

European guideline for the management of sexually acquired reactive arthritis

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INTRODUCTION

Reactive arthritis (RA) is a sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection at a distant site, usually gastrointestinal or genital. RA 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. There is no direct association between SARA and human immune deficiency virus (HIV) infection, despite earlier suggestions of a link^{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 unclear, although it appears to involve an immune response to uro-genital micro-organisms.

SARA appears to occur over 10 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}.

DNA and/or surface antigens of *C. trachomatis*^{8,19–25}, *U. urealyticum*^{24,26} and other mycoplasmas²⁷ 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.

DIAGNOSIS

The diagnosis of SARA involves three major components, comprising evidence of genito-urinary infection, typical clinical features of spondyloarthropathy and extra-genital manifestations, and laboratory investigation.

Clinical, genito-urinary infection

- Sexual intercourse, usually with a new partner, within 3 months prior to the onset of arthritis^{2,7,16}
- A recent history of urethral discharge and/or dysuria in approximately 80% of men with SARA, although considerably fewer women are symptomatic^{7,9,12,13,16}
- Genital infection may be clinically manifest in men by urethritis, urethral discharge, dysuria 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^{7,9,12,13,16}
- Please refer to the relevant guidelines on urethritis, *C. trachomatis* and gonorrhoea.

Clinical, spondyloarthropathy and extra-genital manifestations

- Possible past or family history of spondyloarthritis or iritis^{1,12,17,18,28}
- Onset of first episode 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}
- Pain, with or without swelling and stiffness, almost invariably affecting 1–5 lower-limb joints in an asymmetrical distribution, especially at the knees and feet. Persistent small-joint involvement may be erosive. Upper-limb joint involvement is rare in the absence of psoriasis^{12,16–18}
- Enthesopathy—Pain and stiffness, with or without swelling at the sites of tendon or fascia attachments, especially the Achilles tendon and plantar fascia attachments to the calcaneum, which often results in difficulty in walking. Enthesitis and/or fasciitis occurs in approximately 20% of patients^{1,11,13,16,17}
- Tenosynovitis—Tenderness, with or without swelling over tendon sheaths with pain on movement and crepitus occurs in 30% and classical dactylitis may be seen in 16%^{16,17}
- Low back pain and stiffness is common in the acute episode and sacro-iliitis, with pain on direct sacral pressure, occurs in approximately 10% of patients during the acute episode, although care should be taken to distinguish it from lumbosacral disc disease or other pathology^{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}. Slit-lamp examination is necessary to differentiate between them. Rarely, corneal ulceration, keratitis and intra-ocular haemorrhage may be seen and optic neuritis and posterior uveitis have been described^{1,11,13,17}
- Psoriasiform rash which may be typical plaque or guttate cutaneous psoriasis in 12.5%¹², nail dystrophy in 6–12%^{12,30}, or typical psoriatic lesions of the glans penis or labia (circinate balanitis or vulvitis) in 14–40%^{1,11,13,16,17,30}, tongue (geographical tongue) in about 16%³⁰, or pustular psoriasis on the soles of the feet (keratoderma blennorrhagica) in up to 33%^{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%^{11–13,17}
- Renal pathology, such as proteinuria, microhaematuria and aseptic pyuria, is seen in about 50% and is usually asymptomatic. Glomerulonephritis and IgA nephropathy rarely occur¹⁸
- 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% of patients^{11–13,17}

- Rare manifestations include thrombophlebitis of the lower limbs, subcutaneous nodules, nervous system involvement including meningococcal meningitis and nerve palsies^{1,12,13,17}
- Systemic symptoms of malaise, fatigue, weight loss and fever occur in approximately 10% of patients^{16,18–29}.

Laboratory

The following investigations are essential, often useful or sometimes useful^{6,11–13,16–18,28–31}.

