

2014 European Guideline on the management of sexually acquired reactive arthritis

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2014 European Guideline on the management of sexually acquired reactive arthritis

EM Carlin¹, JM Ziza², A Keat³ and M Janier⁴

Introduction

This guideline is for the use of physicians working in dermatovenereology, sexual health, sexually transmitted infection (STI), genitourinary medicine (GUM) clinics in Europe, henceforth referred to as STI clinics and STI physicians.

Aetiology

Reactive arthritis (ReA) is a sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection at a distant site, usually gastrointestinal or genital.

ReA includes Reiter's syndrome, described as the classic triad of urethritis, arthritis and conjunctivitis, with or without other cutaneous or mucous membrane lesions such as keratoderma blennorrhagica, circinate balanitis/vulvitis, uveitis, oral ulceration, cardiac or neurological involvement.

ReA triggered by a gastrointestinal infection may have any of the features outlined above, including urethritis, but in most cases, enteric infection is also present or has recently occurred. It is most commonly associated with *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* infections but it has also been reported with *Clostridium difficile* and occasionally enteropathic *Escherichia coli* infection. It is difficult to determine the true frequency but reported enteric ReA rates are 1–9% when clinical examination is included and higher rates are seen with *Yersinia* infection.^{1–3}

ReA triggered by an STI is referred to as sexually acquired reactive arthritis (SARA). It can include any of the features described above but enteric infection is not present. Lower genital tract infections, either urethritis or cervicitis, are most commonly associated with the condition and objective features of SARA have been reported in 0.8–4% of cases.^{4–7} The place of upper genital tract infection, such as prostatitis and salpingitis, is unresolved. A rising incidence of spondyloarthritis, including ReA, in association with the human immune deficiency virus (HIV) has been seen

in sub-Saharan Africa, although this does not appear to be the case in Caucasian populations.^{8–10}

The precise mechanisms linking infective agents with SARA are not clearly understood, so links with specific micro-organisms are partly speculative.

- *Chlamydia trachomatis*, the commonest identifiable cause of non-gonococcal urethritis (NGU), has been the micro-organism most strongly linked to SARA, being identified in 35–69% of cases, using non-nucleic acid amplification tests (NAATs).^{5,11–16}
- *Neisseria gonorrhoeae* has been linked with up to 16% of cases, as distinct from its role in septic, gonococcal arthritis.^{4,17–20} The precise role of this micro-organism in relation to SARA remains unknown.
- *Ureaplasma urealyticum* has been linked with a few cases and may be a cause of SARA in a minority.^{21,22}
- A causal role for other genital tract pathogens and commensals is possible but there is currently insufficient evidence for evaluation.

Mechanisms of pathogenesis in SARA are not completely elucidated but appear to involve an immune response to uro-genital micro-organisms. DNA and/or surface antigens of *C. trachomatis*,^{13,23–29} *U. urealyticum*^{28,30} and other mycoplasmas³¹ may be detected within joint material from individuals with SARA. It is likely that the persistence of viable micro-organisms intra-articularly is an important factor in the causation and perpetuation of the arthritis. It has been shown in chlamydial infection that the organism develops into an unusual, persistent state in the synovium in an aberrant

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form with repressed synthesis of the major outer membrane protein (MOMP) and active production of heat shock protein (hsp), which contributes to the inflammatory response.^{32–34}

SARA appears to occur over 10 times more frequently in men compared to women, although under recognition in women may be a problem.^{3,4,20,35} Possession of the HLA-B27 gene increases susceptibility to SARA and is associated with increased severity of the condition.^{1,5,7,12,15,18,35}

SARA is a ReA and can be associated with other spondyloarthritides; most commonly ankylosing spondylitis, sometimes psoriatic arthritis and rarely inflammatory bowel arthritis due to Crohn's disease or ulcerative colitis. In some cases, the ReA is complicated by ankylosing spondyloarthritis but the converse can also occur.

Clinical features

Epidemiological data suggests that SARA may be under or mis-diagnosed.³⁶ However, the following pointers will help clinicians to identify and diagnose the condition. It should be noted that most individuals with SARA do not have features of all three of the classic triad described earlier.

