Seminar

Bacterial septic arthritis in adults

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Symptoms and signs of septic arthritis are an important medical emergency, with high morbidity and mortality. We review the changing epidemiology of septic arthritis of native joints in adults, encompassing the increasing frequency of the disorder and its evolving antibiotic resistance. We discuss various risk factors for development of septic arthritis and examine host factors (tumour necrosis factor α, interleukins 1 and 10) and bacterial proteins, toxins, and enzymes reported to be important determinants of pathogenesis in mouse models. Diagnosis of disease is largely clinical, guided by investigations and the opinion of skilled clinicians. We emphasise the need for timely medical and surgical intervention—most importantly, through diagnostic aspiration of relevant joints, choice of suitable antibiotic, and appropriate supportive measures. Management is growing in complexity with the advent of novel and antibiotic-resistant causative microorganisms and within the current climate of increased immunosuppression. Findings from animal models and patients are shedding light on disease pathogenesis and the possibility of novel adjunctive treatments, including systemic corticosteroids, cytokines and anticytokines, and bisphosphonates.

Introduction

The presentation of a patient with one or more hot swollen joints is a common medical emergency. Such symptoms have a broad differential diagnosis, and, although not the most typical, the most serious cause is septic arthritis. This disease has substantial morbidity and mortality.

Diagnosis of septic arthritis can be challenging even for doctors skilled in the management of musculoskeletal disease. Usually, patients present in the primary-care or emergency-room setting, and doctors working in these areas could have had little training in rheumatic disease. Delayed or inadequate treatment can lead to irreversible joint destruction and, even in expert hands, case-fatality is generally around 11%. This frequency is raised in polyarticular disease, with estimates as high as 50%.[1] Moreover, resistance to conventional antibiotics is a growing difficulty.

Search strategy and selection criteria

We did a systematic search of work published in English in the following databases: Cochrane Library, Medline (1951 to Aug 31, 2008), Embase (1974 to Aug 31, 2008), and the National Electronic Library for Health. Selection of papers for full-text review depended on adherence to defined inclusion and exclusion criteria (outlined in detail in reference 41, search updated to Aug 31, 2008). In brief, we used search terms including: "infectious arthritis", "meta-analysis", "randomised controlled trial", "controlled clinical trial", "evaluation studies", "therapy", "diagnosis", "epidemiology", "microbiology", "radiography", and the names of the main causative bacteria in septic arthritis. The reference lists of retrieved articles and of review articles from key authors and journals were hand-searched to confirm the sensitivity of the defined search strategy. Authors were invited to contribute additional references. We excluded papers in which children younger than age 16 years were assessed; studies on reactive arthritis, chronic sepsis, osteomyelitis, spinal infection, and prosthetic joint infection; and reviews and case reports. We evaluated the methodological quality of selected papers with criteria set out by the clinical effectiveness and evaluation unit of the UK Royal College of Physicians.

Epidemiology

Accurate information about the epidemiology of septic arthritis is limited by several factors. First, data are mainly from retrospective cohorts, because the uncommon nature of the disorder makes prospective studies logistically difficult. Second, case-definitions generally restrict cases to those that are proven bacteriologically. Although this approach has nosological advantages, there are practical limitations. In patients in whom septic arthritis is strongly suspected clinically, the subsequent diagnosis might or might not be established microbiologically, and, historically, this situation has led to difficulties with disease categorisation.

Usual case-definition relies on modified criteria used by Newman[2] and requires one of four points to be met: (1) isolation of a pathogenic organism from an affected joint; (2) isolation of a pathogenic organism from another source (eg, blood) in the context of a hot red joint suspicious of sepsis; (3) typical clinical features and turbid joint fluid in the presence of previous antibiotic treatment; and (4) postmortem or pathological features suspicious of septic arthritis. However, case-series differ in their exclusion criteria. These typically include orthopaedic, gonococcal, tuberculous, and paediatric infections. Despite these considerations, several conclusions about epidemiology can be drawn.

The incidence of proven and probable septic arthritis in western Europe is 4–10 per 100 000 patient-years per year.[3–6] This rate is amplified in disadvantaged groups from northern Europe[1] and in Australia, where prevalence is 29 cases per 100 000 of the aboriginal Australian population, with a relative risk of 6·6 compared with the white Northern Territory Australian population.[3] The incidence of septic arthritis seems to be rising, and this increase is linked to augmented orthopaedic-related infection[6] and an ageing population, more invasive procedures being undertaken, and enhanced use of immunosuppressive treatment.

