Aetiology

Reactive arthritis (ReA) is a sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection at a distant site, usually gastro-intestinal or genital. ReA triggered by a sexually transmitted infection (STI) is referred to as sexually acquired reactive arthritis (SARA). This includes sexually acquired Reiter’s syndrome, described as the 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.

Most commonly lower genital tract infections, either urethritis or cervicitis, are associated with SARA with objective features of SARA being present in 0.8-4% of cases.\(^1\)-\(^3\) The place of upper genital tract infection, such as prostatitis and salpingitis, is unresolved. Previously, it was suggested that infection with the human immune deficiency virus (HIV) was directly associated with SARA but current evidence suggests this is not so.\(^4\),\(^5\)

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 techniques.\(^2\),\(^6\)-\(^9\)

- *Neisseria gonorrhoeae* has been linked with up to 16% of cases, as distinct from its role in septic, gonococcal arthritis.\(^1\),\(^10\)-\(^13\) 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.\(^14\),\(^15\)

- 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 also unclear, although it appears to involve an immune response to uro-genital micro-organisms. SARA appears to occur over ten times more frequently in men compared to women, although under recognition in women may be a problem.\(^1\),\(^13\),\(^16\),\(^17\) Possession of the HLA-B27 gene increases susceptibility to SARA by up to 50 fold.\(^2\),\(^7\),\(^11\),\(^16\),\(^18\) It is also now clear that DNA and/or surface antigens of *C. trachomatis*,\(^8\),\(^19\)-\(^25\) *U. urealyticum*,\(^24\),\(^26\) and other mycoplasmas\(^27\) may be detected within joint material from individuals with SARA. It is possible that
the persistence of viable micro-organisms intra-articularly is an important factor in the causation and perpetuation of the arthritis.

**Clinical Features**

**History**

- There may be a past or family history of spondyloarthritis or iritis.\(^1,12,17,18,28\)

- Sexual intercourse, usually with a new partner, within 3 months prior to the onset of arthritis.\(^2,7,16\)

**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.\(^1,2,12,16,17\)

- A recent history of urethral discharge and/or dysuria in approximately 80% of men with SARA, although considerably fewer women are symptomatic.\(^9,7,12,13,16\)

- Pain, with or without swelling and stiffness, at one or more (usually fewer than 6) joints, especially at the knees and feet.\(^12,16-18\)

- 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 approximately 20% of patients.\(^1,11,13,16,17\)

- Painful movements may also result in 30% from tenosynovitis and in 16% painful swelling of a toe or finger (dactylitis) may occur.\(^16,17\)

- Low back pain and stiffness is common in the acute episode and sacro-iliitis occurs in approximately 10% of patients during the acute episode.\(^1,11-13,16,17,29,30\)

- Irritable eyes, with or without redness, photophobia or a reduction in visual acuity. Conjunctivitis occurs in 20-50% of patients with SARA but iritis is less common occurring in around 2-11% of patients.\(^1,11-13,16,17,30\) Other eye lesions occur rarely.\(^1,11,13\)

- Systemic symptoms of malaise, fatigue and fever occur in approximately 10% of patients.\(^16,18\)

**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. Infection may be asymptomatic, particularly in women.\textsuperscript{7,9,12,13,16}

- 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.\textsuperscript{12,16-18}

- 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.\textsuperscript{1,11,13,16,17}

- Tenosynovitis. Tenderness, with or without swelling over tendon sheaths and crepitus on movement. Classical dactylitis may be seen.\textsuperscript{16,17}

- Pain on direct sacral pressure may indicate acute sacro-ililitis\textsuperscript{1,11,13,16,17}. Care should be taken to distinguish this from lumbosacral disc disease or other pathology.

- Pain and redness of the eye is usually due to conjunctivitis, or rarely iritis.\textsuperscript{1,11-13,16,17,30} Slit lamp examination is essential to differentiate them. Rarely, corneal ulceration, keratitis and intra-ocular haemorrhage may be seen and optic neuritis and posterior uveitis have been described.

