Bone and joint infections

Catherine J Mathews

Abstract

The joint is a common site of musculoskeletal infection in adults. Septic arthritis is the most serious, although not the most frequent, cause of a hot swollen joint or joints. The diagnosis rests principally on clinical suspicion. Investigation of suspected joint sepsis is urgent in order to avoid significant morbidity and mortality. This review will cover the aetiology, pathogenesis, clinical features, investigation and management of native joint sepsis in adults, and will highlight the gaps in the evidence base regarding its pharmacological management and suggest some areas for future research. It will briefly cover osteomyelitis, which is much more common in young children than it is in adults.

Keywords Antibiotics; arthritis; infection; osteomyelitis; sepsis

Septic arthritis

The presentation of a patient with one or more hot swollen joints has a broad differential diagnosis (Table 1). It can be challenging to make the diagnosis of joint infection even for practitioners experienced in the management of musculoskeletal disease. Such patients should be considered a medical emergency because septic arthritis, although not the most common cause, is a serious condition that carries a significant morbidity and mortality. If treatment is delayed or suboptimal then the outcome can be irreversible joint destruction. Moreover, the mortality is up to 11%, increasing to figures as high as 50% in polyarticular sepsis.[1]

Epidemiology

Estimates of the incidence of septic arthritis are limited by several difficulties relating to research methodology.[2] Most data are generated from retrospective cohorts. Prospective studies are difficult to conduct due to the infrequent nature of the condition. It is also difficult to categorize the disease consistently as, even in patients in whom septic arthritis is strongly suspected, the subsequent diagnosis might not be firmly established microbiologically. Newman's 1976 modified criteria are those most commonly used to define the diagnosis and require one of four conditions to be met:

- isolation of a pathogenic organism from an affected joint
- isolation of a pathogenic organism from another source in the context of a hot, red, swollen joint where sepsis is suspected
- clinical features of joint sepsis and turbid synovial fluid in the presence of previous antibiotic therapy or
- pathological features suspicious of septic arthritis at post mortem.[3]

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Differential diagnosis of the acute hot joint

Differential diagnosis	Clues to this diagnosis
Septic arthritis	Short history, 1–2 weeks, pain and restriction of movement of affected joint(s)
Crystal arthritis (gout, pseudogout)	First metatarsophalangeal joint suggests gout. History of diuretic use, particularly in older women, suggests pseudogout
Trauma	History, bloody joint aspirate
Haemarthrosis	History, bloody joint aspirate
Systemic inflammatory arthritis (rheumatoid arthritis, seronegative arthritis)	Systemic symptoms, multiple joint involvement ± axial skeleton; psoriasis; inflammatory bowel disease; gastrointestinal or genitourinary infection; conjunctivitis/uveitis.
Extra-articular pathology (tenosynovitis, bursitis)	Full range of movement of the joint. Visible inflammation of extra-articular structures

Table 1

The incidence of definite and probable septic arthritis in western Europe is 4–10 per 100,000 patient-years per year.[4,5] The incidence of septic arthritis globally is rising and this has been linked with an ageing population, increased use of immunosuppressive agents, musculoskeletal prostheses and surgical procedures.

Septic arthritis can affect all age groups but is more common in the elderly and the very young. Further risk factors for the development of septic arthritis are summarized in Table 2.[6] It is much more likely to develop in a joint that is already abnormal. Previous joint damage inflicted by rheumatoid arthritis, osteoarthritis or crystal arthritis will predispose individuals to sepsis in the affected joint(s). Prosthetic joints are also at higher risk of superimposed infection. Other documented risk factors include intravenous drug abuse, alcoholism, diabetes mellitus, and skin infection or ulceration.

Instrumentation of a joint, either using a needle or by surgical arthroscopy, has been implicated as a cause of septic arthritis but studies suggest that cases are relatively rare. The incidence has been quoted at about four cases per 10,000 injections and a prevalence of 14 per 10,000 arthroscopic procedures.[7] In the

Risk factors for the development of septic arthritis

Underlying joint pathology (e.g. rheumatoid arthritis, osteoarthritis)
Prosthetic joint
Low socioeconomic status
Intravenous drug abuse
Alcoholism
Diabetes mellitus
Previous intra-articular injection or instrumentation
Cutaneous ulceration
Immunosuppression

Table 2

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context of immunosuppression for inflammatory arthritis, disease-modifying pharmacological treatment can predispose some patients with rheumatoid arthritis to joint sepsis. The introduction of anti-tumour necrosis factor-α (anti-TNF-α) agents has seen an increased risk of septic arthritis in this cohort. The absolute risk is still small, but there is an approximate doubling of the incidence that is attributable to the drug therapy itself.[8]