Panel: Risk factors for development of septic arthritis

- Rheumatoid arthritis or osteoarthritis
- Joint prosthesis
- Low socioeconomic status
- Intravenous drug abuse
- Alcoholism
- Diabetes
- Previous intra-articular corticosteroid injection
- Cutaneous ulcers

Although all ages can be affected, septic arthritis is a disease that usually arises in elderly people and very young children. Previous joint pathology (eg, rheumatoid arthritis, osteoarthritis, crystal arthropathy, and other forms of inflammatory arthritis) predisposes individuals to development of sepsis. Quantification of this increased risk is hard to establish, but it seems likely that rheumatoid arthritis presents a greater risk than osteoarthritis. A prospective study from Amsterdam, in which more than 7000 patients were followed up for 3 years with 37 incident cases of sepsis, showed that risk factors for development of septic arthritis included age older than 80 years, diabetes, rheumatoid arthritis, and recent joint surgery.[7] Raised prevalence in patients on haemodialysis has also been reported and could be around 500 cases per 100 000 patients.[8] Rheumatological risk factors remain important, however, even in this group.

Skin infection is an important risk factor for septic arthritis.[7] Joint injection with corticosteroids has been suggested as an important cause of septic arthritis, but is rare. The precise risk is difficult to quantify, but it is probably about four cases per 10 000 injections.[6] Postarthroscopic septic arthritis has a prevalence of around 14 per 10 000 procedures (0·14%).[6] Moreover, disease-modifying drug treatment can predispose some patients with rheumatoid arthritis to septic arthritis,[9] but to date, antagonists of tumour necrosis factor α for rheumatoid arthritis do not seem to have altered the frequency of septic arthritis. The panel summarises typical risk factors for development of septic arthritis.

In all age and risk groups, the most frequent causative organisms identified are *Staphylococcus aureus* followed by other gram-positive bacteria, including streptococci.[4,5,10] Different microbes increase in importance in specific risk groups, but even in these populations, the most typical organisms remain *S aureus* and streptococci. Findings of studies have noted consistently a worrying increase in meticillin-resistant *S aureus* (MRSA) infection in several health-care systems, and particularly in intravenous drug abusers,[1] elderly people, and individuals with infections related to orthopaedic procedures.[10] The constant evolution of microorganisms has also led to emergence of new resistant strains of MRSA. These strains have been isolated from community-associated infections and have become a major problem in the USA and are starting to be seen in Europe and the UK.[11,12] They have a different antibiotic sensitivity from hospital-acquired MRSA and from isolates from intravenous drug abusers in Europe.[12,13]

Intravenous drug abusers are especially susceptible to mixed bacterial infections, fungal infections, and unusual organisms. Immunosuppression has been suggested as an important risk factor for development of septic arthritis but the precise extent of this risk is unclear. Researchers studying patients with HIV infection conclude that the risk of septic arthritis relates to intravenous drug abuse rather than HIV status.[14,15]

The frequency of gram-negative organisms is amplified in the older population, presumably because of an increased prevalence of comorbidities such as urinary-tract infections and cutaneous ulceration.[5,7] A slight rise in invasive *Haemophilus* infection in adults has also been suspected.[10]

Traditionally, gonococcal infection has been emphasised as a cause of septic arthritis, particularly in young adults. Several studies, however, have established that this organism is a rare cause of so-called dermatitis-arthritis syndrome in Europe and North America.[1,4,5,10,16] In fact, in detailed studies with PCR techniques, *Neisseria meningitidis* is by far the most typical cause of dermatitis-arthritis. *Neisseria gonorrhoeae* is still prevalent in other parts of the world, such as aboriginal communities in Australia[3] and Rwanda.[17] This change needs to be considered when contact tracing and in development of prophylactic regimens.

Pathogenesis

Infection can be introduced into a joint either as a result of haematogenous spread or by direct inoculation, occurring with trauma or iatrogenically. Bacteraemia is more likely to arise in immunosuppressed individuals and patients admitted to hospital, particularly those who have invasive procedures, intravascular devices, or urinary catheters. Infection will most probably become established if the patient is immunosuppressed or the joint is damaged.[4]

Beyond traditional risk factors for sepsis, key advances in our understanding of the pathogenesis of septic arthritis have come from work in animals. Tarkowski and colleagues have developed an experimental mouse model of septic arthritis mediated by *S aureus*.[18] This model parallels pathogenesis of human disease closely in that the pathogen is introduced haematogenously by intravenous injection. More than 90% of mice develop septic arthritis within 24 h of inoculation and their joints have a severe degree of bone erosion similar to changes seen in the human septic joint. This model has been used to study both host and bacterial virulence factors implicated in the establishment of joint infection. Figure 1 shows a

