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7
Septic Arthritis

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I. INTRODUCTION

Septic arthritis is an inflammation of the joint space, synovial fluid, synovium, and articular cartilage caused by a variety of microorganisms. Acute infections are generally caused by pyogenic bacteria and called *acute bacterial* or *septic arthritis*. The process is generally acute and constitutes a medical emergency; if it is untreated for even 24 to 48 hours, permanent joint damage may result. Common pyogenic bacteria including *Staphylococcus aureus*, *Streptococcus* spp., *Haemophilus influenzae*, and *Neisseria gonorrhoeae* cause the vast majority of episodes. The aerobic gram-negative bacilli and anaerobes account for additional cases.

Chronic infections are most often caused by mycobacteria or fungi. Sterile or reactive arthritis is an inflammatory reaction that is generally secondary to infection in another part of the body. It may be associated with infection preceding hepatitis or postgastrointestinal infections with *Salmonella* or *Shigella* spp.

Nearly 10% of the patients who have nongonococcal bacterial arthritis may die with the infection and one-third of the survivors are afflicted with residual loss of function in the involved joint. It afflicts all age groups and has a predilection for immunocompromised patients. Important questions regarding the therapy of septic arthritis include the duration of antibiotic treatment, the mode of joint drainage, and the role of physical therapy.

II. MICROBIOLOGICAL CHARACTERISTICS

Virtually every bacterial organism has been reported to cause septic arthritis. The specific etiological agent in any given patient can be anticipated by identifying the patient's age, host factors, and presence of prior disease (Table 1). *Staphylococcus aureus* has been the most common cause of nongonococcal bacterial arthritis over the course of the last four decades (1,2). In 1990 an increased incidence of gram-negative organisms, especially *Escherichia coli* and *Pseudomonas aeruginosa*, in the elderly debilitated population was reported (3).

S. aureus causes most cases of bacterial arthritis in human immunodeficiency virus–(HIV)-positive patients who are intravenous drug users. However, HIV infection predisposes patients to joint infections with opportunistic as well as common pathogens (4–6).

In patients with sickle cell disease, *Salmonella* spp. as well as gram-positive and other gram-negative bacteria have been isolated from infected joints. In the neonate with prolonged hospitalization and instrumentation, coagulase-negative staphylococci, gram-negative enteric bacteria, and fungi have been isolated. *N. gonorrhoeae* is the most common cause of acute joint infection in young adults between 15 and 40 years of age in the United States.

Historically, *H. influenzae*, *S. aureus*, and group A streptococci were the most common causes of infectious arthritis in children below 2 years of age. However, the overall incidence of *H. influenzae* as a cause of septic arthritis is decreasing because of the *H. influenzae* type b (Hib) vaccine now given to children (7). A 1997 study of 165 cases of acute hematogenous osteomyelitis or septic arthritis treated in the years before and after the advent of the Hib vaccine demonstrated that musculoskeletal infections due to this bacterial species were reduced to nearly nonexistent levels (8). Therefore, the coverage of *H. influenzae* as part of the empirical antibiotic coverage may no longer be needed in the management of acute septic arthritis in Hib-vaccinated children. While *H.*

Table 1 Causative Organism in Septic Arthritis by Age in Years (Percentages)

	2 Yr	2–15 Yr	16–50 Yr	75 Yr
Staphylococcus aureus	35	50	15	75
Streptococcus pyogenes	15	20	5	5
Streptococcus pneumoniae	10	10	–	5
Haemophilus influenza, type B	35	2	–	–
Neisseria gonorrhoeae	–	10	10	–
Others	5	8	10	15
Gram-negative bacilli	5	7	9	15
Anaerobes	–	1	1	–

influenzae has lost its predominance as the most commonly identified gram-negative pathogen in pediatric populations, the normal oropharyngeal resident of young children *Kingella kingae* may have taken its place, specifically in patients less than 24 months of age (9–12). In fact, a 1979 study found that nearly half of the clinical isolates from acute septic arthritis patients less than 2 years old were *K. kingae* (12). However, these results have yet to be seen in other regions. Clinical data suggest that the organism may gain access to the bloodstream in the course of an upper respiratory infection or stomatitis (13). In children above the age of 2, *S. aureus*, streptococci, *H. influenzae*, and *N. gonorrhoea* have usually been isolated (14–16), but *H. influenzae* may have also lost its predominance in this patient age group as mentioned previously (10).

Microbiological associations exist with concomitant disease states. Septic arthritis after cases of infectious diarrhea may be caused by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp. (17,18). However, these cases may reflect a form of reactive arthritis. A rare form of migrating polyarthritis may be caused by *Streptobacillus moniliformis*. In HIV-infected patients, *S. aureus* continues to be the most common isolate (approximately 30%) (6). However, there is an increased number of opportunistic pathogens isolated from this patient subset, including *Streptococcus pneumoniae*, mycobacterial species, and fungal species (14,16). Anaerobic bacteria have been seen primarily after surgical arthroplasty or traumatic injuries of the extremities (19). *Bacteroides* species appear to attack the sternoclavicular and sacroiliac joints. Table 2 summarizes the relationship between certain epidemiological situations and the infecting agents.