History

- There may be a past or family history of spondyloarthritis, iritis, psoriasis, inflammatory bowel disease or SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis).^{3,4,7,19,37}
- Sexual intercourse, usually with a new partner, within 3 months prior to the onset of arthritis.^{5,12,35}

Symptoms

- Onset of arthritis within 30 days of sexual contact in 88% of patients with a mean interval of 14 days between the onset of genital tract symptoms and arthritis.^{3,4,5,19,35}
- A recent history of urethral discharge and/or dysuria in approximately 80% of men with SARA, although considerably fewer women are symptomatic.^{12,14,19,20,35}
- Pain, with or without swelling and stiffness, at one or more (usually fewer than six) joints especially at the knees, ankles and feet. The upper limb joints are much less commonly involved. The arthritis is usually asymmetrical and is inflammatory with morning stiffness and nocturnal pain.^{1,3,7,16,19,35}

- Pain and stiffness at entheses, especially the posterior and plantar aspect of the heels, which often results in difficulty in walking. Enthesitis and/or fasciitis occurs in up to 40% of patients.^{3,4,16,18,20,35}
- Painful movements may also result in 30% from tenosynovitis and in 16% painful swelling of a toe or finger (dactylitis) may occur.^{3,16,35}
- Low back pain and stiffness is common in the acute episode. Sciatalgia and sacral pain can occur and sacro-iliitis occurs in approximately 10% of patients during the acute episode.^{1,3,4,16,18–20,35,38,39}
- Irritable eyes, with or without redness, photophobia or a reduction in visual acuity. Conjunctivitis occurs in 20–50% of patients with SARA, often bilateral and preceding the arthritis by a few days, but iritis is less common occurring in around 2–11% of patients.^{3,4,7,18–20,35,39} Other eye lesions occur rarely.^{4,18,20}
- Systemic symptoms of malaise, fatigue and fever occur in approximately 10% of patients.³⁵

Physical signs

- Genital infection. Manifest in men by urethritis, urethral discharge and/or epididymo-orchitis and in women by muco-purulent cervicitis, with or without easily-induced cervical bleeding and/or abdominal pain. Proctitis in both sexes. Infection may be asymptomatic, particularly in women.^{12,14,19,20,35}
- Arthritis, almost invariably affecting 1–5 lower limb joints in an asymmetrical distribution. Persistent small joint involvement may be erosive. Upper limb involvement is rare in the absence of psoriasis.^{3,7,19,35}
- Enthesopathy. Tenderness, with or without swelling at the sites of tendon or fascial attachments, especially the Achilles tendon and plantar fascia attachments to the calcaneum.^{3,4,7,18,20,35}
- Tenosynovitis. Tenderness, with or without swelling over tendon sheaths and crepitus on movement. Classical dactylitis may be seen.^{3,35}
- Pain on direct sacral pressure may indicate acute sacro-iliitis.^{3,4,18,20,35} Care should be taken to distinguish this from lumbosacral disc disease or hip involvement.
- Pain, irritation and redness of the eye are usually due to conjunctivitis, or rarely iritis.^{3,4,7,18–20,35,39} Slit lamp examination is required to differentiate between them but pain is more commonly a feature of iritis. Rarely, corneal ulceration, keratitis and intra-ocular haemorrhage may be seen and optic neuritis and posterior uveitis have been described.^{3,4,7,18,20}

