

Sexually acquired reactive arthritis

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ABSTRACT

Sexually acquired reactive arthritis (SARA) may present acutely to general physicians. It is important to consider the condition and to identify key features in the history and examination so that appropriate investigations are taken and optimum treatment is given. Involvement of relevant specialists in the management is essential and where sexually transmitted infections are identified, partner notification is required.

Introduction

Sexually acquired reactive arthritis (SARA) is a reactive arthritis (ReA) triggered by a sexually transmitted pathogen in the genital tract. It may also include inflammation of the tendons and fascia and have other systemic manifestations.

Reiter's syndrome described the classic triad of urethritis, arthritis and conjunctivitis, with or without other cutaneous or systemic involvement, but is no longer used in current practice.

SARA should be considered with any acute arthritis, especially in a young adult. In such cases it is important to screen for sexually transmitted infections (STIs) and treat appropriately.

Management may require input from several specialities depending on the symptoms and severity.

Aetiology

Establishment of SARA appears to involve an immune response to an infective pathogen and alteration of its usual state to allow it to persist in the synovium in an aberrant form while generating an inflammatory response. It is unclear why some individuals develop STI complications, including SARA, and why not all STIs are associated with the condition.

Lower genital tract infections, either urethritis or cervicitis, are most commonly associated with the condition, with objective features of SARA in 0.8–4% of cases;^{1,2} although this now appears to be much lower in clinical practice.

The most frequently reported infection is *Chlamydia trachomatis* in up to two-thirds of cases^{3,4} and *Neisseria gonorrhoeae* has been reported in up to 16%,¹ independent of its potential to cause septic arthritis.

It has been suggested that ocular strains of *C trachomatis* (trachoma), rather than genital strains, are preferentially associated with SARA⁵ but more work is needed to substantiate this and to determine whether ocular serovars are associated with genital tract infection. *Mycoplasma genitalium*, which can cause urethritis, and *Ureaplasma urealyticum* have been reported in a few cases of SARA but a causal role in the development of SARA has not been established.⁶

Risk factors for SARA

There are several predisposing factors for SARA.

- > Gender: SARA appears to occur over ten times more frequently in men compared to women but under-recognition or milder disease in women may be a factor.
- > HLA-B27: The gene is 10 times more common in those with SARA and is associated with more severe disease.³
- > HIV infection: A rising incidence of spondyloarthritis, including ReA, has been seen in sub-Saharan Africa in association with HIV. Similar observations have not been seen in Caucasian populations.

Associations with SARA

There is a recognised association with other spondyloarthritides, most commonly with ankylosing spondylitis but also with psoriatic arthritis, inflammatory bowel arthritis and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis).

Hence, there may be a personal or family history of spondyloarthritis, iritis, psoriasis, inflammatory bowel disease or SAPHO.

Clinical presentation

There is a history of sexual intercourse, usually with a new partner, within three months of arthritis symptoms.³

Most men give a recent history of genital symptoms of urethral discharge, dysuria and/or testicular pain or swelling. The genital symptoms occur on average 14 days before the arthritis develops.^{1,3}

Women are more likely to be asymptomatic but may describe altered vaginal discharge, inter-menstrual or post-coital bleeding, pelvic pain or deep dyspareunia.

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Rectal STIs, including gonorrhoea and chlamydia, may be asymptomatic but can present with rectal discharge, bleeding, discomfort and tenesmus.

Joint pain, with/without swelling and stiffness, especially at the knees, ankles and feet is described.³ It is typically inflammatory in nature with morning stiffness and nocturnal pain. The distribution is usually asymmetrical and affects less than six joints.

Other musculoskeletal symptoms include:

- > enthesitis and fasciitis (20–40%), which may cause difficulty in walking^{1,3,4}
- > tenosynovitis (30%) and dactylitis (16%)^{3,4}
- > low back pain and stiffness is common and sacro-iliitis occurs in approximately 10% of patients.