Investigations which are essential

- Full screening for STIs, including *C. trachomatis* and *N. gonorrhoeae*
- Microscopic confirmation of urethritis in men by a Gram-stained urethral smear demonstrating ≥ 5 polymorphonuclear leucocytes (PMNLs) per high power ($\times 1000$) microscopic field, or ≥ 10 PMNLs per high power ($\times 1000$) microscopic field on a first-void urine sample
- Acute phase response tests 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 RA 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).

Prognosis

- In the majority of individuals with SARA the disease is self-limiting with a mean first-episode duration of 4–6 months^{1,16,17,30}. The complications of SARA are principally due to aggressive arthritis and are more likely if the individual possesses the HLA-B27 gene^{11,16}

- Approximately 50% have recurrent episodes at variable intervals^{1,12,17,28}
- Chronicity with symptoms persisting for more than one year occurs in approximately 17% of patients¹⁷
- Erosive joint damage especially affects the small joints of the feet with 12% exhibiting foot deformities, although severe deformity is rare¹
- 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^{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 disease²⁹. It is unclear whether the development of ankylosing spondylitis is a complication of the RA 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^{11-13,28}.

MANAGEMENT

General

- The principles of management are governed by the expectation that SARA is a self-limiting condition in the majority of patients
- Screening for STIs is essential and 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, or where epidemiological treatment is required
- Treatment is directed at several distinct elements of the condition and dermatovenereologists are advised to liaise with and/or refer to other relevant specialists, including rheumatologists and ophthalmologists, for all patients with significant involvement of extra-genital systems outside their areas of expertise. In particular, it is advised that all patients with SARA are referred to an ophthalmologist, if possible, for slit-lamp assessment
- 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.

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^{16,30,32-34}.

Arthritis

For summary of treatment see Figure 1.

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^{18,35-37}
- Physical therapy with the use of cold pads to alleviate joint pain and oedema^{18,35-37}
- NSAIDs are well established as efficacious agents in many inflammatory arthritides and form the mainstay 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^{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-randomized placebo-controlled trials (RPCTs) of its use in SARA^{18,35,37,41-44}.

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

As above plus:

- Systemic corticosteroids. If used, consideration should be given to anti-osteoporosis prophylaxis. Corticosteroids are valuable as short courses, usually beginning with oral doses of 10-25 mg 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^{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