- Psoriasiform rash which may be typical plaque or guttate cutaneous psoriasis in 12.5%,¹⁹ nail dystrophy in 6–12%,^{19,39} typical lesions of psoriasis on the glans penis or labia (there may also be erosive circinate balanitis or vulvitis, which may occur without other features of ReA) in 14–40%,^{3,4,15,18,20,35,39} tongue (geographical tongue) in about 16%,³⁹ or pustular psoriasis on the soles of the feet (keratoderma blennorrhagica) in up to 33%.^{3,4,7,15,18–20,35,39} The latter may rarely occur on the palms of the hands. Stomatitis and oral ulceration occur in approximately 10%.^{3,15,18–20}
- Heart lesions are almost invariably asymptomatic although tachycardia, left ventricular dilatation, and rarely pericarditis and aortic valve disease may occur. Electrocardiographic abnormalities, including conduction delay, are recorded in 5–14% of patients.^{3,15,18–20,40}
- Renal pathology, such as proteinuria, microhaematuria and aseptic pyuria, which may be due to concurrent urethritis, is seen in about 50%. It is usually asymptomatic and glomerulonephritis and IgA nephropathy rarely occur.^{1,41}
- Very rare manifestations include thrombophlebitis of the lower limbs, subcutaneous nodules, nervous system involvement including meningoencephalitis and nerve palsies.^{3,4,19,20}
- Fever and weight loss occur in a minority of patients, approximately 10%.^{16,35,38}

Complications

In the majority of individuals with SARA, the disease is self-limiting with a mean first episode duration of 4–6 months followed by full recovery.^{3,4,7,16,35,39} Approximately 50% have recurrent episodes at variable intervals.^{3,4,7,19,37} The complications of SARA are principally due to aggressive arthritis and are more likely if the individual possesses the HLA-B27 gene.^{7,15,18,35,42}

- Chronicity with symptoms persisting for more than one year in approximately 17% of patients.³
- Erosive joint damage especially affects the small joints of the feet with 12% exhibiting foot deformities, although severe deformity is very rare, unless there is co-existing psoriasis.⁴
- Persistent locomotor disability occurs in approximately 15%, due principally to erosive damage with deformity of the metatarsophalangeal, ankle or knee joints, or as a consequence of sacro-iliitis or spondylitis.^{18,37} Heel and foot involvement is particularly associated with subsequent disability. No accurate estimates of the prevalence of ankylosing spondylitis are available although it has been described in up to 23% of patients with severe disease and sacro-iliitis has been reported in 37% of patients over a 15-year follow up period.^{16,38} It is unclear whether the development of ankylosing spondylitis is a complication of the ReA or the independent development of two conditions in the same genetically predisposed population, as SARA, ReA, ankylosing spondylitis, inflammatory bowel arthritis and SAPHO are all types of spondyloarthritis and belong to the same collection of conditions.
- Inadequately treated, or recurrent, acute anterior uveitis may lead rapidly to cataract formation and blindness in a minority.^{18–20,37}

Diagnosis

The diagnosis of SARA involves three components.

- Recognition of the typical clinical features of spondyloarthritis. It is important to consider and differentiate SARA from a septic arthritis. Features suggestive of a septic arthritis include the rapid onset of an intensely painful, swollen, warm, red joint with fever and chills. Usually, only one joint is affected with septic arthritis but, in some cases, there may be more.
- Demonstration of evidence of genito-urinary infection by the identification of:
 - Urethritis in men. Urethral discharge, dysuria and/or epididymo-orchitis may be present. Asymptomatic cases with *C. trachomatis* are relatively common, occurring in up to 50% of men. Microscopic confirmation is by a Gram-stained urethral smear demonstrating ≥ 5 polymorphonuclear leucocytes (PMNLs) per high power ($\times 1000$) microscopic field (averaged over five fields with the greatest concentration of PMNLs), and/or ≥ 10 PMNLs per high power ($\times 1000$) microscopic field on a Gram-stained preparation from a centrifuged sample of a first void urine (averaged over five fields with the greatest concentration of PMNLs).
 - Muco-purulent cervicitis in women. Post-coital or intermenstrual bleeding, dysuria, purulent vaginal discharge, purulent or muco-purulent endocervical exudate, with or without easily-induced cervical bleeding, and/or lower abdominal/pelvic pain may be present. However, cervical infection with *C. trachomatis* is frequently asymptomatic, occurring in about 70% of women.
 - Rectal infection in men and women. This may present with anal discharge and/or anorectal discomfort due to proctitis but most infections are asymptomatic.

- The identification of genital pathogens, particularly *C. trachomatis* (including serovar L) or *N. gonorrhoeae*. Full screening for STIs is essential from sites, as indicated by the sexual history.
- Refer to relevant guidelines on NGU, *C. trachomatis*, gonorrhoea, and STI screening.^{43–45}
- Investigation of specificity and activity of arthritis.