Table 2 Relationships Between Organisms and Underlying Epidemiological Conditions

Organisms	Epidemiological condition
Neisseria gonorrhoeae	Menstruation or pregnancy
Neisseria meningitis	Chronic meningococcemia
Haemophilus influenza	Children less than 2 years
Pasteurella multocida	Cat or dog bite
Eikenella corrodens	Human bite
Fusobacterium nucleatum	
Streptobacillus moniliformis	Rat bite
Borrelia burgdorferi	Tick exposure
Brucella spp.	Ingestion of nonpasteurized dairy products
Sporothrix schenkii	Injury: rose thorns, splinters, moist soil
Mycobacterium marinum	Trauma in aquatic environment
Staphylococcus aureus or	Intravenous drug abuse
Pseudomonas aeruginosa	
Mycobacterium kansasii	Monoarticular synovitis

III. PREDISPOSING CONDITIONS

Table 3 lists some of the predisposing factors for infectious arthritis. Intravenous (IV) drug abuse appears to be a risk factor for the development of bacterial arthritis. *S. aureus*, *P. aeruginosa*, and *Serratia marcescens* have been isolated. In these IV drug abusers there was an increased frequency of infection of the sacroiliac joints, sternal articulations, and pubic symphysis (20). Chronic inflammation and joint damage as seen in gout, osteoarthritis, and rheumatoid arthritis are predisposing factors for joint infection. Joint trauma, joint surgery, and presence of a joint prosthesis are also risk factors because damaged joints act as a nidus for bacterial infection. Patients with chronic underlying illnesses (systemic lupus erythematosus, diabetes, renal failure, HIV, etc.) have suppressed or defective immune functions and are susceptible to increased bacterial infections.

Table 3 Predisposing Factors in Infectious Arthritis

Adults
Immunosuppressive therapy
Joint trauma
Penetrating injury
Intra-articular injections (rare)
Preexisting arthritis
Osteoarthritis
Rheumatoid arthritis
Crystal-induced arthritis
Presence of joint prosthesis
Arthroscopic procedures (rare)
Serious chronic illness
Cancer
Systemic lupus erythematosus
Chronic liver disease
Diabetes
Human immunodeficiency virus
Hemoglobinopathy
Intravenous drug abuse
Children
Trauma
Contiguous osteomyelitis
Systemic illnesses

IV. PATHOGENESIS

There are three modes by which a joint space may be seeded in both children and adults; the most common cause is hematogenous. Roughly 50% of patients with septic arthritis have concomitant positive blood culture findings. A primary source such as otitis and endocarditis should be sought. Although not all episodes of bacteremia result in joint infection, the risk for the development of infection is increased by local factors in the joint (e.g., recent trauma, rheumatoid arthritis, preexisting joint disease) systemic factors in the host (e.g., parenteral drug abuse, corticosteriod use, immunosuppressive medication, malignancy) or finally properties of the infecting organism (e.g., gram-positive cocci as the etiological agent of nongonococcal septic arthritis).

A small percentage of cases result from direct inoculation of the joint space, either accidentally (e.g., atypical mycobacteria, actinomyces) or iatrogenically (e.g., arthrocentesis, instillation of corticosteroids). In children, septic arthritis can develop from a contiguous infection such as osteomyelitis. Septic arthritis may also result from the spread of a contiguous infection (*Mycobacterium tuberculosis*) in adults.

Once the synovium is seeded, the resulting inflammatory reaction may result in rapid destruction of the articular cartilage. The drainage to the joint results from increased intra-articular pressure and the release of proteolytic enzymes from the polymorphonuclear leukocytes, which degrade the cartilage (21,22). Since this cartilage is avascular and unable to regenerate, permanent damage results.

Endocrine factors seem to play an important role in the pathogenesis of gonococcal infectious arthritis. There is a greater incidence of gonococcal arthritis in women, and women are more susceptible to gonococcal bacteremia during pregnancy, in the postpartum period, and during the first week of the menstrual cycle. Rubella arthritis occurs primarily in postpubertal women and mumps arthritis is seen exclusively in postpubertal men (23).

Recovery from various systemic infections has been associated with a reactive arthritis related to the immune response. The postinfectious arthritis that follows gastrointestinal infections with *Shigella, Salmonella, Campylobacter*, and *Yersinia* spp. occurs most often in persons with human leukocyte antigen B27 (HLA-B27) histocompatibility antigen (24). Inpatients with hepatitis C infection arthritis secondary to antigen-antibody complex formation may develop.

V. CLINICAL FEATURE OF BACTERIAL ARTHRITIS

The clinical findings in gonococcal and nongonococcal infectious arthritis in adults are outlined in Table 4. The presenting symptoms in disseminated

Table 4 Comparison of Clinical Findings in Gonococcal and Nongonococcal Bacterial Arthritis

Gonococcal	Nongonococcal
Generally healthy young adults	Generally elderly or immunocompromised
Polyarticular arthritis (> 50% of cases)	Monoarticular arthritis (> 80% of cases)
Tenosynovitis common	Tenosynovitis rare
Rash common	Rash unusual
Blood culture results positive in < 10%	Blood culture results positive in > 50%
Joint culture results positive in < 25%	Joint culture results positive in > 90%
Rapid response to antibiotic treatment	Slow response to antibiotics and drainage
Generally good prognosis	Variable prognosis

Source: Modified From Ref. 39.

gonococcal infections may be insidious; migratory polyarthralgias, fever, dermatitis, urethral or vaginal discharge, and tenosynovitis are the most common findings. Only 30%–40% of these patients have the classic bacterial arthritis symptoms of fever, localized symptoms of warmth, pain, swelling, and tenderness over the involved joint. When tenderness in present, it is often diffuse in its periarticular location in contrast to the "point tenderness" often noted in acute osteomyelitis. Often, there is a palpable joint effusion, and most patients experience decreased active and passive motion of the involved joint, a sign that often distinguishes septic arthritis from bursitis or cellulitis (25). Radiographically the joint capsule may be distended with fluid, accompanied by soft tissue swelling; less commonly destructive changes in the bony structure are evident. The latter may occur with pyogenic arthritis in which there has been delay in diagnosis or in mycobacterial infection or in infections complicated by rheumatoid arthritis.