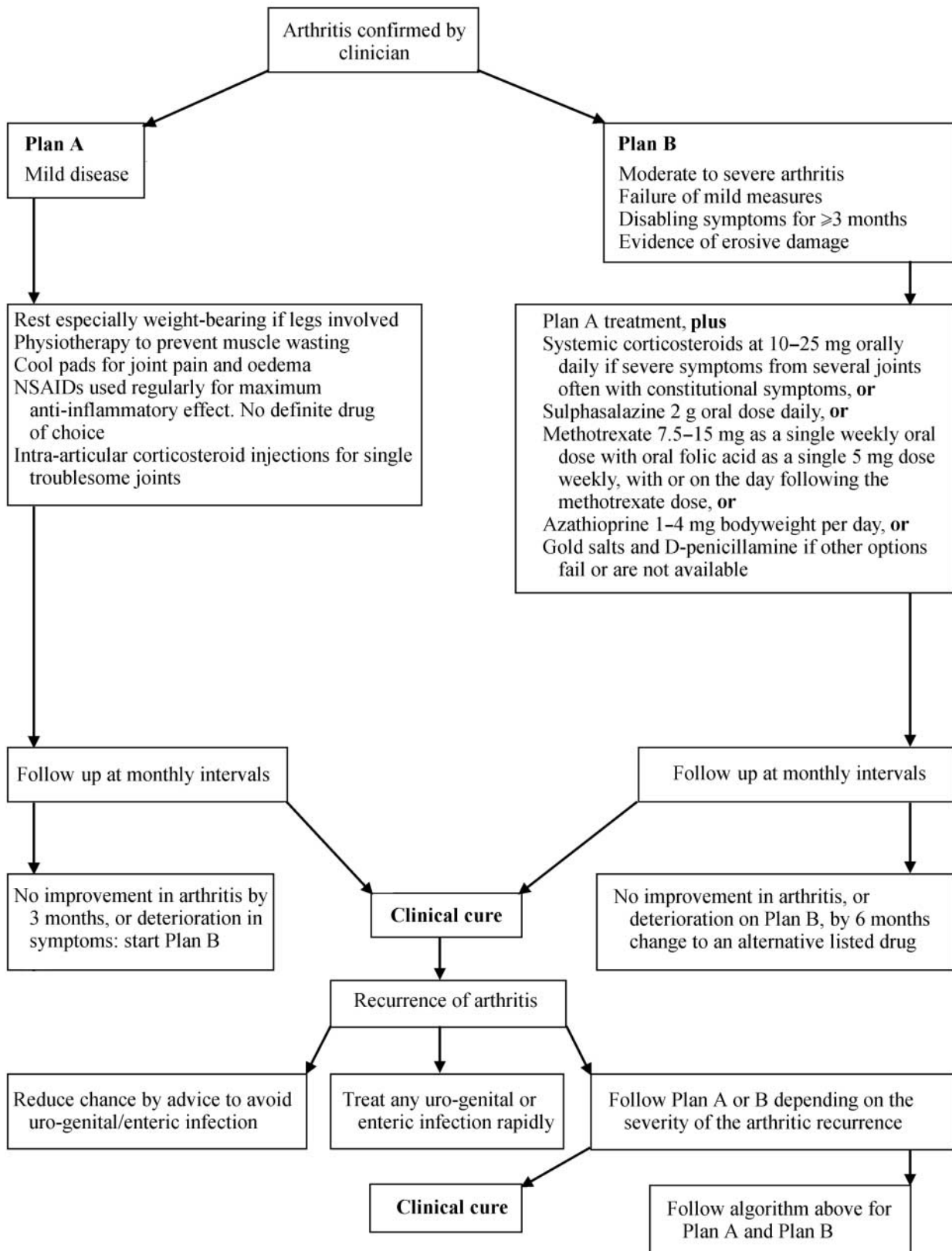


Figure 1. Management of arthropathy in sexually acquired arthritis. NSAID=non-steroidal anti-inflammatory drug

may necessitate cessation of treatment, whereas 2g daily appears equally effective and better tolerated^{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 7.5–15 mg orally as a single weekly dose. Oral folic acid should be given, usually as a single 5 mg 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^{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 1–4 mg/kg/body weight per day may be used^{18,35,53}
- Gold salts and D-penicillamine. These drugs are occasionally used when persistent poly-arthritis is present. No RPCTs have been published concerning their use in SARA^{18,35}
- Antibiotics. Short-course antibiotic therapy used for the treatment of concomitant uro-genital infection may reduce the risk of recurrent arthritis developing in individuals with a history of RA but otherwise there is little evidence of benefit in respect of arthritis^{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 *C. trachomatis*, and in the main antibiotic therapy has been commenced after the arthritis has established. Antibiotics may also have anticollagenolytic properties⁵⁴. 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 while others have identified no benefit⁵⁵⁻⁵⁷. Lyme cycline administered for 3 months, in one study, has been shown to reduce the duration of arthritis in *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^{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^{42,62}
- Surgery. Exceptionally, surgical treatment including synovectomy and arthroplasty, is valuable³⁵.

Enthesitis

For summary of treatment see Figure 2.

- Rest¹⁸
- Physiotherapy and ultrasound
- Orthoses, heel pads or cups for plantar fasciitis
- NSAIDs¹⁸
- Local corticosteroid injection^{37,42,43}
- Radiotherapy for persistent disabling heel pain, exceptionally
- Surgery, exceptionally.

Mucous membrane and skin lesions

For summary of treatment see Figure 3.

