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INFECTION AND ARTHRITIS

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- In acute monoarthritis in adults, joint aspiration and culture remain vital diagnostic procedures
- Prosthetic joint sepsis increasingly involves antibiotic-resistant microorganisms, with 5–15% mortality
- Human immunodeficiency virus (HIV) infection predisposes to musculoskeletal infections but the association with aseptic arthritis is tenuous
- Streptococcal throat infections are now implicated in benign oligoarthritis distinct from rheumatic fever in both adults and children
- Bacteria are detectable in the joints of patients with a wide range of inflammatory arthritis but their pathogenic significance is unclear
- Treatment of established reactive arthritis with antibiotics is probably ineffective

INTRODUCTION

Contrary to earlier expectations, infectious agents are now known, or suspected, to play crucial roles in a wide variety of acute and chronic rheumatic diseases, including those conventionally regarded as aseptic. Joint sepsis is re-emerging as an important cause of morbidity and mortality thanks largely to widespread antibiotic usage and drug resistance, joint replacement surgery, immunosuppressive therapy and human immunodeficiency virus (HIV) infection. In consequence, doctors – whether in general practice, musculoskeletal specialties, Accident & Emergency departments or in general medicine – need to practise rigorous preventive measures, maintain a high index of suspicion and ensure urgent, assiduous, multidisciplinary approaches to treatment.

Viral infections undoubtedly cause both common and uncommon forms of inflammatory arthritis worldwide. In the UK few such cases reach hospitals, most being recognised and managed in general practice. The potential contribution of HIV infection to acute arthritis remains uncertain.

The major chronic inflammatory arthritides are likely to be multifactorial in origin but infective agents may well initiate or perpetuate the joint lesion. Sophisticated developments in techniques for bacterial detection, particularly those involving specific deoxyribonucleic acid (DNA) amplification, as well as the identification of previously unknown microorganisms, have produced surprising results. The demonstration of an essentially septic basis for Lyme disease has had a major impact on the understanding of chronic arthritis. Similarly the demonstration of minute numbers of bacteria in joint samples from patients with reactive and other forms of inflammatory arthritis has led to reappraisal of existing concepts of pathogenesis. As with bacteria, the plot has thickened with the identification of viral DNA sequences embedded within the genome of patients with some rheumatic disorders such as Sjögren’s syndrome, so that the relationship between both exogenous and endogenous viruses and inflammatory rheumatic disease is intriguing but obscure.
SEPTIC ARTHRITIS

Septic arthritis remains an uncommon clinical problem, although dealing with suspected cases of infection is not. Staphylococcus aureus remains the commonest causal agent. More than 90% of strains are now resistant to penicillin and in hospitals an increasing proportion are multiply resistant (MRSA). More concerning still, MRSA strains with intermediate sensitivity to glycopeptide antibiotics (vancomycin and teicoplanin) are now emerging. The presence of a prosthetic joint now ranks among the highest risk factors for joint sepsis, with joint damage such as from rheumatoid arthritis (RA), immunosuppressive treatment, HIV infection and intravenous drug abuse also key predisposing factors.

Management of the acute hot joint

This is one of the most challenging and urgent problems in clinical rheumatology. The differential diagnosis is wide, including trauma, inflammatory arthritis, haemarthrosis, bone or cartilage disorders and infection.1 Urgent investigations to separate crystal synovitis, bacterial infection and traumatic joint derangement from other sub-acute or chronic disorders should be undertaken.

The age of the patient may give clues to the likely diagnosis. In children up to the age of 18 months sepsis must be regarded as likely, whereas in older children trauma must be considered.2 In young, sexually active, adults reactive arthritis and gonococcal arthritis must be strongly considered,3 whereas in older patients crystal arthropathies are likely.4 Severe pain at rest suggests infection or crystal synovitis.

In the management of acute monoarthritis it should be assumed that infection is present until proven otherwise. Fever and systemic upset support the diagnosis of infection, although these may also be seen in acute gout and pseudogout. Assessment for additional risk factors including a primary source for infection, previous joint damage due to arthritis or surgery, immunosuppressive therapy or intercurrent disease including diabetes and HIV infection should raise the index of suspicion further.

The most important investigation remains aspiration of joint fluid for urgent microscopy, culture and crystal examination. Assessment of markers of infection including leucocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be contributory, as may plasma urate estimation and blood cultures. X-rays of affected joints during the acute phase are seldom helpful. Further imaging with isotope, white cell and magnetic resonance imaging (MRI) scans does not usually help distinguish between infection and other causes of joint inflammation.5

The most common causes of non-gonococcal septic arthritis in adults are Staphylococcus aureus (68%), Streptococci (20%), aerobic gram negative organisms (10%) and Haemophilus influenzae (1%).6 Where the microbiological diagnosis is not known, blind parenteral antimicrobial therapy should be instituted with a combination of a penicillin such as cloxacillin and a cephalosporin.7 Where MRSA infection is suspected or confirmed, options would include vancomycin, teicoplanin, aminoglycosides, fusidic acid or quinolones. Blind treatment is best determined in conjunction with a local microbiologist who will be best able to predict likely antibiotic sensitivity. Joint drainage and lavage by an orthopaedic surgeon may reduce joint damage and in a few cases steroid therapy may be helpful.8

