Seminar

Septic arthritis

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Microorganisms have been implicated as the cause of many rheumatic diseases. In most chronic joint disorders, including rheumatoid arthritis, there is no evidence that infectious agents are directly involved. However, we now recognise the important role of microbes in many types of acute and chronic arthritis. During the past two decades, Lyme disease and arthritis associated with HIV infection have emerged as important examples of infectious agents causing arthritis. There has also been greater evidence to support a causal role for various microbes in forms of arthritis that have traditionally been classified as "reactive". However, the most important cause of septic arthritis continues to be acute bacterial arthritis. This seminar will therefore focus on bacterial arthritis, discussing other forms of infectious arthritis primarily in the context of a differential diagnosis.

Bacterial arthritis

Bacterial arthritis is the most rapidly destructive joint disease. The yearly incidence of bacterial arthritis varies from 2 to 10 per 100 000 in the general population to 30–70 per 100 000 in patients with rheumatoid arthritis and in patients with joint prostheses.[1,2] Irreversible loss of joint function develops in 25–50% of patients.[1,3–5] Despite better antimicrobial agents and improved hospital care, the case fatality rate for bacterial arthritis has not changed substantially in the past 25 years, ranging from 5% to 15%.

Pathophysiology

In native joints, bacterial arthritis is usually secondary to the haematogenous seeding of a joint during a transient or persistent bacteraemia. The bacteria enter the closed joint space and within hours trigger an acute inflammatory synovitis. The synovial membrane reacts with a proliferative lining-cell hyperplasia, and there is an influx of acute and chronic inflammatory cells. Release of cytokines and proteases leads to cartilage degradation. Within a few days, irreversible subchondral bone loss can be demonstrated.

Bacteria may be introduced during joint surgery (see below) or, rarely, during joint aspiration or a local corticosteroid injection.[6] Direct puncture wounds such as a bite or stepping on a nail are unusual portals of entry for septic arthritis. In children, a focus of osteomyelitis in the metaphysis or epiphysis may spread to the adjacent joint.

Staphylococci are the most common organisms that cause bacterial arthritis in adults.[3,5] In three recent large series, *Staphylococcus aureus* was the primary cause of bacterial arthritis in 40% of cases from England and Wales,[7] 56% of cases from France,[6] and 37% of cases from tropical Australia[2] (panel 1). *S aureus* cause 80% of joint infections in patients with concurrent rheumatoid arthritis and in those with diabetes. This microbe is also the primary pathogen in hip infections and in polyarticular septic arthritis. *S aureus* elaborate several extracellular and cell-mediated factors that may be important virulence determinants in septic arthritis.[8,9]

Panel 1: **Bacteria that most often cause septic arthritis (% of cases from three countries)**

Bacterium	England and Wales[7]	France[6]	Australia[2]
S aureus	40	56	37
All streptococci	28	10	21
S pneumoniae	10	0	1
Group A	8	9	16
Other	10	1	4
All gram-negative bacilli	19	16	4
H influenzae	7	0	1
E coli	6	9	1
Pseudomonas	2	4	1
Other	4	3	1
N gonorrhoeae	0·6	3	12
Anaerobes	1·4	2	3

Lancefield group A β-haemolytic streptococci are the next most common bacteria isolated from septic joints in adults (panel 1). Group B, C, and G streptococci are important causes of bacterial arthritis in compromised hosts or in patients with serious genitourinary or gastrointestinal infections. Gram-negative bacilli are common causes of bacterial arthritis in intravenous drug users, in the elderly, and in seriously immunocompromised hosts. Gram-negative bacilli and *Haemophilus influenzae* are the most common pathogens in the newborn and in all children under age 5 years. However, *H influenzae* bacterial arthritis is not limited to neonates. Although pneumococcal arthritis has been uncommon in most series during the past 25 years, 10% of bacterial arthritis from England and Wales over a 4 year period from 1990 to 1993 were caused by *S pneumoniae*.[7] Anaerobes are sometimes involved in prosthetic joint infections and in diabetics who develop septic arthritis. In most series, 10–20% of clinically diagnosed bacterial arthritis are never confirmed with positive synovial fluid or blood cultures.[7]

Host factors that predispose to bacterial arthritis include the patient's age, decreased immunocompetence, and preexisting joint disease. Age greater than 80 years, diabetes mellitus, and rheumatoid arthritis were found to be important independent risk factors in a large-scale prospective study from the Netherlands.[1] Rheumatoid

