symptoms improve, to strengthen muscles and improve the range of movement in the affected joints and tendons. Physiotherapy and exercise are particularly important where there is axial involvement^{11,33,69,71–74} (Grade 1D).
- Cold pads may be used to alleviate joint pain and oedema,^{72–74} and ultrasound³³ and orthotics with insoles, cushioning and heel supports may help with enthesitis^{11,33} (Grade 1D).

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Non-steroidal anti-inflammatory drugs are well established as the main stay of therapeutic management for many inflammatory arthritides. It is important that they are used regularly for the maximum anti-inflammatory benefit. No specific NSAID has benefits over others in these circumstances, and individual responses will vary^{31,33,35,41,71–78} (Grade 1B).
- Non-steroidal anti-inflammatory drugs may also be useful for associated constitutional symptoms, and oral or topical options exist for symptoms of enthesitis^{11,31,33,79} (Grade 1D).
- Potential side effects of NSAIDs should be considered – namely, gastrointestinal, renal and cardiovascular.

Non-steroidal anti-inflammatory drugs should be given for the shortest possible time period, particularly in those with other underlying risks factors for toxicity^{33,71,75,79–81} (Grade 1A).

- For individuals at high risk of gastrointestinal bleeding, a cyclooxygenase (COX)-2 selective drug should be used (Grade 1A).
- Risk factors for gastrointestinal bleeding include previous history of the same, age over 65 years, male gender, cigarette smoking, excessive alcohol intake, concomitant oral glucocorticoids, antiplatelet agents and anti-coagulants.⁷⁵ Gastro-protective agents such as proton pump inhibitors or histamine-2 receptor blockers can reduce the gastrointestinal risks.
- Cyclooxygenase-2 selective drugs have been linked with increased cardiovascular risk independent of baseline cardiovascular risk factors.⁸² The greatest risk may be with high doses taken long-term and in those with multiple risk factors for cardiovascular or cerebrovascular disease. Naproxen appears to have the best cardiovascular safety profile.^{75, 83–85}

Corticosteroids

- For single troublesome joints, intra-articular corticosteroid injections are especially valuable. There are no randomised placebo-controlled trials (RPCTs) of their use in SARA^{31,33,35,41,71,72,74,79,86–89} (Grade 1C).
- Local corticosteroid injections can be used for enthesitis, although should be used judiciously at weight-bearing sites^{11,31,41,74,87,88} (Grade 2C).
- Topical corticosteroid preparations can be used for cutaneous or mucosal lesions. Low potency options are preferable for mucosal lesions^{9,30} (Grade 1C). Alternative options for mild to moderate lesions include topical salicylic acid ointments, vitamin D3 analogues such as calcitriol⁹⁰ (Grade 1C) and for more severe lesions retinoids such as acitretin^{31,35,91} (Grade 1C).
- Topical corticosteroid eye drops, or oral corticosteroids, and mydriatics are used to treat uveitis. Posterior uveitis usually requires more aggressive therapy.³¹ All patients with eye symptoms should have a slit lamp examination and be managed with specialist ophthalmological advice (Grade 1A).
- Systemic corticosteroids may be valuable where there are several joints involved or where severe constitutional symptoms arise. They can be given orally, as a single intramuscular injection, or occasionally as an intravenous bolus. There are no RPCTs of use of corticosteroids in SARA, but they have been demonstrated to reduce inflammation in rheumatoid arthritis^{31,33,71,72} (Grade 2D). If systemic corticosteroids are used, consideration should be given to osteoporosis prophylaxis, although this is unlikely to be required if a short course or single injection is used.^{92–94}

Disease modifying anti-rheumatic drugs

- These are indicated where there are disabling joint symptoms that have persisted for over 3 months, earlier where there is severe disease, or where erosive joint damage is identified.
- Sulphasalazine has been shown to reduce the severity and duration of peripheral joint synovitis, although it may not influence long-term recovery. There may also be some benefits in early sacroiliitis but not in established ankylosing spondylitis. High doses of 3 g daily may be associated with significant toxicity, particularly gastrointestinal, whereas 2 g daily appears to be equally effective and better tolerated. The dose of sulphasalazine should be titrated upwards until an effective dose is reached^{31,35,72,79,95–99} (Grade 1B).
- Methotrexate is favoured by many physicians because of the ease of weekly oral administration and the favourable responses seen in rheumatoid disease and psoriatic arthritis. The main effect of methotrexate is seen in the peripheral joints and entheses. It may be helpful with severe mucous membrane and skin lesions, although its side effects also include mouth ulceration and gastrointestinal intolerance. There is no proven efficacy of methotrexate in the treatment of axial or spinal joint disease. In addition, there are no published RPCTs of its use in SARA. Doses range from 7.5 to 15 mg orally as a single weekly dose. This can be increased to 25 mg orally in resistant arthritis. It may also be given as an intramuscular preparation. It is important to give oral folic acid, usually as a single 5–15 mg dose weekly, at 24 h following the methotrexate dose^{31,35,71–73,79,91} (Grade 1B).

