

Septic arthritis: current diagnostic and therapeutic algorithm

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Current Opinion in Rheumatology 2008, 20:457–462

Purpose of review

To propose and discuss an evidence-based algorithm for the diagnosis and treatment of bacterial septic arthritis. Also, to review the recent literature on emerging management strategies and discuss the potential impact of these developments on clinical practice.

Recent findings

Evidence-based guidelines have recently been published to assist in the diagnosis and management of suspected and confirmed septic arthritis. All suspected septic joints should be aspirated and the synovial fluid examined by microscopy for the presence of crystals and microorganisms. There is controversy surrounding the diagnostic utility of quantifying the synovial fluid white cell count, with two recent systematic reviews reaching opposite conclusions. The emergence of multidrug resistant pathogens has led to a search for alternative antimicrobial agents such as linezolid. Studies in animals and children have suggested that corticosteroid therapy may be a useful adjunct to conventional antibiotic therapy. Research using experimental murine models of septic arthritis is also generating novel immunotherapeutic targets as potential adjuncts to antibiotic regimens.

Summary

There is a striking paucity of high-quality evidence upon which to base guidelines on the management of the hot-swollen joint. Ultimately, the diagnosis of septic arthritis rests on the opinion of a clinician experienced in the assessment of musculoskeletal disease. Future research may provide alternative investigative and treatment strategies to improve the accuracy of diagnosis as well as the outcome in this group of patients.

Keywords

diagnosis, linezolid, management, novel immunotherapies, septic arthritis, synovial fluid

Curr Opin Rheumatol 20:457–462
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1040-8711

Introduction

The clinical presentation of a patient with one or more hot-swollen joints is a common medical emergency. Although the differential diagnosis is broad, the most serious potential cause is bacterial septic arthritis because this has a mortality of approximately 10%, as well as significant morbidity [1]. In this study we define septic arthritis as joint infection caused by pathogenic inoculation of the joint either directly or more commonly by haematogenous spread. Delayed or suboptimal management of joint sepsis can lead to irreversible joint damage and permanent disability [2]. Thus it is vital that the diagnosis of bacterial infection is made rapidly, and that treatment is started promptly.

One of the difficulties surrounding the assessment of joint infection is that patients often present to clinicians who are inexperienced in the management of musculoskeletal disease. Prognosis is optimized when the diagnosis is made quickly and appropriate treatment is given. Even when management is correct, a significant number

of cases result in irreversible joint damage and, in some patients, overwhelming septicemia.

Clinical features of septic arthritis

Our recent review of the literature revealed that, despite the use of laboratory investigations, the ‘gold standard’ for the diagnosis of septic arthritis is the level of clinical suspicion of a physician experienced in the diagnosis and management of rheumatic disease [3••]. Typically septic arthritis presents with a short 1–2 week history of pain, swelling, heat and restricted movement in the affected joint(s). There is a common misconception that septic arthritis affects one joint only, but evidence suggests that in up to 22% of cases the presentation is polyarticular [4]. Large joints are more commonly affected than small joints and in up to 60% of cases the hip or the knee is involved.

There are well documented risk factors the identification of which should raise the threshold of suspicion for the diagnosis of joint infection. Any joint that has been

rendered structurally abnormal by the presence of underlying inflammatory or degenerative arthritis is at a higher risk of becoming infected. When there is preexisting polyarticular inflammatory arthritis such as rheumatoid arthritis (RA), a septic joint will have symptoms that are out of proportion to the disease activity detected in other joints. Patients with RA are more likely to develop joint sepsis both due to the disease process itself and due to the immunosuppressive therapy that they receive [5^{*}]. The advent of biological therapies in the treatment of RA has increased the number of skin and soft tissue infections, but as yet there are no reports of an increase in the incidence of septic arthritis in this group of patients [6,7].

Other risk factors for the development of joint sepsis include:

- (1) Joint prostheses [1,8]
- (2) Intravenous drug abuse [1,9]
- (3) Alcoholism [9]
- (4) Diabetes [2,9]
- (5) Previous intra-articular corticosteroid injection [10]
- (6) Cutaneous ulcers [8]

The predominant causative pathogens in septic arthritis are *Staphylococcus aureus* and Streptococcus, accounting for up to 91% of cases [1]. In the elderly, the immunocompromised and in those patients who have had intravascular devices or urinary catheters inserted, infection with a Gram-negative enteric bacillus is more common.