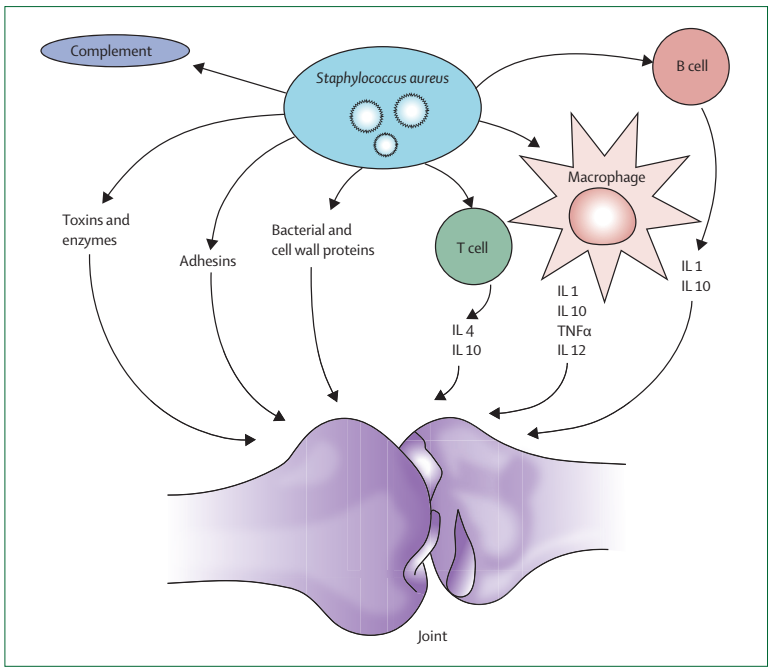

Figure 1: **Pathogenesis of staphylococcal septic arthritis**
TNFα=tumour necrosis factor α. IL=interleukin. Adapted from ref 30, with permission of Future Medicine.

representation of the pathogenesis of staphylococcal septic arthritis.

Host factors

By genetic manipulation of animal models to induce disease, host factors affecting the response to *S aureus* can be studied. Genetic deletion of macrophage-derived cytokines (including lymphotoxin α, tumour necrosis factor [TNF] α, and interleukin 1 receptor) reduces host protection in *S aureus* sepsis, causing increased morbidity and mortality.[19,20] Similarly, absence of the anti-inflammatory cytokine interleukin 10 in knockout mice seems to amplify the frequency and severity of staphylococcal joint disease secondary to reduced clearance of pathogens.[21] By contrast, the interleukin 4 knockout mouse is associated with diminished incidence and mortality, which could be attributable to the role of interleukin 4 in enhancement of bacterial growth or reduction of bacterial clearance from the joint space.[22]

The role of these cytokines has yet to be fully investigated in human septic arthritis. However, data from these murine studies suggest that similar work in patients would prove useful to show not only that the cytokines TNFα and interleukins 1 and 10 could be vital to mount an effective immune response to *S aureus* infection but also that genetic variation in expression of these cytokines might play a part in differential susceptibility to, and severity of, septic arthritis. Similarly, genetic variation leading to high expression of interleukin 4 might lead to increased susceptibility to septic arthritis.

Bacterial factors

S aureus produces many virulence factors, including diverse extracellular toxins, enzymes, and other cell-associated components. These factors have been studied in Tarkowski's murine model by genetic deletion or mutation,[18] and results indicate that certain extracellular virulence factors have a crucial role in promotion of erosive joint damage in septic arthritis.[23] Components of the bacterial cell wall also modulate bacterial virulence. For example, studies of *S aureus* strains deficient in staphylococcal protein A have resulted in less severe disease in mice.[24] Specific oligonucleotide sequences within bacterial DNA also contribute to inflammatory processes in septic joints, and synthetic analogues of these sequences trigger joint inflammation and might play a part in both aseptic and septic arthritis.[25]

The virulence of bacterial molecules can be studied by immunisation of animals with purified concentrates of bacterial components. By this approach, specific bacterial adhesins that facilitate *S aureus* infection have been well characterised.[26] For example, inactivation of adhesins through vaccination with either recombinant collagen adhesin or fibrinogen-binding adhesin-clumping factor A results in a protective effect in mice subsequently challenged intravenously with *S aureus*.[27,28] Similarly, in an alternative murine model developed by Tissi and colleagues,[29] factors implicated in pathogenesis of group B streptococcal infection have been evaluated.[30] These data from animal models show that, in addition to variable host-susceptibility factors, considerable bacterial variability exists that could account for why some infections are mild and self-limiting and others are severe or fatal.

Some strains of *S aureus* are positive for the virulence factor Panton-Valentine leucocidin (PVL) cytotoxin, which enables them to survive in neutrophils. Such strains have been associated with fulminant infections, including joint infections in previously healthy patients, and a higher rate of complications than PVL-negative strains.[31,32] The rise in PVL-positive MRSA strains has accounted for an increase in the frequency of joint infections in some areas of the USA.[11]

Diagnosis

Clinical features

Ideally, septic arthritis is confirmed by detection of bacteria in synovial fluid, but predominantly, diagnosis is clinical, depending on informed integration of history, examination, and results of investigations.[2] Most studies are hospital-based and include individuals in whom synovial fluid culture fails to grow bacteria but in whom clinical suspicion is high. This situation often arises when patients present with acute arthritis and evidence of infection elsewhere.[5,33,34]

Individuals with septic arthritis typically present with a 1–2 week history of a red, painful, and restricted joint.[1,16,33] Some factors, including low virulence causative organisms and fungal and mycobacterial infections, can delay presentation.[1,35] In the context of pre-existing arthritis, the affected joint or joints will show signs that are out of proportion to disease activity detected in other joints. Generally, large joints (typically in the leg) are affected,[5,33] but in most studies up to 20% of patients have more than one joint affected.