Septic arthritis is generally monoarticular and weight-bearing joints are most commonly affected (Table 5). Nearly half of the cases of septic arthritis in adults involve the knee joints, followed in descending order of frequency by the hip, elbow, ankle, wrist, shoulder, sternoclavicular joint, sacroiliac joint, and small joints of the hands and feet. Joints involved in acute pyogenic arthritis are usually warm, tender, and erythematous. Ninety percent of patients have joint effusions associated with general constitutional symptoms such as malaise and fever. Misleading symptoms may also be seen in bacterial arthritis of the hip and sacroiliac joints, where pain may be referred to the abdomen or knee. In older individuals with a history of chronic degenerative joint disease, a definitive diagnosis may be delayed because symptoms are erroneously attributed to the underlying condition rather than to an infectious process. In neonates, the clinical features of infectious arthritis are those of septicemia or fever of unknown origin.

Table 5 Frequency of Joint Involvement in Bacterial Arthritis

Site	Children (%)	Adults (%)
Knee	40	50
Hip	20	25
Ankle	15	7
Elbow	15	10
Wrist	5	7
Shoulder	5	5
Interphalangeal and metacarpal	1	1
Sternoclavicular	1	8
Sacroiliac	0	2

The clue to diagnosis here is a careful physical examination that may reveal localized swelling, pain on palpation or passive movement of the joint, and decreased movement of the extremity.

Pustular skin lesions similar to those commonly observed in disseminated gonococcemia have been described in patients with meningococcal arthritis (26,27) and in occasional patients with septic arthritis due to group A streptococci (28) and *H. influenzae* (12). Polyarticular nongonococcal infection occurs in 10%–20% of adults and children with septic arthritis (12). In contrast, more than one joint is involved in the majority of patients with gonococcal arthritis (29).

VI. DIAGNOSIS

The traditional "index of suspicion" remains the most important factor in the diagnosis of septic arthritis. Table 6 outlines the proper evaluation of a patient with suspected septic arthritis. The diagnosis is established by a complete history, including an epidemiological one; physical examination; and by examination and culture of the synovial fluid. Peripheral blood leukocyte counts are visually elevated in children but are often within normal limits in adults. Many patients display elevated C-reactive protein levels and erythrocyte sedimentation rates. A suspicion of septic arthritis mandates an arthrocentesis of the suspected joint and careful examination of the synovial fluid, if there is no contraindication (Table 7). Synovial fluid is analyzed for total and differential leukocyte count, crystals, glucose, and mucin clot (30). Other parameters include protein, complement, pH, color, and turbidity. However, there is significant overlap of all these findings among different types of inflammatory arthritis, for example septic, rheumatoid, gouty, and pseudogouty. In septic arthritis, the leukocyte count is usually greater than 50,000 per cubic millimeter with more than 90% of the cells polymorpho-

Table 6 Diagnostic Evaluation of a Patient with Septic Arthritis[a]

History
Physical examination
Joint fluid aspiration
Leukocyte count
Crystals
Synovial glucose level
Gram stain
Culture (aerobic, anaerobic, fungus, mycobacteria)
Culture other sites
Blood cultures
Blood tests
Peripheral WBC
Erythrocyte sedimentation rate
C-reactive protein
Blood sugar
Roentgenograms (routine, CT, MRI, radionuclide scans)
Response to treatment

[a]WBC, white blood cell count; CT, computed tomography; MRI, magnetic resonance imaging.

nuclear leukocytes. The glucose is less than 60% of simultaneous serum glucose, mucin clot is poor, and protein levels are elevated. The appearance is cloudy or turbid with a yellow to green hue.

Synovial fluid from any adult with monoarticular arthritis should be examined by compensated polarizing light microscopy for negatively birefringent (uric acid) and positively birefringent calcium pyrophosphate dihydrate crystals to

Table 7 Analysis of Synovial Fluid for Differing Forms of Infectious Arthritis

Condition	Leukocytes, n/mm	Predominant Cell Type	Glucose ratio, synovial fluid to blood	Diagnostic smear, % cases
Normal	200–600	Mononuclear	0.8–1.0	0
Bacterial arthritis	10,000–100,000	> 90% PMN[a]	< 0.5	> 90
Fungal arthritis	3,000–30,000	70% PMN	> 0.5	< 0.5
Tuberculous arthritis	10,000–20,000	50%–70% PMN[a]	0.5–1.0	< 20
Reactive	3,000–10,000	Mononuclear	0.8–1.0	0

[a]PMN, polymorphonuclear leukocyte cells.

rule out crystalline joint disease. However, simultaneous bacterial infection and crystalline disease has been reported (31).

The ultimate diagnosis of septic arthritis is made through identification of the infecting organism, either by Gram stain of the synovial fluid or through culture. Prior antibiotic therapy may result in a negative culture or Gram stain finding. If the Gram stain result is negative it is important to do an acid-fast stain for mycobacteria and a potassium hydroxide wet mount for fungi. Cultures of synovial fluid fail to grow organisms in a substantial number of patients in whom there is a clinical diagnosis of septic arthritis. Several reasons have been proposed for the inability to obtain positive culture results, including prior use of antibiotics, inadequate anaerobic cultures, standard of the microbiology laboratory, changing patterns of the organisms involved and their cultural characteristics, and failure to obtain blood for culture or to perform a sufficient number of arthrocentesis.

Skin lesions, particularly those that can be aspirated and examined on Gram stained smears, can provide a clue as to the presence of bacteremia (meningococcal, gonococcal, or staphylococcal) and indicate a specific organism.

