Gonococcal and Nongonococcal Bacterial Infections

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Acute inflammation of one or more joints is a common cause of emergency medical evaluation, being one of the most important reasons for suspecting septic arthritis. Delayed or inadequate treatment can lead to irreversible joint destruction. Most septic arthritis is caused by bacterial infections. The most common cause of acute bacterial arthritis is gonococcal or nongonococcal infection of the joints. The term acute bacterial arthritis usually denotes not only most of the bacterial arthritis's caused by bacterial infection but also those caused by fungal and mycobacterial infection. This chapter is a review of the risk factors, pathogenesis, clinical manifestations, diagnosis, and treatments of nongonococcal and gonococcal arthritis. Other infections associated with arthritis, such as prosthetic joint infections and fungal and mycobacterial arthritis, have unique clinical manifestations and will not be covered in this chapter.

Nongonococcal and gonococcal arthritis are the most dangerous and destructive forms of acute arthritis. They are usually curable, but their associated morbidity and mortality are still significantly high in patients with prosthetic joints, patients with underlying rheumatoid arthritis, elderly patients, and patients with multiple severe comorbidities [1].

Risk Factors

The existing experimental evidence suggests that healthy joints are very resistant to infections, in contrast with diseased and prosthetic joints. Recognizing the influence of systemic, local, and social risk factors is of crucial importance. These factors increase the risk of bacteremia or reduce the body's ability to eliminate infectious organisms from the joint [2, 3].

Systemic disorders that affect the host's response by impairing the immune system include diabetes mellitus, pre-existing rheumatoid arthritis, liver disease, chronic renal failure, malignancies, intravenous drug abuse, hemodialysis, alcoholism, acquired immunodeficiency syndrome, hemophilia, organ transplantation, and hypogammaglobulinemia [4–8].

Local risk factors, such as damage of a specific joint, may be the result of earlier trauma, which in turn may be related to acupuncture procedures, joint surgery, or arthroscopy. The presence of cutaneous ulcers, skin infections [9], a prosthetic knee or hip joint, or previous damage to the joint architecture caused by rheumatoid arthritis, osteoarthritis, or crystal arthropathies (e.g., gout) [10] is an important predisposing factor for septic arthritis. Age is another important factor; newborns and elderly people, especially those older than 80 years, are particularly vulnerable [11–16]. Social risk factors include low socioeconomic status and occupational exposure to animals with brucellosis [17] in patients that inhabit regions where this zoonosis is still a public health issue [18]; furthermore, certain racial groups are significantly at higher risk of acquiring tuberculosis (e.g., people from India) [19].

Tuberculosis reemerged in developed countries in recent decades as a result of mass immigrations from endemic areas elsewhere, increasing the numbers of immunocompromised individuals, which also include those with AIDS. There has also been an increase in infection rates associated with drug abuse, homelessness, therapeutic noncompliance, and the emergence of drug-resistant mycobacteria [20]. Intravenous drug users are high-risk subjects and are more likely to have fungal, polymicrobial, or septic arthritis, which are much less frequent in the general population [21]. In some cases, these risk factors are compounded, meaning, for example, that patients with rheumatoid arthritis treated with immunosuppressive medications or steroids are at higher risk of

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infection. Sometimes it is difficult to distinguish between an infection and inflammatory synovitis, especially when the patient is receiving steroid therapy.

A study in the Netherlands identified risk factors for bacterial arthritis. In almost half of the patients, bacterial infections were present in abnormal joints. More than 25% of the infected joints in patients with available clinical information contained prosthetic or osteosynthetic material. All but one of 22 adult patients with hip infection had a prosthesis. About 20% of the adult had rheumatoid arthritis; those patients accounted for 5 of 16 polyarticular cases. The authors of the study looked for clinical factors that would be amenable to prophylaxis. Infected skin lesions, which were present in 38 of 60 adult patients with an identifiable infection source, were considered the most common cause of hematogenous bacterial arthritis in patients with rheumatoid arthritis (16 of 22 cases). Invasive nonsterile medical interventions in places distant from the affected joints accounted for seven cases, all but one in native joints [22, 23].