Management

Information, explanation and advice for the patient

Patients should be given a detailed explanation of their condition and this should be reinforced by giving them clear and accurate written information.^{15,43,46}

In the majority of patients, SARA is a self-limiting disease and this should be explained. However, information on the long-term implications should also be provided.

Sexual intercourse (including oral sex) should be avoided by the patient until they and their partner(s) have completed treatment and follow-up for any genital infection identified.

Further investigation

The following investigations are essential, often useful or sometimes useful.^{1,3,7,11,15,16,18–20,35,37–39,46–49} Close liaison between STI physicians and rheumatologists is recommended and the patient should be referred to other specialists where there is significant extra-genital involvement. In particular, those with ocular or visual symptoms should be referred to an ophthalmologist for eye and slit lamp assessment.

Essential

- Synovial fluid analysis for cell count, Gram stain, crystals, culture (where septic arthritis is suspected).
- Full screening for STIs, including HIV.
- Acute phase response such as, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
- Full blood count (FBC).
- Urinalysis (to check for renal pathology).

Investigations, which are often useful

- Liver and kidney function tests.
- HLA-B27.
- X-rays of affected joints, spine and sacro-iliac joints.
- Ultrasonography of affected joints or entheses.
- Electrocardiogram.
- Ophthalmic evaluation including slit lamp assessment.

Investigations, which are sometimes useful

- Blood cultures.
- Stool culture (if enteric ReA is suspected).
- Magnetic resonance imaging of sacro-iliac joints.
- Synovial biopsy.
- Echocardiogram.
- Exclusion tests for other diseases with rheumatological features, for example, rheumatoid factor and anti-cyclic citrullinated peptide antibodies (anti-CCP) (rheumatoid arthritis), autoantibodies (systemic lupus erythematosus), plasma urate (gout), chest X-ray and serum angiotensin-converting enzyme (ACE) level (sarcoidosis).

Therapy

Therapy is directed at several distinct elements of the condition. It is advisable that advice/assessment is obtained from relevant specialists as indicated above.

Constitutional symptoms

- Rest.
- Non-steroidal anti-inflammatory drugs (NSAIDs).

Genital infection

- Antimicrobial therapy for any genital infection identified should be as in uncomplicated infection. Refer to the relevant infection guidelines.^{43–45} Whether short course antibiotic treatment of the acute genital infection influences the non-genital aspects of SARA is controversial, with the probability being that it does not once the arthritis is manifest. (Ib, A)^{35,39,50,51}

Arthritis

First line therapy

- Rest with the restriction of physical activity, especially weight-bearing activity where leg joints are involved. Use physiotherapy, as necessary, to prevent muscle wasting and, when symptoms improve, to strengthen muscles and improve the range of movement in the affected joints. Physiotherapy and exercise are particularly important where there is axial involvement. (IV, C)^{7,33,46,52–55}
- Physical therapy with the use of cold pads to alleviate joint pain and oedema. (IV, C)^{52–54}
- NSAIDs are well established as efficacious agents in many inflammatory arthritides and form the main

stay of therapeutic management. It is important that they are used regularly to achieve the maximum anti-inflammatory effect. There is no definite drug of choice and the individual response varies between individuals. (IIB, B)^{1,7,15,16,46,52–54,56–59}

NSAIDs have significant gastrointestinal, renal and cardiovascular side effects. All individuals should be assessed and a cyclo-oxygenase (COX)-2-selective drug should be used for those at high risk of upper gastrointestinal complications, such as gastrointestinal bleeding. Adding gastro-protective agents, such as misoprostol, histamine-2 blockers and a proton pump inhibitor (PPI), to non-selective NSAIDs, can also reduce the gastrointestinal risks. Individuals at the highest risk of gastrointestinal complications are those with a history of upper gastrointestinal disease or haemorrhage and those over 65 years of age. Other factors, associated to a lesser extent, with an increased risk are male gender, cigarette smoking, heavy alcohol use, concomitant oral glucocorticoids, anticoagulants, thienopyridines or low dose aspirin.⁵⁶