Biologic agents

- Tumour necrosis factor (TNF) alpha blockers, of which there are a number, are highly effective in the treatment of rheumatoid arthritis,^{81,100–103} ankylosing spondylitis,^{11,69,81,103–109} psoriatic arthritis,^{11,69,81,103,104,107,109–112} and skin lesions,^{69,103,107,109–112} other spondyloarthritides,^{79,107,113,114} and related enthesitis.^{109,111} They have also been reported to reduce the frequency of episodes of uveitis when treating ankylosing spondylitis.^{31,103,107,109,115–118}
- There are side effects with TNF alpha blockers including infusion reactions; an increased risk of infection, including tuberculosis; development of autoantibodies; systemic lupus erythematosus and vasculitis; demyelinating disease and worsening congestive cardiac failure. There is no proven risk for solid cancer and lymphoma development, but caution is necessary for cutaneous malignancies, and frequent skin examination is required.^{79,103,105,107,119,120}
- Experience of the use of biological agents in the treatment of ReA, including SARA, is limited, and no large or controlled studies are available. Early reports are encouraging, and it does not appear that they reactivate the

infective trigger in patients with ReA.^{31,121} However, the place of such therapy in SARA is not yet established^{11,33,35,79,107,122–129} (Grade 2C).

- New treatments for seronegative spondyloarthritis including axial spondyloarthritis and psoriatic arthritis include IL-17A inhibitors^{130,131} and JAK inhibitors¹³² have shown effectiveness in rheumatoid arthritis. No data are currently available on their potential effect in SARA.

Rare treatments

Medical synovectomy

- Procedures involving yttrium-90, osmic acid, samarium-153 or rhenium-186 have shown short-term benefit in symptomatic chronic single-joint synovitis, but their advantage over intra-articular corticosteroids has not been confirmed¹³³ (Grade 2D).

Radiotherapy

- This is exceptionally used for severe, disabling heel pain from enthesitis¹¹ (Grade 2D).

Surgery

- In certain circumstances, surgical procedures such as synovectomy and arthroplasty may be valuable. It has been suggested that a 3-month course of azithromycin be given alongside the synovectomy, but this trial did not include a placebo arm, so benefit cannot be confirmed^{72,134} (Grade 2D).

Low dose TCAs

- Severe postinflammatory pain and fatigue can be treated with low dose tricyclic drugs such as amitriptyline 10–25 mg nocte (Grade 2D).

Pregnancy and breastfeeding

- Many drugs are not licensed in pregnancy or during breastfeeding and should be avoided unless the potential benefit outweighs the risk.
- Recommended and alternative treatment regimens for individual STIs in pregnancy can be found in the relevant STI guidelines on the BASHH website (www.bashh.org/guidelines).
- Non-steroidal anti-inflammatory drugs have the potential to cause reversible subfertility by the luteinised unruptured ovarian follicle syndrome.¹³⁵ If used regularly during pregnancy, particularly in the third trimester, they may result in premature closure of the foetal ductus arteriosus, oligohydramnios, delayed onset and increased duration of labour.^{136,137} Advice on breastfeeding depends on the specific NSAID being used.¹³⁸
- Prolonged use of corticosteroids carries a risk of intrauterine growth restriction and foetal adrenal suppression. Systemic effects to the baby from breastfeeding are unlikely unless the mother is taking more than 40 mg of prednisolone (or equivalent) a day. With higher doses, appropriate monitoring of infant adrenal function is recommended¹³⁷ (Grade 1A).