The most frequent causative agent identified microbiologically in septic arthritis is *Staphylococcus aureus*, in all age and risk groups.[4,5,9] The second most common organisms are other Gram-positive bacteria, predominantly streptococci. In certain risk groups other organisms rise in prevalence, although *S. aureus* and streptococci remain the most common. Intravenous drug abusers have an increased susceptibility to atypical bacteria and fungal infections. Gram-negative organisms are more frequent seen in the elderly, which may be a result of comorbidities including urinary tract infections and skin ulceration.[5,6] Gonococcal infection, though frequently quoted as a cause of septic arthritis in young adults, has been established as a relatively rare cause of so-called dermatitis-arthritis syndrome in North America and Europe.[1,4] Studies using PCR methods have revealed that *Neisseria meningitidis* is the most common cause of this syndrome.[2]

Hospital-acquired meticillin-resistant *S. aureus* (MRSA) infection is on the increase as a cause of septic arthritis, particularly in patients who have other risk factors for infection.[1,9] New strains of community-acquired MRSA have also been identified both in the Europe and in North America, and these have different antibiotic sensitivities than the hospital-acquired organisms.[2]

Pathogenesis

There are two ways by which infection can be introduced into a joint. The most common route is via haematogenous spread. Less commonly, a joint may be directly inoculated by organisms either as a result of trauma, or iatrogenically via needling or arthroscopy. In patients who are immunosuppressed, or who have had invasive procedures, an established bacteraemia is more likely and can result in established joint infection, particularly if the patient has a joint that is already damaged.[4]

Key advances have been made in the understanding of the pathogenesis of septic arthritis through work in experimental mouse models of both staphylococcal and streptococcal disease.[10,11] Genetic manipulation of these animal models has revealed that the elimination of host factors including macrophage-derived cytokines (e.g. lymphotoxin-α, TNF-α, and interleukin-1 receptor) and anti-inflammatory cytokines (e.g. interleukin-10) can increase the severity of septic arthritis as well as causing increased morbidity and mortality. Conversely, the absence of interleukin-4 appears to confer a protective effect. Bacterial factors including proteinaceous cell wall components and bacterial adhesins appear to modulate bacterial virulence. Data from both animal models indicate that considerable variability exists from one pathogen to another.[12]

Clinical features

The diagnosis of septic arthritis principally rests on the clinical features. Typically, individuals with septic arthritis present with a short, 1–2 week history of one or more red, painful, restricted joints.[3] Presentation may be more insidious if fungal or mycobacterial pathogens are causative.[1,13] Large joints are more likely to be affected than small ones, with the lower limb being more commonly affected than the upper limb. Although septic arthritis is often thought of as affecting one joint only, in most studies up to 20% of patients have a polyarticular presentation.[9] In patients who have underlying rheumatic disease, the infected joint will typically show signs that are out of proportion to the disease activity detected in other joints.

Symptoms of systemic upset are not a prerequisite for the diagnosis of septic arthritis. Fever and rigors at presentation occur much less commonly that might be expected and the diagnosis of septic arthritis must not be ruled out on the basis of their absence.[1,13]

Laboratory investigation

There is no single investigation with anything approaching 100% sensitivity for the diagnosis of septic arthritis.[14] For this reason the diagnosis principally rests on clinical suspicion. To maximize the chances of confirming the diagnosis and obtaining a causative organism together with its antibiotic sensitivities, the affected joint(s) must be aspirated.[15] Synovial fluid, if it is obtained, can be the key to diagnosis and should be sent for Gram stain and culture. Gram staining of synovial fluid may identify the pathogenic organism in 50% of cases, this percentage rising to 67% after culture.[5] Joint aspiration should always be performed before starting antibiotic therapy and sent fresh to the laboratory for processing.

Blood should also always be cultured to maximize the microbiological yield.[15] One study has shown that blood cultures were positive in 24% of cases in which the synovial fluid had revealed a causative organism. More telling, however, was the 9% of cases in which synovial fluid culture was negative but blood culture was positive.[5] Any other potential source of sepsis, such as skin, urine, throat or genitourinary system should also be swabbed and cultures requested to aid accurate diagnosis. All microbiological specimens should be taken before the commencement of empirical antibiotic therapy.

Several potential serological and synovial markers have been studied over the years in what has, so far, been a fruitless search for a means to discriminate between infective and non-infective joint inflammation. Thus far, none has had sufficient predictive value to become established in routine clinical practice.[16]

White cell count, erythrocyte sedimentation rate and serum C-reactive protein concentration should all be measured, although they may well be normal in the presence of joint sepsis and do not discriminate between infectious and non-infectious inflammation.[15,16] If raised, however, they have a role in monitoring the response to antibiotic treatment. It is also prudent to check renal and liver function at presentation.[15] Abnormal function of either of these organs indicates a poorer prognosis in septic arthritis. In addition, results indicating reduced kidney or liver function may influence the choice, or dose, of antibiotic therapy.

Some studies have suggested that quantification of the synovial fluid white cell count may help to discriminate between infectious and non-infectious causes of joint inflammation.[17] Others, however, have not corroborated these data and this area remains controversial. A cell count greater than 50,000 cells

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