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Panel 2: **Characteristics of gonococcal and non-gonococcal bacterial arthritis**

Characteristic	Gonococcal arthritis	Other bacterial arthritis
Patient profile	Young, healthy sexually active >female	Newborn or elderly; compromised host; rheumatoid or other systemic arthritis
Initial presentation	Migratory polyarthralgia; tenosynovitis, dermatitis	Single hot, swollen painful joint
Polyarticular	40–70%	10–20%
Recovery of bacteria	<50% synovial fluid, <10% blood	>90% synovial fluid, 50% blood
Response to antibiotics	Within a few days; outcome excellent	Takes weeks; joint drainage must be adequate; outcome often poor

arthritis is the most common joint disease associated with bacterial growth. Repeated intraarticular corticosteroid injections also increase the risk of bacterial arthritis. HIV infection has been associated with mycobacterial and fungal as well as bacterial joint infections.[11] Septic arthritis is sometimes mistakenly diagnosed as a haemarthosis in HIV patients with haemophilia.[12]

In the USA, disseminated gonococcal infection (DGI) is the most common form of bacterial arthritis in young, healthy sexually active adults (panel 2). It is an uncommon cause of bacterial arthritis in Europe, and in most countries the incidence varies with the patients' socioeconomic status (panel 1). For example, Australian aboriginals, in comparison with non-aboriginals, have a greater prevalence of all forms of septic arthritis, especially gonococcal arthritis.[2] Disseminated infection develops in 1–3% of untreated gonorrhoea.

Clinical manifestations

Non-gonococcal bacterial arthritis usually presents with the abrupt onset of a single hot, swollen, and very painful joint (panel 2).[3] The knee is the site of infection in 50% of cases but any joint may be involved. Hip infections are more common in young children.[2] The hip is often held in a flexed and externally rotated position and there is extreme pain on motion. It is often difficult to detect an effusion of the hip or the shoulder although the joint is frequently warm and very tender. Both passive and active range of motion cause considerable discomfort. 10% of infections involve the sacroiliac joint;[6] these are especially difficult to spot on physical examination and imaging studies have an important role in the diagnosis.[13] 10–20% of infections are polyarticular, usually two or three joints. Polyarticular septic arthritis is most likely to occur in patients with rheumatoid arthritis or a systemic connective-tissue disease or in patients with overwhelming sepsis.[14] Most patients are febrile, although chills and spiking fevers are unusual, except in young children. A source of infection, often from the skin, lungs or bladder, will be found in 50% of cases.

The initial most common symptoms in DGI are migratory polyarthralgias, tenosynovitis, dermatitis, and fever (panel 2).[15,16] Less than half of patients with DGI will present with a purulent joint effusion, most often of the knee or wrist. Multiple tendons of the wrist, ankles, and small joints may be inflamed and very tender. The skin lesions are typically multiple, painless macules and papules, most often found on the arms or legs or on the trunk.

Diagnosis

The definitive diagnosis of bacterial arthritis requires identification of bacteria in the synovial fluid by Gram's stain or by culture. Clinical suspicion of joint sepsis should prompt immediate synovial fluid aspiration. If synovial fluid cannot be obtained with closed needle aspiration, the joint should be aspirated again, with imaging guidance for joints that are not very accessible, such as hips, shoulders, or sacroiliac joints. Such joints may require surgical arthrotomy to obtain synovial fluid or tissue. A Gram's stain should be done and fluid sent to the microbiology laboratory for culture (figure 1). The synovial fluid culture is positive in 90% of cases of non-gonococcal bacterial arthritis[3] but Gram stains are positive in only 50%, and clumps of stain or cellular debris may be mistaken for bacteria. Most infected joint effusions are purulent or very inflammatory with an average leucocyte count of $50–150\times10^9$/L, predominantly polymorphonuclear cells. The synovial fluid glucose is often depressed and lactic acid and lactate dehydrogenase levels are raised, but such values may be seen in inflammatory joint disease too. Blood cultures are positive in 50–70% of patients with non-gonococcal bacterial arthritis.[7]

