Curr Rheumatol Rep (2013) 15:332
DOI 10.1007/s11926-013-0332-4

Clinical Management of Septic Arthritis

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Abstract Septic arthritis is a rheumatologic emergency as joint destruction occurs rapidly and can lead to significant morbidity and mortality. Accurate diagnosis can be particularly challenging in patients with underlying inflammatory joint disease. This review outlines the risk factors for septic arthritis and summarizes the causative bacterial organisms. We highlight advances in antibiotic management with a focus on new drugs for methicillin-resistant *Staphylococcus aureus* (MRSA) and discuss the use of adjunctive therapies for treatment of septic arthritis in adults.

Keywords Septic arthritis · Clinical management · Antibiotic management · Diagnosis · Treatment · Joint drainage · Prosthetic joint infections · Steroids · MRSA · Bisphosphonates · Risk factors · Linezolid · Daptomycin · Ceftaroline · Quinupristin-dalfopristin

Introduction

Acute bacterial arthritis, or "septic arthritis", is a rheumatologic emergency. Bacterial replication in the joint and the ensuing inflammatory process can lead to rapid local joint destruction, and may be accompanied by systemic infection. The clinician's prompt recognition of the infected joint and implementation of appropriately targeted therapy is therefore critical to limit the morbidity and mortality associated with these infections. Incidence in the United States appears to be increasing [1], although there are no population-based studies to substantiate this assertion. This apparent increase may be attributed to a rise in orthopedic procedures and an aging population with more systemic illness and underlying joint disease [2, 3]. It is precisely those patients who are at greatest risk of septic arthritis—those with pre-existing inflammatory joint disease—for whom accurate diagnosis and therapy can be particularly challenging. The increased use of immune modulating agents for a variety of autoimmune inflammatory conditions has made diagnosis and management even more difficult. This review will discuss the evolving management of septic arthritis in adults.

This article is part of the Topical Collection on *Infections and Arthritis*

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Risk Factors for Septic Arthritis

Abnormal joint architecture is the most important risk factor for septic arthritis as seen in patients with rheumatoid arthritis (RA), crystal-induced, and Charcot's arthropathy [3, 4]. For reasons that are not entirely clear, the risk of septic arthritis in a patient with RA is increased 4- to15-fold irrespective of therapy [3, 5, 6]. One hypothesis to explain the increased risk is that patients with RA may have reduced bactericidal activity of synovial fluid and defective phagocytosis by polymorphonuclear cells [7–9]. Additionally, the abnormal joint architecture may allow microorganisms to escape normal phagocytosis [10]. The link between septic arthritis and gout is less frequently reported in medical literature, perhaps due to the episodic nature of gout flares [11] or to under-diagnosis resulting from the similar clinical presentations of septic arthritis and gout [12, 13].

Although underlying joint disease is the primary risk factor for septic arthritis, disease-modifying anti-rheumatic drugs (DMARDs) that may limit joint destruction due to rheumatologic disease appear to paradoxically increase the risk of joint infection. A retrospective review of patients with RA treated with tumor necrosis factor inhibitors (anti-TNF) and non-biologic DMARDs demonstrated incidence rates of septic arthritis as 4.2/1,000 patient-years and

Published online: 17 April 2013

1.8/1,000 patient-years, respectively. Anti-TNF use in RA was associated with a doubling of risk of septic arthritis compared to non-biologic DMARD agents [14•].

The frequency of procedure-related septic arthritis has also risen in recent years as a result of more intraarticular procedures being performed. Orthopedic interventions may introduce contaminated fluids resulting in increased incidence of septic arthritis. This increase has been demonstrated in Europe, where a retrospective study of septic arthritis showed that bacterial joint infections were iatrogenic in 41.8 % of adult cases; the incidence of SA increased from 4.2 cases/100,000 in 1990 to 11.0 cases/100,000 in 2002 [2]. Prior studies have suggested that intraarticular steroids [15] and hyaluronate injections [16] increase the risk of joint infection as was seen in a recent case of septic arthritis following injection of a knee with contaminated steroids [17•].

