REVIEW

When is arthritis reactive?

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Reactive arthritis is an important cause of lower limb oligoarthritis, mainly in young adults. It is one of the spondyloarthropathy family; it is distinguishable from other forms of inflammatory arthritis by virtue of the distribution of affected sites and the high prevalence of characteristic extra-articular lesions. Many terms have been used to refer to this and related forms of arthritis leading to some confusion. Reactive arthritis is precipitated by an infection at a distant site and genetic susceptibility is marked by possession of the HLA-B27 gene, although the mechanism remains uncertain. Diagnosis is a two stage process and requires demonstration of a temporal link with a recognised "trigger" infection. The identification and management of "sexually acquired" and "enteric" forms of reactive arthritis are considered. Putative links with HIV infection are also discussed. The clinical features, approach to investigation, diagnosis, and management of reactive arthritis are reviewed.

criteria this feature is absent.^{7,8} The term undifferentiated spondylarthropathy is used in cases of unclassified HLA-B27 associated peripheral arthritis or enthesitis.⁹

For practical purposes the term reactive arthritis refers to the same condition as the term Reiter's syndrome, the latter being eponymously linked to Hans Reiter, who in 1916 described a febrile illness associated with purulent conjunctivitis, urethritis, and polyarthritis after an episode of bloody diarrhoea.¹⁰ In fact the association between reactive arthritis and infection was recognised well before Reiter's description. Despite this long history, extensive literature, and remarkable recent advances in genetics and microbiology the precise role of infection in reactive arthritis remains unclear. It is clear, from reporting of cases of arthritis during sporadic genitourinary infections and outbreaks of diarrhoeal illnesses over several centuries, that certain infections on some but not all occasions trigger the disease.^{2,10-14}

EPIDEMIOLOGY

The true incidence of the condition is probably underestimated as milder forms of the condition go under recognised. The condition occurs worldwide, predominantly affects young adults in the 20-40 age group, and affects men more so than women (ratio 3:1). The risk of developing reactive arthritis is about 50 times greater in those people who are HLA B27 positive.¹⁵ The incidence in Europe is estimated at 30/100 000.¹⁶ Around 1% of patients with non-gonococcal urethritis and up to 3% of patients with bacterial enteric infection subsequently develop reactive arthritis.¹⁶⁻¹⁸ Remarkably the incidence of arthritis in outbreaks of diarrhoeal infections varies from 0% to 3%-4% even when strains of the infecting agent are ostensibly similar.^{17,19}

AETIOPATHOGENESIS

Making a causal link between a micro-organism and a disease process is an age old problem. It is clear that Koch's postulates are insufficient for this purpose and new suggestions as to how causality could be ascribed to an infectious agent have been proposed more recently.²⁰ The notion that reactive arthritis is caused or triggered by particular infections is based on several strands of evidence. Most persuasive of these is epidemiological data from outbreaks of bacterial diarrhoea.^{12-14,21} Further supportive evidence in individual cases includes identification of specific infections by isolation of micro-organisms, serology, and identification of microbial components in synovial fluid during episodes of arthritis.²²⁻²⁴ A large number of candidate

Reactive arthritis should be high up in the differential diagnosis whenever a young adult presents with acute arthritis affecting the knees, ankles, or heel pain. It is a systemic inflammatory disorder characterised by aseptic arthritis, which is triggered by an infection at a distant site, usually occurring in genetically susceptible people.¹ The most frequent infectious triggers are those arising from the genitourinary, gastrointestinal, and possibly the respiratory tracts. In contrast with other infection related arthritides, such as meningococcal sepsis and rheumatic fever, its natural history is independent of antibiotic therapy. Several terms and definitions have been formulated for this type of arthritis as well as its subtypes (box 1).¹⁻⁶ These reflect the uncertainties concerning the role of infection in causing this clinical syndrome: more importantly, it is implicit in the term "reactive" that a preceding infection, which triggers the onset of symptoms, is shown.