In contrast, the synovial fluid Gram's stain is positive in less than 25% of patients with gonococcal arthritis, and culture is positive in only 50%.[15,16] The skin lesions and blood rarely yield positive cultures in DGI. Therefore, a presumptive diagnosis of DGI is often made based on the characteristic signs and symptoms and a identification of *Neisseria gonorrhoeae* from a genitourinary source. Genitourinary cultures are positive in 70–90% of patients with DGI.[15,16]

The failure to recover *N gonorrhoeae* from a site of dissemination may be partly explained by the fastidious in vitro growth requirements of *N gonorrhoeae*. Immune mechanisms may also be responsible for the sterile synovitis and dermatitis.[16] The polymerase chain reaction (PCR) has been used to detect *N gonorrhoeae* in patients with clinically typical but culture-negative gonococcal arthritis.[17] The presence of gonococcal DNA, even in culture-negative synovial fluid, suggests that viable bacteria do indeed provoke the synovitis associated with DGI. In a case of staphylococcal arthritis, PCR demonstrated persistent *S aureus* DNA in the synovial fluid for 10 weeks despite adequate antibiotic treatment and sterile synovial fluid.[18] Identification of bacterial DNA by PCR will be most useful in patients with partly treated or culture-negative bacterial arthritis and in "reactive" arthritis.

A peripheral blood leucocytosis and a raised erythrocyte sedimentation rate (ESR) are present in most patients with septic arthritis but these tests are very non-specific. Measurement of ESR or C-reactive protein may be more helpful in children with possible septic hips.[6,19] In acute septic arthritis, radiographs initially do not reveal destructive joint lesions but are useful in detecting a joint effusion and in demonstrating concurrent osteomyelitis or arthritis.[20] Characteristic juxtaarticular osteoporosis and bone erosions take weeks to develop. Scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI) are far more sensitive than plain films in early septic arthritis. CT is most useful to detect effusions and to guide the joint aspiration of the hip, sternoclavicular, and sacroiliac joints. MRI demonstrates adjacent soft-tissue oedema and abscesses

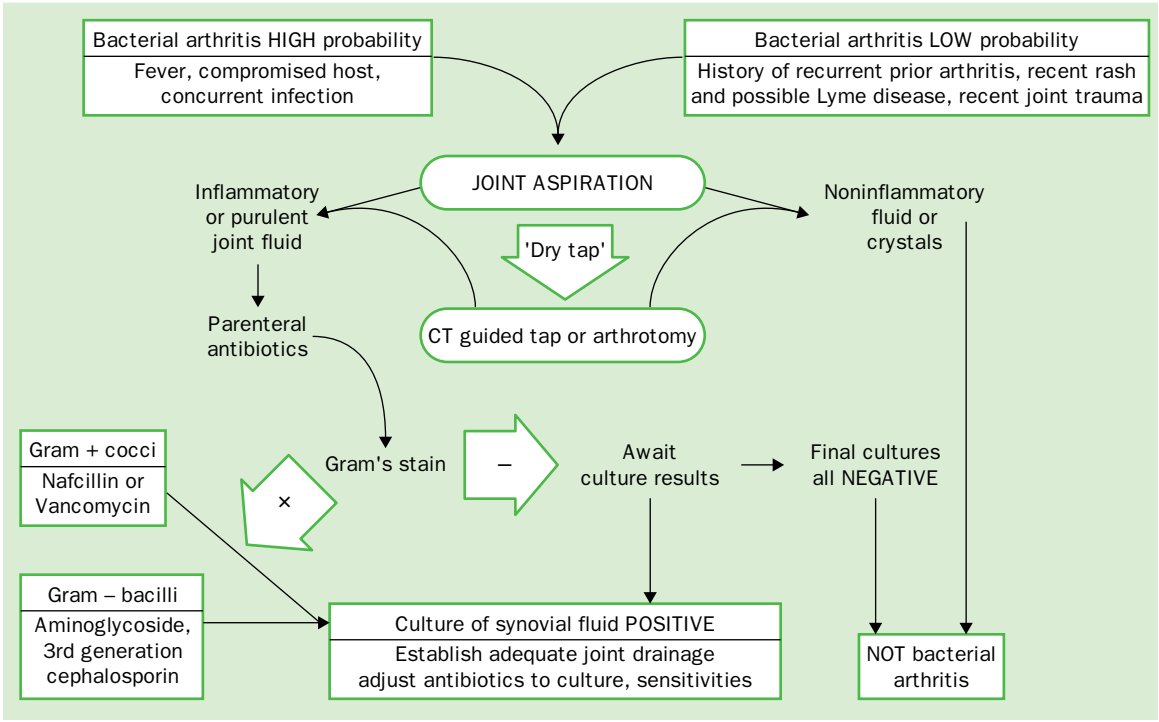

Figure 1: **Algorithm for evaluating hot, swollen joint**

and may be especially helpful in detecting septic sacroiliitis.[20]