Causative Organisms

Determining the causative pathogen is paramount in delivering optimally effective and targeted antimicrobial therapy. A wide range of bacteria can be pathogenic in septic arthritis. *S. aureus* is the most commonly identified organism and is often associated with cellulitis, abscesses, endocarditis, chronic osteomyelitis, and drug abuse. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging problem particularly in intravenous (IV) drug users, the elderly, and orthopedic-associated infections [18–20]. Once a problem limited to healthcare settings, MRSA infections acquired in the community without healthcare risk factors are now prevalent. These infections often demonstrate increased suppurative complications and prolonged fever and hospitalization compared to infections caused by MSSA [21, 22]. Vancomycin-intermediate *S. aureus* (VISA, vancomycin MIC 4–8 ug/ml) and *S. aureus* with reduced vancomycin susceptibility (SA-RVS, vancomycin MIC $\geq$ 2 ug/ml) septic arthritis have been reported in patients with frequent exposure to health-care facilities, antecedent vancomycin exposure, and a history of prior MRSA infection [23, 24].

Gram-negative organisms are cultured from approximately 5–20 % of patients with bacterial septic arthritis and are seen primarily in children, the elderly, immunosuppressed and IV drug users [3, 25•, 26, 27]. The prevalence of multidrug resistant enterobacteriaceae has risen over the past decade with the emergence of organisms that produce extended-spectrum β-lactamases [ESBL) and carbapenemases [28]. Some carbapenemase-producing *Enterobacteriaceae* (CRE) are resistant to all available antibiotics, though fortunately there are few reports of septic arthritis caused by these organisms in the United States. While, historically, gonococcal infection was a common cause of dermatitis-arthritis syndrome in young sexually active adults, [18, 29] recent data suggests that this organism is now a less common cause of septic arthritis in Europe and North America [19, 20, 30, 31].

In patients with RA, *S. aureus* remains the most frequently reported organism and accounts for approximately 60–75 % of joint infections [10, 14•, 32]. In addition to *S. aureus*, patients on anti-TNF therapy also suffer from infections due to intracellular organisms including *Listeria* and *Salmonella*. Furthermore, Gram-negative species accounted for 50 % of the organisms in patients on non-biologic DMARDS and 10 % of species in patients receiving anti-TNF therapy [14•]. Other pathogen-specific clinical scenarios are highlighted in Table 1.

Diagnosis and Antibiotic Management

The diagnosis of bacterial arthritis should be considered in any patient with acute mono- or oligoarticular arthritis. A widely accepted case definition for bacterial septic arthritis was proposed by Newman, and requires one of four points to be met: (1) isolation of an organism from an affected joint, (2) isolation of an organism from another source with a concomitant swollen, hot joint, (3) clinical features and turbid joint fluid in the presence of previous antibiotic therapy, and (4) histologic or radiologic evidence consistent with septic arthritis [33, 34]. However, because these criteria are nonspecific, the differential diagnosis of acute monoarthritis should remain broad especially when underlying systemic inflammatory arthritis, previous antibiotic exposure or immunosuppressive agents cloud the diagnostic picture.

Most cases of septic arthritis occur by hematogenous spread of microorganisms to the synovial membrane of one or more joints. Therefore, blood cultures are an essential component of the initial diagnostic evaluation in patients with suspected septic arthritis. Whenever possible, the clinician should obtain at least two sets of blood cultures before initiating antibiotic therapy.

One systematic review showed that the combination of synovial fluid white blood cell (WBC) count and percentage of polymorphonuclear cells (PMNs) was the best diagnostic tool for predicting bacterial arthritis before synovial culture test results are known [35]. A synovial fluid leukocyte count of greater than 50,000 cells/mm^3 is often used to as a diagnostic predictor of septic arthritis. However, a lower WBC can be encountered in the setting of septic arthritis, especially in those who are pretreated with antibiotics or are immunosuppressed [1, 35, 36]. In patients with underlying inflammatory arthritis such as RA or gout, there is substantial overlap in diagnostic values for septic and inflammatory arthritis. Therefore, a sudden increase in inflammation in one or two joints out of proportion to disease activity should raise suspicion of complicating bacterial arthritis. One