Due to a combination of factors the aetiology of septic arthritis is changing. The increasing incidence of surgical arthroplasty provides a prosthetic environment where coagulase-negative staphylococci, which are unusual pathogens in native joint sepsis, are able to flourish [11]. This often establishes low-grade infection and subsequent prosthesis failure. It is a matter of concern that the ability of organisms to develop antibiotic resistance is highlighted by the recent emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) in patients who do not have traditional risk factors for MRSA acquisition. CA-MRSA has been responsible for cases of musculoskeletal sepsis in both North America (USA) and the United Kingdom (UK) and requires alternative antimicrobial strategies to the more common healthcare-associated MRSA [12,13]. In addition, the increase in both iatrogenic immunosuppression and HIV infection means that more unusual organisms such as mycobacteria are increasing in incidence [14–16].

Investigation of suspected septic arthritis

The key to the diagnosis of suspected septic arthritis is prompt microscopic analysis and culture of synovial fluid

aspirated from the affected joint(s). This enables the diagnosis of both septic and crystal arthritis, the latter being an alternative cause of an acutely hot-swollen joint. Synovial fluid Gram staining and microscopy gives a positive result in only 50% of cases of septic arthritis [2]. Subsequent fluid culture increases the yield although, even so, a joint can be septic even in the absence of positive microscopy or culture.

Controversy surrounds the use of the synovial fluid white cell count (WCC) in attempting to differentiate between sepsis and other causes of joint inflammation. A retrospective study in 2002 [17] looked at 202 patients with suspected septic arthritis. Those with a synovial fluid WCC of more than 50 000/mm³ had a proven diagnosis of sepsis in 47% of cases. Those with a synovial fluid WCC of more than 100 000/mm³ had the diagnosis confirmed in 77% of cases. The authors concluded that, although a synovial fluid WCC of less than 50 000/mm³ reduced the likelihood of the diagnosis of sepsis, it could not rule it out conclusively.

Last year two further studies have revisited this issue. A retrospective cohort study by Li *et al.* [18] looked at the serum WCC, erythrocyte sedimentation rate (ESR) and the synovial fluid WCC in 156 adult and paediatric patients who had undergone arthrocentesis. Of those, 10% had septic arthritis confirmed microbiologically, and the remaining 90% had a variety of other inflammatory conditions or no diagnosis confirmed. The authors concluded that of the three tests, the synovial fluid WCC was the most informative. The diagnostic utility of the test was optimal using a threshold of 17 500/mm³ above which the diagnosis of sepsis could be made with a sensitivity of 83% and a specificity of 67%. The positive likelihood ratio at this level was 2.5 with a negative likelihood ratio of 0.25.

Margaretten *et al.* [19^{*}] systematically reviewed the literature and examined 14 studies including a total of 653 patients presenting with a peripheral monoarticular arthritis that could be septic. They assessed the diagnostic utility of factors in the history and clinical examination as well as a variety of laboratory investigations. They confirmed that there is limited evidence to suggest that any clinical feature is significantly specific for septic arthritis. They also concluded that neither the absence of a fever nor a normal serum WCC, ESR or C-reactive protein (CRP) could reliably exclude the diagnosis of sepsis. None of these factors changed the pretest probability of septic arthritis. They did show, however, that a higher synovial fluid WCC increased the likelihood of the diagnosis of joint sepsis. They concluded that counts of less than 25 000/mm³, more than 25 000/mm³, more than 50 000/mm³ and more than 100 000/mm³ gave a septic arthritis likelihood ratio of 0.32, 2.9, 7.7 and

28.0, respectively. They did not, however, suggest that this test could be relied upon, but emphasized that it should be used in conjunction with clinical findings to influence management of suspected septic arthritis before Gram stain and culture results are known.

Our own guidelines on the management of septic arthritis published in 2006, based on a systematic review of the literature, recommended that the gold standard for the diagnosis of septic arthritis rested on the level of clinical suspicion of a physician experienced in the management of patients with musculoskeletal disease [20]. No investigation was thought to be of sufficient specificity to clinch the diagnosis beyond a reasonable doubt. Moreover, not all laboratories have the facilities to measure accurately a synovial fluid WCC.