Differential diagnosis

Other rheumatic disorders

Physicians should always consider the possibility of concurrent septic arthritis in patients with chronic joint disease who present with one or two new inflamed joints. Septic arthritis is most likely in patients with long-standing rheumatoid arthritis (panel 2), and in such patients treatment is often delayed because it is wrongly assumed that the joint symptoms are related to an exacerbation of the underlying rheumatoid arthritis.[10] The patient will often be afebrile and the presentation indolent. Diagnostic delay is an important contributor to the poor outcome of septic arthritis in rheumatoid arthritis, which carries a 30–50% case-fatality rate. If one or two joints become suddenly inflamed in a patient with rheumatoid arthritis or with another connective tissue disease, it should be assumed that the joint is septic until proven otherwise.

Gout and pseudogout (calcium pyrophosphate dihydrate deposition disease) are the two most important forms of acute arthritis that mimic bacterial arthritis.[21] A history of recurrent monoarthritis, typical podagra, or radiological evidence of chondrocalcinosis are most predictive of crystal-induced arthritis (panel 3). However, demonstration of the characteristic urate crystals of gout or the calcium pyrophosphate dihydate crystals of pseudogout are the only definitive diagnostic tests. Rarely, patients will have concurrent crystal-induced arthritis and bacterial arthritis,[22] so the synovial fluid should be cultured and examined for crystals in the evaluation of an acute effusion of unknown aetiology (figure 1).

Other infectious diseases

Mycobacterial arthritis—During the past decade mycobacterial and fungal arthritis have reemerged, partly related to the worldwide epidemic of HIV infection. 80% of joint infections in England and Wales from 1990 to 1992 were due to mycobacteria.[7] Mycobacterial and fungal arthritis both present with the slow onset of a chronic monoarthritis (panel 3). In both, there is a predilection for weight-bearing joints and the spine. There are usually no systemic symptoms. Joint swelling is marked but signs of acute joint inflammation are absent or mild. At the time of diagnosis, plain radiographs usually demonstrate joint-space narrowing and bone erosions. The synovial fluid is inflammatory with leucocyte counts of $10–30\times10^9$/L. Synovial fluid

Panel 3: **Differential diagnosis of bacterial arthritis**

Condition	Key clinical features	Most definitive tests
Mycobacterial or fungal arthritis	Insidious onset monoarthritis	Synovial fluid, tissue culture, histology
Viral arthritis	Polyarthritis, fever, rash	Serology
HIV infection	Sterile, acute synovitis or reactive arthritis	Always first consider septic joint and/or a haemarthrosis; serology
Lyme disease	History of erythema migrans, endemic Lyme area	Serology
Reactive arthritis	Recent gastrointestinal/ genitourinary infection, enthesopathy, skin lesions uveitis, conjunctivitis	Radiological sacroiliitis HLA-B27
Endocarditis	Fever, heart murmur, septic and sterile synovitis	Blood culture; septic joint more common in intravenous drug users
Rheumatoid arthritis	Rarely may cause a "pseudoseptic" arthritis	Always culture synovial fluid if acute rheumatoid arthritis
Gout, pseudogout	Prior history of acute arthritis, podagra	Demonstration of crystals in synovial fluid