Guidelines have been produced for the management of the acute hot joint, though their usefulness is dependent on the clinical situation.9 In patients with a monoarthritis in which an early diagnosis is not made, the most frequent eventual diagnosis is spondyloarthropathy followed by RA.10

Prosthetic joint sepsis

The use of prosthetic joint surgery is growing rapidly. Between 0.5% and 2.3% of prostheses become infected over the 10 years following the procedure. Early infections, within a month of surgery, arise as a result of direct contamination of the wound; late infections occurring more than 12 months post-operatively usually result from haematogenous spread from a distant source of infection. Coagulase-negative Staphylococci and Staphylococcus aureus are the commonest causal microorganisms, followed by Streptococci and enterobacteriaceae.11 Antibiotic-resistant strains such as MRSA and vancomycin-resistant Enterococci (VRE) are becoming increasingly common. Presentation is typically acute, with fever, malaise and soft tissue swelling, but symptoms may be subtle, especially in elderly and debilitated patients with pain and tenderness with or without a fluctuant mass.

The enhanced susceptibility of prosthetic joints to infection relates partly to the ease with which bacteria attach to prosthetic material12 and partly to other susceptibility factors including immobility and susceptibility to infections at other sites, including the urinary tract and skin.

The incidence of prostatic infection can be minimised by scrupulous exclusion of any potential sources of infection pre-operatively, adoption of ultra-clean air systems, suitable theatre clothing,9 systemic antibiotic prophylaxis and use of antibiotic-impregnated cement.14,15

The diagnosis of prosthetic joint infection firstly requires a high index of suspicion. Plain radiographs may show a resorption zone around implants as a late feature.
99mTc bone scanning may indicate changes before x-ray abnormalities appear, but ultimately the diagnosis requires aspiration of the joint or synovial biopsy under scrupulously sterile conditions. There is little evidence to suggest that further investigation with white cell scanning improves management.16

Treatment of infected joint implants is complicated and requires considerable experience. Treatment may include long-term antibiotic treatment, debridement, revision arthroplasty, arthrodesis and amputation.17 The decision as to which approach or combination of approaches to take must be based on the general condition of the patient, the soft tissue and bone quality around the wound and the identity and sensitivity of the microorganism involved.18 Current practice favours a two-stage procedure with initial meticulous removal of the infected prosthesis followed by a prolonged course of antibiotics with a view to eventual revision arthroplasty.

Despite the advances in prosthetic joint surgery and the antibiotics available to prevent and treat sepsis, the mortality of prosthetic joint sepsis remains around 5% for knee and 15% for hip – those with antibiotic-resistant microorganisms having an especially poor prognosis.19

VIRAL INFECTION AND ARTHRITIS

A wide range of viruses have been implicated as causing inflammatory arthritis. Human parvovirus and hepatitis B virus remain the most common viral precipitators of arthritis in Europe and the USA, although alphaviruses are major causes worldwide. In the summer, outbreaks of erythema infectiosum in children are associated with sporadic self-limiting poly- or oligoarthritis usually among adult contacts. Transient anaemia due to erythroid maturation arrest is highly characteristic and the diagnosis is confirmed by the finding of a raised titre of parvovirus IgM antibody.20,21 Hepatitis C virus is associated with a range of autoimmune phenomena.21,22 Retrovirus infection has provoked considerable interest in recent years, HIV 1 and 2, human T-cell lymphotrophic virus 123 and human endogenous retroviruses24 all having been implicated in chronic arthritic conditions.

Human immunodeficiency virus and rheumatic lesions

A wide range of rheumatic lesions have been described in individuals with HIV infection, with or without demonstrable immunodeficiency.25 Lesions described include non-specific oligoarthritis, arthralgia, reactive arthritis, psoriatic arthritis, the diffuse infiltrative lymphocytosis syndrome, vasculitis, polymyositis/dermatomyositis, and joint, bone and muscle sepsis, in addition to forms of vasculitis and the presence of a range of autoantibodies. Early reports focused on forms of aseptic inflammatory arthritis, particularly reactive arthritis, psoriatic arthritis and undifferentiated oligoarthritis. Such studies suggested that these conditions were more common in HIV-infected individuals and that HIV-induced immunodeficiency predisposed to more aggressive arthritis, although there have been few controlled studies to support these contentions.

More recent reports have focused on the presence of musculoskeletal infections in this population. The incidence of musculoskeletal sepsis ranges from 0.3 to 3.6%25 and it is clear that major risk factors for bacterial sepsis include a CD4 count of <250/mm3, intravenous drug use, haemophilia and additional sources of infection including trauma and in-dwelling catheters. The range of bacteria isolated is broadly similar to the range involved in HIV-negative individuals, Staphylococcus aureus, Streptococcus pneumoniae and Mycobacterium tuberculosis being the principal agents.26 Very low CD4 cell counts (< 100/mm3) predispose especially to atypical opportunistic pathogens. Rapid diagnosis and early effective treatment leads to successful outcome in the majority of patients, the mortality rate of bacterial joint sepsis in this population being less than 3%.