- Sulphasalazine carries a theoretical risk of neonatal haemolysis in the third trimester, so it should be used with caution in pregnancy and during breastfeeding, and with maternal folate supplementation¹³⁷ (Grade 1A).
- Methotrexate and retinoids are both teratogenic and therefore contraindicated in pregnancy and breastfeeding. Women and men, with their female partners, should avoid conception for at least 6 months after methotrexate use according to advice from the manufacturer. Women taking retinoids should be advised about use of effective contraception for 1 month before, during and at least 1 month after, but in some cases, such as acitretin, up to 3 years after¹³⁷ (Grade 1A).
- Tumour necrosis factor blockers and other biologic therapies should only be used under advice of the appropriate specialist as advice varies depending on the specific medication.¹³⁸

In HIV-positive individuals

- There is no evidence to suggest that treatments should be any different in HIV-positive individuals. Drug interactions and overlapping toxicities with antiretrovirals should be considered (<https://www.hiv-druginteractions.org/checker>).

Reactions to treatment

- There are many treatment options described in this guideline with key side effects highlighted. However, we recommend referring to the British National Formulary (<https://www.medicinescomplete.com>) or Summary of Product Characteristics for full details and to check on interactions with other concomitant medications.

Follow-up

Follow-up for specific STIs should be as for uncomplicated infections. In certain cases, this will include follow-up for test of cure, or repeat screening. See BASHH STI guidelines for further information (www.bashh.org/guidelines).

Follow-up may be useful to confirm adherence to treatment and clarify the risk of reinfection. Where a test of cure is not required, this follow-up could be done over the telephone.

Follow-up for extra-genital features should be under the guidance of the relevant specialist.

Sexually acquired reactive arthritis is a self-limiting disease in the majority of individuals, with mean duration of symptoms of 4–6 months. However, 50% of patients may experience recurrent episodes at variable time intervals, particularly those individuals who are HLA-B27 positive, which is a recognised predictor of disease chronicity and severity in spondyloarthritis.^{16,18,19,29,30,33,35,39,41,43,104, 139}

Up to 17% will develop chronic symptoms lasting over 12 months,²⁹ and 15% will experience persistent locomotor

disability. The latter is principally due to erosive joint damage and resultant deformity.^{18,39}

Ocular involvement with uveitis may lead to cataracts and rapid loss of vision in a minority^{18–20,39} and hence the need for expert ophthalmological input.

Contact tracing and treatment

Contact tracing for specific STIs should be performed according to BASHH guidelines (www.bashh.org/guidelines), with reference to look back periods. Patients should be informed of the importance of partner notification and supported to do this by appropriately trained professionals.

Patients who present as a sexual contact of a known STI should be offered epidemiological treatment and screening for all STIs.

Auditable outcomes

- Proportion of patients with clinical diagnosis of SARA tested for STIs (chlamydia, gonorrhoea, HIV and syphilis as a minimum). Performance standard was 97%.
- Proportion of patients treated with recommended regimen for confirmed STI. Performance standard was 97%.
- Proportion of patients offered information (written or digital) about their diagnosis and management. Performance standard was 97%.
- Proportion of patients with eye symptoms referred for specialist ophthalmologist advice on the same day. Performance standard was 97%.
- Proportion of patients with significant peripheral joint or spinal joint symptoms discussed with/referred to rheumatology within 1 week. Performance standard was 97%.
- Proportion of patients invited for test of cure or repeat screening for specific STI diagnosed in accordance with relevant BASHH STI Guidelines. Performance standard was 97%.

Recommendations for further research

- Investigation of the significance of *M. genitalium* and SARA.
- Elucidation of the current frequency and type of *C. trachomatis* and *N. gonorrhoeae* in synovial fluid of individuals with SARA.
- Evaluation of antibiotic duration for the treatment of genital chlamydia where SARA is also present.
- A protocol for a Cochrane systematic review has been established to evaluate this contentious area, and this needs to be progressed.¹⁴⁰

Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure specification of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

Review arrangements

An author group will be invited by the BASHH CEG to review and revise the guideline in 2025 using the BASHH framework for guideline development. However, addenda may be issued sooner than 2025, particularly if relevant new data are available relating to testing or treatment options.

Acknowledgements

We thank the patient representative who has reviewed the document. We acknowledge and thank Dr Andrew Keat, Dr Kate Nambiar and Mrs Alison Darley for their valuable contributions to this guideline.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without funding being sought or obtained. All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG.

Membership of the clinical effectiveness group

Current membership of the BASHH Clinical Effectiveness Group is available at <https://www.bashh.org/guidelines>.