- No treatment for mild lesions
- Keratolytic agents, such as topical salicylate or corticosteroid preparations, in mild to moderate cases^{18,52}
- Calcipotriol cream/ointment in mild to moderate cases⁶³
- Methotrexate, if severe lesions^{18,52}
- Retinoids, such as acitretin, if severe lesions^{18,64}.

Eye lesions

- Should be managed with ophthalmology advice. Slit-lamp assessment is essential to diagnose uveitis, which if untreated may result

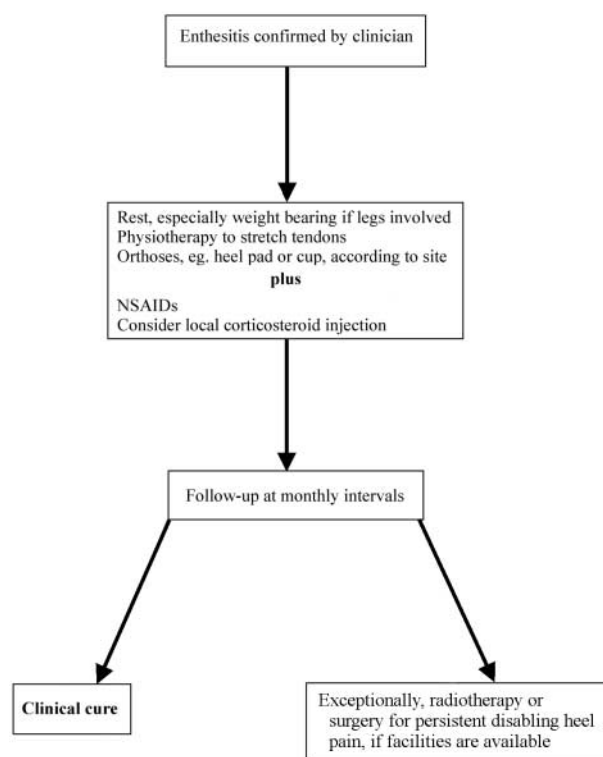


Figure 2. Management of enthesitis in sexually acquired reactive arthritis. NSAID=non-steroidal anti-inflammatory drug