Table 1 Pathogen-specific clinical scenarios for septic arthritis

Clinical History	Joint Involvement	Pathogen
Cellulitis, skin infection [86]	Monoarticular, polyarticular	*S. aureus, Streptococcus*
Sexually active	Polyarticular	*N. gonorrhea*
Elderly patients with UTI, skin breakdown [87]	Monoarticular	Gram-negative rods
Intravenous drug abuse [41]	Sternoclavicular, Sacroiliac, Pubic symphysis	*Pseudomonas*, *S. aureus*
Gardening, plant thorn injuries [88, 89]	Monoarticular: knee, hand, wrist	*Pantoea agglomerans*, *Nocardia asteroides*, *Sporothrix schenckii*
Rheumatoid arthritis [14•]	Monoarticular	*S. aureus*
Anti-TNF therapy [14•]	Monoarticular	*Salmonella*, *Listeria*
Unpasteurized dairy products [1]	Sacroiliac joint, Monoarthritis, Oligoarthritis of lower extremity	*Brucellosis*
Animal bites [90]	Small joints (fingers, toes)	*Pasteurella multocida*, *Capnocytophaga canimorsus*, oral aerobes/anaerobes
Southwestern US, Central and South America, primary respiratory illness	Knee	*Coccidioides immites*
Tick bite, erythema migrans, flu-like illness [91]	Oligoarthritis: knee, large joints	*Borrelia burgdorferi*

prospective study evaluated clinical symptoms and laboratory markers of culture proven (n=47) and suspected (n=35) septic arthritis and found no significant difference in history, clinical exam, laboratory markers or mortality between the two groups, thereby highlighting the importance of treating for bacterial arthritis if the clinical suspicion is high even in the absence of positive cultures [37].

A new tool being utilized for diagnosis or confirmation of infectious arthritis is universal microbe nucleic acid amplification and sequencing by polymerase chain reaction (universal PCR). This molecular diagnostic tool is especially useful when cultures are negative or antibiotic therapy is administered prior to arthrocentesis. However, the utility is limited by slow turn around time, lack of a gold standard, and high rates of false positives or contamination [38]. While real-time universal PCR is under development, it has not been validated in large studies and is not available for commercial use [39].

There are no randomized controlled trials that have evaluated one antimicrobial agent over another or the optimal duration of antibiotic treatment for septic arthritis. A large meta-analysis did not show an advantage of one therapeutic regimen over another for native joint infection, [40] and therefore initial antibiotic therapy is selected based upon patient clinical presentation (Table 1) and Gram stain results (Table 2). When septic arthritis is suspected, empiric antimicrobial therapy is warranted until culture data are available, even in the setting of a negative Gram stain. Furthermore, for patients with a high clinical suspicion of septic arthritis and negative cultures who are responding to empiric therapy, continuing a full treatment course of antibiotics may be prudent.

Choice of empiric treatment depends on the clinical presentation, host risk factors, and knowledge of local prevalence of drug-resistant pathogens. In patients presenting with acute monoarticular arthritis and a negative Gram stain who are at high risk for sexually transmitted diseases (STD), ceftriaxone plus azithromycin or doxycycline can be used empirically for treatment of infections due to *Gonococcus* and *Chlamydia*. However, in the setting of a negative Gram stain and no clear STD risk, empiric therapy should include ceftriaxone plus an agent active against MRSA. In the elderly, immunocompromised, and patients with previous exposure to a healthcare setting, a rational empiric choice would be vancomycin combined with a 4th generation cephalosporin (cefepime) for broader spectrum Gram-negative activity. If a patient has a history of a previous ESBL or if this organism is suspected, the antibiotic choice should include a carbapenem, a quinolone, or cefepime (Table 2). Injection drug users should be treated initially with drugs such as vancomycin plus an antipseudomonal ß-lactam that are active against MRSA and environmental gram-negative bacilli [25•, 41]. Vancomycin is a reasonable empiric therapy for patients with known MRSA risk factors including hemodialysis, diabetes, recent hospitalization, incarceration, or residence in a long-term care facility. Septic arthritis associated with human, dog or cat bites should receive a beta-lactam/beta-lactamase inhibitor combination such as ampicillin-sulbactam for activity against anaerobes and oral flora [1]. Once the causative organism is identified and antimicrobial susceptibilities are available, antibiotic therapy should be narrowed appropriately.

