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Advances in the Management of Bacterial Septic Arthritis

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Abstract and Introduction

Abstract

The acute hot, swollen joint is a common medical presentation. It has a broad differential diagnosis, the most serious of which is bacterial septic arthritis. This article will discuss the epidemiology and pathogenesis of bacterial septic arthritis. The emergence of newer pathogenic organisms with changing antibiotic sensitivities will also be reviewed. The role that experimental animal models have played in clarifying some of the pathogenetic pathways of disease, as well as providing potential targets for novel therapies, will be presented. The clinical criteria for diagnosis will be discussed as well as the role of serum and synovial investigations to aid diagnosis. A guideline for antibiotic therapy will be shown as well as evidence suggesting that therapies, such as adjunctive corticosteroids, bisphosphonates and cytokine therapies, could improve the prognosis of septic arthritis. This article emphasizes that the diagnosis of septic arthritis rests principally on maintaining a high level of clinical suspicion. Early diagnosis with prompt and appropriate investigation and treatment is the mainstay of reducing the morbidity and mortality associated with the disease.

Introduction

The clinical presentation of a patient with one or more hot, swollen joints is common. The differential diagnosis is broad but the most serious potential cause is bacterial septic arthritis. The management of bacterial septic arthritis relies on early recognition, diagnosis and timely drainage of purulent material, together with prompt administration of antibiotic therapy. If the diagnosis is not made rapidly then the treatment of septic arthritis may be delayed, which can lead to substantial morbidity due to catastrophic joint damage,[1] as well as significant mortality due to overwhelming septicemia.[2]

The differential diagnosis of bacterial septic arthritis includes inflammatory arthritis, crystal arthropathy, trauma, hemarthrosis and degenerative joint disease. Even in the hands of experienced physicians, the crucial diagnosis of septic arthritis can be a difficult one to confirm. Despite advances in laboratory techniques, efforts are still being made to find a synovial or serum investigation of sufficient sensitivity and specificity to clinch the diagnosis. In addition, the emergence of unusual and resistant organisms makes the management of septic arthritis an ongoing challenge.

Epidemiology & Pathogenesis of Bacterial Septic Arthritis

The annual incidence of septic arthritis remains four to ten cases per 100,000 patient-years per year in western Europe.[1–3] The estimated incidence of septic arthritis in industrialized countries is six per 100,000 of population per year.[3] If patients have underlying joint disease, or prosthetic joints, the incidence increases to approximately 30–60 per 100,000 of the population per year.[4,5] There are no specific incidence data available for septic arthritis in developing countries. There are two age groups that are particularly susceptible to septic arthritis: young children and the elderly. Other at-risk groups for the development of septic arthritis include the immunocompromised, patients with diabetes, patients who are on hemodialysis[6] and intravenous drug users.[2,7] Any joint that carries underlying pathology, such as in rheumatoid arthritis, osteoarthritis or if a joint is prosthetic, has a significantly higher risk of developing intra-articular sepsis.[1,2,7,8] Lower socioeconomic status, alcoholism, previous intra-articular steroid injection and cutaneous ulceration have also been documented as significant risk factors.[8] Interestingly the incidence of septic arthritis appears to be rising, which could be attributable to the increasing use of immunosuppression, an aging population and the rise in frequency of invasive investigative and therapeutic procedures across all specialities.[3]

There are two main possible routes by which pathogens can enter the joint: by direct inoculation into the joint or, much more commonly, by hematogenous spread following a septicemic or bacteremic episode. Direct invasion of pathogens into the joint can result from orthopedic procedures and joint surgery, joint aspiration, intra-articular injection and via intra-articular extension from a nearby contiguous source. A community-based prospective survey showed that the most common causes of direct pathogen invasion are orthopedic procedures including joint surgery and arthroscopy, followed by trauma.[8] This survey also revealed that infected cutaneous lesions are the most common focus of infection that leads to hematogenous spread and secondary joint involvement. Lower respiratory tract infections and urinary tract infections were the second and the third most common sources leading to secondary bacterial septic arthritis.[8] Septic arthritis due to intra-articular injection is uncommon with an estimated prevalence of four cases per 10,000 injections,[3] while the prevalence of septic arthritis following arthroscopic procedures is estimated at 14 cases per 10,000 procedures (0.14%).[3]