- Psoriasiform rash which may be typical plaque or guttate cutaneous psoriasis in 12.5\textperthousand,\textsuperscript{12} nail dystrophy in 6-12\textperthousand,\textsuperscript{12,30} or typical psoriatic lesions of the glans penis or labia (circinate balanitis or vulvitis) in 14-40\textperthousand,\textsuperscript{1,11,13,16,17,30} tongue (geographical tongue) in about 16\textperthousand,\textsuperscript{30} or pustular psoriasis on the soles of the feet (keratoderma blennorrhagica) in up to 33\textperthousand.\textsuperscript{1,11-13,16,17,30} The latter may rarely occur on the palms of the hands. Stomatitis and oral ulceration occur in approximately 10\textperthousand.\textsuperscript{11-13,17}

- Heart lesions are almost invariably asymptomatic although tachycardia and rarely pericarditis and aortic valve disease may occur. Electrocardiographic abnormalities, including conduction delay, are recorded in 5-14\textperthousand of patients.\textsuperscript{11-13,17}

- Renal pathology, such as proteinuria, microhaematuria and aseptic pyuria, is seen in about 50\textperthousand and is usually asymptomatic. Glomerulonephritis and IgA nephropathy rarely occur.\textsuperscript{18}

- Rare manifestations include thrombophlebitis of the lower limbs, subcutaneous nodules, nervous system involvement including meningoencephalitis and nerve palsies.\textsuperscript{1,12,13,17}

- Fever and weight loss occur in a minority of patients, approximately 10\textperthousand.\textsuperscript{16,18,29}
Complications

In the majority of individuals with SARA the disease is self-limiting with a mean first episode duration of 4-6 months.\textsuperscript{1,16,17,30} Approximately 50% have recurrent episodes at variable intervals.\textsuperscript{1,12,17,28} The complications of SARA are principally due to aggressive arthritis and are more likely if the individual possesses the HLA-B27 gene.\textsuperscript{11,16}

- Chronicity with symptoms persisting for more than one year in approximately 17% of patients.\textsuperscript{17}

- Erosive joint damage especially affects the small joints of the feet with 12% exhibiting foot deformities, although severe deformity is rare.\textsuperscript{1}

- 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.\textsuperscript{11,28} 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.\textsuperscript{29} 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.

- Inadequately treated, or recurrent, acute anterior uveitis may lead rapidly to cataract formation and blindness in a minority.\textsuperscript{11-13,28}

Diagnosis

The diagnosis of SARA involves three components.
- Recognition of the typical clinical features of spondyloarthropathy.
- 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 are not infrequent. Microscopic confirmation is by a Gram stained urethral smear demonstrating >= 5 polymorphonuclear leucocytes (PMNLs) per high power (x1000) microscopic field, or >= 10 PMNLs per high power (x1000) microscopic field on a first void urine sample.
  - Muco-purulent cervicitis in women. A purulent or muco-purulent endocervical exudate, with or without easily induced cervical bleeding, and/or lower abdominal pain may be present. However, cervical infection is frequently asymptomatic.
  - The identification of genital pathogens, particularly \textit{C. trachomatis} or \textit{N. gonorrhoeae}. Full screening for STIs is essential.
• Please refer to the relevant guidelines on NGU, *C. trachomatis* and gonorrhoea.

• Investigation of specificity and activity of arthritis.

**Management**

**General advice**

The principles of management are governed by the expectation that SARA is a self-limiting disease in the majority of patients.

Patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment and follow-up for any genital infection identified.

Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.

**Further investigation**

The following investigations are essential, often useful or sometimes useful.\(^6,11-13,16-18,28-31\) Genito-urinary medicine (GUM) specialists are advised to liaise with and/or refer to other specialists including rheumatologists, ophthalmologists and dermatologists for all patients with significant involvement of extra-genital systems. It is advised that all patients with SARA are referred to an ophthalmologist, if possible, for slit lamp assessment. Essential investigations should be performed by GUM specialists whilst other investigations are suggested following appropriate referral.