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References

- Schumacher HR Jr, Magge S, Cherian PV, et al. Light and electron microscopic studies on the synovial membrane in Reiter's syndrome. Immunocytochemical identification of chlamydial antigen in patients with early disease. *Arthritis Rheum* 1988; 31: 937–946.
- Taylor-Robinson D, Gilroy CB, Thomas BJ, et al. Detection of Chlamydia trachomatis DNA in joints of reactive arthritis patients by polymerase chain reaction. *Lancet* 1992; 340: 81–82.
- Rahman MU, Cheema MA, Schumacher HR, et al. Molecular evidence for the presence of chlamydia in the synovium of patients with Reiter's syndrome. *Arthritis Rheum* 1992; 35: 521–529.
- Bas S, Griffais R, Kvien TK, et al. Amplification of plasmid and chromosome chlamydia DNA in synovial fluid of patients with reactive arthritis and undifferentiated seronegative oligoarthritis. *Arthritis Rheum* 1995; 38: 1005–1013.
- Branigan PJ, Gérard HC, Hudson AP, et al. Comparison of synovial tissue and synovial fluid as the source of nucleic acids for detection of Chlamydia trachomatis by polymerase chain reaction. *Arthritis Rheum* 1996; 39: 1740–1746.
- Li F, Bulbul R, Schumacher HR Jr, et al. Molecular detection of bacterial DNA in venereal-associated arthritis. *Arthritis Rheum* 1996; 39: 950–958.
- Nikkari S, Puolakkainen M, Yli-Kerttula U, et al. Ligase chain reaction in detection of chlamydia DNA in synovial fluid cells. *Br J Rheumatol* 1997; 36: 763–765.
- Vittecoq O, Schaefferbeke T, Favre S, et al. Molecular diagnosis of ureaplasma urealyticum in an immunocompetent patient with destructive reactive polyarthritis. *Arthritis Rheum* 1997; 40: 2084–2089.
- Tully JG, Rose DL, Baseman JB, et al. Mycoplasma pneumoniae and mycoplasma genitalium mixture in synovial fluid isolate. *J Clin Microbiol* 1995; 33: 1851–1855.
- Gérard HC, Branigan PJ, Schumacher HR, Jr, et al. Synovial chlamydia trachomatis in patients with reactive arthritis/Reiter's syndrome are viable but show aberrant gene expression. *J Rheumatol* 1998; 25: 734–742.
- Rihl M, Klos A, Köhler L, et al. Infection and musculoskeletal conditions: reactive arthritis. *Best Pract Res Clin Rheumatol* 2006; 20: 1119–1137.
- Gérard HC, Whittum-Hudson JA, Carter JD, et al. The pathogenic role of Chlamydia in spondyloarthritis. *Curr Opin Rheumatol* 2010; 22: 363–367.
- Gerard HC, Stanich JA, Whittum-Hudson JA, et al. Patients with Chlamydia-associated arthritis have ocular (trachoma), not genital, serovars of C. trachomatis in synovial tissue. *Microb Pathog* 2010; 48: 62–68.
- Perry MEO and White JA. Three cases of reactive arthritis secondary to lymphogranuloma venereum. *J Clin Rheumatol* 2015; 21(1): 33–34.
- Mason E, Wray L, Foster R, et al. Reactive arthritis at the Sydney sexual health centre 1992-2012: declining despite increasing chlamydia diagnoses. *Int J STD AIDS* 2015; 27: 882–889.
- Csonka GW. The course of Reiter's syndrome. *Br Med J* 1958; 1: 1088–1090.
- Rosenthal L, Olhagen B and Ek S. Aseptic arthritis after gonorrhoea. *Ann Rheum Dis* 1980; 39: 141–146.
- Leirisalo M, Skylv G, Kousa M, et al. Followup study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum* 1982; 25: 249–259.
- Kousa M. Clinical observations on Reiter's disease with special reference to the venereal and non-venereal aetiology. *Acta Derm Venereol Suppl (Stockh)* 1978; 58(Suppl S1): 1–36.
- Csonka GW. Workshop I. Features and prognosis of Reiter's syndrome. Clinical aspects of Reiter's syndrome. *Ann Rheum Dis* 1979; 38(Suppl): 4–7.