While susceptibility to septic lesions in immunosuppressed individuals seems to be genuinely increased, uncertainty remains as to whether other rheumatic lesions occur more commonly in HIV-infected populations than in otherwise healthy individuals.

INFECTION IN ASEPTIC ARTHRITIS

It seems highly likely that infective agents also play roles in the causation of other forms of inflammatory arthritis in which conventional features of infection are absent. In reactive arthritis and rheumatic fever epidemiological and biological links with episodes of infection are strong. In consequence they hold out the tantalising prospect of understanding the mechanism linking infection and aseptic arthritis and have therefore been the subject of considerable research activity in recent years.27,28

Over the same time period a plethora of new, highly sensitive techniques have promised to allow the detection of bacteria, or bacterial components, in joint samples even when cultures are negative. Such techniques include assays for endotoxin, use of monoclonal and polyclonal antibodies, mass spectrometry and DNA amplification techniques. Crucially, such techniques have demonstrated the presence of bacterial membrane antigens, DNA and ribonucleic acid (RNA) in joint samples from patients with conventionally aseptic arthritis and so beg the
question as to whether bacteria identified actually cause or perpetuate the arthritis. Studies have focused on reactive arthritis, in which such a mechanism appears likely, but more recently have also included other forms of chronic arthritis including rheumatoid disease. Use of techniques based on the polymerase chain reaction (PCR), in particular, have produced some startling results which are difficult to understand.

**Reactive arthritis**

The clinical and epidemiological links between reactive arthritis and specific infections have been known for several decades. However, it seemed that the more recent identification of bacterial antigens and DNA within inflamed joints would provide, at last, the missing link that would explain the pathogenesis. Thus far, sadly not.

There is a wide consensus that outer membrane proteins, DNA, and probably RNA, of *Chlamydia trachomatis* are present in joint tissue from some patients with reactive arthritis. Although searches for bacterial DNA in such samples have been unrewarding. These findings seem consistent with clinical and microbiological evidence and also with immunological studies of lymphocyte sensitisation in the joint.

However, recent reports have thrown these findings into confusion. Chlamydial DNA has been reported in joint samples from patients with RA in whom recent infection appears unlikely and from asymptomatic subjects. Bacterial RNA from a very wide range of bacteria has been detected in joint samples from patients with reactive arthritis following these infections, although diligent searches for bacterial DNA in such samples have been unrewarding. These findings seem consistent with clinical and microbiological evidence and also with immunological studies of lymphocyte sensitisation in the joint.

It remains unclear whether PSRA is a homogeneous condition or whether there is significant linkage with human leucocyte antigen (HLA) B27. Studies of streptococcal antigen deposition in inflamed tissue have yet to be reported. There are grounds for considering penicillin treatment and prophylaxis in both children and adults with PSRA following GAS infection, though there are no clear studies to support this. Eradication of infection is appropriate when non-group-A streptococci have been implicated, though there is no case for prophylactic treatment in this group.

**Antibiotic treatment of aseptic arthritis**

The long-standing assumption that inflammatory arthritis may be initiated or perpetuated by infectious agents has spawned considerable interest in antimicrobial chemotherapy. Moreover, the finding of potentially viable bacteria in joint material from patients with reactive and other forms of arthritis has added weight to such expectations. In consequence, several investigators have explored the potential of, necessarily blind, antibiotic treatment of arthritis.

There have been a number of trials of antibiotic therapy in patients with inflammatory arthritis, including RA. Early studies did not show any benefit of antibiotics in RA, although subsequent studies in patients with severe RA showed modest improvement with tetracyclines. More recently, in a double-blind placebo-controlled study, minocycline therapy in the first 6 months after diagnosis of seropositive RA produced a 50% improvement or more in 65% of patients after 6 months. Four-year follow-up of this patient group demonstrated that 50% of patients treated with minocycline had not required therapy with disease-modifying anti-rheumatic drugs (DMARDs) or steroid. The maximum benefit in responders was seen at 9 months. Previous studies in patients with established...
RA have also shown benefit from minocycline treatment, although of a smaller magnitude. The mechanism by which tetracyclines might be effective in RA remains unclear, matrix metalloproteinase inhibition, immunomodulatory effects and inhibition of angiogenesis may all play a role.

The rationale for antibiotic treatment has been more evident in reactive arthritis. The use of short courses of antibiotic treatment (up to 3 weeks) to eradicate genital tract infection remains logical. However, short courses of antibiotic treatment have not been shown to be of benefit to the arthritis. Use of ciprofloxacin for periods of 3 months to 1 year have not been shown to be beneficial in reactive arthritis following gastrointestinal infection, although of a smaller magnitude. The mechanism by which tetracyclines might be effective in RA remains unclear, matrix metalloproteinase inhibition, immunomodulatory effects and inhibition of angiogenesis may all play a role.

The occurrence of reactive arthritis. Further collaborative studies are in progress, though it is of interest that no studies have yet addressed the issue of whether antibiotic treatment eradicates microorganisms from the joint.

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