Extra-articular symptoms include:

- > irritable eyes, conjunctivitis (30%) and less commonly uveitis, which is more likely if pain is present (2–11%)^{1,3,4,7,8}
- > skin manifestations include psoriasiform rash (12%) with genital lesions, circinate balanitis/vulvitis (14–40%), pustular psoriasis on the soles of the feet (keratoderma blennorrhagica) (5–33%), geographical tongue (16%), oral ulceration (10%) and nail dystrophy (6–12%)^{1,3,4,7,8}

Key points

Sexually acquired reactive arthritis (SARA) is a reactive arthritis (ReA) triggered by a sexually transmitted pathogen in the genital tract. It may include other systemic manifestations involving tendons, fascia, skin/mucous membranes, and the eyes.

General physicians should not shy away from asking about genital symptoms and sexual contacts. They should examine specifically for genital signs, and test for sexually transmitted infections, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, from sites according to sexual practice and symptoms.

In those with ocular or visual symptoms it is essential to identify uveitis as this can rapidly progress to irreversible visual loss. Slit-lamp examination may reveal cells in the anterior chamber in active iritis and synechiae with other lesions in recurrent scarring disease.

Treatment is given for identified infection with antibiotics and for arthritis with non-steroidal anti-inflammatory drugs. Second-line therapy is reserved for more severe arthritis or where first-line therapy fails. Other manifestations may also require specific treatment.

Most cases are self-limiting and resolve within 4–6 months but 50% have recurrent episodes and up to 17% have chronic symptoms. Advise patients about safer sexual practices and good food hygiene to avoid potentially 'triggering infections' in the future.

KEYWORDS: Sexually acquired, reactive arthritis, Reiter's syndrome, sexually transmitted infection, uro-genital infection ■

Box 1. Rare clinical features

Cardiac:

- > left ventricular dilatation, pericarditis, aortic valve disease.

Renal:

- > glomerulonephritis, IgA nephropathy.

Neurological:

- > meningoenzephalitis, nerve palsies.

Other:

- > thrombophlebitis, subcutaneous nodules.

Systemic symptoms of malaise, fatigue, weight loss and fever are seen in some patients (10%) and electrocardiographic abnormalities may occur (5–14%).⁸

Renal pathology, such as proteinuria, microscopic haematuria and aseptic pyuria, which may be due to concurrent urethritis, is common (50%) but is usually asymptomatic.⁴

Good clinical examination is essential, specific features to look for are listed in Table 1.

Other clinical features are rare (Box 1).

Management in the acute medical setting

The diagnosis of SARA depends on recognising the typical features of spondyloarthritis and genital infection with a sexually transmitted pathogen.

Close liaison between STI physicians, rheumatologists and the microbiology department is advised to ensure appropriate specimens are obtained (Box 2 and Table 2) and to achieve optimum management. Those with ocular or visual symptoms should be referred to an ophthalmologist for ocular assessment, including slit-lamp assessment.

The condition and prognosis should be fully discussed with the patient.

Treatment

Antimicrobial therapy for genital tract infections should be as in uncomplicated infection. Rapid treatment may reduce the risk of arthritis developing.⁹ It is controversial whether treatment alters the natural history of extra-genital aspects of SARA with the most likely position being that it does not once the arthritis is established. Extended antibiotic courses of 3–12 months and combination antibiotic regimens have been trialled but conclusive evidence of benefit with respect to arthritis is lacking.^{10–13}

Comprehensive guidelines on the management of STIs and guidance on 'look back periods' have been produced by the British Association for Sexual Health and HIV and should be followed with respect to specific infections.^{14,15}

Partner notification and management will be required for all diagnosed STIs, using standard 'look-back periods', to avoid re-infection, and the patient should be advised to avoid all sexual contact until they and their sexual partner(s) have completed treatment.

First-line treatment of arthritis and other musculoskeletal manifestations includes simple measures such as rest, orthotics

Box 2. Essential investigations

STI tests

- > NAAT for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (vulvo-vaginal sample in women, urine in men; throat and rectal samples depending on sexual history and symptoms).
- > If *N gonorrhoeae* NAAT is positive further samples for culture confirmation and sensitivity are required.
- > NAAT for *Mycoplasma genitalium* if available, particularly important for men with urethritis (endocervical sample in women, urine in men).
- > Urethral (men) or endocervical (women) samples for Gram staining and culture if genital symptoms are present.
- > HIV antibody test (fourth generation – antigen/antibody)

Synovial fluid analysis

- > Cell count, Gram stain, crystals.
- > Culture (where septic arthritis is suspected).