Table 2 Empiric therapy for septic arthritis

Gram stain	**Antimicrobial** (Dose adjust for renal function)
Gram-positive cocci	Vancomycin 15–20 mg/kg (actual body weight) administered IV q 8–12 h
Gram-negative cocci (concern for *Neisseria*)	Ceftriaxone 1 g IV q 24 h + azithromycin 1 g PO x 1 (or doxycycline 100 mg PO BID×7 days)
Gram-negative rods	Ceftazidime 2 grams IV q 8 h, cefepime 2 grams IV q 8–12 h, piperacillin/tazobactam 4.5 g IV q 6 h, or a carbapenem (imipenem 500 mg IV q 6 h, meropenem 1 g IV q 8 h, doripenem 500 mg IV q 8 h)
	B-lactam allergy:
	Aztreonam 2 g IV q 8 h or fluoroquinolone (ciprofloxacin 400 mg IV q 12 h or levofloxacin 750 mg IV q 24 h)
Gram-stain negative	Concern for STD associated: ceftriaxone 1 g IV q 24 h + azithromycin 1 g PO×1 day (or doxycycline 100 mg PO BID× 7 days)
	No STD risk:
	Vancomycin 15–20 mg/kg IV q 8–12 h + ceftriaxone 1 g IV q 24 h or vancomycin 15–20 mg/kg IV q 8–12 h plus cefepime 2 g IV q 8–12 h (for elderly, immunocompromised, healthcare-associated)

(Data from [1, 34, 62, 92])

Special Consideration: MRSA

MRSA septic arthritis is occurring more frequently in the community and health care settings, with rising rates of quinolone and clindamycin resistance [42, 43]. Glycopeptides have been the standard therapy for MRSA infections, but rising minimum inhibitory concentrations (MIC) for MRSA [44] and intolerance of vancomycin have resulted in the need for new antibiotics to treat this organism. Linezolid, daptomycin, quinupristin-dalfopristin and ceftaroline all have activity against MRSA, but published experience with these drugs for treatment of septic arthritis is limited to case reports, and observational or open-labeled studies. Furthermore, there are limited data to support use of these alternative antibiotics for bacteremic septic arthritis, with the exception of daptomycin [45••].

Linezolid

Linezolid is an oxazolidinone antibiotic with bacteriostatic activity against gram-positive organisms. It has 100 % oral bioavailability, and has adequate tissue penetration. One study demonstrated that linezolid reaches infected tissue compartments around joints and bones in concentrations twice the MIC_{90} for common Gram-positive pathogens. However, in this study, bone concentrations of linezolid below the MIC_{90} were observed, highlighting the importance of adequate surgical debridement [46]. However, a second study measured bone penetration of linezolid 90 min after standard dosing and demonstrated mean drug concentrations of at least twice the serum MIC_{90} for Gram-positive organisms in synovial fluid, synovium and cancellous bone [47]. No randomized trials examining linezolid use in septic arthritis have been done, so outcome data can only be extrapolated from anecdotal cases, small series, and open-label comparisons. A study on the compassionate use of linezolid for 52 patients with *S. aureus* bone or joint infections described a successful outcome in 69 % of patients [48]. In 25 patients with SA-RVS infections, 6 had septic arthritis or osteomyelitis and demonstrated improved clinical outcome when switched from vancomycin to linezolid. Limitations of this study include the extent of surgical debulking, disease localization and inability to compare prior treatment and duration of therapy [49]. A case report describes a MRSA (vancomycin susceptible) knee arthritis that failed to respond to a 14-day course of teicoplanin plus rifampicin but demonstrated clinical improvement with a subsequent 3-week course of linezolid [50]. Furthermore, an open-label study recently evaluated oral linezolid in *S. aureus*, *Coagulase-negative S. aureus* (CONS) and enterococcal osteomyelitis and prosthetic joint infections and demonstrated clinical and microbiological success in all cases [51].