**Essential**

- Full screening for STIs.
- Acute phase response such as, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or Plasma viscosity (PLV).
- Full blood count.
- Urinalysis.

**Investigations which are often useful**

- Liver and kidney function tests.
- HLA-B27.
- X-rays of affected joints and sacro-iliac joints.
- Electrocardiogram.
- Echocardiogram.
- Ophthalmic evaluation including slit lamp assessment.
Investigations which are sometimes useful

HIV antibody test.
Blood cultures.
Stool culture (if enteritic ReA is suspected).
SeroLOGY specific for C. trachomatis.
Synovial fluid analysis for cell count, Gram stain, crystals, and culture.
Synovial biopsy.
Exclusion tests for other diseases with rheumatological features, for example, rheumatoid factor (rheumatoid arthritis), plasma urate (gout), chest X-ray and serum angiotensin-converting enzyme (ACE) level (sarcoidosis).

Treatment

Treatment 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. Please refer to the relevant infection guidelines. 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) 16,30,32-34

Arthritis

First line therapy

• Rest with the restriction of physical activity, especially weight bearing activity where leg joints are involved. Balance with the use of physiotherapy to prevent muscle wasting. (IV, C) 18,35-37

• Physical therapy with the use of cold pads to alleviate joint pain and oedema. (IV, C) 18,35-37

• 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. (IIb, B) 18,35-40

- Intra-articular corticosteroid injections, especially valuable for single troublesome joints. May also be used for inflamed sacro-iliac joints. Proven value in other inflammatory arthritides but there are no randomised placebo-controlled trials (RPCTs) of its use in SARA. (IV, C) 18,35,37,41-44

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

- As above +

- Systemic corticosteroids. If used, consideration should be given to anti-osteoporosis prophylaxis. Corticosteroids are valuable as short courses usually beginning with oral doses of 10-25mg daily where severe symptoms arise from several joints, often in the presence of constitutional illness. In rheumatoid arthritis it has been shown to suppress inflammation but there are no RPCTs of its use in SARA. (IV, C) 18,35,45-47

- Sulphasalazine. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Its effect is maximum on peripheral articular manifestations. Sulphasalazine reduces the duration of active synovitis but probably does not influence ultimate recovery. High doses, 3g daily, are associated with significant toxicity, especially gastrointestinal, which may necessitate cessation of treatment, whereas 2g daily appears equally effective and better tolerated. (Ib, A) 18,35,48-51

- Methotrexate. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Doses range from 7.5-15mg orally as a single weekly dose. Oral folic acid should be given, usually as a single 5mg dose weekly, with or on the day 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. Only case reports of its use in SARA have been published. (IV, C) 18,35,36,52

- Azathioprine. Indicated where disabling symptoms persist for 3 or more months, or evidence of erosive joint damage is present. Doses of 1-4mg/kg/body weight per day may be used. (III, B) 18,35,53

- Gold salts and D-penicillamine. These drugs are occasionally used when persistent polyarthritis is present. No RPCTs have been published concerning their use in SARA. (IV, C) 18,35
• Antibiotics. Short course antibiotic therapy for the treatment of concomitant uro-genital infection 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 arthritis. (Ib, A)\(^{16,30,32-34}\) Longer course antibiotic therapy has been considered. However, many studies have had small numbers of individuals with SARA, often the trial antibiotic has been ciprofloxacin, a drug with low efficacy against \textit{C. trachomatis}, and in the main antibiotic therapy has been commenced after the arthritis has established. Antibiotics may also have anticollagenolytic properties.\(^{54}\) Conflicting results have been obtained, with one study identifying a non-significant improvement in SARA with 3 months treatment with ciprofloxacin compared to placebo, albeit with a diminishing effect after 12 months, whilst others have identified no benefit.\(^{55-57}\) Lymecycline administered for 3 months, in one study, has been shown to reduce the duration of arthritis in \textit{C. trachomatis} triggered SARA, but no such effect was seen in a comparative study of 2 weeks versus 4 months of doxycycline therapy.\(^{58,59}\) The role of long term antimicrobial therapy, particularly in non-chlamydial SARA, is not yet established. (Ib, A)\(^{33,55-61}\)