Acute phase response

- > Erythrocyte sedimentation rate or C-reactive protein.

Other

- > Full blood count.
- > Urinalysis.

NAAT = nucleic acid amplification test; STI = sexually transmitted infection.

and regular non-steroidal anti-inflammatory drugs (NSAIDs). There is no definitive NSAID of choice and the individual response to medication varies.

NSAIDs have significant gastrointestinal (GI), renal and cardiovascular (CV) side effects and appropriate assessments

Table 1. Examination essentials

Systemic examination	Features to identify
Genital	Men: urethritis, urethral discharge, epididymal / testicular tenderness or swelling, proctitis. Women: muco-purulent cervicitis, cervical motion / adenexal / pelvic tenderness, proctitis.
Musculoskeletal	Tender, swollen joints (1–5) with reduced range of movements; asymmetric distribution; swollen toes / fingers (1 or more) and tendons with crepitus on movement; tenderness at entheses; pain on direct sacral pressure; impaired gait and mobility.
Eyes	Conjunctival redness; abnormal visual acuity; slit-lamp examination – if uveitis, corneal ulceration, keratitis or intra-ocular haemorrhage are suspected.
Skin and mucous membranes	Psoriasiform rash; erosive circinate balanitis or vulvitis; geographical tongue; keratoderma blennorrhagica; stomatitis and oral ulceration; nail dystrophy.

Table 2. Other investigations which may be required

Often useful	Sometimes useful
Liver and renal function tests	Blood cultures
HLA-B27	Stool culture (if enteric ReA suspected)
X-rays of affected joints	MRI of sacro-iliac joints
Ultrasound of affected joints or entheses	Synovial biopsy
ECG	Echocardiogram
Ophthalmic examination with slit lamp assessment	Exclusion tests for other diseases with rheumatological features: <ul style="list-style-type: none"> > rheumatoid factor and anti-cyclic citrullinated peptide antibodies (rheumatoid arthritis) > autoantibodies (systemic lupus erythematosus) > plasma urate (gout) > chest X-ray and serum angiotensin-converting enzyme level (sarcoidosis).

ECG = electrocardiogram; MRI = magnetic resonance imaging; ReA = reactive arthritis.

should be made before prescribing these drugs. Those at risk of GI toxicity may benefit from concurrent gastroprotective agents. All NSAIDs may be associated with increased CV events, with the likely exception of naproxen, which has a more favourable CV safety pattern. NSAIDs should always be used at the lowest effective dose for the shortest time period possible.

Corticosteroid injections may be useful for single troublesome joints, including the sacro-iliac joint, and enthesitis.

Second-line therapies are reserved for those who have moderate/severe arthritis, or where there is erosive joint damage, or who have failed first-line therapy. Individuals falling into this group should be referred for specialist rheumatology assessment.

The most common second line therapies⁴ are disease-modifying antirheumatic drugs:

- > sulphasalazine¹⁶
- > methotrexate¹⁷
- > azathioprine.¹⁸

Less common therapies are:

- > systemic corticosteroids
- > tumour necrosis factor (TNF)- α blockers: experience in SARA is limited although they are well established in treating other spondyloarthritides and they do not appear to reactivate the infective trigger¹⁹
- > gold salts and D-penicillamine are rarely used.

Surgical interventions are rarely required for musculoskeletal problems but can include synovectomy and arthroplasty.

Mild skin and mucous membrane lesions do not require any specific treatment. Topical keratinolytic agents, corticosteroids, and vitamin D3 analogues are options for mild/moderate cases, while more severe situations may require methotrexate, retinoids or TNF- α blockers.

Eye lesions should be managed with ophthalmological advice and uveitis should be treated promptly with topical or oral corticosteroids and mydriatics to reduce the risk of blindness. In severe cases TNF- α blockers may be considered.