Symptoms related to systemic infection are less common than might be expected. In a prospective analysis of patients in whom bacteria were cultured from synovial fluid, a history of fever was recorded in 34%, sweats in 15%, and rigors in only 6%.[1] Similarly, a fever (>37·5°C) at presentation is detected in only about 60% of cases,[1,16,34,35] indicating that (contrary to popular medical opinion) raised temperature is not a prerequisite for diagnosis of septic arthritis.

Laboratory investigations

Blood should always be cultured before starting antibiotic treatment to boost the chances of obtaining causative organisms.[36] In one study, blood cultures were positive in 24% of cases in whom organisms were identified in the synovial fluid, and in a further 9% of patients, blood cultures were the only source of a positive microbiological diagnosis.[5] In blood samples of individuals with septic arthritis, erythrocyte sedimentation rate, C-reactive protein concentration, and white-cell count are usually raised. However, normal values for these variables at presentation have been reported; thus absence of an acute-phase response does not exclude septic arthritis.[1,37,38]

White-cell count, erythrocyte sedimentation rate, and serum C-reactive protein concentration might not distinguish septic arthritis from other forms of acute arthritis,[39] but amounts of procalcitonin in serum could be useful for differentiation.[40] This variable is the latest in a series of potential serological and synovial markers to be studied over the years in the search for a means to discriminate between infective and non-infective joint inflammation. To date, none has had sufficient sensitivity, specificity, or predictive value to be taken into routine clinical practice.[39]

Nevertheless, white-cell count, erythrocyte sedimentation rate, and C-reactive protein concentration should be measured, because when raised they are useful to monitor response to treatment. Moreover, because renal and liver abnormalities are poor prognostic factors in septic arthritis, and abnormal function could affect antibiotic choice, both should be assessed at presentation.[36,41] When indicated by a patient's history, skin ulcer, urine, throat, and genitourinary cultures might be appropriate to aid accurate diagnosis before antibiotic treatment.[36]

Many researchers have attempted to identify ways in which analysis of synovial fluid can help to differentiate the various forms of acute arthritis. Synovial fluid aspiration, if it yields positive results, can be the key to diagnosis of septic arthritis, with gram stain and culture guiding choice of antibiotic treatment. In one study, gram staining of synovial fluid identified the causative organism in 50% of cases, rising to 67% after culture.[5] Specimens should always be taken before antibiotic treatment is started and sent fresh for appropriate microbiology culture.[42–44] Debate is ongoing about whether inoculation of synovial fluid directly into blood-culture bottles increases diagnostic yield over conventional agar culture. Our own conclusion is that no evidence supports this strategy: the laboratory should process all specimens.[36]

Historically, the skill of joint aspiration has been undervalued compared with other general internal medical techniques, and traditionally, junior medical staff are reluctant to aspirate joints in the emergency room. However, aspiration is a vital step for assessment of a hot swollen joint (just as lumbar puncture is for suspected meningitis), and a competent clinician needs to be found urgently to aspirate any acutely hot swollen joint when sepsis is a possibility. The only exception to this rule is suspected sepsis of a prosthetic joint, which should always be aspirated with full aseptic precautions in an operating theatre.

To diagnose crystal arthritis, samples of synovial fluid should be examined by polarising microscopy (ideally, compensated polarising-light microscopy), preferably in laboratories with adequate standardisation and quality control.[45,46] However, because artificial crystals can form on