Imaging studies of septic arthritis can only be used to support or refute a clinical suspicion of the disease and should not be used as an absolute diagnostic indicator. Radiographs taken in the first 7 to 10 days of infection are of little diagnostic help because they show only distention of the joint capsule and periarticular swelling. Initial films should nevertheless be obtained before arthrocentesis because one needs a baseline for comparison. Septic arthritis may be a consequence of preexisting osteomyelitis or the presence of intra-articular gas (rare) that would suggest *Clostridium* spp.; in prosthetic joint infections, it can often demonstrate loosening of the prosthesis, which would be revealed radiographically. Follow-up films are important in evaluating the extent of articular damage. The presence of chondrocalcinosis on radiography should not dissuade anyone from the diagnosis of septic arthritis.

Ultrasonography is capable of showing both intra- and extra-articular abnormalities not apparent by plain radiography and is a very powerful tool to detect early fluid effusions and to guide initial joint aspiration and drainage procedures (32,33). Even small collections of fluid (1–2 mL) can be accurately detected (33). Non–echo-free effusions (due to clotted hemorrhagic collections) are very characteristic of a septic joint. It has been suggested that the presence of only an echo-free effusion (caused by transient synovitis and fresh hemorrhagic effusions) may rule out the diagnosis of septic arthritis (33). This imaging technique is also useful for detecting collections of fluids in deep joints, including the hip. In addition, the status of the intra-articular compartment, joint capsule, bony surface, and adjacent soft tissues, and the patient's response to therapy can be monitored. When one considers that this imaging technique is also noninvasive, inexpensive, easy to use, and devoid of irradiation or any other known

complications, more clinicians should use ultrasonography in the diagnosis of septic arthritis in the future.

A triple-phase radionuclide bone scan is the best earliest radiographic diagnostic test for septic arthritis. It shows increased activity around an infected joint. However, these findings are nonspecific and can be detected in other forms of infectious arthropathies.

Like radiographs, computed tomography (CT) scans have limited use during the early stages of septic arthritis. However, these scans may allow the visualization of joint effusion, soft tissue swelling, and periarticular abscesses. In addition, they are more sensitive than plain radiographs in the imaging of joint space widening due to localized edema, bone erosions, foci of osteitis, and scleroses. This scanning technique may be useful in the diagnoses of arthritis cases that are difficult to assess, including infections of the hip, sacroiliac, and sternoclavicular joints. In addition, they may assist in guiding joint aspiration, selecting the surgical approach, and monitoring therapy in these difficult infections (34).

Magnetic resonance imaging (MRI) has become a useful diagnostic tool for the early determination of the extent of musculoskeletal infection (35,36). As with CT, MRI may be particularly useful in aiding the diagnosis of joint infections that are difficult to access, such as sacroiliitis (37). MRI displays greater resolution for soft tissue abnormalities than CT scans or radiographs and greater anatomical detail than radionuclide scans. The spatial resolution of MRI makes it useful in visualizing joint effusion and differentiating between bone and soft tissue infections. The main disadvantages to MRI are high cost, lack of universal availability, imaging interference due to metal implants, and lower resolution of calcified bone structures and cortex (38). However, neither CT nor MRI can differentiate between infectious and noninfectious joint effusions.

VII. DIFFERENTIAL DIAGNOSIS

The diagnosis of septic arthritis should be considered for any patient who has acute monoarticular arthritis (Table 8). A number of factors should be included in the differential diagnosis of septic arthritis:

1. Acute crystal-induced arthritis may resemble suppurative arthritis but can be distinguished readily by the presence of crystal in the synovial fluid.
2. Early rheumatoid arthritis, acute rheumatic fever, or Reiter's syndrome may mimic septic arthritis, particularly when only one or a few joints are involved. Joint fluid analysis is necessary to distinguish these processes from invasive infection.

Table 8 Differential Diagnosis of Septic Arthritis

Septic arthritis
Gonococcal
Nongonococcal
Nonsuppurative infectious arthritis
Mycobacteria
Fungal
Viral (hepatitis, rubella)
Syphilis
Mycoplasma
Lyme
Bacterial endocarditis
Sexually acquired reactive arthritis
Enteric arthritis
Acute rheumatic fever
Rheumatoid arthritis exacerbation
Crystal-induced arthritis
Septic bursitis
Polyarticular septic arthritis (PASA)

3. Acute arthritis involving one or several joints may occur in patients with sickle cell disease, usually along with other evidence of sickle cell crisis. Acute arthritis caused by sickle cell disease must also be distinguished from septic arthritis, osteomyelitis, aseptic bone infarctions, and gout. In acute arthritis that is caused by sickle cell disease, the synovial fluid finding is a noninflammatory process with a white blood cell (WBC) count of less than $1000/mm^3$ and mononuclear cells predominating (39).
4. Osteomyelitis must be considered in the differential diagnosis because it may have preceded joint involvement and may mimic septic arthritis by virtue of associated periarticular soft tissue swelling.
5. In any patient with rheumatoid arthritis in whom fever and disproportionate involvement of one or more joints develops bacterial infection should be suspected.
6. Unilateral sacroiliac pain with fever should point to a possible diagnosis of sacroiliac pyarthrosis.
7. Patients with septic bursitis experience fever and an acute painful swelling that may in some cases be mistaken for septic arthritis.
8. Trauma commonly precedes septic bursitis.
9. The diagnosis of Lyme arthritis in patients who live in endemic areas is based on a history of exposure to ticks, a history of erythema

chronicum migrans, or diagnostic serum titers of antibody to *Borrelia burgdorferi*.

10. Twenty-five percent of patients with infective endocarditis have an acute, sterile synovitis tenosynovitis, arthralgias, and myalgias (40). Bone or joint infections have been reported in 15% of cases in many series and are more common in intravenous drug users.

VIII. TREATMENT

Septic arthritis is a medical emergency that requires prompt diagnosis and treatment within 24 to 48 hours of onset of symptoms. Delaying therapy for more than 7 days commonly results in incomplete recovery, permanent disability, and death. Successful management consists of four elements: prompt diagnosis, appropriate antimicrobial therapy, drainage of the joint space, and rehabilitative therapy.