An Italian study [24] drew attention to the fact that the reported incidence of septic arthritis varies from 2 to 5 cases per 100,000 persons per year among the general population to 70 cases per 100,000 persons per year among patients with rheumatoid arthritis. Indeed, individuals with rheumatoid arthritis are at particularly high risk of developing septic arthritis. This may be due to several reasons: diseased joints are more prone to bacterial colonization and rheumatoid arthritis (RA), while the prescribed treatments with corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biological therapies can have a negative effect on the immune functions required for protection against pathogens. Steroids and DMARDs seem to affect the synovial leukocyte count, and the leukocyte count in the synovial fluid of RA patients with septic arthritis is indeed lower than in patients with septic arthritis without underlying rheumatic diseases. It can be difficult to diagnose septic arthritis in RA patients because the development of a hot, painful joint is often mistaken for a relapse of the underlying joint disease, leading to a delayed diagnosis.

Common Risk Factors for Septic Arthritis [25]

- Systemic disorders
  - Rheumatoid arthritis
  - Diabetes mellitus
  - Liver diseases
  - Alcoholism
  - Chronic renal failure
  - Malignancies
  - Intravenous drug abusers
  - Hemodialysis patients
  - Acquired immunodeficiency syndrome
  - Hemophilia
  - Organ transplantation
  - Hipogammaglobulinemia
  - Immunosuppressive drugs and glucocorticosteroids
  - Biologic agents
- Local factors
  - Direct joint trauma
  - Recent joint surgery
  - Open reduction of fractures
  - Arthroscopy
  - Acupuncture procedure
  - Rheumatoid arthritis in a specific joint
  - Osteoarthritis
  - Prosthetic joint in knee or hip
- Age: elderly >80 years old or newborns
- Social factors
  - Occupational exposure to animals (brucellosis)
  - Low social income: tuberculosis

Pathogenesis

Septic arthritis is usually the result of direct inoculation or of an occult bacteremia that spread to the joint. The synovium is a highly vascular tissue with no basement membrane beneath the intimal layer, which makes it vulnerable to bacteremia [26]. Microorganisms such as staphylococci and streptococci may gain access to the bloodstream from their initial innocuous location when the integrity of the skin and the natural mucosal barriers is disrupted by injury or disease. Gram-negative septic arthritis is probably caused by bacteremia from the gastrointestinal or urinary tracts. Some bacteria, such as *Neisseria gonorrhoeae*, are particularly likely to infect a joint during a bacteremia episode [27]. In some cases, septic arthritis is the result of penetrating trauma such as bite wounds, foot injuries caused by stepping on nail, or an errant injection in drug users. Penetrating traumas, including those caused by plant thorns and wood slivers [28], are the most common means of infection of the small joints of hands and feet [22].

Arthroscopy and therapeutic joint injections with corticosteroids are sometimes, but rarely, complicated by septic arthritis. Furthermore, bacteria may gain access into the joint during joint surgery. Orthopedic surgeons often encounter patients with joint infections that are the result of trauma or surgical procedures. Examples include the accidental introduction of foreign bodies into a joint, arthroscopic surgery, open reduction of fractures involving joints, and arthroplasties [29]. Most cases of septic arthritis are caused by gram-positive bacteria. Enteric gram-rods

account for 43% of community-acquired bacteremia, but only for 10% of septic arthritis cases [30, 31].

This is likely due to the superior ability of gram-positive bacteria to bind to connective tissue and extracellular matrix proteins. *S. aureus*, the most common causative agent of septic arthritis, produces bacterial surface proteins that mediate adherence to extracellular matrix proteins and are known as "microbial surface components recognizing adhesive matrix molecules." Staphylococcal strains that are deficient in microbial surface components recognizing adhesive matrix molecules have been found to be less arthritogenic in animal models [32].

In septic arthritis patients, joint damage can be caused by bacterial invasion, host inflammation, and tissue ischemia. Bacterial enzymes and toxins cause direct damage to cartilaginous tissue. Cartilage may suffer "collateral" damage when host neutrophils release active oxygen species and lysosomal proteases. Cytokines activate host matrix metalloproteinases, resulting in the autodigestion of cartilaginous tissue. Ischemic injury also plays a role in this process. Cartilage is avascular and thus highly dependent on the diffusion of oxygen and nutrients from the synovium. When purulent exudates accumulate around a joint, pressure increases and synovial blood flow is compromised, resulting in cartilage anoxia [33]. Under these conditions, cartilage synthesis is inhibited, the degradation of cartilaginous tissue accelerates, and irreversible bone loss occurs [27], as shown by a case of septic arthritis of hip joint where a delayed presentation of more than 3 weeks predicted higher joint damage and led to the need for excision arthroplasty [34].