Staphylococcus aureus and other Gram-positive organisms such as streptococci remain the most common pathogenic organisms in bacterial septic arthritis. The emergence of antibiotic-resistant strains, such as β-lactam-resistant *Streptococcus pneumoniae*, ceftriaxone-resistant strains of gonococci, Panton-Valentine leucocidin-positive methicillin-resistant *S. aureus*,[9–11] as well as increasingly atypical organisms has made the management of septic arthritis a real challenge. There have been recent case reports of the identification of organisms such as *Streptococcus suis* (swine pathogen), *Kingella kingae*, *Fugobacterium necrophorum* and *Clostridium cadaveris* in the synovial fluid of patients with septic arthritis.[12–15] Certainly there are patient groups that are more at risk of harboring atypical organisms, such as elderly patients, immunocompromised patients and intravenous drug abusers. Intravenous drug abusers are susceptible to mixed bacterial infections as well as fungal infections and the incidence of Gram-negative infection is demonstrably higher in the older population, presumably due to the presence of comorbidities, such as skin ulceration and urinary tract infection.[1,8]

Advances in our understanding of the pathogenesis of septic arthritis, as well as clues to future therapeutic options, have emerged from animal studies using experimental mouse models of both staphylococcal and streptococcal septic arthritis.[16] Tarkowski and colleagues model of staphylococcal arthritis closely mimics the pathogenesis of human disease. The pathogen is injected intravenously and the joints are thereby inoculated via hematogenous spread.[17] As soon as bacteria invade the blood stream, various virulence factors, such as extracellular toxins, enzymes, adhesins, bacterial and cell wall proteins, are produced, which initiate the inflammatory process via T-cell, B-cell and macrophage stimulation. As a consequence, proinflammatory molecules including TNF-α, IL-1β and IL-6, immunomodulatory (IL-4, IL-12) and anti-inflammatory (IL-4 and IL-10) cytokines are produced by monocytes, macrophages and synovial fibroblasts.[17–19] Experimental manipulation of this mouse model has shown that the degree of joint damage and the severity of disease, including the resulting mortality, can be altered by genetically manipulating these host factors. For example, the depletion of proinflammatory cytokines (such as IL-1 and TNF-α) using knockout mice increases the mortality rate in *S. aureus* septic arthritis. Tissi and colleagues mouse model of streptococcal B-mediated septic arthritis similarly sheds light on the molecular pathogenesis of disease, showing that the lack of B7-1 and B7-2 immunoregulatory molecules modulates the severity of group B streptococcal sepsis.[20]

The role of Toll-like receptors (TLR), a class of proteins within the innate immune system, has been discussed in recent studies in the context of both Gram-positive and -negative septic arthritis.[21,22] Papathanasiou *et al.* showed higher levels of both TLR mRNA expression and MMP-13 mRNA expression in chondrocytes isolated from septic joints compared with normal chondrocytes suggesting that modulation of TLR-mediated signalling could be a potential future therapeutic target in the prevention of cartilage damage in septic arthritis.[22]

Much of this experimental work is, of course, confined to the laboratory at present. The translation of these findings from bench to bedside, however, could herald the development of novel therapeutic options for the treatment of septic arthritis.

Diagnosis of Bacterial Septic Arthritis

The initial suspicion of the diagnosis of septic arthritis comes with the typical clinical presentation of a short, 1–2 week duration of an acutely hot and swollen joint (or joints).[23] On examination, the joint is often not only swollen but almost invariably has extreme limitation of range of movement. Although traditionally thought of as a monoarticular process, septic arthritis can be polyarticular in up to 22% of cases.[24] Polyarticular presentations can therefore mimic inflammatory arthritis but typically a septic joint in this context will be symptomatic to an extent that is out of proportion to the overall disease activity in the rest of the joints.