Prognosis

SARA is a self-limiting condition in the majority of cases with full resolution within 4–6 months on average, although 50% of patients may experience recurrent episodes and up to 17% have chronic symptoms persisting for more than one year.^{1,3,4}

Joint-related complications of SARA relate to aggressive arthritis, and are more common in individuals who are positive for the HLA-B27 gene. Persistent locomotor disability occurs in approximately 15% of cases.

Ankylosing spondylitis has been described in up to 23% of patients, although it is unclear if this is a complication of SARA or a coexisting disease in a genetically predisposed population.²⁰

Uveitis that is inadequately treated, or recurrent, may result in cataract formation and irreversible visual loss in some cases.

Follow-up

Follow-up should be under the guidance of the relevant specialist and depends on the severity of the symptoms and on the genital infection identified.

It is important that patients are actively involved in their care, including self-management, and they should be advised to avoid potentially 'triggering infections' in the future. These may be genital or enteric. Therefore, safer sexual practice and good food hygiene should be discussed.

Summary

SARA can present with a wide range of manifestations. Although it is self-limiting in most individuals, some will have long-term consequences and disability. It is important to recognise the condition and coordinate treatment with relevant specialists to achieve optimum management. ■

References

- Csonka GW. The course of Reiter's Syndrome. *Br Med J* 1958;1:1088–90.
- Rich E, Hook EW III, Alarcón GS, Moreland LW. Reactive arthritis in patients attending an urban sexually transmitted diseases clinic. *Arthr Rheum* 1996;39:1172–7.
- Keat AC, Maini RN, Pegrum GD, Scott JT. The clinical features and HLA associations of reactive arthritis associated with non-gonococcal urethritis. *QJM* 1979;48:323–42.
- Colmegna I, Cuchacovich R, Espinoza LR. HLA-B27-associated reactive arthritis: pathogenetic and clinical considerations. *Clin Microbiol Rev* 2004;17:348–69.
- 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 Pathogen* 2010;48:62–8.
- Taylor-Robinson D, Keat A. Observations on Chlamydia trachomatis and other microbes in reactive arthritis. *Int J STD & AIDS* 2015;26:139–44.
- Popert AJ, Gill AJ, Laird SM. A prospective study of Reiter's syndrome. An interim report on the first 82 cases. *Br J Vener Dis* 1964;40:160–5.
- Csonka GW. Clinical aspects of Reiter's syndrome. *Ann Rheum Dis* 1979; 38 Suppl:4–7.
- Bardin T, Enel C, Cornelis F *et al*. Antibiotic treatment of venereal disease and Reiter's syndrome in a Greenland population. *Arthr Rheum* 1992;35:190–4.
- Barber CE, Kim J, Inman RD, Esdaile JM, James MT. Antibiotics for treatment of reactive arthritis: a systemic review and metaanalysis. *J Rheumatol* 2013;40:916–28.
- Kvien TK, Gaston JSH, Bardin T *et al*. Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study. *Ann Rheum Dis* 2004;63:1113–9.
- 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;62:1298–307.
- Laasila K, Laasonen L, Leirisalo-Repo M. Antibiotic treatment and long term prognosis of reactive arthritis. *Ann Rheum Dis* 2003;62:655–8.
- British Association for Sexual Health & HIV. *Guidelines*. Macclesfield: BASHH, 2016. Available online at www.bashh.org/guidelines [Accessed 19 February 2016].
- McClellan H, Radcliffe K, Sullivan A, Ahmed-Jushuf I. 2012 BASHH statement on partner notification for sexually transmissible infections. *Int J STD & AIDS* 2013;24:253–61.
- 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. *Arthr Rheum* 1996;39:2021–7.
- Owen ET, Cohen ML. Methotrexate in Reiter's disease. *Ann Rheum Dis* 1979;38:48–50.
- Calin A. A placebo controlled, crossover study of azathioprine in Reiter's syndrome. *Ann Rheum Dis* 1986;45:653–5.
- 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;63:1274–80.
- Good AE. Reiter's syndrome: long-term follow-up in relation to development of ankylosing spondylitis. *Ann Rheum Dis* 1979;38 Suppl:39–45.

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