Reactive arthritis is a member of the spondyloarthropathy family (box 2). This group of conditions are associated with the HLA-B27 gene and is characterised by shared rheumatic features including enthesitis, sacroiliitis, peripheral arthritis, and associated extra-articular lesions notably psoriasis, uveitis, and inflammatory bowel disease. Previous criteria have proposed the importance of the absence of IgM rheumatoid factor but in clinical practice this seldom influences the diagnosis and in more recent

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Box 1 Definitions

Reactive arthritis

Aseptic inflammatory arthritis, triggered by infection at a distant site in genetically susceptible people¹

Reiter's syndrome (classic definition)

A triad of urethritis, conjunctivitis, and arthritis secondary to an infectious dysentery²

Reiter's syndrome (ACR definition)*

Episode of peripheral arthritis of more than one month's duration occurring in association with urethritis or cervicitis³

Uroarthritis

Reactive arthritis secondary to a urinary tract infection⁴

Sexually acquired reactive arthritis (SARA)

Reactive arthritis associated with a recent sexually transmitted infection⁵

Rheumatic fever†

Multisystem inflammatory disease with "carditis" after a group A streptococcal pharyngitis

*American College of Rheumatology (ACR) definition.

†Diagnosis established using modified Jones criteria.⁶

micro-organisms have been found in individual cases although only shigella, campylobacter, salmonella, and yersinia infections have been implicated in epidemiological studies of outbreaks.^{1 13 14} Of many probable genitourinary pathogens only *Chlamydia trachomatis* is consistently implicated in sporadic cases of sexually acquired reactive arthritis (SARA).²⁵ The possibility that reactive arthritis may be started by upper respiratory tract infections caused by *Streptococcus pyogenes* and other bacteria has been raised and is far from clear.²⁶ In addition anecdotal studies have implicated a large number of possible triggers although their genuine significance is impossible to establish with confidence (box 3).

The finding that antibiotics seem to have little impact on the established disease process after the inciting infection suggests a triggered, self perpetuating inflammatory response.¹ Microbial components have been found within the inflamed synovium suggesting a direct role for the microbe in the pathogenesis of arthritis. The ability of certain micro-organisms to evade specific immune clearing mechanisms may be the basis for persisting antigens and injury within the joint. The best studied in this context is *Chlamydia trachomatis*, an intracellular bacterium well known for its capacity for latent infection.²⁷ Possible mechanisms of ineffective clearance of micro-organisms from the joint include reduced expression of self major outer membrane protein (MOMP) antigens, down regulation of host major histocompatibility proteins, and induced apoptosis of host T cells.²⁸ Presentation of chlamydial antigen by joint fluid antigen presenting cells has been seen and mononuclear cells obtained from synovial fluid react strongly to micro-organisms thought to cause reactive arthritis suggesting an antigen driven T cell specific response within the joint.²⁹

HLA-B27, a class one major histocompatibility complex gene is strongly associated with the spondylarthropathies.¹⁵ The HLA-B27 protein is complexed with β_2 microglobulin and is expressed on the surface of many cells. They are essential for presenting processed antigens to CD8 positive lymphocytes and eliciting specific immune responses. The gene is present in 95% of patients with ankylosing spondylitis and in 45%–90% of patients with reactive arthritis. It is associated with more severe and prolonged disease.³⁰ Several hypotheses linking HLA-B27 and infection have been proposed including the following:

Box 2 The spondylarthropathy family

- Ankylosing spondylitis
- Psoriatic arthritis
- Enteropathic arthritis
- Reactive arthritis
- Juvenile ankylosing spondylitis
- Undifferentiated spondylarthropathy

Box 3 Micro-organisms in reactive arthritis

Genitourinary tract

- Probable
 - *Chlamydia trachomatis*
- Possible
 - *Neisseria gonorrhoeae*
 - *Mycoplasma fermentans*
 - *Mycoplasma genitalium*
 - *Ureaplasma urealyticum*

Gastrointestinal tract

- Probable
 - *Shigella flexneri*
 - *Salmonella enteritidis*
 - *Salmonella typhimurum*
 - *Yersinia enterocolitica*
 - *Yersinia pseudotuberculosis*
 - *Campylobacter jejuni*
- Possible
 - *Escherichia coli*
 - *Cryptosporidium*
 - *Entamoeba histolytica*
 - *Giardia lamblia*
 - *Brucella abortus*
 - *Clostridia difficile*