Although the diagnosis of septic arthritis rests primarily on clinical findings, there are laboratory investigations that can be helpful in guiding diagnosis.[25] But as the recent literature review by Carpenter *et al.* has demonstrated, there is still very little in the way of diagnostic tests that significantly and confidently alter the post-test probability of the diagnosis of septic arthritis over and above one's initial clinical hunch.[26] The identification of pathogens in the synovial fluid remains the crucial investigation in the diagnosis of septic arthritis.[16] Any acute hot swollen joint should always be aspirated before the initiation of antibiotics and sent for urgent Gram stain and culture. Warfarinization is not an absolute contraindication to joint aspiration[23] and nor is the presence of overlying cellulitis.[27] The only absolute contraindication to simple needle aspiration in suspected septic arthritis is if the joint is prosthetic in which case aspiration should always be performed under strict aseptic conditions in an operating theater.[16,23]

In a patient with septic arthritis due to hematogenous spread, cultures of extra-articular infective sources can provide invaluable information on the primary focus of infection and therefore guide antibiotic therapy.[23] Blood should always be cultured, and urine, sputum, skin and urethral discharge should be cultured based on the patient's clinical history and presentation irrespective of their body temperature,[23] as the absence of fever does not rule out septic arthritis.[1,2]

Routine serological tests may not be useful in the diagnosis of septic arthritis. No studies have demonstrated a significant level of sensitivity or diagnostic accuracy for the serum white cell count (WCC) in septic arthritis. In addition, the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not reliably raised in cases of joint sepsis. Moreover, it is not always easy to differentiate between inflammatory and septic arthritis on the basis of serum inflammatory markers.[26] Markers such as C-reactive protein and ESR may well not be useful in distinguishing between the two. Serological tests including the total WCC, neutrophil count and inflammatory markers such as C-reactive protein and ESR are probably more reliable for monitoring purposes than as diagnostic tools.[26]

Serum procalcitonin is an inflammatory marker that rises significantly in response to bacterial infection.[28] Detectable levels of procalcitonin can rise to 100 ng/ml (compared with levels less than 10 pg/ml in the healthy population) in severe infections and procalcitonin has a half-life of 25–30 h. Higher levels of serum procalcitonin are associated more with Gram-negative than Gram-positive bacteremias and higher levels are seen when the source of joint sepsis is systemic rather than local infection. However, the use of procalcitonin as a marker for septic arthritis is limited by its poor sensitivity.[28,29]

Interestingly, among the synovial markers, synovial lactate dehydrogenase could be a useful diagnostic tool for differentiating septic arthritis and inflammatory arthritis. There is some evidence to suggest that a threshold of >10 mmol/l could be of diagnostic utility. However, the effectiveness of synovial lactate dehydrogenase in the diagnosis of septic arthritis in the acute setting remains to be established.[30,31] The utility of other synovial inflammatory markers, such as glucose and synovial procalcitonin, in diagnosis of septic arthritis is still controversial.

A raised synovial WCC (sWCC) is not an uncommon finding in bacterial septic arthritis. This synovial marker has been regarded as a potentially useful discriminator between bacterial septic arthritis and other causes of joint inflammation. In 2004, Trampuz *et al.* showed that prosthetic knee septic arthritis produces a lower sWCC than native joint bacterial septic arthritis.[32] Two studies in 2007 suggested that a threshold of 50,000 cells/μl might be discriminatory.[33,34] In 2008, Ghanem *et al.* suggested that the sWCC, as well as the synovial white cell differential

counts, could be useful adjuncts to blood inflammatory markers with cutoff values of a sWCC of 1100 cells/10^{-3} cm^3 and a neutrophil percentage of greater than 64% perhaps being diagnostic of septic arthritis.[35] However, there are also studies that have suggested that the sWCC is not a useful diagnostic marker if the clinician is trying to differentiate between crystal and bacterial septic arthritis.[36–38] The recent review by Carpenter *et al.* concluded that a sWCC of greater than 90% has no significant effect if one is attempting to calculate the probability of septic arthritis (sensitivity: 60%, specificity: 78%, + likelihood ratio: 2.7, - likelihood ratio: 0.51).[26]