Clinical Features

Bacterial arthritis generally involves acute onset of localized pain, tenderness, swelling, and decreased range of joint motion. Gonococcal and nongonococcal arthritis produce characteristic signs and symptoms that can be easily used to make a diagnosis. Acute infectious arthritis is usually monoarticular but can easily overlap with other causes of polyarthralgia, mainly because monoarthritis is frequently the form in which polyarticular diseases present themselves. In patients with monoarthritis, a differential diagnosis should consider two other conditions: trauma and crystal-induced arthropathies [35]. In 80–90% of cases, only one joint is affected [36].

Nongonococcal arthritis usually appears in patients with a short history of high fever and leucocytosis. Most importantly, it manifests as a single, hot, swollen, and intensely painful joint, mainly one of the large ones, with more than 50% of cases involving a knee [37]. Approximately 20% of nongonococcal arthritis cases are polyarticular, affecting 2–3 large joints, although this is observed mainly in patients with chronic degenerative diseases such as rheumatoid arthritis and osteoarthritis [26, 35].

It is not easy to make a clinical and laboratory diagnosis of nongonococcal bacterial arthritis. Clinical manifestations such as high-grade fever are only present in 58% of the cases [4], even though low-grade fever may be present in approximately 90% of the patients; regarding leucocytosis, it is only found in 50% of the patients [38]. In patients with rheumatoid arthritis or in patients under treatment with corticosteroids or immunosuppressive drugs, joint pain may be masked, which can delay diagnosis.

Gonococcal infection is the most common cause of monoarthritis in sexually active young adults. The female to male ratio is 3:1, which might be explained by the fact that women are more frequently affected by asymptomatic, and thus untreated, genito-urinary tract infections [39–41]. Disseminated gonococcal infection affects 0.5–3% of patients with mucosal infection; these patients usually present severe polyarthritis that may resolve spontaneously [42]. This type of infection is associated with a characteristic triad of clinical components that includes migratory polyarthralgia; dermatological lesions, usually in the form of macules, papules, and tenosynovitis, the latter of which often affects multiple joints simultaneously (particularly wrists, fingers, ankles, and toes); and systemic inflammatory symptoms [43, 44].

This type of infectious arthritis usually presents in two forms, one as the classic triad defined above, also called arthritis dermatitis syndrome, and the other as a localized septic arthritis, an asymmetric polyarticular or monoarticular disease that appears in less than 50% of patients, usually affecting the knees, ankles, and wrists. Tenosynovitis usually affects wrists, ankles, and other small joints and is usually very painful; its most common dermatological features are non-painful macules or papules in arms or legs, although no specific location has been described [43].

Recent exposure to sexual activity should raise suspicion of the presence of this type of arthritis. Even though a positive gram stain of synovial fluid is found in less than 50% of the patients with this condition, cervical, urethral, and rectal cultures should be simultaneously obtained to increase the likelihood of a positive diagnosis, mainly by looking for the presence of *N. gonorrhoeae* [43]. Table 3.1 shows a summary of the clinical characteristics of gonococcal and nongonococcal arthritis.

Diagnosis

The methods to diagnose bacterial arthritis have not changed substantially in the last decades, and reaching a diagnosis continues to be challenging. The diagnosis is still mainly based on culturing and isolating the pathogen, and great

Table 3.1 Clinical characteristics of gonococcal and nongonococcal arthritis

Characteristics	Gonococcal	Nongonococcal
Patient profile	Young sexually active adults, mainly women	Newborns or chronic diseased adults (diabetes, RA, OA)
Presentation	Migratory polyarthritis Dermatitis, tenosynovitis	Single joint affectation
Joint affection	Polyarticular approx. 50%	Oligoarticular approx. 90%
Positive culture	Less than 50%	Nearly 90%
Prognosis	Good with adequate antibiotic therapy	Usually bad prognosis, requiring joint drainage in most cases

Modified from: Goldenberg [27]

Table 3.2 Clinical and laboratory data suggestive of infectious arthritis

Key clinical data	Joint fluid characteristics
Recent onset of fever, general malaise	More than 50,000 cells/mL
Arthralgia and synovitis (mono/polyarticular)	More than 90% polymorphonuclear cells
Risk factors for infectious arthritis	Positive gram stain and culture Low glucose and high lactate

Modified from Shirtliff and Mader [36]

emphasis is put on differentiating between the two major types of infectious arthritis, which is the subject of this review. It is generally agreed that gonococcal arthritis is one of the main causes of septic arthritis and that differentiating it from nongonococcal arthritis is of great importance due to the associated prognostic and outcome factors.