Respiratory tract

- Possible
 - *Streptococcus pyogenes*
 - *Chlamydia pneumoniae*
 - *Chlamydia psittaci*

- Arthritogenic peptide theory—HLA-B27 binds unique peptides of microbial or self origin and presents them to CD8 positive T cells.³¹
- Molecular mimicry—antibodies against foreign antigens arise during bacterial infection and cross react with HLA-B27. HLA-B27 has been shown to have sequence homology with peptides from enterobacter, chlamydia, and cytokeratin.^{32 33}
- HLA-B27 assembly—aberrant transit of HLA-B27 heavy chains results in increased cell surface expression and activation of several pro-inflammatory mechanisms. HLA-B27 is unique in its ability to form homodimers, which may function as an abnormal peptide presenting structure.³³

- Auto-display— β_2 microglobulin free and peptide free HLA-B27 heavy chains undergo a helix-coil transition between the $\alpha 2$ and $\alpha 3$ domains of the molecule displaying specific residues (identical to an HLA-B27 ligand) that occupy its own binding cleft. Such interactions within and between HLA-B27 molecules may trigger an inflammatory signal³⁴

Other susceptibility genes including HLA-B39, HLA-B60, and HLA-DR1 are also associated with reactive arthritis particularly in those cases, which are negative for HLA-B27.

Ultimately, however, the mechanisms by which interactions between microbes and susceptibility genes lead to arthritis remain obscure.

CLINICAL FEATURES

Reactive arthritis ranges from a mild localised condition to a severe multisystem disease, which may be accompanied by fever, malaise, and weight loss. Involvement of the joints ranges from a transient monoarthritis to a widespread polyarthritis involving the peripheral and axial joints with or without characteristic extra-articular lesions, particularly enthesopathy, psoriasiform mucosal, and cutaneous lesions, inflammatory eye disease, and cardiovascular lesions. Occasionally, the family history reveals other members of the spondylarthropathies, psoriasis, or inflammatory bowel disease. A history or evidence of recent infection, usually within one to four weeks of the arthritis, is critical to the diagnosis.

Musculoskeletal manifestations

Arthritis occurs in 95% of cases and usually presents as an acute, asymmetrical, lower limb oligoarthritis (involving one to five joints), principally affecting the knees, metatarsophalangeal (MTP) joints, and ankles. Synovitis of the small joints particularly the MTP joints may be erosive.³⁵ Involvement of the interphalangeal joints with digital tendonitis and probably multiple enthesal lesions gives rise to dactylitis or "sausage digits". It is highly unusual for upper limb joints to be involved. Histological appearances of involved joints are non-specific being indistinguishable from the changes seen in rheumatoid arthritis.^{36 37}

Lower back and buttock pain is not unusual in the acute stage of the illness. This may be attributable to sacroiliitis but the real origin of such symptoms is often difficult to establish. Some patients subsequently progress to develop ankylosing spondylitis and in a few, evidence of the disease in the form of limited spinal movements or radiological syndesmophytes may already be evident. Radiographs may show syndesmophytes in the presence or absence of spinal symptoms.^{38–40} Enthesitis, defined as inflammation of ligaments or tendons at their point of attachment to bone, is highly characteristic and is the defining lesion of the spondylarthropathies. Enthesitis gives rise to localised pain, swelling, and tenderness. The plantar aponeurosis (plantar fasciitis) and Achilles' tendon attachments to the calcaneum are most commonly affected, often giving rise to heel pain and difficulty walking. Enthesitis of the patella tendon and pelvic tendons may also give rise to knee and pelvic pain respectively. Enthesitis may be associated with adjacent osteitis detectable by magnetic resonance imaging.⁴¹

Skin and nail involvement

Keratoderma blenorrhagica affects 5%–10% of patients and is highly characteristic of reactive arthritis. Histologically, appearances are identical to pustular psoriasis. Early pustular lesions may become hyperkeratotic and scaly and coalesce into larger psoriatic plaques.⁴² This may be associated with psoriatic onychodystrophy of the toe nails. Circinate balanitis is characterised by painless, shallow psoriasiform lesions over

the glans or shaft of the penis. In circumcised men the rash is less moist and consists of hyperkeratotic psoriatic plaque-like lesions that resemble keratoderma. Both lesions may occur recurrently in isolation from arthritis. Erythema nodosum is not a cutaneous manifestation of reactive arthritis in itself, but may occur during episodes of enteric reactive arthritis especially after yersinia and salmonella infection. There is no association with HLA-B27.⁴³