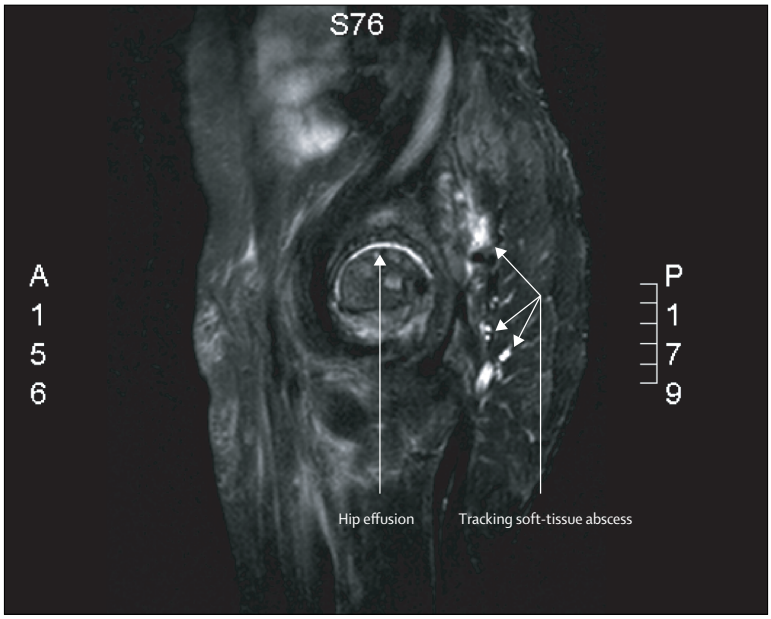

Figure 2: **MRI of staphylococcal septic arthritis of left hip, with fluid collections between planes of gluteal muscles**
Arrows indicate fluid collections.

	Proven (n=47)	Suspected (n=35)
Age (years)	66·5 (58·0–74·0)	64·0 (45·0–71·0)
Symptoms		
Pain	39 (83%)	31 (89%)
Fever	16 (34%)	20 (57%)
Rigors	3 (6%)	6 (17%)
Risk factors		
Primary joint disease	32 (68%)	18 (51%)
Leg ulcers	5 (11%)	3 (9%)
Chest infections	7 (15%)	4 (11%)
Investigations		
White-cell count (×10⁹/L)	14·4 (9·0–18·0)	14·0 (11·0–21·0)
C-reactive protein (mg/L)	175 (102–239)	224 (121–252)
Erythrocyte sedimentation rate (mm/h)	71·5 (42·0–102·0)	84·0 (62·0–110·0)
Supportive treatment		
Admission to intensive-care unit	3 (6%)	3 (9%)
Central venous line	9 (19%)	8 (23%)
Outcome		
Mortality at 3 months	4 (9%)	3 (9%)
Mortality at 2 years	12 (26%)	7 (21%)

Data are median (IQR) or number (%). Data taken from reference 35; mortality data provided by M Gupta.

Table 1: **Comparison of clinical variables and outcomes between proven (synovial fluid culture-positive) and suspected (culture-negative) septic arthritis**

refrigeration, samples should be processed immediately or stored at room temperature before analysis.[36]

Whether quantification of the synovial white-cell count is helpful for diagnosis is controversial. Some researchers have suggested that this variable is a useful discriminator of septic arthritis, citing a level greater than 50 000 cells per µL as a threshold,[47,48] but others have reported that this measure cannot distinguish between crystal and septic arthritis.[49–51] Concentrations of procalcitonin in synovial fluid are raised in septic arthritis,[52] but whether this marker can accurately discriminate septic arthritis from other forms of acute arthritis remains to be established.

Imaging

In several studies of septic arthritis, radiographs, technetium bone scans, CT, and MRI have been examined in the hope of identifying an investigation that will discriminate septic from other forms of acute arthritis. Although these techniques can be used to assess the presence and extent of inflammation, destruction, and tissue response, they cannot accurately distinguish between infective and other causes of acute inflammatory arthritis. However, MRI can help to assess both coexistent osteomyelitis, which might indicate a need for orthopaedic intervention,[36] and deep joints (such as the hip or sacroiliac joint) in patients with septicaemia with localised musculoskeletal pain. Furthermore, MRI will also indicate any tracking of purulent material into surrounding soft tissues from a primary joint infection (figure 2).

Proven versus suspected disease

Diagnosis of septic arthritis is straightforward when bacteria are isolated from synovial fluid. However, absence of organisms on gram stain, or a subsequently negative synovial fluid culture, does not exclude the diagnosis, although it does make it less likely, and expert rheumatological advice should be sought.[41] Such advice might be needed because false-negative gram stains and cultures of synovial fluid can occur, for example, with fastidious organisms or if antibiotic treatment was started before culture was done.

How do patients with septic arthritis from whom bacteria are isolated from synovial fluid compare with individuals from whom microorganisms are not cultured? One study showed that patients' history, joint distribution, clinical examination, and acute-phase response did not differ significantly.[35] Furthermore, predisposing causes, underlying diagnoses, complication rate, need for additional supportive treatment (such as dialysis or admission to intensive care), and acute and long-term mortality between groups were also closely similar (table 1). Importantly, in patients in whom bacteria were not isolated from the joint, microorganisms were detected in blood culture in 11% and from other sources in 7%, reinforcing the importance of appropriate cultures.

Prognosis

Mortality for septic arthritis varies in different studies, but seems to be around 11% for monoarticular sepsis.[36] In one study, a poor functional outcome was recorded in 24% and osteomyelitis in a further 8%, emphasising the need for both early diagnosis and improvements in current management strategies.[5]

Management

In view of the 11% mortality rate for septic arthritis, patients should be admitted to hospital for prompt assessment, supportive care, and intravenous antibiotic treatment, along with measures to aspirate pus from the joint. If evidence indicates septic shock or organ failure, patients should be treated in appropriate critical-care facilities.