A. Antimicrobial Therapy

The clinical setting, epidemiological history, age of the patient, and results of the Gram stain of the joint fluid initially determine selection of antibiotics. Selection may later be modified on the basis of culture and sensitivity findings (Table 9).

The synovial tissue is very vascular and does not have a basement membrane. These characteristics facilitate the penetration of antimicrobial agents from blood into infected and uninfected inflamed joints. Synovial fluid concentrations of most antibacterials generally average at least 60% to 70% of serum drug concentrations at the time of peak serum concentrations and frequently exceed those in serum immediately before the subsequent systemic dose in patients with septic arthritis (41–43). In order for therapy to be effective, it is assumed that the antibacterial concentration attained in synovial fluid should exceed the usual amount required to inhibit the growth of the infecting bacteria.

Optimal concentrations of antibacterial agents in body fluids are particularly important in the immunocompromised host because recovery from the infected site depends to a large extent on the effectiveness of the antibacterials. In any host, a peak antibacterial concentration that exceeds the minimal inhibitory concentration of the infecting organism 5- to 10-fold and a measurable trough concentration has an excellent predictive value for a favorable outcome. Ceftriaxone should be used to treat gonococcal arthritis in most areas, since penicillin-resistant strains are being increasingly reported.

The route and duration of antibiotic therapy are still controversial in the treatment of septic arthritis. Parenteral antibiotics obtain adequate levels in the joint fluid, and intra-articular injection of antibiotics is not indicated for the

Table 9 Choice of Antibiotics in Therapy of Septic Arthritis[a]

Organism	Drug of choice	Dose (IV)	Alternative drug	Dose (IV)
Neisseria gonorrhoeae	Ceftriaxone	2 g q24 h	Doxycycline	100 mg q12 h
Staphylococcus aureus	Nafcillin	8–12 g, total 2–3 g q6 h	Vancomycin or imipenem	1 g q12 h
Streptococcus pneumoniae	Penicillin G	2 Million units q4–6 h	Erythromycin	0.5–1.0 g q6 h
Escherichia coli	Ceftriaxone	2 g q24 h		
Proteus mirabilis	Cefotaxime or Ceftriaxone	2 g q6–8 h 2 g q24 h	Imipenem or ciprofloxacin	0.5–1.0 g q6 h 400 mg IV q12 h
Pseudomonas aeruginosa	Ceftazidime and Tobramycin	2 g q24 h 8 mg/kg/qday		
No organisms seen Healthy young patient	Ceftriaxone	2 g q24 h	Imipenem	0.5–1.0 g q6 h
Older patient with underlying disease	Imipenem and Tobramycin	0.5–1 g q6 h 5 mg/kg/qday	Vancomycin[b] and ciprofloxacin	1 g q12 h and 400 mg q12 h

[a] Dosages for nonallergic patients with normal renal function. IV, intravenous.
[b] Vancomycin used only for methicillin-resistant *Staphylococcus* spp.

therapy of bacterial arthritis. In fact, intra-articular antibiotics may produce a chemical synovitis. Parenteral antibiotics should be given for 14 days or longer; the only exception is gonococcal arthritis, in which the organisms are usually very sensitive and 7 days suffices. However, when the organism is difficult to eradicate (such as *S. aureus* or gram-negative bacilli), parenteral treatment should be given for 4 weeks. Parenteral antibiotics can be changed to oral antibiotics if there is a good clinical response, but serum and synovial fluid concentrations of oral antibiotics must be bactericidal for effective therapy. For patients with nongonococcal infectious arthritis, most physicians administer antibiotics intravenously for 2 weeks, followed by 1 to 2 weeks of oral antibiotics. When the infection is difficult to eradicate, parenteral therapy is given for 4 weeks or for 2 weeks followed by a 4- to 6-week course of oral antibiotics. In gonococcal arthritis, parenteral therapy can be changed to oral therapy in 3 to 4 days if there is a good clinical response.

The effectiveness of treatment can be determined by serial examinations of the synovial fluid. Sterility should be achieved within a few days, but the leukocyte count may take a week to drop markedly. Few controlled studies assessing the optimal duration, dose, or route of administration of antibiotics in nongonococcal arthritis exist (41).

B. Surgical Therapy

Draining the infected joint allows removal of debris and toxin, which if allowed to accumulate would result in the destruction of the articular surfaces and the formation of adhesions. There are several methods available to achieve drainage, ranging from closed-needle aspiration to open drainage (Table 10). However, there are no universally accepted standards for drainage.

The joint should be aspirated by needle as often as required to remove pus, which contains enzymes that destroy cartilage. Repeated aspirations may be required for 7 to 10 days until the leukocyte count decreases and the synovial fluid remains sterile. Knees, ankles, wrists, and elbows usually can be drained adequately by needle aspiration. However, deep joints such as hips, shoulders, axial joints, and the sternoclavicular joint often necessitate open surgical drainage. Indications for open surgical drainage include the following:

1. Presence of loculations incompletely removed by repeated aspirations, especially when *S. aureus* is the pathogen
2. Persistently high neutrophil counts (>25,000 per cubic millimeter) in the joint fluid or positive culture results despite appropriate antibiotic treatment and multiple closed aspirations
3. Hip and other deep joint infections that cannot be aspirated with a needle

Table 10 Comparison of Drainage Procedures

	Aspiration	Tidal irrigation	Arthroscopy	Arthrotomy
Location	Bedside	Bedside	Operating room	Operating room
Anesthesia	Local	Local	Regional/general	Regional/general
Joint accessibility	Limited to large superficial joints; requires repeated aspirations	Limited to large superficial joints	Limited to large joints	All joints
Drainage capability	Modest	Modest	Excellent	Excellent
Adhesion lysis	No	No	Yes	Yes
Synovectomy	No	No	Yes	Yes
Morbidity	Minimal	Minimal	Moderate	Significant
Recovery time	Short	Short	Short	Prolonged
Cost	Inexpensive	Inexpensive	Modest	Expensive

After open drainage, the wound should be allowed to heal by secondary closure and antibiotic therapy should be continued for another week.