Treatment of septic arthritis

All cases of septic arthritis should be treated with prompt anti-microbial therapy. Non-pharmacological treatment may also be indicated. The evidence guiding both medical and surgical management strategies is, however, sparse.

Choice of antibiotic

There is a striking lack of evidence to guide the optimal management of septic arthritis. There is a consensus of expert opinion that the mainstay of treatment should be prompt removal of any purulent material together with appropriate antibiotic therapy [20]. There is little to guide the choice, the route or the duration of antibiotic treatment. A meta-analysis of antibiotic therapy for joint sepsis showed no clinical or bacteriological advantage of one therapeutic regimen over another [21]. Current antibiotic choices should be made based on the likely aetiological organism and subsequently modified in light of culture and sensitivity results. It is prudent always to discuss antibiotic treatment with local microbiology experts to gain extra guidance based on local demographics. A summary of

suggested empirical treatment in the UK is presented in Table 1 [20]. It is clear that the choice of first line antibiotic may be different in the USA, and ideally national microbiological societies in each country should advise on the best first choice antibiotic.

Falagas *et al.* [22] recently reviewed the evidence for using linezolid in adults with bone and joint infection. Linezolid is a bacteriostatic antibiotic. Bactericidal antibiotics are often preferred to those that are bacteriostatic due to the relatively poor blood supply to bone. Linezolid, however, has advantages in that it is available in an oral formulation with almost 100% bioavailability. This could potentially decrease the need for inpatient treatment in such patients. In addition, the emergence of an increasing number of infections that are due to drug resistant microbes, including MRSA and even Vancomycin-RSA, means that linezolid may be a welcome addition to the antimicrobial armamentarium.

The evidence regarding the safety and efficacy of linezolid administration for the treatment of patients with musculoskeletal infection due to multidrug resistant Gram-positive cocci was reviewed. Studies included pharmacokinetic evaluation, case reports and case series but no randomized controlled trials. The authors concluded that linezolid appeared to be an effective treatment for patients with bone and joint infections secondary to drug resistant Gram-positive cocci. Reported side-effects included bone marrow suppression and irreversible peripheral neuropathy both occurring after a prolonged treatment.

In recent years a number of social and political pressures have led to measures designed to reduce hospital admissions and inpatient lengths of stay. In this context Esposito *et al.* [23] published in 2007 an analysis of a large database to identify the most convenient and successful diagnostic and therapeutic approach to bone and joint infection. In Italy, a National Outpatient Parenteral Antibiotic Therapy

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

Patient group	Antibiotic choice
No risk factors for atypical organisms.	Flucloxacillin 2 g q.i.d. i.v. Local policy may be to add fusidic acid 500 mg t.i.d p.o., or gentamicin i.v. If penicillin allergic, Clindamycin 450–600 mg q.i.d., or 2nd or 3rd generation cephalosporin.
High risk of Gram-negative sepsis (elderly, frail, recurrent UTI, recent abdominal surgery).	2nd or 3rd generation cephalosporin e.g. cefuroxime 1.5 g t.i.d. Local policy may be to add flucloxacillin. Discuss allergic patients with microbiology – Gram stain may influence antibiotic choice.
MRSA risk (known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors determined locally).	Vancomycin and 2nd or 3rd generation cephalosporin.
Suspected gonococcus or meningococcus.	Ceftriaxone, or similar dependent on local policy or resistance.
Intravenous drug users	Discuss with microbiologist.
ITU patients, known colonization of other organs (e.g. cystic fibrosis)	Discuss with microbiologist.

Antibiotic choice will need to be modified in the light of results of Gram stain and culture. It should also be reviewed locally by microbiology departments. ITU, intensive therapy unit; MRSA, methicillin-resistant *S. aureus*; p.o., orally; q.i.d., four times daily; t.i.d., three times daily; UTI, urinary tract infection. Reproduced with permission from [20].

(OPAT) Registry was set up in 2003. The premise of OPAT is that, in patients who are otherwise healthy, a course of prolonged intravenous therapy can be administered in an outpatient setting thus improving quality of life for the patient as well as reducing hospital costs. A study of the OPAT registry between 2003 and 2005 allowed 239 cases of bone and joint infection to be analysed. The authors reported that clinical success was high, particularly using intravenous teicoplanin and intravenous ceftriaxone, and that side-effects were mild occurring in 11% of cases. In addition, both patients and doctors reported a high degree of satisfaction with the OPAT regimen. Such outpatient intravenous antibiotic regimes may become increasingly popular.