21. Taylor-Robinson D and Keat A. Observations on *Chlamydia trachomatis* and other microbes in reactive arthritis. *Int J STD AIDS* 2015; 26(3): 139–144.
22. Horner PJ and Martin DH. Mycoplasma genitalium infection in men. *J Infect Dis* 2017; 216: S396–S405.
23. Taylor-Robinson D, Gilroy CB, Horowitz S, et al. *Mycoplasma genitalium* in the joints of two patients with arthritis. *Eur J Clin Microbiol Infect Dis* 1994; 13(12): 1066–1069.
24. Schaeferbeke T, Renaudin H, Vernhes JP, et al. Ureaplasma urealyticum and reactive arthritis. *Clin Rheumatol* 1995; 14: 252.
25. Horowitz S, Horowitz J, Taylor-Robinson D, et al. Ureaplasma urealyticum in Reiter's syndrome. *J Rheumatol* 1994; 21: 877–882.
26. Kennedy SL, Murira J and Wenham CY. A case of reactive arthritis secondary to sexually acquired *Shigella flexneri*. *Oxf Med Case Rep* 2017; 2017: 210–211.
27. Chen M, Delpech V, O'Sullivan B, et al. *Shigella sonnei*: another cause of sexually acquired reactive arthritis. *Int J STD AIDS* 2002; 13(2): 135–136.
28. Public Health England. Laboratory surveillance of non-travel associated *Shigella* spp. infection in adult males, England: 2004 to 2017. *Health Protection Report* 2017. 11(42). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662498/hpr4217_shgll-nntrvl.pdf.
29. Keat A. Reiter's syndrome and reactive arthritis in perspective. *N Engl J Med* 1983; 309: 1606–1615.
30. Keat AC, Maini RN, Pegrum GD, et al. The clinical features and HLA associations of reactive arthritis associated with non-gonococcal urethritis. *Q J Med* 1979; 48: 323–342.
31. Leirisalo-Repo M, Repo H and Hochberg MC. Reactive arthritis: clinical features and treatment. In: Silman AJ, Smolen JS, Weinblatt ME, et al. (eds) *Rheumatology*. 5th ed. Philadelphia: Mosby Elsevier; 2011. Section 8: Infection-related rheumatic diseases, 110, pp. 1113–1120.
32. Keat AC, Maini RN, Nkwazi GC, et al. Role of *Chlamydia trachomatis* and HLA-B27 in sexually acquired reactive arthritis. *Br Med J* 1978; 1: 605–607.
33. Hamdulay SS, Glynne SJ and Keat A. When is arthritis reactive?. *Postgrad Med J* 2006; 82: 446–453.
34. Martin DH, Pollock S, Kuo CC, et al. *Chlamydia trachomatis* infections in men with Reiter's syndrome. *Ann Intern Med* 1984; 100: 207–213.
35. Colmegna I, Cuchacovich R and Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. *Clin Microbiol Rev* 2004; 17: 348–369.
36. Stein CM and Davis P. Arthritis associated with HIV infection in Zimbabwe. *J Rheumatol* 1996; 23: 506–511.
37. Clark MR, Solinger AM and Hochberg MC. Human immunodeficiency virus infection is not associated with Reiter's syndrome. Data from three large cohort studies. *Rheum Dis Clin North Am* 1992; 18: 267–276.
38. Adizie T, Moots RJ, Hodkinson B, et al. Inflammatory arthritis in HIV positive patients: a practical guide. *BMC Infect Dis* 2016; 16: 100.
39. Csonka GW. Long-term follow-up and prognosis of Reiter's syndrome. *Ann Rheum Dis* 1979; 38(Suppl): 24–28.
40. Kousa M, Saikku P, Richmond S, et al. Frequent association of chlamydial infection with Reiter's syndrome. *Sex Transm Dis* 1978; 5: 57–61.
41. Flores D, Marquez J, Garza M, et al. Reactive arthritis: newer developments. *Rheum Dis Clin North Am* 2003; 29: 37–59. vi.
42. Good AE. Reiter's syndrome: long-term follow-up in relation to development of ankylosing spondylitis. *Ann Rheum Dis* 1979; 38(Suppl 1): 39–45.
43. Popert AJ, Gill AJ and Laird SM. A prospective study of reiter's syndrome. An interim report on the first 82 cases. *Br J Vener Dis* 1964; 40: 160–165.
44. Hannu T, Nieminen MS, Swan H, et al. Cardiac findings of reactive arthritis: an observational echocardiographic study. *Rheumatol Int* 2002; 21: 169–172.
45. Kontinen YT, Bergroth V, Nordström D, et al. IgA nephropathy in reactive arthritis. *J Rheumatol* 1987; 14: 1070–1071.
46. 2015 BASHH CEG guidance on tests for Sexually Transmitted Infections. Available at <https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf>
47. International Union Against Sexually Transmitted Infections Treatment Guidelines (Europe). Available at <https://iusti.org/treatment-guidelines/>
48. British Association For Sexual Health and HIV guidelines. Available at <https://www.bashh.org/guidelines>
49. Centers for Disease Control and Prevention 2015 Sexually Transmitted Diseases Treatment Guidelines. Available at <https://www.cdc.gov/std/tg2015/default.htm>
50. 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: 1299–1302.
51. 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: 190–194.
52. Nordström D, Lindy O, Lauhio A, et al. Anti-collagenolytic mechanism of action of doxycycline treatment in rheumatoid arthritis. *Rheumatol Int* 1998; 17: 175–180.
53. 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.
54. Sieper J, Fendler C, Laitko S, et al. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled study. *Arthritis Rheum* 1999; 42: 1386–1396.
55. 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: 565–570.
56. Kvien TK, Gaston JS, Bardin T, et al. Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study. *Ann Rheum Dis* 2004; 63: 1113–1119.
57. Smieja M, MacPherson DW, Kean W, et al. Randomised, blinded, placebo controlled trial of doxycycline for chronic seronegative arthritis. *Ann Rheum Dis* 2001; 60: 1088–1094.
58. 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: 1894–1897.