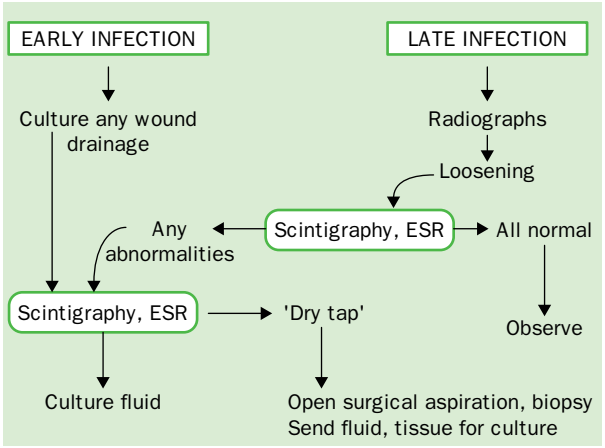

Figure 2: **Algorithm for evaluating possible prosthetic joint infection**

cultures are positive in 80–90% of tuberculous arthritis and culture of the synovial tissue is positive in 94%. Caseating or noncaseating granulomas are present in 90% of synovial biopsies. Fungal arthritis may present as a self-limited acute polyarthritis in normal hosts with recent exposure to a fungal infection. The chronic monoarthritis is seen primarily in immunocompromised hosts. When present, associated fungal skin lesions are the primary clue to diagnosis. The synovial fluid or synovial tissue cultures are positive in 90% of suspected cases. Antituberculous or antifungal agents usually eradicate mycobacterial or fungal arthritis although surgical joint debridement may be necessary.

Viral arthritis—Most forms of viral arthritis present with an acute polyarthritis, with fever and a characteristic rash (panel 3). Parvovirus, hepatitis B and C virus, and rubella virus are the most common. Small and large joints are involved and the differential diagnosis includes conditions such as acute rheumatoid arthritis, acute rheumatic fever, or gonococcal arthritis. HIV infection may be associated with a wide variety of rheumatic disorders, including Reiter's syndrome, psoriatic arthritis, vasculitis and Sjögren's-like syndrome.[23] A subacute monoarthritis or oligoarthritis which mimics infection or gout has been described (panel 3). HIV infection is an important risk factor for infectious arthritis, including typical bacterial as well as gonococcal and mycobacterial arthritis.[11]

Lyme disease—Lyme disease may present with a chronic monoarthritis, especially of the knee. Earlier cardinal symptoms include the typical erythema migrans skin lesion and transient polyarthralgias with viral-like features, including fever, headaches, and a variety of neurological signs (panel 3). The chronic arthritis occurs at a median of 6 months after the erythema migrans. Joint effusions may be massive but often resolve without treatment and then recur. Chronic persistent synovitis develops in 20% of patients with untreated Lyme disease. The serological tests are confirmatory but many false-positive results may occur if the test is ordered in patients who do not manifest the typical clinical features of Lyme disease. Oral or parenteral antibiotics are generally effective but antibiotic failures do occur in chronic Lyme arthritis regardless of mode or length of therapy.

Reactive arthritis—By definition, reactive arthritis has been classified as a sterile joint inflammation that may be related to a distant infection. There is a strong association with other seronegative spondyloarthropathies, including classic Reiter's syndrome, psoriatic arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease. The familial clustering of these rheumatic diseases is related to possession of the histocompatibility antigen HLA-B27 in 50–95% of cases. Recent gastrointestinal or genitourinary infection, in the context of an acute, sterile arthritis, suggests the diagnosis of a reactive arthritis. Presence of an enthesopathy, skin and mucous membrane lesions, uveitis or conjunctivitis and predilection for the sacroiliac joints are important clinical features of these conditions (panel 3). Although there is no definitive test, microbiological and serological tests for possible pathogens (eg, *Yersinia, Salmonella, Campylobacter* and *Chlamydia* spp) are important in the setting of an acute arthritis. Poststreptococcal arthritis is considered by many to be a form of reactive arthritis and also should be considered in the appropriate clinical setting. Recent synovial fluid PCR studies have demonstrated persistent microbial antigens in reactive arthritis.

Infective endocarditis—An acute, sterile synovitis or tenosynovitis as well as arthralgias and myalgias are common in bacterial endocarditis. Musculoskeletal symptoms are the presenting manifestations of infective endocarditis in 25% of patients.[24] Joint or bone infection are present in 15% of cases in some series.[24] These infections are much more common in intravenous drug users and may involve more than one joint (panel 3).