COX-2-selective drugs used long-term have been linked with increased cardiovascular risk and so should be avoided in those at high cardiovascular risk, such as those with established ischaemic heart disease or cerebrovascular disease. This may extend to all NSAIDs although naproxen appears to have the best cardiovascular safety.^{56,60–62} Therefore, it is advised that treatment is given for the shortest time period possible and avoided or modified in at-risk patients. (Ia, A)^{7,46,56,63–65}

- Intra-articular corticosteroid injections are especially valuable for single troublesome joints, sometimes given under radiological control. They may also be used for inflamed sacro-iliac joints. They have proven value in other inflammatory arthritides but there are no randomised placebo-controlled trials (RPCTs) of their use in SARA. (IV, C)^{1,7,15,16,46,52,54,65,66–69}

Second line therapy (moderate/severe arthritis/failure of first line)

As above +

- Systemic corticosteroids. If used, consideration should be given to anti-osteoporosis prophylaxis. (Ia, A)^{70–72} This is unlikely to be required with a short course or single bolus therapy. Corticosteroids are valuable where severe symptoms arise from several joints, often in the presence of constitutional illness, either as a short course of oral prednisolone 10–30 mg daily or as a single intramuscular dose of depot methyl prednisolone 80–120 mg. Intravenous bolus preparations may also be used. In rheumatoid

arthritis, it has been shown to suppress inflammation but there are no RPCTs of its use in SARA. (IV, C)^{1,7,46,52}

- Sulphasalazine. Indicated where disabling symptoms persist for three or more months, or evidence of erosive joint damage is present. Sulphasalazine reduces the severity and duration of peripheral joint synovitis but probably does not influence ultimate recovery. There may also be some benefits in early sacroiliitis but not in established ankylosing spondylitis. High doses, 3 g daily, are associated with significant toxicity, especially gastrointestinal, which may necessitate cessation of treatment, whereas 2 g daily appears equally effective and better tolerated. The effective dose must be reached by progressive increments. (Ib, A)^{1,15,52,65,73–77}
- Methotrexate. Indicated where disabling symptoms persist for three or more months, or earlier in cases of severe disease or where evidence of erosive joint damage is present. Doses range from 7.5–15 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. Oral folic acid should be given, usually as a single 5–15 mg dose weekly, at 24 h following the methotrexate dose. 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. There are no published RPCTs of its use in SARA. (IV, C)^{7,15,46,52,53,65,78}
- Azathioprine. Indicated where disabling symptoms persist for three or more months, or evidence of erosive joint damage is present. Doses of 1–4 mg/kg/body weight per day may be used. (III, B)^{15,52,65,79}
- Gold salts and D-penicillamine. These drugs are now rarely used. No RPCTs have been published concerning their use in SARA. (IV, C)^{15,52}
- Biological agents. Tumour necrosis factor (TNF) α blockers, such as infliximab, etanercept and adalimumab, are highly effective in the treatment of rheumatoid arthritis,^{64,80–83} ankylosing spondylitis,^{33,42,55,64,83–88} psoriatic arthritis^{33,42,55,64,83,86,88,89–91} and other spondyloarthritis.^{65,86,92,93}

There are side effects with TNF α 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.^{65,83,84,86,94,95}

Experience of the use of biological agents in the treatment of ReA, including SARA, is limited and there are no large or controlled studies available.

Early reports are encouraging and it does not appear that they re-activate the infective trigger in patients with ReA.^{1,96} However, the place of such therapy in SARA is not yet established. (IV, C)^{7,15,33,36,65,86,97–103}