Limitations of linezolid include risk of bone marrow suppression [52], peripheral neuropathy and rare cases of optic neuropathy seen after 2 weeks of drug administration [53]. Additionally, linezolid inhibits monoamine oxidase and thus can potentiate serotonin syndrome if given to patients taking selective serotonin re-uptake inhibitors [54]. Linezolid is considered inferior to vancomycin for MRSA bloodstream infection and therefore would not be

an appropriate choice for septic arthritis with associated bacteremia [45••].

Daptomycin

Daptomycin is a lipopeptide antibiotic with bactericidal activity against Gram-positive organisms, including MRSA and vancomycin-resistant enterococcus (VRE). The FDA approved daptomycin for treatment of skin and soft tissue infections and right-sided *S. aureus* endocarditis. There is limited data on the efficacy of daptomycin for septic arthritis although in vitro data suggests that this drug has adequate bone penetration [55]. With regards to clinical data, one of the largest studies evaluated 22 patients with septic arthritis in a retrospective multicenter observational cohort. All of the patients had Gram-positive pathogens and 64 % of cultures demonstrated MRSA. Cure was achieved in 41 % of patients and 50 % demonstrated clinical improvement at the end of therapy. Confounders included concurrent infections at other body sites and lack of information regarding the infected joint and surgical interventions undertaken [56]. In a randomized, prospective study evaluating daptomycin versus vancomycin or a semi-synthetic penicillin plus gentamicin for *S. aureus* bacteremia, 11 patients in the daptomycin treatment group and 5 patients in the comparator group were found to have concomitant septic arthritis. In this subgroup analysis, successful outcome was seen in 64 % of patients treated with daptomycin and 60 % of patients treated in the comparator arm, further supporting the use of daptomycin for *S. aureus* septic arthritis [57]. Adverse reactions associated with daptomycin include muscle toxicity requiring weekly monitoring of CPK levels [58]. Rare cases of drug-induced eosinophilic pneumonia [59] and acute renal failure have also been reported [60]. Although there are limited data evaluating the efficacy of daptomycin in septic arthritis, it appears to be a reasonable choice as an alternative treatment for MRSA septic arthritis.

Quinupristin-Dalfopristin

Quinupristin-dalfopristin is a streptogramin antibiotic that inhibits ribosomal protein synthesis in susceptible bacteria including *Enterococcus faecium*, MSSA, MRSA and *Streptococcus pyogenes*. A cohort of 27 patients with MRSA infection (44.4 % with bone and joint infections) who were intolerant or failing prior therapy were treated with quinupristin-dalfopristin. The overall response rate was 66.7 % for the evaluable cohort with lower response seen in patients with bacteremia, respiratory infections and endocarditis [61]. Limitations of this drug include painful arthralgias in 2–50 % of patients and local phlebitis requiring the medication to be administered via a central line [62]. Given the limited clinical data and toxicity of quinupristin-dalfopristin, this drug should be reserved for patients without other viable treatment options.

Ceftaroline

Ceftaroline is a parenteral 5th generation cephalosporin with activity against MRSA. It is FDA approved for MRSA skin and soft tissue infections and community- acquired pneumonia. One retrospective review demonstrated microbiological and clinical cure in 6 of 10 patients with deep-seated MRSA infections; 2 patients had both septic arthritis and MRSA bacteremia [63]. Ceftaroline is a promising new option for severe MRSA infections and is well tolerated without serious toxicities. However, prospective trials are needed to establish the use of ceftaroline in MRSA septic arthritis and define appropriate dose and duration of therapy.