59. 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. *Arthr Rheum* 1997; 40(Suppl 1): S143.
60. Putschky N, Pott HG, Kuipers JG, et al. Comparing 10-day and 4-month doxycycline courses for treatment of Chlamydia trachomatis-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006; 65: 1521–1524.
61. Dreses-Werringloer U, Padubrin I, Zeidler H, et al. Effects of azithromycin and rifampin on Chlamydia trachomatis infection in vitro. *Antimicrob Agents Chemother* 2001; 45: 3001–3008.
62. Carter JD, Valeriano J and Vasey FB. Doxycycline versus doxycycline and rifampin in undifferentiated spondyloarthritis, with special reference to chlamydia-induced arthritis. A prospective, randomized 9-month comparison. *J Rheumatol* 2004; 31: 1973–1980.
63. Carter JD, Espinoza LR, Inman RD, et al. Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. *Arthritis Rheum* 2010; 62: 1298–1307.
64. Leirisalo-RepoPaimela ML, Julkunen H, Peltomaa R, et al. A 3-month, randomised, placebo-controlled study with combination antimicrobial therapy in acute reactive arthritis. *Arthritis Rheum* 2001; 44(Suppl): S91.
65. Yli-Kerttula T, Luukkainen R, Yli-Kerttula U, et al. Effect of a three month course of ciprofloxacin on the late prognosis of reactive arthritis. *Ann Rheum Dis* 2003; 62: 880–884.
66. Laasila K, Laasonen L and Leirisalo-Repo M. Antibiotic treatment and long term prognosis of reactive arthritis. *Ann Rheum Dis* 2003; 62: 655–658.
67. Pott HG, Wittenborg A and Junge-Hülsing G. Long-term antibiotic treatment in reactive arthritis. *Lancet* 1988; 1: 245–246.
68. Barber CE, Kim J, Inman RD, et al. Antibiotics for treatment of reactive arthritis: a systematic review and metaanalysis. *J Rheumatol* 2013; 40: 916–928.
69. Anandarajah A and Ritchlin CT. Treatment update on spondyloarthritis. *Curr Opin Rheumatol* 2005; 17: 247–256.
70. NICE guideline [NG65]. Spondyloarthritis in over 16s: diagnosis and management. Published February 2017. Available at: <https://www.nice.org.uk/guidance/ng65>
71. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European standing committee for international clinical studies including therapeutics (ESCSIT). *Ann Rheum Dis* 2007; 66: 34–45.
72. Toivanen A and Toivanen P. Epidemiologic, clinical, and therapeutic aspects of reactive arthritis and ankylosing spondylitis. *Curr Opin Rheumatol* 1995; 7: 279–283.
73. Cuellar ML and Espinoza LR. Management of spondyloarthritis. *Curr Opin Rheumatol* 1996; 8: 288–295.
74. Leirisalo-Repo M. Prognosis, course of disease, and treatment of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998; 24: 737–751. viii.
75. Patrono C. Non-steroidal anti-inflammatory drugs. In: Hochberg MC, Silman AJ, Smolen JS, et al. (eds) *Rheumatology*. 5th ed. Philadelphia: Mosby Elsevier; 2011. Section 4: Principles of management, 50, pp. 485–493.
76. Juvakoski T and Lassus A. A double-blind cross-over evaluation of ketoprofen and indomethacin in Reiter's disease. *Scand J Rheumatol* 1982; 11: 106–108.
77. Dougados M, Nguyen M, Caporal R, et al. Ximoprofen in ankylosing spondylitis. A double blind placebo controlled dose ranging study. *Scand J Rheumatol* 1994; 23: 243–248.
78. Wienecke T and Göttsche PC. Paracetamol versus non-steroidal anti-inflammatory drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2004; (1): CD003789.
79. Palazzi C, Olivieri I, D'Amico E, et al. Management of reactive arthritis. *Expert Opin Pharmacother* 2004; 5: 61–70.
80. Medicines & Healthcare products Regulatory Agency Guidance. Cox-2 selective inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs): Cardiovascular safety. Published January 2015. Available at <https://www.gov.uk/government/publications/cox-2-selective-inhibitors-and-non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-safety/cox-2-selective-inhibitors-and-non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-safety>
81. National Institute for Health and Care Excellence. NSAIDs – prescribing issues. Last revised April 2020. Available at <https://cks.nice.org.uk/topics/nsaids-prescribing-issues/>
82. British National Formulary. Non-steroidal anti-inflammatory drugs – NSAIDs and cardiovascular events. Available at: <https://bnf.nice.org.uk/treatment-summary/non-steroidal-anti-inflammatory-drugs.html>
83. McGettigan P and Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006; 296: 1633–1644.
84. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006; 332: 1302–1308.
85. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2009; 2: 155–163.
86. Blyth T, Hunter JA and Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. *Br J Rheumatol* 1994; 33: 461–463.
87. Canoso JJ, Naredo E and Hochberg MC. *Aspiration and injection of joints and periarticular tissues and intraleisional therapy*. In: Silman AJ, Smolen JS, Weinblatt ME, et al. (eds) *Rheumatology*. 5th ed. Philadelphia: Mosby Elsevier; 2011. Section 4: Principles of management, 66, pp. 617–628
88. Calin A. Workshop III. Management of Reiter's syndrome. *Ann Rheum Dis* 1979; 38(Suppl): 96–97.
89. Günaydin I, Pereira PL, Daikeler T, et al. Magnetic resonance imaging guided corticosteroid injection of the sacroiliac joints in patients with therapy resistant spondyloarthritis: a pilot study. *J Rheumatol* 2000; 27: 424–428.
90. Thiers BH. The use of topical calcipotriene/calcipotriol in conditions other than plaque-type psoriasis. *J Am Acad Dermatol* 1997; 37: S69–S71.
91. Owen ET and Cohen ML. Methotrexate in Reiter's disease. *Ann Rheum Dis* 1979; 38: 48–50.