Other unusual cutaneous lesions include painless, shiny ulcer-like lesions on the palate, tongue, and mucosa of the cheeks and lip, geographical tongue and pyoderma gangrenosum.^{44–46}

Ocular involvement

Conjunctivitis occurs in 30% of patients and is a key factor of the "Reiter's triad".⁴³ This usually occurs early in the episode, often preceding arthritis by a few days. It tends to be bilateral and mild and is often ignored. Some patients, however, complain of red eyes, crusting of the eyelids and ocular discharge that is sterile. The symptoms and signs usually subside within one to four weeks, but occasionally, may progress to episcleritis, keratitis, and corneal ulceration. Rarely patients present with anterior uveitis (iritis).⁴⁶ More commonly this is a separate event occurring asynchronously from the acute episode of arthritis but, because of the risk of rapid onset of blindness in iritis, an urgent ophthalmological examination is indicated whenever there are ocular symptoms.

Genitourinary involvement

SARA is always associated with urethritis or cervicitis, these features may also be present in enteric reactive arthritis. In both instances genitourinary involvement may be asymptomatic. In SARA the history shows recent acquisition of a sexually transmitted infection within four to six weeks. Urethritis usually occurs within one to 21 days after dysentery or sexual exposure but may be unnoticed by the patient.⁴⁷ Generally urethritis precedes conjunctivitis and arthritis but in a few cases the reverse may occur.^{14 48} Dysuria is common and this may be urethral or vaginal discharge with, occasionally, frank haematuria. In a few patients gonococcal infection is present, although this may coexist with a non-gonococcal infection.³⁹ Severe glomerulonephritis and IgA nephropathy are rare complications.⁴⁹

Gastrointestinal involvement

Enteric acquired reactive arthritis occurs within four weeks of an acute diarrhoeal illness. The severity and duration of the diarrhoeal episode does not correlate with the severity and duration of the arthritis so that in some patients with arthritis evidence of gut infection needs to be sought even though symptoms are mild or absent. Asymptomatic acute or chronic lesions in the large and small bowel occur in many patients with other spondylarthropathies including SARA.⁵⁰ These lesions microscopically and macroscopically resemble ulcerative colitis or Crohn's disease and may have a genetic basis.^{51 52}

Cardiac involvement

Clinically apparent involvement of the heart is rare. Transient conduction abnormalities seen on the ECG are not uncommon but are generally of little clinical significance. Proximal (ascending) aortitis affects 1%–2% of patients, particularly those with severe, recurrent disease. This may cause secondary aortic regurgitation, eventually leading to cardiac failure and occasionally death. Valve replacement surgery may be indicated.³⁷ Histologically, aortic valve disease is indistinguishable from endarteritis obliterans. In exceptional circumstances aneurysmal aortic dilatation may occur. There are few case reports of reactive arthritis complicated by

myocarditis and pericarditis.⁵³ With prolonged disease mild to moderate ventricular dilatation may be a complication.⁵⁴

CLINICAL COURSE

The duration of the acute episode of reactive arthritis is variable and evidence from follow up studies is selective. Most patients recover spontaneously within 3–12 months. However, a few develop chronic arthritis. Those with very aggressive episodes of arthritis may develop erosive joint damage leading to secondary arthritis and deformity. In the case of SARA, 30% to 50% of patients have a recurrence of arthritis that is usually related to re-infection. Recurrence of enteric reactive arthritis is much less common. Non-specific arthralgia may well persist for several years after the acute episode has settled. Back pain and enthesopathy may remain a problem. Radiographically verified sacroiliitis, which may be unilateral, affects up to a third of patients with SARA and around 10% of patients with enteric reactive arthritis. It is more common in those with severe prolonged episodes.^{40–55} In some cases this may reflect progression of disease after the initial acute episode. In others it may represent the late development of sacroiliitis or spondylitis as a separate disease in genetically susceptible people. Early changes may not be detectable by radiography but may be shown by magnetic resonance imaging. Episodes of iritis and circinate balanitis may recur independent of other disease features. Factors associated with severe disease have been identified with variable sensitivity and specificity (box 4).⁵⁶ Patients who are HLA-B27 positive seem to have more severe prolonged episodes, a higher prevalence of back pain, and are more likely to have mucocutaneous disease.⁴⁰