It is possible that there may be a role for PCR pathogen-specific probes in the diagnosis of bacterial septic arthritis. A recent study demonstrated the use of a real-time broad-based PCR assay in the acute clinical setting for the identification of microbes by targeting a 16S rRNA gene.[39] The ability to identify organisms within 3 h suggested that a PCR assay might have a high clinical performance in detecting pathogenic microbes compared with traditional culture techniques. Two previous studies, however, have shown that PCR has no advantage over traditional synovial culture in the identification of common bacterial infections (staphylococcus and streptococcus) in the standard laboratory setting.[40,41] However, this nonculture-based PCR technique may be very useful in identifying slow-growing organisms, such as *Mycobacterium tuberculosis*, and fastidious organisms that require specialized environments due to their complex nutritional requirements.

Turning to imaging, there is no imaging technique, which has been shown to reliably diagnose septic arthritis.[23] MRI findings in septic arthritis are nonspecific and it is impossible to differentiate between septic arthritis, inflammatory- and crystal-induced arthritis with imaging methods.[42] However, MRI can be very useful in identifying associated complications of septic arthritis, such as osteomyelitis, surrounding abscesses, soft tissue infections and the presence of foreign bodies.[23,42]

Current Treatment of Bacterial Septic Arthritis

Prompt initiation of appropriate antibiotic therapy and drainage of purulent material remains the mainstay of treatment of bacterial septic arthritis.[16] As there are no randomized controlled trials regarding the duration and choice of antibiotic regimen to date, most published guidelines on the initial empirical choice of antibiotic therapy depend on the individual risk factors for the patient, local drug resistance and the geographic variation of pathogens.[16] Treatment regimes need to be modified depending on subsequent identification of organisms. In the UK, 2 weeks duration of initial antibiotic therapy is recommended with follow-up of at least 4 weeks of oral antibiotics. Antibiotics are advised to be continued until symptoms and signs resolve and the inflammatory markers normalize.[23] Table 1 shows a summary of current UK recommendations for initial antibiotic choice in suspected septic arthritis.[23]

Table 1. Summary of UK recommendations for initial antibiotic choice in suspected septic arthritis.

Patient group	Antibiotic choice
No risk factors for atypical organism	Intravenous flucloxacillin (2 g four-times a day). Local policy might add oral fusidic acid (500 mg three-times a day) or intravenous gentamycin. If allergic to penicillin, use clindamycin (450–600 mg four-times a day) or second- or third-generation cephalosporin
High risk of Gram-negative sepsis (elderly or frail individual, recurrent urinary tract infection, recent abdominal surgery)	Second- or third-generation cephalosporin (e.g., cefuroxine 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 antibiotics choice
MRSA risk (known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors)	Vancomycin plus second- and third-generation cephalosporin
Suspected gonococcus and meningococcus	Ceftriaxone or similar, dependent on local policy or resistance
Intravenous drug abusers	Discuss with microbiologist

Patients in intensive care unit, known colonization of other organs (e.g., 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 a microbiology department.
MRSA: Methicillin-resistant *Staphylococcus aureus*.