• Medical synovectomy using Yttrium-90, osmic acid, or Samarium-153. 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)\(^{42,62}\)

• Surgery. Exceptionally, surgical treatment including synovectomy and arthroplasty, is valuable.\(^{35}\)

**Enthesitis**

• Rest. (IV, C)\(^{18}\)
• Physiotherapy and ultrasound.
• NSAIDs. (IV, C)\(^{18}\)
• Local corticosteroid injection. (IV, C)\(^{37,42,43}\)
• Radiotherapy for persistent disabling heel pain, exceptionally.
• Surgery, exceptionally.

**Mucous membrane and skin lesions**

• No treatment for mild lesions.
• Keratinolytic agents, such as topical salicylate or corticosteroid preparations, in mild to moderate cases. (IV, C)\(^{18,52}\)
• Calcipotriol cream/ointment in mild to moderate cases. (IV, C)\(^{63}\)
• Methotrexate, if severe lesions. (IV, C)\(^{18,52}\)
• Retinoids, if severe lesions. (IV, C)\(^{18,64}\)
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. (IV, C)\textsuperscript{18}

Post-inflammatory pain and fatigue

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

Prophylaxis

- In addition to the advice to avoid unprotected sexual intercourse 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 urogenital or enteric. Hence, safer sexual practice should be discussed and the importance of food hygiene stressed.

Pregnancy and breastfeeding

- All medications should be avoided during pregnancy and breastfeeding where possible.
- Antibiotics. Please refer to the relevant infection guidelines.
- NSAIDs may potentially produce sub-fertility as a result of the leuteinised unruptured ovarian follicle syndrome.\textsuperscript{65} NSAIDs, used regularly during pregnancy, may produce premature closure of the foetal ductus arteriosus, oligohydramnios, delayed onset and increased duration of labour.\textsuperscript{66,67} Advice regarding breastfeeding depends on the specific NSAID being used.\textsuperscript{67}
- Corticosteroids are low risk but if the daily use is 10mg or more, foetal/infant adrenal suppression may occur.\textsuperscript{67}
- Sulphasalazine appears to have only small theoretical risks but should be used with caution in pregnancy and breastfeeding. It may induce oligospermia in men.\textsuperscript{67,68}
- Azathioprine should not be initiated during pregnancy, if possible.\textsuperscript{67}
- 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 6 months after. Women using retinoids should be advised to use adequate contraception for at least one month before treatment, during treatment, and for at least 2 years after stopping treatment.\textsuperscript{67}
• Gold salts should be avoided during pregnancy and breast feeding. Women should avoid conception during and for at least 6 months after treatment.67

Sexual partners

• Partner notification, treatment, and the contact tracing period is dependant on the genital infection identified. Please refer to the relevant infection guidelines.

Follow-up

• GUM follow-up is dependent on the genital infection identified. Please refer to the relevant infection guidelines.
• Extra-genital manifestations should be followed up under the direction of the relevant specialist.

Auditable Outcome Measures

• Duration of inability to work.
• Need for admission to hospital.
• Presence of erosive joint damage.
• Duration to full recovery.
• Number of joint and/or extra-articular recurrences over a 2 year period after the initial episode.
• Presence of long-term disability.

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Conflict of Interest

None.

Evidence Base

In compiling these guidelines evidence has been sought from:
Medline
Biomed
Cochrane Library
Authoritative reviews
Additional papers referenced by articles identified by the search strategy were also reviewed

Searches have been made from 1966 to November 2000 under the following headings:

- Reactive arthritis
- Reiter’s syndrome
- Infectious arthritis
- Spondyloarthropathy

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