Treatment of bacterial arthritis

The treatment of acute bacterial arthritis requires antibiotics and joint drainage (figure 1). The initial choice of antibiotics should be based on the Gram's stain and the age and risk factors of the patient. If the Gram's stain is negative, empirical therapy should usually include antimicrobial activity against *S aureus* and streptococci.[25] Ceftriaxone, 1 g parenterally every 24 h, or ceftizoxime or cefotaxime, 1 g parenterally every 8 h, are the initial antibiotics of choice for suspected DGI.[26] In most situations, broad-spectrum parenteral antibiotics should be started and definitive therapy can be modified based on the culture and sensitivity of the synovial fluid or blood culture isolate. Combinations of a β-lactam and an aminoglycoside or second-generation quinolone have been widely used in the treatment of gram-negative bacilli and susceptible staphylococcal arthritis.[6] Most antibiotics penetrate well into inflamed joints during either parenteral or oral administration. Usually intravenous antibiotics are administered for 2–4 weeks. Shorter courses of treatment and oral antibiotics are often effective in children and in adults with gonococcal arthritis. Intraarticular antibiotic instillation is not required and such therapy may cause a chemical synovitis.

Many joints can be drained with closed needle aspiration, although daily aspiration may be necessary at first.[27] Arthroscopy is often preferred in knee or shoulder infections because of more adequate irrigation and better visualisation of the joint. If joint drainage cannot be maintained by needle aspiration or arthroscopy, open surgical drainage is necessary.[2,6] Initial open surgical drainage is recommended in hip infections, especially in

children. Immediate joint mobilisation (eg, by means of continuous passive motion devices) will prevent contractures and promote nutrition to the articular cartilage. The addition of corticosteroids to antibiotics ameliorates the course of experimental *S aureus* arthritis.[28] However, there are no prospective clinical trials of nonsteroidal antiinflammatory drugs or corticosteroids as adjuncts in the treatment of septic arthritis.

Prosthetic joint infection

Pathophysiology

The rate of infection ranges from 0·5% to 2% for hip and knee replacements. Early-onset infections are usually the results of perioperative wound contamination and are most often caused by coagulase-negative staphylococci. Infections that begin later than three months after the joint implant are usually haematogenously acquired. *S aureus*, streptococci, gram-negative aerobes, and anaerobes are the most common bacteria in late-onset prosthetic joint infections. When certain bacteria attach to the prosthetic material, they elaborate an exopolysaccharide, a glycocalyx.[29] Bacteria that lie deep within this biofilm are protected against host phagocytes and are highly resistant to antibiotics. The protective biofilm may explain the indolent nature of prosthetic joint infections and the difficulty there is in eradicating the infection unless the prosthesis is removed. The most important risk factor for prosthetic joint infection is revision arthroplasty, which carries a 5–10% risk of infection. Others are rheumatoid arthritis, diabetes, and immunosuppressive medications.

Clinical manifestations, diagnosis

Infections within the first few months of surgery usually present with pain, erythema, and drainage at the wound site. However, late-onset infections present with gradually progressive joint pain. Fever and other signs of infection are uncommon. Measurement of acute-phase reactants is useful only if there is a significant change since the operation. Radiological evidence of joint loosening is often present but does not differentiate mechanical from septic loosening.

Therefore, if there is any index of suspicion of prosthetic joint infection, the joint must be aspirated for microbiological evaluation (figure 2). This can generally be accomplished by closed needle aspiration of the knee, but hips often require arthrotomy to obtain material for culture. Preoperative hip arthrography and joint aspiration has been useful. Fluid and any periprosthetic tissue should be sent for aerobic and anaerobic culture. Intraoperative frozen section histology has also been recommended.

Treatment

Treatment usually requires the surgical removal of all bioprosthetic components. Rarely, early-onset infections can be eradicated by debridement and a long course of parenteral antibiotics. Patients with late-onset infection will most often require removal of the prosthesis, extensive debridement, and a later replacement arthroplasty. High-risk patients or those refusing replacement arthroplasty have been treated with long-term suppressive antimicrobial therapy. Antibiotic therapy is based on a definitive microbiological diagnosis. Generally, six weeks of parenteral antibiotics are recommended for prosthetic joint infections.

Conclusion

The outcome of bacterial arthritis has not changed much in the past few decades despite more effective antibiotics and improved methods of joint drainage. Permanent joint damage develops in 50% of cases and mortality is 10–16%.[2,6,7] Outcome is directly related to host factors, such as prior joint damage, and to virulence of the infecting organism. The large number of total joint arthroplasties being done have resulted in joint prostheses becoming the most important risk factor in septic arthritis. Physicians must always first consider septic arthritis in the evaluation of any acute arthritis.

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