Antibiotic treatment

Evidence on which to base choice or duration of antibiotic treatment for septic arthritis is scarce, and to the best of our knowledge, no randomised trials have been done. A large meta-analysis of antibiotic treatment for joint sepsis failed to show an advantage of any one therapeutic regimen over another for native joint infection.[53] Consensus suggests the mainstay of treatment should be prompt removal of any purulent material and appropriate antibiotic treatment.[36]

Table 2 summarises UK guidelines on initial antibiotic choice; this guidance is appropriate for the UK only because, in other settings, suitable antibiotic treatment must account for geographic variation in organisms and resistance patterns. In principle, however, the antibiotic regimen should be based on likelihood of the organisms involved and current local sensitivity patterns, modified subsequently by results of gram stain and culture. Because probable pathogens in all risk groups are *S aureus* and streptococci, initial antibiotic treatment before organism identification should have bactericidal activity against these bacteria. Suitable choices include β-lactamase-stable penicillins, such as flucloxacillin or cloxacillin, or the cephalosporins.[36]

Modification of choice of empirical treatment could be appropriate to include activity against MRSA in patients at risk, such as nursing-home residents or recent hospital inpatients, or where the local incidence of community-associated MRSA is greater than 10%.[54] Glycopeptides (eg, vancomycin) are active against most MRSA strains. For difficult infections, such as those affecting prosthetic joints, glycopeptides are used in combination with rifampicin or fusidic acid, because glycopeptides infiltrate poorly into joint and bone tissue. Clindamycin penetrates well into bone and joint tissue, and can be used as an alternative in macrolide-sensitive strains.[54]

Novel antibiotics

Resistance to glycopeptides has emerged as a problem in some MRSA strains, particularly in patients with deep-seated chronic infections treated with long-term glycopeptides alone. The organism usually has low-level intermediate resistance and is known as glycopeptide-intermediate *S aureus* (GISA). Emergence of GISA and intolerance to glycopeptides in some patients has led to use of new agents for gram-positive osteoarticular infections, because they have extended activity to include these multidrug-resistant strains.

Daptomycin and linezolid are gram-positive antibiotics from two new classes of antimicrobials, which have been licensed on the basis of results of studies in skin and soft-tissue infections. As far as we know, no randomised trials have been done to compare effectiveness and safety of these new antibiotics with traditional treatments for osteoarticular infections.[55–57] Linezolid is an oxazolidinone antibiotic with bacteriostatic activity against gram-positive organisms, and it can be administered orally because it has 100% bioavailability. With treatment for longer than 2 weeks, linezolid has been associated with significant risk of reversible bone-marrow suppression and peripheral neuropathy, and a small but more worrying risk of optic neuropathy.[56] Daptomycin is a lipopeptide antibiotic with bactericidal activity against gram-positive organisms, including those in the stationary phase of growth, and is licensed for complicated skin and soft-tissue infections and right-sided endocarditis. It must be given intravenously and is associated with toxic effects in muscle in about 0·4–2·5% of cases. No formal studies have been done in osteoarticular infections, and emergence of resistance has been described in prolonged courses of treatment.[55]

Gram-negative enterobacteriaceae are most usually seen as a cause of septic arthritis in elderly people or immunosuppressed patients. Unfortunately, multidrug resistance is a major problem, particularly in *Escherichia coli*, which is the most common cause of community and health-care-associated infection.[58] Resistance is associated with extended-spectrum β-lactamases, which expand resistance to third-generation cephalosporins (eg, ceftriaxone) and are usually associated with resistance mechanisms to other classes of antibiotics that are often used to treat gram-negative infections. International prevalence of multiresistant enterobacteriaceae positive for extended-spectrum β-lactamases has risen greatly over the past decade. These organisms are now a major cause of both community and healthcare-associated bacteraemia and

	Antibiotic choice
No risk factors for atypical organisms	Intravenous flucloxacillin (2 g four times a day). Local policy might add oral fusidic acid (500 mg three times a day) or intravenous gentamicin If allergic to penicillin, use clindamycin (450–600 mg four times a day) or second-generation or third-generation cephalosporin
High risk of gram-negative sepsis (elderly or frail individual, recurrent urinary-tract infection, recent abdominal surgery)	Second-generation or third-generation cephalosporin (eg, cefuroxime 1·5 g three times a day). Local policy might add flucloxacillin. Discuss strategy for patients allergic to specific antibiotics with microbiologist. Gram stain could affect antibiotic choice
MRSA risk (known MRSA, recent inpatient, nursing-home resident, leg ulcers or catheters, or other risk factors)	Vancomycin plus second-generation or third-generation cephalosporin
Suspected gonococcus or meningococcus	Ceftriaxone or similar, dependent on local policy or resistance
Intravenous drug abusers	Discuss with microbiologist
Patients in intensive-care unit, known colonisation of other organs (eg, cystic fibrosis)	Discuss with microbiologist

Antibiotic choice will need to be modified after results of gram stain and culture, and should be reviewed locally by microbiology departments. MRSA=meticillin-resistant *Staphylococcus aureus*.