Arthroscopy and open arthrotomy should be considered when lysis of adhesions or synovectomy is being considered, when there is adjacent osteomyelitis, or when a trial of aspiration is unsuccessful (44–47). Arthroscopy can be also used to obtain synovial tissue for culture and histological testing when aspirated synovial fluid culture findings are negative and a bacterial identification is important to further treatment. This procedure is particularly valuable with fastidious organisms (44,48,49). Tidal irrigation, consisting of repeated distention and irrigation of the joint, may eliminate the need for surgical drainage (46).

C. Rehabilitation

Removable splints or casts, physical therapy, and active exercises are important for optimal recovery. Recently there has been support for early and aggressive mobilization after septic arthritis. However, weight bearing should be prevented until all signs of inflammation subside. Maintaining the joint in a position of maximal function by strict immobilization is not required. In fact, clinical observations have revealed deleterious effects of prolonged immobilization on synovial joints, including stiffness, pain, muscle atrophy, disuse osteoporosis, and later degenerative arthritis. Early continuous passive motion has the following benefits: prevention of adhesions and pannus formation, improvement in cartilage

nutrition through increased diffusion of synovial fluid, enhancement of clearance of enzymes in purulent exudate from the infected joint, and stimulation of chondrocytes to synthesize the various synovial matrix components (50,51). It has been recommended that passive range of motion be started during the first week of treatment, followed by active motion as soon as the patient permits it, usually within 1 or 2 weeks (50–52). Isometric exercise should be started on the first postoperative day, followed by range of motion exercise 1 or 2 days after removal of the drainage catheters (48).

Overall, the optimal time for initiating isometric exercise or range of motion exercise is not certain and remains controversial. Splinting versus continuous passive motion treatment for a joint with pyarthrosis is also controversial.

IX. COURSE OF ILLNESS AND PROGNOSIS

A permanent loss in joint function is seen in approximately 40% of patients with nongonococcal septic arthritis but ranges between 10% and 73% (2,53–55). Certain clinical findings are associated with poor prognosis (Table 11). The mortality rate associated with this disease is usually between 5% and 20% and is often a result of the transient or chronic bacteremia that causes most of the cases of septic arthritis and underlying host factors (malignancy, neonate, rheumatoid arthritis, etc.) (2,53–56). Septic arthritis in patients with rheumatoid arthritis (RA) has a mortality rate of about 20%, and a large proportion of survivors are left with diminished joint function. Case fatality rates are much higher among those with polyarticular septic nongonococcal arthritis (PASA) versus those with monoarticular infection (30% versus 4%, respectively) (57). Patients who have PASA have a very poor prognosis, which is due to the associated bacteremia and reduced ability to resist the infection. However, PASA may result in very high rates of mortality in patients infected with staphylococcal species (up to 56% mortality rate) and those with a concomitant diagnosis of rheumatoid arthritis (up to 49% mortality rate) (37).

Table 11 Predictors of Poor Outcome with Bacterial Arthritis

Age above 60 years
Infection in hip and shoulder
Severe underlying disease (rheumatoid arthritis, malignancy, etc.)
Duration of symptoms before treatment >1 week
Persistently positive culture results after 7-day course of appropriate therapy
Demonstrated bacteremia

The prognosis for patients suffering from gonococcal arthritis is very favorable with a rapid diminution of symptoms and a full return of joint function. In rare cases of DGI (1%–3%), complications such as endocarditis, pericarditis, osteomyelitis, pyomyositis, perihepatitis, and meningitis may occur.

The outcome in patients with septic arthritis due to some of the more virulent organisms such as superantigen-producing *S. aureus* and certain gram-negative bacilli is poor in spite of optimal therapy (58). The elderly demonstrate a high mortality rate (19%–23%) associated with septic arthritis since these patients often have preexisting medical conditions (e.g., diabetes mellitus) and joint diseases (e.g., osteoarthritis and rheumatoid arthritis) (3,59–61).

X. SPECIAL FORMS OF ARTHRITIS

In patients who experience fever, rash, lymphadenopathy, arthritis, or arthralgia, a viral cause should be considered. Arthropathy may be acute, subacute, or chronic. The most common viral diseases associated with arthropathy are rubella, mumps, hepatitis B, Epstein-Barr virus (associated with symptoms of infectious mononucleosis), parvovirus B19 (produces erythema infectiosum, (fifth disease), alpha viruses (Ross River virus in Australia, Chikungunya in Southeast Asia), and parvovirus (in the United Kingdom) (Table 12). Synovial fluid samples reveal an abundant presence of mononuclear leukocytes, and normal joint glucose and lactate levels are usually found (44,62). Clinical and epidemiological clues often lead the clinician to appropriate serological studies via antibody titers.

Tuberculosis Arthritis

Tuberculosis arthritis is a rare form of extrapulmonary tuberculosis that occurs in less than 1% of tuberculosis patients. However, with the advent of acquired immunodeficiency syndrome (AIDS) an increased incidence of articular involvement can be expected in these immunocompromised patients. Articular involvement is the result of either dissemination of infection from the original pulmonary primary focus or reactivation of a previously seeded by quiescent skeletal focus.