In a recent survey of UK-based rheumatologists and orthopedic surgeons (74 rheumatologists and 77 orthopedic surgeons, total 151), the vast majority of clinicians (80% of rheumatologists and 82% of orthopedic surgeons) reported that they would use antibiotics for a minimum of 6 weeks including 2 weeks of intravenous therapy in the treatment of bacterial septic arthritis. The majority would seek microbiological advice to guide their treatment. However, only 7% of rheumatologists and 4% of orthopedic surgeons would continue antibiotics until inflammatory markers normalized.[43]

Combined with antibiotics, removal of septic material from the joint space is mandatory in the management of septic arthritis.[16,44] Either arthroscopic washout, open drainage or repeated closed needle aspiration can be used. According to the UK survey already quoted, 76% of rheumatologists and 65% of orthopedic surgeons would prefer to employ an arthroscopic washout. 22% of rheumatologists and 27% of orthopedic surgeons would prefer closed-needle aspiration. Only a minority of doctors would prefer an open joint washout.[43] In reality, so far, there is no randomized controlled trial with results that can identify which method is superior.[45]

Future Developments

There is an interesting debate emerging on the use of adjunctive corticosteroids in the treatment of septic arthritis. Two randomized, double-blind, placebo-controlled trials in 2003 and 2011 revealed that concomitant dexamethasone use in the treatment of septic arthritis in children shortened the fever, hospital stay and duration of disease compared with those treated with antibiotics alone. Odio *et al.* enrolled 123 children with septic arthritis into their study and a 4-day course of dexamethasone 0.2 mg/kg was administered intravenously every 8 h given in combination with antibiotic treatment compared with a second treatment group who received antibiotic therapy alone.[46] Harel *et al.* included 49 children with septic arthritis and 0.15 mg/kg of dexamethasone intravenously was given for 4 days.[47] Children who received concomitant dexamethasone therapy had a favorable outcome compared with those without dexamethasone therapy. However, there are no equivalent studies conducted in adult patients with bacterial septic arthritis.

In animal models, the use of intraperitoneal bisphosphonates has been shown to be effective in the reduction of bone destruction. This is thought to be due to the effect of bisphosphonates on skeletal osteoclastic activity in experimental *S. aureus*-induced arthritis. Again, there are no human studies to date.[48]

A recent animal study in 2011 showed that the combination of anti-TNF-α (etanercept) therapy and antibiotic therapy (cloxacillin) has beneficial effects on the outcome of staphylococcal arthritis and sepsis.[49] An arthritogenic dose and a septic dose of *S. aureus* were inoculated into two groups of mice and the arthritic frequency and arthritic index were measured along with mortality. A reduction in arthritic frequency (68 vs 89%; $p = 0.07$) and arthritic index (0.9 vs 1.67; $p = 0.015$) was observed in the mice who had combination treatment compared with the mice given antibiotics alone at day 10 and 14. In the group of animals who received the septic dose of *S. aureus*, more than 60% of the mice in the combination treatment group survived and recovered completely, while all the mice treated with cloxacillin alone died within a week. The authors commented on the potential danger of the inadequate use of antibiotics when combined with anti-TNF-α therapy since anti-TNF-α therapy has been associated with the development of certain infections, including septic arthritis itself.[49] The recent review by Galloway *et al.* revealed that there is increased risk of *S. aureus* septic arthritis in patients with rheumatoid arthritis who are treated with anti-TNF-α therapy and the risk is highest in the early months of treatment.[50] There are also studies that have raised the awareness of the increased risk of sepsis in patients treated with anti-TNF-α therapy.[51,52]

Two experimental mouse models of staphyloccal and streptococcal septic arthritis have already been presented in this paper. It is worth noting that these studies not only shed light on the pathogenesis of disease but also provide ideas for potential novel targets for adjunctive therapies in the treatment of joint sepsis. Tarkowski's *S. aureus* model demonstrates a possible beneficial role for cytokines such as IL-1, IL-10, TNF-α and lymphotoxin-α.[16–19] Tissi's model of group B streptococcal arthritis has shown that both IL-10 and IL-12 can ameliorate both the morbidity and mortality associated with disease.[53,54] In addition, more recent work from Tissi's group has shown that a lack of B7-1 and B7-2 immunoregulatory molecules can modulate the severity of group B streptococcus sepsis in their mouse model.[20]

These animal studies have suggested that the use of cytokines in both staphylococcal and streptococcal bacterial septic arthritis could enhance the disease outcome in human patients although the work has yet to be translated into human studies.