Table 2: **Summary of UK recommendations for initial antibiotic choice in suspected septic arthritis**

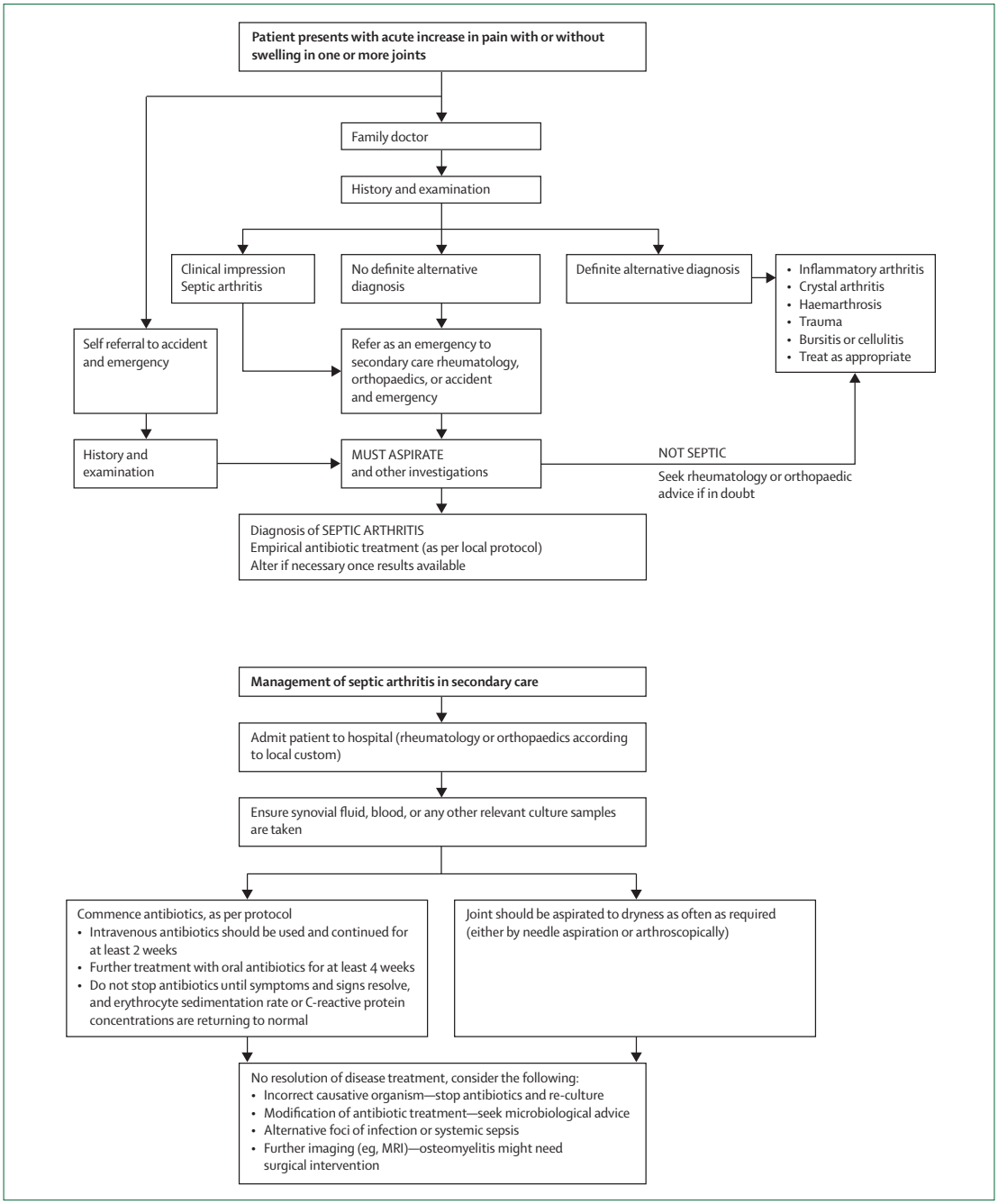

Figure 3: **Diagnostic and treatment algorithms for management of the hot swollen joint**
Adapted from ref 36, with permission of Oxford University Press.

urosepsis, and are starting to be seen in joint sepsis. Multiresistant bacteria make the choice of empirical treatment difficult and increase the need to use carbapenems, such as meropenem.[58–62]

The need for empirical treatment of *N gonorrhoeae* or *Haemophilus influenzae* type b will depend on local epidemiology. Routine cover for these microorganisms is not indicated in western Europe in the absence of specific clinical markers because these bacteria are currently uncommon causes of septic arthritis in this region. With national and international variation in possible causative organisms and sensitivity rates,

empirical antibiotic treatment and guidelines for septic arthritis should be developed locally in accordance with sensitivity patterns and probable causative organisms, and these should be reviewed and updated regularly.[36] The safest option in view of the complexity of causative organisms and resistance patterns is to treat cases of suspected or proven septic arthritis with close involvement of microbiologists.