Other Novel Agents with Activity Against MRSA

Telavancin is a parenteral lipoglycopeptide antibiotic with activity against MRSA and is FDA approved for treatment of complicated skin and skin structure infections. There is limited literature on the use of telavancin in MRSA septic arthritis although there are case reports describing successful use of telavancin for treatment of MRSA osteomyelitis and methicillin-resistant *Staphyloccocus epidermidis* prosthetic joint infections [64, 65]. Adverse reactions to this drug include taste disturbance, QTC prolongation, nausea, vomiting, elevated creatinine, and teratogenicity in women of childbearing age. Tigecycline is a derivative of minocycline with an added substituent that blocks bacteria from using efflux pumps, thereby expanding the antibacterial spectrum of this drug to include MRSA and other resistant Gram-negative infections. It is licensed for the treatment of skin and soft tissue infections, community-acquired pneumonia and intra-abdominal infections. Limitations of this antibiotic include emerging resistance during therapy. A recent meta-analysis of 10 published and 3 unpublished randomized controlled trials of tigecycline showed a significant overall increase in mortality and non-cure rates with tigecycline use for indications for which it is approved and marketed (skin and soft tissue infection, community acquired pneumonia and intra-abdominal infections), as well as for non-FDA-approved indications (MRSA and vancomycin-resistant enterococcus infections, hospital acquired pneumonia, and diabetic foot infections)[66••].

Duration and Route of Therapy

There are limited data defining the appropriate duration of therapy for septic arthritis. Gonococcal arthritis is usually treated with 7–14 days of ceftriaxone. Patients should also

receive 1 g of azithromycin orally or doxycycline 100 mg orally twice daily for 7 days for dual coverage of gonococcal infection and potential *Chlamydia trachomatis* co-infection [67, 68]. Non-gonococcal bacterial arthritis generally requires 2–4 weeks of parenteral antimicrobials, although recommended duration varies depending on the expert group. The UK guidelines recommend parenteral therapy for 2 weeks followed by 4 weeks of oral therapy [26]. *S. aureus* infection and Gram-negative septic arthritis requires 4 weeks of parenteral therapy [45••, 69]. If the Gram-negative organism is susceptible to fluoroquinolones, oral therapy with ciprofloxacin or levofloxacin can be considered as an alternative to IV during the latter half of the treatment course due to the high bioavailability of these agents [40, 69]. Whereas patients with hardware-associated joint infections generally require suppressive antimicrobial therapy if prosthetic material is retained, most patients with native joint septic arthritis respond clinically to appropriate antimicrobial agents and joint drainage. There is a paucity of data describing the proportion of individuals that require long-term suppressive antimicrobial treatment for control of infection in native joint septic arthritis.

Hardware-Associated Joint Infections

Presence of foreign material in the joint space increases the risk of infection and decreases the chance of treatment success. Biofilm formation allows infecting organisms to evade both host immune defenses and antibiotic effect. The biofilm creates a haven for bacteria where they transition to a less metabolically active state. Therefore, antibiotics that depend on cellular replication for their mechanism of action are often ineffective. Additionally, prosthetic material allows for better microbial adhesion decreasing the efficacy of drainage by arthrocentesis and irrigation [70]. For these reasons, patients with prosthetic joint infections treated with antibiotics and closed drainage often experience relapse or antibiotic failure due to resistant organisms. The timing of the infection in relation to placement of the prosthesis, the causative organisms and its antimicrobial susceptibility, the patient's surgical risk and immune status weigh into the decision to remove hardware. Infections identified less than 30 days after arthroplasty can often be managed by surgical debridement with retention of prosthesis, exchange of polyethylene liners and a long course of IV antibiotics. However, prosthetic joint infections identified later than 1 month nearly always require full explant of the prosthetic material to achieve a cure. Biofilm active antibiotics such as quinolones, rifampin, or azithromycin have been utilized in combination with other standard antibiotics especially in those with retained prosthesis [72]. Duration of treatment for prosthetic joint infections depends on what type of surgical treatment plan was employed, but usually is no shorter than 6 weeks of IV antibiotics followed by oral suppressive therapy. Best efforts to identify causal organisms to enable targeted antimicrobial therapy should be employed for the greatest chance of cure. A more detailed discussion of the management of prosthetic joint infections can be found in the recently published guidelines of the Infectious Disease Society of America (IDSA) [71••].