92. Homik J, Suarez-Almazor ME, Shea B, et al. Calcium and vitamin D for corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 1998; 2(2): CD000952.
93. Cranney A, Welch V, Adachi J, et al. Calcitonin for preventing and treating corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 2000; 1: CD001983.
94. Homik J, Cranney A, Shea B, et al. Bisphosphonates for steroid induced osteoporosis. *Cochrane Database Syst Rev* 1999; (1): CD001347.
95. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995; 38: 618–627.
96. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulfasalazine and placebo in the treatment of reactive arthritis (Reiter's syndrome). A department of veterans affairs cooperative study. *Arthritis Rheum* 1996; 39: 2021–2027.
97. 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: 32–36.
98. Clegg DO, Reda DJ and Abdellatif M. Comparison of sulfasalazine 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: 2325–2329.
99. Braun J, Zochling J, Baraliakos X, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006; 65: 1147–1153.
100. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. *N Engl J Med* 2000; 343: 1594–1602.
101. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343: 1586–1593.
102. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46: 1443–1450.
103. Reimold AM. New indications for treatment of chronic inflammation by TNF-alpha blockade. *Am J Med Sci* 2003; 325: 75–92.
104. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002; 136: 896–907.
105. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; 359: 1187–1193.
106. Gorman JD, Sack KE and Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002; 346: 1349–1356.
107. Braun J and Sieper J. Biological therapies in the spondyloarthritides—the current state. *Rheumatology (Oxford)* 2004; 43: 1072–1084.
108. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 2136–2146.
109. Kavanaugh A, Tutuncu Z and Catalan-Sanchez T. Update on anti-tumor necrosis factor therapy in the spondyloarthropathies including psoriatic arthritis. *Curr Opin Rheumatol* 2006; 18: 347–353.
110. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; 356: 385–390.
111. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005; 64: 1150–1157.
112. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3279–3289.
113. van der Bosch F, Kruithof E, Baeten D, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (infliximab) versus placebo in active spondyloarthropathy. *Arthritis Rheum* 2002; 46: 755–765.
114. Kruithof E, De Rycke L, Roth J, et al. Immunomodulatory effects of etanercept on peripheral joint synovitis in the spondyloarthropathies. *Arthritis Rheum* 2005; 52: 3898–3909.
115. Rosenbaum JT and Smith JR. Anti-TNF therapy for eye involvement in spondyloarthropathy. *Clin Exp Rheumatol* 2002; 20(Suppl 28): S143–S145.
116. Braun J, Baraliakos X, Listing J, et al. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; 52: 2447–2451.
117. Theodossiadis PG, Markomichelakis NN and Sfrikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. *Retina (Philadelphia, Pa)* 2007; 27: 399–413.
118. Levy-Clarke G, Reed G and Nussenblatt R. Is anti-tumor necrosis factor therapy effective in reducing uveitis flares in patients with spondyloarthropathies? *Nat Rev Rheumatol* 2007; 3: 376–377.
119. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N Engl J Med* 2001; 345: 1098–1104.
120. Baeten D, Kruithof E, van den Bosch F, et al. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis* 2003; 62: 829–834.
121. Meyer A, Chatelus E, Wendling D, et al. Safety and efficacy of anti-tumor necrosis factor α therapy in ten patients with recent-onset refractory reactive arthritis. *Arthritis Rheum* 2011; 63: 1274–1280.
122. Carter JD. Treating reactive arthritis: insights for the clinician. *Ther Adv Musculoskelet Dis* 2010; 2: 45–54.
123. Flagg SD, Meador R, Hsia E, et al. Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial. *Arthritis Rheum* 2005; 53: 613–617.