Duration of antibiotic treatment

High-quality data are scarce that show the best duration of antibiotic treatment for septic arthritis, with the exception of treatment for *N gonorrhoeae* (a 1-week course of a third-generation cephalosporin is indicated). Treatment is usually given for up to 6 weeks, with the first 2 weeks administered intravenously followed by a switch to oral treatment if an oral option exists and clinical signs, symptoms, and inflammatory markers are settling.[36] Use of OPAT (outpatient parenteral antimicrobial treatment) with antibiotics with a long half-life—eg, ceftriaxone and teicoplanin—has risen over the past decade. OPAT enables early discharge and follow-up if the patient is otherwise well, but parenteral treatment is still needed. This technique is especially useful when a suitable oral option is missing, and it has been used successfully for difficult infections, including septic arthritis. OPAT needs to be delivered by dedicated teams with adequate supervision and follow-up of patients.[63]

Needle aspiration and surgical interventions

In addition to antimicrobial treatment, successful management of acute septic arthritis requires removal of intra-articular pus. Evidence for the mode of drainage that should be used is scarce. Options include closed-needle aspiration and surgical aspiration via arthroscopy. Only one study identified by our search strategy compared needle aspiration with surgical intervention directly, and no evidence was available to enable us to recommend one treatment strategy over another.[64] Both arthroscopy and needle aspiration, however, seem to have a favourable outcome, and expert opinion is that these techniques should be repeated until pus no longer accumulates. Figure 3 presents an algorithm of current UK guidelines for diagnosis and management of septic arthritis.

Future developments

Even when antimicrobial treatment for septic arthritis is timely and appropriate, it is not always sufficient to prevent permanent joint damage and overwhelming sepsis. Therefore, novel therapeutic options are warranted. Development of experimental models of bacterial arthritis has led to important progress in understanding of disease pathogenesis. These animal models have not only shed light on the pathogenic mechanisms underlying disease development but also presented potential targets for immunotherapy of septic arthritis.

An experimental *S aureus* model has already been described (see Pathogenesis).[18] It shows that much of the morbidity in mice (after the initial bacterial insult) is attributable to the host T-cell-mediated immune system. Perhaps counterintuitively, a growing body of evidence suggests that the immune system in septic arthritis, while essential to survival, also causes some joint destruction.[65]

Corticosteroids

Suppression of an excessive immune response with corticosteroids could be a more effective treatment regimen for *S aureus* septic arthritis than use of antibiotics alone. Tarkowski and colleagues[65] showed that, in mice treated with intraperitoneal cloxacillin together with intraperitoneal corticosteroid, prevalence, severity, and mortality associated with septic arthritis induced by *S aureus* inoculation was significantly reduced compared with mice treated with intraperitoneal cloxacillin alone.

123 children were enrolled into a double-blind, randomised, placebo-controlled trial assessing dexamethasone treatment for haematogenous septic arthritis. A short course of low-dose dexamethasone (0·2 mg/kg intravenously every 8 h for 12 consecutive doses), given in conjunction with antibiotic treatment, reduced duration of disease course and extent of residual joint damage and dysfunction compared with antibiotics alone.[66] An equivalent study has not yet been done in adults, but such work would be useful and would need to consider also the possibility of adverse outcomes from use of steroids, such as impaired effectiveness of antibiotics.

Cytokines and bisphosphonates

Work on the Tarkowski mouse model has shown other potential immunotherapeutic targets in septic arthritis. For example, deletion of bacterial virulence factors can reduce severity of disease. Similarly, identification of host-response cytokines has indicated that TNF α antagonists and recombinant interleukin 10 could both be used as adjuncts to antibiotic treatment.[19–21]

Addition of bisphosphonates to an intraperitoneal treatment regimen of corticosteroids and antibiotics seems to add further clinical benefit in the animal model. This finding could be due to a decrease in osteoclast activity and a consequent reduction in skeletal destruction.[67]

The animal model developed by Tissi and colleagues has also been used to show that other potential immunotherapies, such as adjunctive interleukin 10[68,69] or interleukin 12,[69] could enhance disease prognosis. However, none of these cytokine, anticytokine, or bisphophonate therapeutic approaches has yet been studied in patients, and we would not advocate their use outside of a randomised clinical trial.

Contributors
CJM did the literature search, informed by discussion with all authors. All authors were involved in writing sections of the report, and all edited, checked, and approved the final version.

Conflicts of interest
We declare that we have no conflicts of interest.

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