Adjunctive Therapies

Drainage

Removal of bacteria and inflammatory debris from the joint is an essential component of the management of infectious arthritis. The most effective method of drainage has yet to be clearly delineated given a paucity of quality studies. Closed needle aspiration has historically been the method used in less severe cases and in distal, smaller joints. It is less invasive than surgical drainage and may be associated with faster functional recovery, but it has not been associated with shorter length of stay or decreased mortality [73]. Additionally, lysis of adhesions or drainage of loculated infection is not possible with needle aspiration. When surgical drainage is employed, one must consider arthroscopy versus open arthrotomy. There is no definitive evidence to recommend one over the other and most studies focus on a specific joint [74–76]. Historically, infected hip joints have been drained by open arthrotomy due to deeper anatomy and risk of dislocation or osteonecrosis, but newer arthroscopy and irrigation techniques have been shown to be as safe and effective as open drainage [77]. Open arthrotomy is recommended under specific situations such as in joints with pre-existing severe articular disease, associated osteomyelitis, or when conservative methods have failed [78]. Butt et al. conducted a survey of US rheumatologist and orthopedic surgeons inquiring which method they would recommend for drainage of an infected joint. Fifty (65 %) surgeons and 56 (76 %) rheumatologists recommended arthroscopic joint washout as their preferred method of joint drainage, with 21 (27 %) surgeons and 16 (22 %) rheumatologists recommending serial closed needle aspiration. Three surgeons and one rheumatologist recommended open arthrotomy [79].

Steroids

Joint destruction in infectious arthritis is driven primarily by the inflammatory response to the invading organism. With this in mind, systemic corticosteroid administration has been considered as adjunctive therapy. Sakiniene administered intraperitoneal corticosteroid with cloxacillin to mice, which

resulted in a lower prevalence and severity of arthritis as well as a lower mortality when compared with the mice treated with cloxacillin alone [80]. In a double-blinded, placebo-controlled study, children with septic arthritis who received IV dexamethasone plus antibiotics exhibited a shorter duration of illness with less residual joint damage and dysfunction than those treated with antibiotics alone [81]. A smaller double-blinded randomized controlled study showed that antibiotic plus systemic corticosteroid administration was associated with a shorter duration of IV antibiotics and shorter hospital stay in children [82]. There are no published data on systemic steroid use in adult patients from which to draw similar conclusions. An animal model has investigated intraarticular corticosteroid use in septic arthritis, however this has not been sufficiently studied in humans to warrant routine use. Rabbits with experimental *Staphylococcus epidermidis* received systemic antibiotics or systemic antibiotics plus intraarticular steroids. The steroid group had less pronounced synovial inflammation than those receiving antibiotics alone. Additionally, there was no evidence of worsening of infection or joint destruction when the intraarticular corticosteroids were co-administered with antibiotics [83, 84].

Bisphosphonates

Bisphosphonate therapy has been investigated in animal models as an adjunct to decrease bone loss in infectious arthritis. Verdrengh infected mice with *S. aureus* and treated them with antibiotics, bisphosphonates, or combination of antibiotics, bisphosphonates and systemic steroids. Mice treated with combination therapy of antibiotics and bisphosphonate had higher bone mineral density, less severe arthritis and a lower level of osteoclastic activity than those treated with antibiotics or bisphosphonate alone. Osteoclastic activity was further reduced with addition of corticosteroids [85].

Conclusions

Septic arthritis is a medical emergency that requires rapid diagnosis and treatment to avoid morbidity and mortality. Underlying inflammatory joint disease, the use of immune-modulating agents, and orthopedic procedures are risk factors for developing septic arthritis and may be contributing to the rising incidence seen in the United States. *S. aureus* is the most frequent causative pathogen, and MRSA is emerging as an important cause of community- and hospital-acquired septic arthritis. Although glycopeptides remain the mainstay of therapy for MRSA infection, intolerance to vancomycin and increasing resistance has resulted in the need for new antibiotics to treat MRSA infections. Joint drainage is paramount in the management of septic arthritis. More data are needed before other adjunctive therapy such as steroids and bisphosphonates can be recommended for treatment.

Conflict of Interest Katie A. Sharff declares that she has no conflict of interest.

Eric P. Richards declares that he has no conflict of interest.

John M. Townes declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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