Summary

Infection remains one of the leading causes of mortality in the UK, and bacterial septic arthritis is one of the more serious musculoskeletal medical emergencies. The key to preventing the morbidity and mortality associated with bacterial septic arthritis depends on awareness of risk factors and the early diagnosis and timely investigation and management of patients suspected of having joint sepsis. The emergence of newer pathogenic organisms with changing antibiotic sensitivities has made the management of bacterial septic arthritis even more challenging. The future of the management of bacterial septic arthritis may include the use of adjunctive therapies such as corticosteroids, cytokines or bisphosphonates, all of which have had promising results in animal studies as well as some human trials in children. Whether some of these novel targeted therapies could reduce the disease burden in adult bacterial septic arthritis in humans remains to be seen.

Sidebar

Executive Summary

Clinical Presentation of Septic Arthritis

- The clinical presentation of a patient with one or more hot, swollen joints is a common one, however, the most serious potential cause is bacterial septic arthritis although differential diagnosis is broad.
- The management of bacterial septic arthritis relies on early recognition, diagnosis and timely drainage of purulent material together with prompt administration of antibiotic therapy.

Epidemiology & Pathogenesis

- The annual incidence of septic arthritis remains four to ten cases per 100,000 patient-years per year in western Europe. The estimated incidence of septic arthritis in industrialized countries is six per 100,000 of the population per year. The incidence increases to approximately 30–60 per 100,000 of the population per year in patients with underlying joint disease and prosthetic joints.
- There are two main routes by which pathogens can enter the joint: by direct inoculation into the joint or, more commonly, by hematogenous spread following a septicemic or bacteremic episode.
- *Staphylococcus aureus* and other Gram-positive organisms, such as streptococci, remain the most common pathogenic organisms. The emergence of antibiotic-resistant strains as well as increasingly atypical organisms has made the management of septic arthritis a real challenge.
- There are patient groups that are more at risk of harboring atypical organisms, such as elderly patients, immunocompromized patients and intravenous drug abusers.

Diagnosis of Bacterial Septic Arthritis

- The initial suspicion of the diagnosis of septic arthritis comes with the typical clinical presentation of a short, 1–2 week duration of an acutely hot and swollen joint (or joints).
- Any acute hot swollen joint should be always aspirated before the initiation of antibiotics and sent for urgent Gram stain and culture.

Current Treatment of Bacterial Septic Arthritis

- Prompt initiation of appropriate antibiotic therapy and drainage of purulent material remains the mainstay of treatment of bacterial septic arthritis.
- There are no randomized controlled trials regarding the duration and choice of antibiotic regimen to date.
- Initial empirical choice of antibiotic therapy depends on the individual risk factors, local drug resistance and the geographic variation of pathogens.

Future Development

- Concomitant dexamethasone therapy had a favorable outcome compared with those without dexamethasone in pediatric studies, however, there are no equivalent studies conducted in adult patients.
- In animal models, use of intraperitoneal bisphosphonates has been shown to be effective in the reduction of bone destruction.
- Combination of anti-TNF-α (etanercept) therapy and antibiotic treatment (cloxacillin) has been shown to be beneficial on the outcome of staphylococcal arthritis and sepsis in a recent animal study from 2011.
- Whether these novel targeted therapies could reduce the disease burden in adult bacterial septic arthritis in humans remains to be seen.

Summary

- The key to preventing the morbidity and mortality associated with bacterial septic arthritis depends on awareness of risk factors, early diagnosis, timely investigation and management of patients suspected of having joint sepsis.

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Papers of special note have been highlighted as: • of interest •• of considerable interest