Most patients recover fully. However, reactive arthritis can have an important impact on functional status. Heel and foot involvement is an important predictor of poor functional outcome and disability, highlighting the need to treat at an early stage in the disease course. Death from complications of reactive arthritis is extremely rare but is occasionally attributable to cardiac disease or amyloidosis.⁵⁷

MAKING THE DIAGNOSIS

The diagnosis entails first identifying the presence of a spondylarthropathy and then showing a relation with a recent initiating infection. Exclusion of other diagnoses is an essential element of the diagnostic process (table 1).

Diagnosing a spondylarthropathy

The history and examination shows characteristic features such as lower limb asymmetrical peripheral arthritis, buttock pain suggestive of sacroiliitis, enthesitis, and associated extra-articular lesions. A family history of a spondylarthropathy feature such as iritis or inflammatory bowel disease,

while not common, supports the diagnosis. Routine investigations yield non-specific results summarised in box 5. Joint imaging is of limited value and is usually not helpful in the early course of the disease. Radiographs of affected sites are usually normal or show non-specific changes such as periarticular osteopenia and soft tissue swelling. With recurrent disease joint erosions may develop. Areas of osteopenia with the appearance of erosions at tendinous or fascial insertion sites show active enthesitis. Subsequently these give rise to characteristic bony spurs, most typically at the plantar fascia attachment to the calcaneum. Existing heel spurs may point to previous episodes of spondyloarthopathy. Radiographs of the sacroiliac joints are usually normal during the acute episode as changes take many months to appear. Magnetic resonance imaging may, however, permit early diagnosis of sacroiliitis.⁵⁷ Ultrasonography may also be useful in identifying early peripheral joint or enthesitis lesions but is of limited availability.⁵⁸ Diagnostic criteria for spondyloarthopathy have been proposed (box 6).⁷

Identifying a recent infection

This is crucial for a diagnosis of reactive arthritis. The history should carefully assess preceding abdominal, genitourinary, or respiratory symptoms and the likelihood of contact with such infections. A full sexual history including details of sexual contacts must be obtained when SARA is suspected. Bacterial gut pathogens should be sought by stool cultures even if diarrhoea is absent or has resolved. Serodiagnosis of these infections is not generally possible except in the case of yersinia infections.

When the history or symptoms raise the possibility of sexually transmitted infection, the patient should be assessed by a genitourinary physician. Smear testing for evidence of urethritis or cervicitis, or both, is essential along with contact tracing when appropriate. *Chlamydia trachomatis* infection has been particularly linked to SARA but exclusion of other sexually transmitted infections is equally important.

In some patients with SARA *Chlamydia trachomatis* membrane proteins, DNA and RNA can be detected in joint material from affected sites and there may be raised serological responses to chlamydial antigens. Some authors have used the term “chlamydia induced reactive arthritis” to describe these patients although the demonstration of these features does not carry any identifiable advantage in terms of clinical management.⁵⁹ Thus, although these findings may have important implications for the pathogenesis of the arthritis and it is important to identify and eradicate active infections there is no place for searching for intra-articular bacterial antigens and DNA or chlamydial serology in routine rheumatological practice.

MANAGEMENT

As most patients will recover fully or with minor sequelae, treatment should be planned accordingly. The aims of management are to reduce pain and inflammation, minimise disability, and prevent relapse or progression to chronic disease. This requires a multidisciplinary approach involving physiotherapists, occupational therapists, and podiatrists as well as clinicians. European guidelines for the management of SARA have been published.⁶⁰

Antimicrobial treatment

Appropriate antibiotic treatment of acute genitourinary infection along with contact tracing and treatment of sexual partners is essential. Conversely, antibiotic treatment of bacterial diarrhoea, other than in exceptional circumstances, is best avoided. However, the identification of microbes, or microbial elements, in the joint and their possible persistence at other sites raised the possibility that effective antimicrobial therapy might prevent or curtail episodes of reactive arthritis.