At present, patients suffering from tuberculosis arthritis who are not infected with HIV are 30 to 60 years of age, whereas we formerly saw it in children and adolescents. Both *M. tuberculosis* and atypical mycobacteria (*M. intracellulare* and *M. kansasii*) have been responsible for joint infection (28,63,64). Predisposing factors in the development of articular involvement include joint trauma, systemic illness (e.g., systemic lupus erythematosus, HIV, diabetes mellitus), narcotic addiction, and intra-articular injection of corticosteroids. Usually, the infection is monoarticular (spine, hips, knees, ankles) and is characterized by insidious onset, weight loss, and low-grade fever. Although

Table 12 Clinical and Epidemiological Features of Viral Arthritis

Viral agent	Occurrence/symptoms	Affected joints	Physical findings
Rubella	Adult females	Small joints of hands and feet, knees, wrists, and ankles	Joint pains near onset rash
Mumps	Adult males	Symmetrical polyarthritis of large and small joints	Joint pains within 1 week of parotids
Parvovirus B19	60% Adults, 10% children with erythema infectiosum	Metocarpophalangeal, proximal interphalangeal polyarthritis	Rash of EI
Hepatitis B	Preicteric phase	Symmetrical hands, knees, ankles	Urticaria
Arthropodiborne alpha virus Chikungunga ("that which bends up")	East Africa/India; abrupt onset of fever and chills	Large joints	Maculopapular rash over trunk and extensor surface extremities
Onyong-nyong (weakening of the joints)	East Africa (Uganda)	Symmetrical involvement of large joints	

examination of synovial fluid can detect acid-fast organisms in about 20% of culture-positive joint effusions, an open synovial biopsy definitely establishes the diagnosis. Resting of the inflamed joint during the acute stage followed by 18 to 24 months of antituberculosis therapy is the principal therapeutic measure. Débridement, synovectomy, or even joint fusion may be required if there has been extensive destructive change.

C. Fungal Arthritis

Fungal arthritis is rare and generally follows a chronic indolent course. Fungal arthritis can be divided into two groups: the mycostic agents that produce primary invasive systemic infections, such as *Histoplasma*, *Coccidioides*, and *Blastomyces* spp., and those that produce opportunistic infections, such as *Candida*, *Cryptococcus*, and *Sporothrix* spp. (65–68). Fungal arthritis is monoarticular; the knee is the most commonly affected joint, followed by the wrists and elbows. The patients have swollen joints, limited motion, chronic pain, and migratory arthritis. The definitive diagnosis is made by synovial biopsy and culture. The treatment of choice is still intravenous amphotericin B. Data are still lacking on the newer oral antifungals, fluconazole and itraconazole.

D. Syphilitic Arthritis

Arthritis can occur in congenital, secondary (rare), or tertiary syphilis. Children and teenagers with congenital syphilis may have only a painless synovitis with effusion in the knees and elbows. Neuropathic joint disease, most commonly involving the knees, and gummatous osteoarthritis of the large joints occur in tertiary syphilis. The treatment of choice is penicillin given in a dosage appropriate for the particular stage of syphilis.

E. Mycoplasma Arthritis

Septic arthritis has resulted from infection with *Mycoplasma hominis*, *Mycoplasma pneumoniae*, and *Ureaplasma urealyticum*. In some patients who have hypogammaglobulinemia polyarthritis resembling rheumatoid arthritis develops; in others acute septic arthritis develops (69). Mycoplasmas and ureaplasmas have been cultured from their joint fluids (70–72). The condition is responsive to antibiotic treatment with tetracycline or erythromycin.

F. Reactive Arthritis

An inflammatory joint response to extra-articular rather than intra-articular presence of microorganisms may be defined as *reactive arthritis* (73). Therefore,

although infection can be demonstrated at a distant site, joint inflammation occurs without traditional evidence of sepsis at the affected joint(s). Most cases are associated with the major histocompatibility complex antigen HLA-B27. Also, patients usually have recent microbial infections in distal sites that include the gastrointestinal (e.g., *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp.), genitourinary (e.g., chlamydia and mycoplasmas), and respiratory (e.g., *Streptococcus pyogenes*) tracts (24). Patients have a sterile, inflamed joint and may also demonstrate enthesopathy, uveitis, conjunctivitis, or skin and mucous membrane lesions (28). Specifically, poststreptococcal reactive arthritis can follow group A streptococcal infection; it causes nonmigratory arthritis, lack of response to aspirin or nonsteroidal anti-inflammatory agents, and presence of extra-articular manifestations, including vasculitis and glomerulonephritis (74).

Studies in 1999 utilizing immunofluorescence, immunohistochemical, and polymerase chain reaction (PCR) techniques detected persistent microbial antigens within joints affected with reactive arthritis (73). These results may be explained by one hypothesis that describes the presence of bacteria and/or their antigens as a reflection of the persistence of small numbers of latent, nonculturable microbes in the joint space. This hypothesis may be valid in specific cases (e.g., chlamydia-triggered reactive arthritis) since the early administration of tetracycline therapy may reduce the length of disease and the associated articular damage (75). However, antibiotics are usually ineffective, especially when given at later stages of reactive arthritis. Therefore, another hypothesis is that the detection of microbial products may reflect only the natural filtering action of the synovium and the subsequent concentration of these products, thereby stimulating inflammation.

G. Prosthetic Joint Infections

The increased use of implanted prosthetic joints has provided a physiological niche for pathogenic organisms to cause septic arthritis. In fact, prosthetic joint implantation or replacement is the single most common cause of joint infections. The prevalence of infection after total knee or hip arthroplasty is estimated to be approximately 1%–2%; the incidence rate can climb to 4.4% in patients who have rheumatoid arthritis (76).

Prosthetic joint infections are manifested differently according to the length of time since placement of the device (77,78). Infections occurring within the first 3 months after surgery usually result from intraoperative wound contamination by coagulase-negative staphylococci. Typical signs of early joint infection are pain, erythema, wound drainage, hematoma formation, and superficial necrosis of the incision. Fever is an unreliable indicator of the presence of infection.