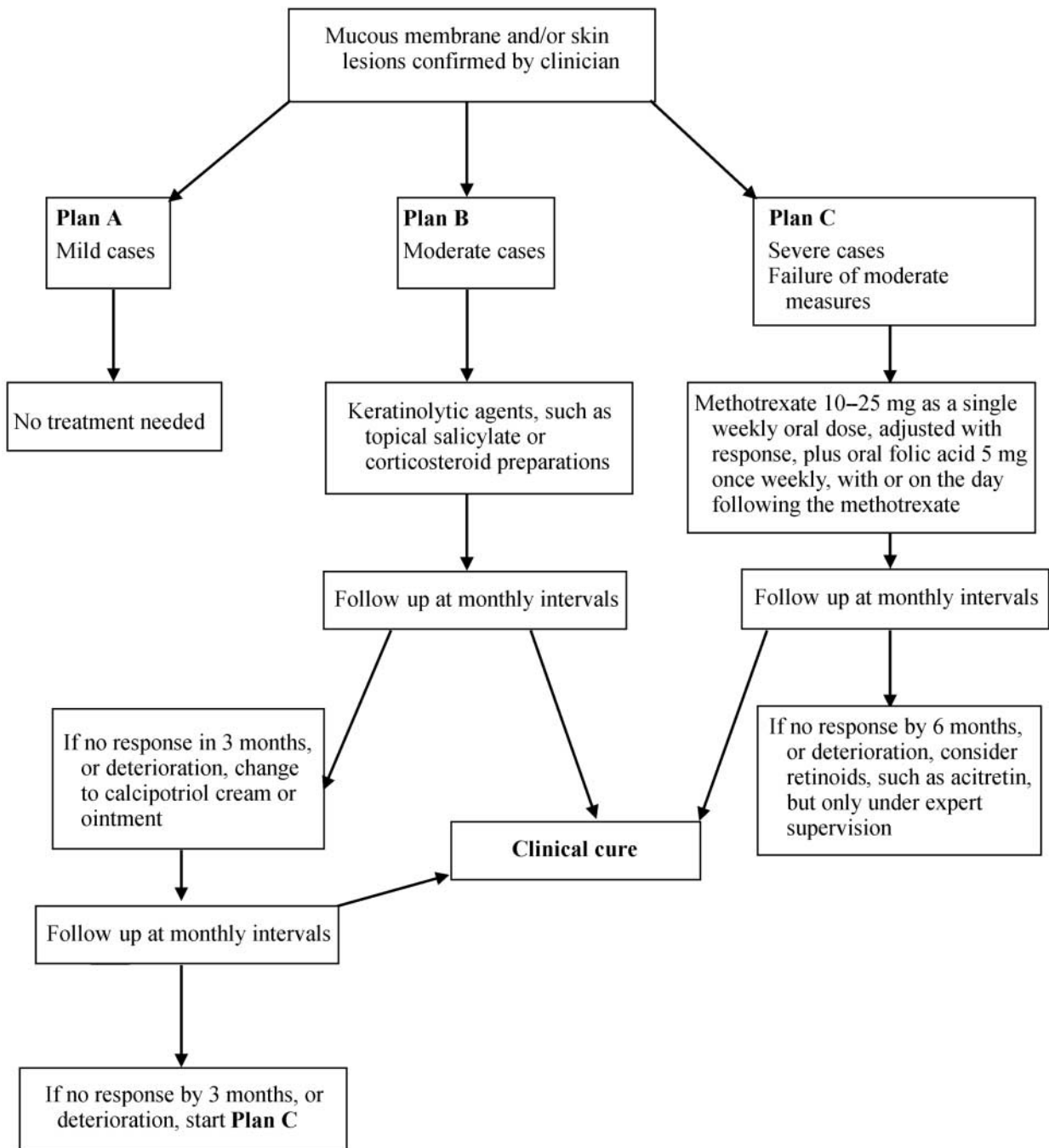


Figure 3. Management of mucous membrane and skin lesions in sexually acquired reactive arthritis

in irreversible visual loss. Therapy for uveitis consists of corticosteroid eye drops or oral corticosteroids, and mydriatics¹⁸.

Post-inflammatory pain and fatigue

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

Special situations

Pregnancy and breastfeeding

- Avoid all medications 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 luteinized unruptured

ovarian follicle syndrome⁶⁵. NSAIDs, used regularly during pregnancy, may produce premature closure of the fetal ductus arteriosus, oligohydramnios, delayed onset and increased duration of labour^{66,67}. Advice regarding breastfeeding depends on the specific NSAID being used⁶⁷

- Corticosteroids are low-risk but prolonged or repeated systemic treatment increases the risk of intra-uterine growth retardation and fetal/infant adrenal suppression may occur. Systemic effects in the breastfeeding infant are unlikely, provided the maternal dose of prednisolone is less than 40 mg daily⁶⁷
- Sulphasalazine appears to have only small theoretical risks but should be used with caution in pregnancy and breastfeeding. It may induce oligospermia in men^{67,68}
- Azathioprine should not be initiated during pregnancy, if possible⁶⁷
- 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, such as acitretin, should be advised to use adequate contraception for at least one month before treatment, during treatment, and for at least 2 years after stopping treatment⁶⁷
- Gold salts should be avoided during pregnancy and breastfeeding. Women should avoid conception during and for at least 6 months after treatment⁶⁷.

Prevention of recurrence

- Prevention of re-activation of SARA can be promoted by information concerning the avoidance of potential 'triggering infections' in the future, either uro-genital or enteric. Hence, safer sexual practice should be discussed and the importance of food hygiene explained.

MANAGEMENT OF PARTNERS

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

FOLLOW UP

- Genitourinary medicine 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 (see Figures 1–3)
- Parameters to be assessed include clinical symptoms and signs, the efficacy of treatment, microbiological and/or laboratory tests.

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