Box 4 Predictors of severe disease at presentation

- Arthritis of the hip
- Erythrocyte sedimentation rate >30 mm in first hour
- Poor response to non-steroidal anti-inflammatory drugs
- Lumbar spine stiffness
- Dactylitis
- Oligoarthritis
- Onset <16 years of age
- Hip arthritis or more than three factors at presentation associated with severe disease

Table 1 Differential diagnosis

Diagnosis	Key distinguishing features/ investigations
Gout	Urate crystals on joint aspiration
Rheumatoid arthritis	Symmetrical arthritis Rheumatoid factor, anti-CCP antibodies, erosions on radiography/ultrasound
Psoriatic arthritis	Psoriatic rash, nail changes
Inflammatory bowel disease	Colonoscopy and biopsy White cell scan
Septic arthritis	Joint aspiration, microscopy, Gram stain and culture Blood cultures
Infective endocarditis	Echocardiography, blood cultures
Sarcoidosis	Chest radiograph, lymph node or target organ biopsy, serum ACE, calcium
Rheumatic fever	History and examination, ASOT, DNase B antibodies, modified Jones' criteria ⁶
Lyme disease	Serology, synovial fluid polymerase chain reaction
Syphilis	Dark field microscopy, serology
Tuberculosis	Aspiration, synovial biopsy, culture

Anti-CCP; cyclic citrullinated peptide antibodies.

Unfortunately, despite many studies, the situation remains unclear. Several aspects of this important facet of reactive arthritis need consideration, chiefly: can antibiotics prevent arthritis, and do prolonged courses of antibiotics shorten or ameliorate episodes.

Clearly, many patients develop SARA after starting or completing antibiotic treatment sufficient to eradicate the local genitourinary infection.⁶¹ In a single observational study appropriate treatment of sexually transmitted infection seemed to reduce the likelihood of arthritis.⁶² Undoubtedly prompt treatment of genitourinary infection makes sense, although the issue of true prophylactic value is unresolved. Short courses of antibiotics (one to two weeks) do not seem to influence the course or duration of either SARA or enteric reactive arthritis.^{61–65} The position is less clear with prolonged courses of treatment. Treatment for three months with lymecycline seemed to shorten episode duration in chlamydia induced reactive arthritis but not in enteric forms.⁶⁶ Similarly combinations of doxycycline and rifampicin for durations of nine months seemed beneficial in undifferentiated spondylarthropathy.⁶⁷ Conversely, however, no significant effect on episode duration or severity was shown in placebo controlled studies of three month courses of ciprofloxacin and azithromycin.^{68–72} Long term outcome has only been investigated by one study, which found that patients treated with a three month course of ciprofloxacin at diagnosis were less likely than those who received placebo to have persistent arthritis after seven years of follow up.⁷³

In clinical practice it is clear that eradication of genitourinary infection is important but that there is no place for long term antibiotic treatment in routine management of reactive arthritis. But many questions remain. Some antimicrobial agents may exert a therapeutic effect by virtue of their anticollagenolytic and anti-inflammatory properties and might yet be useful.⁷⁴ Moreover, it remains unknown whether long term treatment actually eradicates persistent forms of bacteria that may underlie continuing arthritis.

Anti-inflammatory therapy

Single troublesome joint or enthesitis lesions may be effectively and safely treated by local corticosteroid injection, provided that sepsis is excluded. However, you should avoid injecting at the Achilles tendon attachment itself, instead targeting the inflamed bursa if present. Challenging sites are more effectively injected under ultrasound guidance.