Late infections may occur from 3 months to many years after surgery. Such infections usually result from hematogenous seeding of the device followed by

bacterial production of a biofilm, which protects organisms from host immunity and antibiotics. Most patients have a prolonged indolent course of joint pain. Fever and leukocytosis are usually absent. The most common bacteria in late infection are *S. aureus*.

H. Septic Bursitis

Patients with septic bursitis report fever and an acute painful swelling that may in some cases be mistaken for septic arthritis. Skin trauma commonly precedes septic bursitis. The olecranon and the prepatellar bursae are the most common sites of septic bursitis. A skin wound can often be identified as the portal of entry, and most of these infections are due to *S. aureus*. The bursal fluid is usually purulent, the Gram stain smear result is often positive, and the synovial fluid culture result indicates a definite diagnosis. Antibiotics and drainage should be initiated immediately.

I. Lyme Disease

Lyme disease may produce a chronic monoarthritis, especially of the knee (79). Earlier cardinal symptoms include the typical erythema migrans skin lesion and transient polyarthralgias with virus-like features, including fever, headaches, and a variety of neurological signs. 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 test results are confirmatory but many false-positive results may occur if the test is ordered for patients who do not manifest the typical clinical features of Lyme disease.

The diagnosis of Lyme arthritis in patients who live in endemic areas is based on a history of exposure to ticks and a history of erythema chronicum migrans. Culture of *Borrelia burgdorferi* from specimens in Varbour-Stoemer-Kelly medium permits a definitive diagnosis; an antibody response to *B. burgdorferi* by enzyme-linked immunosorbent assay (ELISA) is also available (80,81). Parenteral antibiotics are generally effective, but antibiotic failures do occur in chronic Lyme arthritis regardless of mode or duration of therapy.

J. Polyarticular Septic Arthritis

Acute bacterial arthritis is most often monoarticular. However, polyarticular infection occurs in 5% to 8% of pediatric cases and in 17% to 19% of nongonococcal adult cases. *N. gonorrhoeae, B. fragilis, H. influenzae, S. pneumoniae, Streptococcus* spp., and *S. aureus* are species with a predilection for polyarticular involvement; *S. aureus* accounts for half of all cases (57,82).

Prior disease in multiple joints predisposes to the development of polyarticular sepsis (e.g., 18%–35% of rheumatoid arthritis patients with joint infection have polyarticular involvement) (57). Polyarticular sepsis may not present florid systemic or local features (28,83), and poorer prognosis is related to older age (75 years), rheumatoid arthritis, or staphylococcal infection. The overall mortality rate (30%) has not changed over several decades.

K. Human Immunodeficiency Virus

Although patients infected with HIV demonstrate a higher prevalence of musculoskeletal infections than the general population (approximately 60 cases per 100,000 versus 2–10 cases per 100,000 yearly incidence rates, respectively), it is unclear whether this higher occurrence is due to the viral disease or to the increased incidence of intravenous drug abuse and multiple transfusions in this patient population (6,55,84). Intravenous drug users are at risk for septic arthritis and HIV infection (85). HIV-positive patients who were also intravenous drug users had involved sites other than the hips, knee, and sacroiliac and sternocostal joints and organisms isolated other than *S. aureus*, *C. albicans*, and *M. tuberculosis* (86–89). Most HIV-positive patients do not have profound immunodeficiency at the time of septic arthritis (86). *Salmonella* spp. septic arthritis has also been reported in patients with HIV infection (89).

L. Septic Arthritis in the Elderly

In 1990, 12% of the population of the United States, or 32 million people, was 65 or older. By the year 2050, 64 million Americans will be 65 and over (3,59). The older patient is more likely to display some of the systemic factors that impair host defense. The most common comorbidities among adults with septic arthritis are diabetes mellitus, cirrhosis, chronic renal failure, rheumatoid arthritis, and neoplastic disease (1). Other major risk factors for infectious complications are associated with the management of these chronic ilinesses, including invasive diagnostic procedures, surgical interventions, and use of immunosuppressive drugs.

The aging process in itself can lead to the decline of immune function and increased susceptibility to infectious diseases (61). The decline in immunity in the elderly causes a generalized reduction in the immune response to foreign antigens. The greater susceptibility to infections is due to the effects of age on the immune system and immune suppression caused by age-related illnesses. Specifically, the deficient immune response to foreign antigens results from the loss of thymic and T-lymphocyte function (mainly related to the production and response to interleukin 2 [IL-2]) and associated decrease in antibody production by B cells (90). Underlying joint disease (e.g., osteoarthritis or rheumatoid

arthritis) is another indicator that despite optimal treatment, the patient will have a poor prognosis (57,83). This poor prognosis is often due to a delayed diagnosis since the clinical symptoms of septic arthritis are often mistaken for symptoms related to the preexisting joint disease.

XI. CONTROVERSIES AND CONCLUSIONS

There are a number of unknowns in the treatment of septic arthritis, which are due to a lack of randomized double-blind comparative studies. They are as follows:

1. Route of administration and duration of treatment have not been established.
2. The preferred method of drainage (needle aspiration, open drainage, or arthroscopy) has not been adequately studied.
3. The advantages of splinting versus continuous passive motion treatment and the optimal time for initiating isometric and range of motion exercises are unknown.

With further study of some of the intricacies of septic arthritis treatment, some conclusions can be drawn:

1. Infectious arthritis attacks all age groups and has a predilection for immunocompromised patients.
2. The age of the patient and underlying medical condition provide important clues to the causative infectious agent.
3. Successful management depends on prompt diagnosis, appropriate antimicrobial therapy, and drainage of the joint space.
4. Initially, the choice of antibiotics is often empirical at the onset of therapy and may be changed when culture and sensitivity data are available.

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