- Antibiotics

- Standard short course antibiotic therapy used for the treatment of concomitant uro-genital infection^{43–45} may reduce the risk of recurrent arthritis developing in individuals with a history of ReA, but otherwise there is little evidence of benefit in respect of the duration, severity or course of the arthritis. (Ib, A)^{16,35,39,50,51}
- Longer course antibiotic therapy has been considered. However, many studies have had small numbers of individuals with SARA and mostly antibiotic therapy has been commenced after the arthritis has become established. Antibiotics may also have anticollagenolytic properties.¹⁰⁴ Conflicting results have been obtained, with one study by Lauhio et al. identifying that lymecycline given for three months reduced the duration of arthritis in *C. trachomatis*-triggered SARA.¹⁰⁵ However, no significant effect was seen in placebo-controlled studies of three-month courses of ciprofloxacin, azithromycin or doxycycline, a 12-month course of ciprofloxacin, nor in placebo-controlled comparative studies of short-course versus four months of doxycycline therapy.^{106–112}
- There are theoretical *in vitro* advantages of using combination antimicrobial therapy with rifampicin in terms of persistent chlamydial eradication.¹¹³ *In vivo*, one study identified significant improvements in arthritis and back pain in those treated for three months with doxycycline and rifampicin compared with doxycycline alone.¹¹⁴ Another study identified improvements in patients receiving six months of combination therapy with either doxycycline and rifampicin or azithromycin and rifampicin, compared to rifampicin alone.¹¹⁵ In addition, more patients in the combination groups became negative for *C. trachomatis* by PCR. However, others have shown no benefit in a combined placebo-controlled study with ofloxacin and roxithromycin.¹¹⁶
- The effect of longer term therapy on the late prognosis of arthritis has been evaluated. One study has shown that 8% of those treated with a three-month course of ciprofloxacin, compared to 41% in a placebo group, had developed chronic disease when assessed 4–7 years

later.¹¹⁷ However, this has not been confirmed by a 10-year follow-up study of patients treated with lymecycline, despite the benefits seen initially.¹¹⁸

- The role of combination or longer term antimicrobial therapy in SARA is not yet established and further studies are needed. A protocol for a Cochrane systematic review has been established to evaluate this contentious area. (Ib, A)^{7,16,55,105–112,114–121}
- Medical synovectomy using Yttrium-90, osmic acid, Samarium-153 or Rhenium-186. All have been shown to have short-term benefit in chronic mono-articular synovitis. Advantages over intra-articular corticosteroid injections have not been confirmed. (Ib, A)¹²²
- Surgery. Exceptionally, surgical treatment including synovectomy and arthroplasty is valuable. For synovectomy, the concomitant use of azithromycin for three months has been suggested but the study describing this did not include a placebo arm so a definitive benefit could not be confirmed.^{52,123}

Enthesitis

- Rest. (IV, C)
- Physiotherapy and ultrasound.³³
- Orthotics with insoles, cushioning and heel supports. (IV, C)^{7,33}
- NSAIDs, usually oral but occasionally may be useful topically. (IV, C)^{1,7,33,65}
- Local corticosteroid injection. (IV, C)^{1,16,33,54,67,68}
- Radiotherapy for persistent disabling heel pain, exceptionally.³³
- Surgery, exceptionally.
- TNF blockers appear to improve enthesitis associated with other spondyloarthritis, but there are no RPCTs of their use in SARA. (IV, C)^{88,90}

Mucous membrane and skin lesions

- No treatment for mild lesions.
- Keratinolytic agents, such as topical salicylic acid ointments or corticosteroid preparations, in mild-to-moderate cases. Low potency topical corticosteroids are the best option for mucosal sites. (IV, C)^{1,15}
- Vitamin D3 analogues in mild-to-moderate cases. Calcitriol ointment is better tolerated in flexural sites than calcipotriol. The ointment preparation of calcipotriol is available but the cream formulation has been withdrawn. (IV, C)¹²⁴
- Methotrexate, if severe lesions. (IV, C)^{1,15,78}
- Retinoids, such as acitretin, if severe lesions. (IV, C)^{15,125}

- TNF blockers, such as infliximab, adalimumab, etanercept, have been effective for psoriatic skin lesions but no RPCTs have been performed in SARA. (IV, C)^{55,83,86,88–91}

Eye lesions

- Should be managed with ophthalmological advice.
- Slit lamp assessment is essential to diagnose uveitis, which if untreated may result in irreversible visual loss. Therapy for uveitis consists of corticosteroid eye drops or oral corticosteroids, and mydriatics, although posterior uveitis usually requires more aggressive treatment. Limited information is available on the use of TNF blockers for uveitis, especially adalimumab, although they have been reported to reduce the frequency of episodes of uveitis when treating ankylosing spondylitis. Their therapeutic role is not yet known. (IV, C)^{1,83,86,88,126–129}

Post-inflammatory pain and fatigue

- Explanation and patience.
- Low-dose tricyclic drugs, such as amitriptyline 10–25 mg at night, if severe symptoms.