Nondrug treatment

Removal of purulent material from affected joint(s) is considered essential in the effective management of septic arthritis, although this is based on expert opinion rather than any randomized controlled trial [20]. This can either be achieved surgically by arthroscopy or open arthrotomy, or through closed needle aspiration. There is controversy regarding which method is better, and a systematic review of the literature in 2007 did not reveal any prospective studies in adults addressing this question [3**]. The only study in adults to compare needle aspiration with surgical joint drainage was a retrospective analysis of cases records from 1975 suggesting that needle aspiration may, in many cases, be a superior initial mode of treatment for joint sepsis, although the results did not reach statistical significance [24]. Smith *et al.* [25] published a prospective, randomized study of the treatment of shoulder sepsis in children in Malawi. Sixty-one children were randomized to receive either closed needle aspiration or arthrotomy and washout. The clinical outcome in two groups was not statistically different at any stage of the 2-year follow-up, suggesting that closed needle aspiration is a safe and practical alternative to arthrotomy.

A diagnostic and therapeutic algorithm

One of the difficulties in diagnosing septic arthritis is that patients often present to clinicians who are inexperienced in the management of musculoskeletal disease. In addition, as described above, the evidence guiding treatment is scarce. In 2006, the British Society for Rheumatology (BSR) published evidence-based guidelines to give a structured approach to the management of the hot-swollen joint and septic arthritis in particular [20]. The diagnostic and treatment algorithms are presented in Fig. 1. The algorithms can also be accessed, with further detailed annotations to guide the inexperienced clinician, on the BSR website (http://www.rheumatology.org.uk/guidelines/guidelines_other/interactive_hotswollen).

Future management of septic arthritis

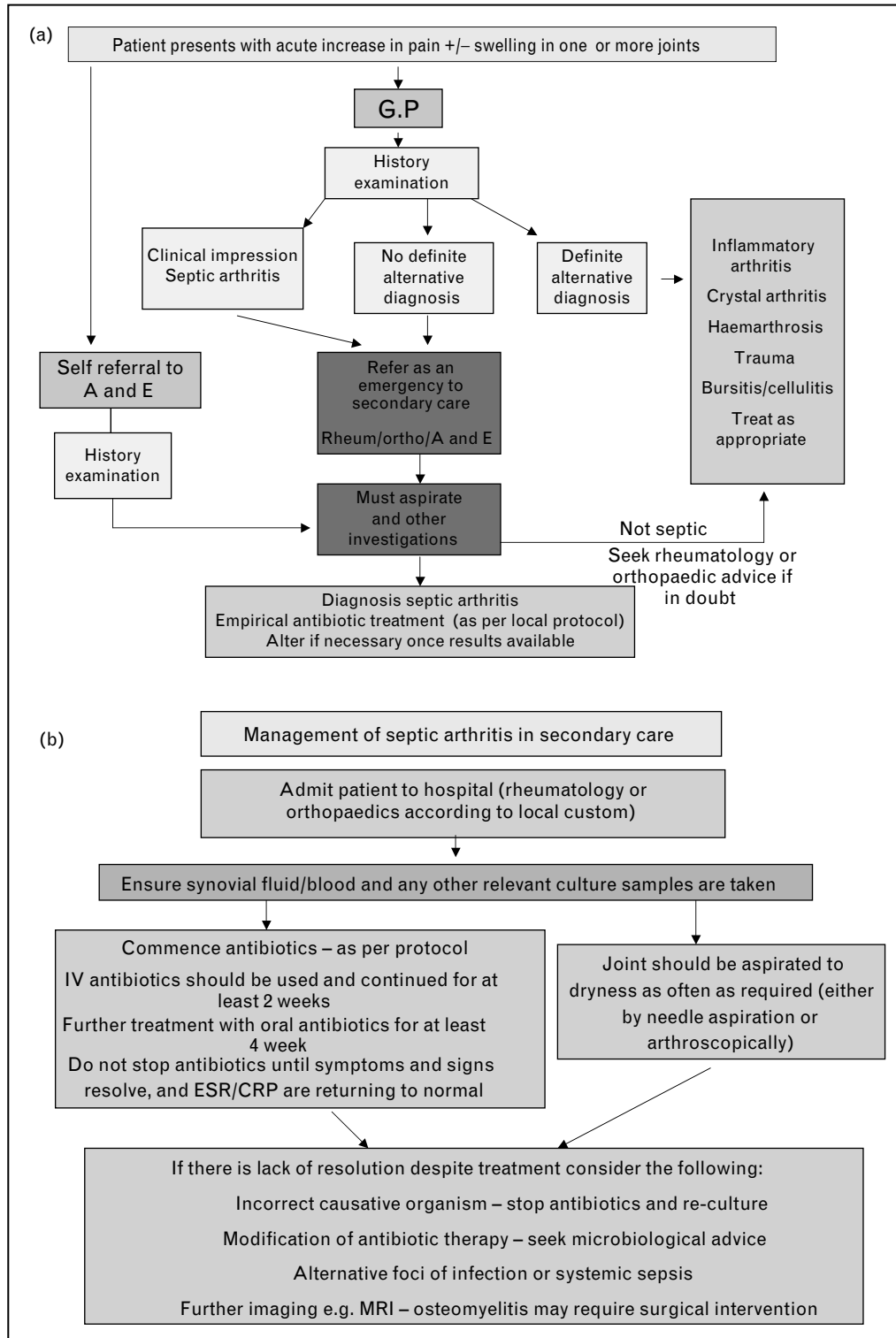
Septic arthritis continues to cause significant morbidity and mortality despite adequate removal of purulent material and prompt, appropriate antibiotic therapy. One fruitful area of current research addresses the concept that successful treatment requires not only the elimination of pathogenic bacteria but also the down-regulation of the heightened immune response that appears to hinder, rather than help, the host's defence mechanisms.