Box 5 Routine investigations in reactive arthritis

Full blood count

Neutrophilic leucocytosis, thrombocytosis, anaemia of chronic disease

Acute phase response

ESR > 60, raised C reactive protein (may normalise with prolonged disease)

Autoantibodies

Negative

Urine analysis

Positive for white cells

Synovial fluid analysis

Polymorphs in acute disease followed by lymphocytes

Synovial biopsy

Polymorph infiltrate indistinguishable from other chronic rheumatic disease

Electrocardiogram

Often normal but may show variable degrees of heart block

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually helpful as first line treatment. There is no evidence to suggest that one NSAID is superior to others in this condition. Although not indicated in current guidelines, more selective COX 2 inhibitors are used effectively in spondylarthropathy in patients at high risk of upper gastrointestinal adverse events.^{75–76} Locally applied NSAIDs may occasionally be useful in the management of enthesitis. Simple and opioid analgesics are useful adjuncts in the management of pain in these patients. In more severe, NSAID resistant, systemic, or prolonged disease, systemic corticosteroid may be used. This may be given as a single intramuscular dose of depot methylprednisolone (80–120 mg) or as a short course of oral prednisolone (10–20 mg once a day), weaned to withdrawal from one week to three months.

Second line agents

In recurrent, chronic, or erosive disease second line agents may be used as in rheumatoid arthritis. Of these sulphasalazine is the best studied and shown to be well tolerated and probably effective for peripheral joint disease.^{77–78} Other agents including methotrexate and leflunomide may be of benefit in the management of the spondylarthropathies although formal evidence for this in reactive arthritis is limited.⁷⁹

Box 6 European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy

- Inflammatory spinal pain or synovitis: asymmetrical predominant in lower limbs

and one or more of the following:

- Positive family history
- Inflammatory bowel disease
- Urethritis, cervicitis, or acute diarrhoea within one month before arthritis
- Buttock pain alternating between right and left gluteal areas
- Enthesopathy
- Sacroiliitis

Anti-TNF therapy has been used successfully on an anecdotal basis in a few patients with severe, chronic disease.⁸⁰ The place of such biological therapy in this condition is however far from established.⁸¹

Other therapies

Physiotherapy is of paramount importance in increasing muscle strength and improving mobility and function. Orthotics including insoles and heel supports may limit pain and improve mobility. Many patients find shoes with substantial cushioning such as trainers comfortable during periods of forefoot or heel pain. Pain management techniques such as transcutaneous electrical nerve stimulation may also be useful for painful localised lesions. Therapy for eye disease should be dictated by ophthalmologists after specialist assessment.

HIV AND REACTIVE ARTHRITIS

Several rheumatic lesions or syndromes are recognised in HIV infected patients (box 7). Reactive arthritis has been reported in up to 11% of HIV infected patients, but the prevalence of arthritis seems to vary between different populations.⁸² Similar to non-HIV cases, peripheral lower limb arthritis and enthesitis are the main presenting features. Synovitis of the knee and dactylitis are the most frequent musculoskeletal manifestations. Cutaneous disease such as circinate balanitis, keratoderma, and urethritis also occur frequently and may be more severe than in non-HIV cases. White patients with HIV related reactive arthritis are usually HLA-B27 positive, whereas non-white patients tend to be negative.^{83–86} After the introduction of HAART therapy (highly active antiretroviral therapy) the frequency of HIV associated spondylarthropathies seems to be unchanged although the severity of cutaneous lesions is milder in cases of reactive arthritis.^{82, 83} Treatment of arthritis in the context of HIV infection firstly requires control with appropriate antiviral therapy. NSAIDs and local corticosteroid injections may also be used as in non-HIV cases. In longstanding cases sulfasalazine is of benefit.⁷¹

SUMMARY

Reactive arthritis is a systemic disorder characterised by aseptic arthritis, which is triggered by a distant infection and usually arises from the genitourinary or gastrointestinal tracts. It is a member of the spondylarthropathy family of diseases of which the pathognomonic lesion is enthesitis. HLA-B27 is the gene linked to this group of diseases although other predisposing genes have been identified. The diagnosis is dependent on identifying features of a spondylarthropathy and a recent infection. Most patients will recover fully, although many experience recurrent episodes.