124. Wechalekar MD, Rischmueller M, Whittle S, et al. Prolonged remission of chronic reactive arthritis treated with three infusions of infliximab. *J Clin Rheumatol* 2010; 16: 79–80.
125. Schafranski MD. Infliximab for reactive arthritis secondary to Chlamydia trachomatis infection. *Rheumatol Int* 2010; 30: 679–680.
126. Kaipainen-Seppänen O, Niinisalo H, Korpilähde T, et al. Treatment of reactive arthritis with infliximab. *Scand J Rheumatol* 2003; 32: 122–124.
127. Meador RJ, Hsia EC, Kitumnuaypong T, et al. Is etanercept (ENBREL) effective in the treatment of reactive and undifferentiated arthritis? *Arthritis Rheum* 2001; 44(Suppl): S348.
128. Gaylis N. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. *J Rheumatol* 2003; 30: 407–411.
129. Carter JD, Gerard HC and Hudson AP. Psoriasiform lesions induced by tumour necrosis factor antagonists: a skin-deep medical conundrum. *Ann Rheum Dis* 2008; 67: 1181–1183.
130. van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018; 392(392): 2441–2451.
131. Mease PJ, Kavanaugh A, Reimold A, et al. Secukinumab provides Sustained Improvements in the signs and symptoms of psoriatic arthritis: final 5-year results from the phase 3 FUTURE 1 study. *ACR Open Rheumatol* 2020; 2(1): 18–25.
132. Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* 2019; 58(Suppl 1): i17–i26.
133. O'Duffy EK, Clunie GP, Lui D, et al. Double blind glucocorticoid controlled trial of samarium-153 particulate hydroxyapatite radiation synovectomy for chronic knee synovitis. *Ann Rheum Dis* 1999; 58: 554–558.
134. Pavlica L, Nikolic D, Magic Z, et al. Successful treatment of postvenereal reactive arthritis with synovectomy and 3 months' azithromycin. *J Clin Rheumatol* 2005; 11: 257–263.
135. Smith G, Roberts R, Hall C, et al. Reversible ovulatory failure associated with the development of luteinized unruptured follicles in women with inflammatory arthritis taking non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1996; 35: 458–462.
136. de Wit W, van Mourik I and Wiesenhaan PF. Prolonged maternal indomethacin therapy associated with oligohydramnios. Case reports. *Br J Obstet Gynaecol* 1988; 95: 303–305.
137. British National Formulary. Available online at <https://www.medicinescomplete.com/#/>
138. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)* 2016; 55(9): 1693–1697.
139. McGonagle D, Aydin SZ, Gül A, et al. 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet disease. *Nat Rev Rheumatol* 2015; 11: 731–740.
140. Siva C, Tanjong GE, Zhou X, et al. Antibiotics for reactive arthritis. (Protocol). *Cochrane Database Syst Rev* 2013; (9): CD006078. Art. No: CD006078.