Pregnancy and breastfeeding

- All medications should be avoided during pregnancy and breastfeeding where possible.
- Antibiotics. Refer to the relevant infection guidelines.^{43–45}
- NSAIDs may potentially produce sub-fertility as a result of the luteinized unruptured ovarian follicle syndrome.¹³⁰ NSAIDs, used regularly during pregnancy, may produce premature closure of the foetal ductus arteriosus, oligohydramnios, delayed onset and increased duration of labour.^{131,132} Advice regarding breastfeeding depends on the specific NSAID being used.¹³²
- Corticosteroids are low risk but with prolonged use in pregnancy there is a risk of intrauterine growth restriction and foetal adrenal suppression. Systemic effects in the breastfeeding infant are unlikely if the maternal dose of prednisolone is less than 40 mg daily. Adrenal function should be monitored in the breastfeeding infant if higher doses are used.¹³²
- Sulphasalazine appears to have only small theoretical risks but should be used with caution in pregnancy and breastfeeding.¹³²
- Azathioprine appears to be safe during pregnancy but should not be initiated during pregnancy, if possible. It should be discontinued if breastfeeding.¹³²

- Methotrexate and retinoids are teratogenic and contraindicated during pregnancy and breastfeeding. Both men and women using methotrexate should avoid conception during drug taking and for at least three months after. Women using retinoids, such as acitretin, should be advised to use effective contraception for at least one month before treatment, during treatment and for at least three years after stopping treatment (oral progestogen-only contraceptives are not considered effective).¹³²
- TNF blockers should be avoided during pregnancy. Women should be advised to use adequate contraception during treatment and this should be continued after the last dose for a duration depending on the half-life of the TNF blocker. Breastfeeding contraindications depend on the specific drug and these should be individually checked.¹³²

Partner notification

- Partner notification, treatment and the contact-tracing period are dependent on the genital infection identified. These are detailed in specific infection guidelines which should be consulted.^{43–45}

Follow-up

- STI follow-up is dependent on the genital infection identified. These are detailed in specific infection guidelines which should be consulted.^{43–45}
- Extra-genital manifestations should be followed up under the direction of the relevant specialist.

Prevention/health promotion

- Sexual intercourse (including oral sex) should be avoided until they and their partner(s) have completed treatment and follow-up for any genital infection identified.
- Patients should be advised to avoid potentially 'triggering infections' in the future, either uro-genital or enteric. Therefore, safer sexual practice should be discussed and the importance of food hygiene stressed.¹

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and

consideration of individual patient circumstances and available resources.

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

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Composition of the European STI guidelines editorial board

See <http://www.iusti.org/regions/Europe/euroguidelines.htm>.

List of contributing organisations

See <http://www.iusti.org/regions/Europe/euroguidelines.htm>.

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Appendix

Search strategy

An extensive literature review was performed using Ovid, Medline, PubMed and Embase from 1966 to January 2014 using the keywords reactive arthritis, sexually acquired reactive arthritis, SARA, Reiter, spondyloarthropathy, spondyloarthritis and infectious arthritis.

The complete Cochrane Library and National Institute for Health and Clinical Excellence were hand-searched in January 2014 for relevant documents.

A review was performed in January 2014 of the relevant European guidelines produced by the International Union Against Sexually Transmitted Infections (<http://www.iusti.org>), UK national guidelines (<http://www.bashh.org>) and guidelines produced by the US Centers for Disease Control (<http://www.cdc.gov/std/>)

Tables of level of evidence and grading of recommendations

See <http://www.iusti.org/regions/Europe/euroguidelines.htm>.