Box 7 Musculoskeletal lesions associated with HIV infection

- Arthralgia
- Reactive arthritis
- Psoriatic arthritis
- Undifferentiated spondylarthropathy
- "HIV associated arthritis" cool oligoarthritis/monoarthritis
- Septic arthritis
- Avascular necrosis of the bone

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F)); ANSWERS AT THE END OF THE REFERENCES

1. Spondylarthropathies are characterised by
 - (A) Enthesitis
 - (B) Positive rheumatoid factor
 - (C) Uveitis
 - (D) Symmetrical joint erosions
 - (E) Presence of HLA-B51
2. Reactive arthritis
 - (A) Is characterised by an aseptic arthritis
 - (B) Predominantly affects the 60–80 age group
 - (C) May be associated with erythema nodosum
 - (D) May be complicated by iritis and corneal ulceration
 - (E) Keratoderma blennorrhagica is a characteristic lesion
3. In enteric forms of reactive arthritis
 - (A) *Yersinia enterocolitica* is a recognised cause
 - (B) Bowel lesions may resemble inflammatory bowel disease
 - (C) Severity of diarrhoea correlates with severity of arthritis
 - (D) Antibiotics are essential in management
 - (E) Stool culture will always show causative organism
4. In cases of reactive arthritis
 - (A) Synovial fluid should be examined whenever possible to exclude septic arthritis
 - (B) NSAIDs are useful in initial management
 - (C) Sulphasalazine is effective treatment for sacroiliitis
 - (D) Antibiotic treatment for local genitourinary infection is essential
 - (E) Presence of HLA-B27 is essential for diagnosis
5. In cases of HIV
 - (A) Reactive arthritis occurs in 25% of patients
 - (B) Psoriatic lesions may be more severe than in non-HIV cases
 - (C) HIV infection is a risk factor for septic arthritis
 - (D) Antiviral therapy improves outcome from reactive arthritis
 - (E) Avascular necrosis is a complication

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ANSWERS

1. (A) T, (B) F, (C) T, (D) F, (E) F; 2. (A) T, (B) F, (C) T, (D) T, (E) T; 3. (A) T, (B) T, (C) F, (D) F, (E) F; 4. (A) T, (B) T, (C) F, (D) T, (E) F; 5. (A) F, (B) T, (C) T, (D) F, (E) T.

WEB TRAWL

Patients frequently attend outpatient clinics either asking where on the web they can access information on their condition, or, more commonly, they arrive at their clinic appointment with information, and sadly, sometimes misinformation, they have downloaded. Being able to direct patients to reputable web sites therefore is likely to become increasingly important. Here are two UK based web sites, which you and your patients may find helpful. Although there is a certain amount of overlap in the information both provide, their approach is slightly different, and some patients, depending on the information they are seeking, may have a preference for one over the other.

<http://www.patient.co.uk> This web site is largely authored by two GPs who aim to provide reliable health related information for the general public, but that may be of interest to all. The home page is clearly laid out, providing a simple list of bullet points detailing the information available, with links as appropriate. The first link is to a comprehensive set of patient information leaflets, these are the same leaflets that many GPs have available for download in the surgeries. For some, foreign language translations and audio versions are available. Another link takes the user to a similarly comprehensive set of information covering different medications. For those wanting more detailed information, links to a number of online medical textbooks are provided, along with one to PubMed allowing Medline searches to be performed. There is also a link to a collection of clinical guidelines—a valuable resource for both patients and health professionals alike. There is also a page for patients to detail their own experiences and anyone may contribute if they so wish. For patients whose GP surgeries are linked to the EMIS system, they may even book an appointment or order a prescription via the web site. Overall this is a simple, easy to use web site providing a wealth of information and is one certainly to be recommended.

<http://www.besttreatments.co.uk> This web site is provided by the *British Medical Journal*, in association with the publication *Clinical Evidence*. From the home page, the user may view information again on a large number of conditions, simply by selecting from a drop down menu. A similar list provides more detailed information aimed at health professionals, but patients may access this information also if they wish. The information for patients is largely written by hospital specialists, many of whom contribute to *Clinical Evidence*, with the information for health professionals consisting of extracts from *Clinical Evidence* itself. Because the web site places a heavy emphasis on evidence based medicine (EBM), it devotes an entire web page to this subject, defining it and explaining its importance. Although designed for patients, health professionals just starting to become familiar with the concept of EBM may also find this of value. A final, smaller section provides information on a number of operations and procedures. This section is by no means comprehensive at present, but no doubt could expand in the future. Overall, again this is a reputable web site that you may confidently recommend to your patients.

Robyn Webber
Web Editor