Recent literature reveals promising developments in experimental mouse models of both Staphylococcal and Streptococcal arthritis [26,27]. This sheds light on components of the immune system, which could, in the future, be targeted therapeutically to create adjunctive treatments for joint sepsis [28*]. Such novel therapies could involve the manipulation of both bacterial virulence and host response factors to improve the outcome. Potential targets include constituents of the bacterial cell wall, molecules involved in bacterial adhesion and oligonucleotide sequences in bacterial DNA [29–31]. In addition the genetic deletion of cell-derived cytokines, using the creation of knockout mice, have been shown to be an elegant way of elucidating the roles of multiple components of the immune system in the host response to bacterial infection [32–38].

As yet none of these molecular treatments has moved into human clinical trials. There is, however, growing evidence from animal models that the use of corticosteroids, in addition to traditional antimicrobial regimens, may improve the outcome. This may seem counter intuitive, given the assumption that corticosteroids suppress the host immune system, but a study [39] in the Staphylococcal murine model suggested otherwise. In this experiment, mice were treated with intraperitoneal corticosteroid and cloxacillin, or cloxacillin alone, 3 days after inoculation with intravenous *S. aureus*. The septic arthritis that resulted in the first group was of reduced prevalence, severity and associated mortality. The explanation could be that an overactive immune response, secondary to the initial septic event, causes damage and that steroid treatment down-regulates this exaggerated native immune response.

The use of corticosteroid treatment has extended to humans too. A double blind, randomized, placebo-controlled trial in 123 children compared the use of low-dose intravenous dexamethasone therapy, given in conjunction with antibiotic therapy, with antibiotic therapy alone [40]. Results showed that the addition of dexamethasone therapy to conventional antimicrobials reduced the duration of the clinical course of septic arthritis as well as decreasing the extent of joint damage and dysfunction.

Figure 1 Diagnostic and treatment algorithms for the management of the hot-swollen joint



CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Reproduced with permission from [20].

Conclusion

Septic arthritis is a diagnosis that rests on the level of clinical suspicion of an experienced physician. Laboratory investigations such as the synovial fluid WCC may help to increase the pretest probability of the diagnosis but should not be relied upon. Our recent systematic review of the literature has generated evidence-based guidelines and an algorithm to guide management of the hot-swollen joint.

In the face of emerging drug resistance future developments may include the use of newer antimicrobials such as linezolid. There may also be a role for adjunctive corticosteroid therapy as well as novel immunotherapeutic agents that have yet to make the transition from the bench to the bedside.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 510–511).

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