In most medical conditions, achieving an accurate diagnosis depends on a combination of clinical data, laboratory information, and radiological images. In the case of infectious arthritis, the diagnosis depends 100% on clinical and laboratory data as shown in Table 3.2.

A definite diagnosis of bacterial arthritis can be established only by visualizing the causative bacteria on a gram-stained smear or by culturing bacteria obtained from the synovial fluid by arthrocentesis. Gram stain and culture of synovial fluid should be obtained as a matter of routing in every case of undiagnosed arthritis, ideally before initiating treatment with antimicrobials. Gram staining of synovial fluid, however, is insensitive for the diagnosis of septic arthritis. Gram stains are positive in 71% of gram-positive cases of septic arthritis [4], in 40–50% of cases of gram-negative septic arthritis [45], and in less than 25% of cases of gonococcal septic arthritis [27]. Synovial fluid cultures are positive in 70–90% of cases of nongonococcal bacterial arthritis [27, 46]. Blood cultures are positive in 40–50% of cases of bacterial arthritis and are the only method of identifying the pathogen in about 10% of cases. Occasionally, an infection in an extra-articular site provides a clue to the etiologic agent infecting the joint. For example, bacterial arthritis is sometimes associated with pneumococcal pneumonia or with a urinary tract infection by *E. coli.*

In gonococcal infections, *N. gonorrhoeae* can be diagnosed by culture or nucleic acid amplification tests (NAATs), and sometimes by gram stain. Cultures of skin lesions are almost always negative, while less than 50% of synovial fluid cultures, and less than one third of blood cultures, are positive. This may be due to the difficulty of culturing these microorganisms. Tenosynovitis and dermatitis, which are associated with disseminated gonococcal infection, may not yield viable organisms; however, they can be easily recovered from the genitourinary tract. Synovial, skin, urethral, cervical, or rectal cultures on Thayer-Martin medium should be made in all cases of patients with clinical features of gonococcal arthritis. Around 50% of patients with gonococcal arthritis have positive cultures from one of the mucosal sites mentioned above [47]. If an associated urethritis is present, a gram stain of the urethral exudate should be collected and examined for the presence of gram-negative diplococci, which are characteristic of *N. gonorrhoeae* infection. Cultures and gram stains of specimens obtained from skin lesions or tendon sheaths are often negative. Due to their superior sensitivity and high specificity, nucleic acid amplification tests (NAATs) have in recent years rapidly replaced cultures as diagnostic tests. In a study of an Australian population with gonococcal arthritis, the most commonly used method to confirm infection was NAAT for *N. gonorrhoeae* in a joint aspirate, followed by urinary NAAT [48]. Ideally, NAATs would be combined with the targeted deferred culture of positive samples for monitoring antimicrobial resistance [49].

The organisms causing nongonococcal septic arthritis in adults are 75–80% gram-positive cocci and 15–20% gram-negative bacilli [4]. The most common organism in native and prosthetic joint infections is *S. aureus*. The next most common group of gram-positive aerobes found in prosthetic joint infections is *Streptococci*, which includes *S. pneumoniae.* The most frequently found groups, after *Streptococcus pyogenes*, are groups B, G, C, and F. Non-group A streptococcal disease is usually present in patients with immunosuppression, diabetes mellitus, malignancy, or severe genitourinary or gastrointestinal infections [50]. Group B streptococcal arthritis is only rarely present in adults; however, it should be considered a serious infection in patients with diabetes and in those with prosthetic hip infections [51]. Infections with gram-negative bacilli are usually found in patients with a history of intravenous drug abuse, in immunocompromised patients, and in very old patients [52]. The most common gram-negative organisms found in these patients are *E. coli* and *P. aeruginosa*.

Infections caused by anaerobes are detected in 5–7% of septic arthritis cases [21, 46]. Common anaerobes found in these patients include *Bacteroides, Propionibacterium acnes*, and various anaerobic gram-positive cocci. If foul-smelling synovial fluid or air is found in the joint space, anaerobic infection should be suspected, and appropriate cultures should be obtained and kept for at least 2 weeks. This type of infection is most frequent in immunocompromised patients, and in patients with wound infections or joint arthroplasty.

Polyarticular septic arthritis is much less common than the monoarticular variant [36]. Many patients with polyarticular septic arthritis have one or more comorbidities, and some have been intravenous drug abusers. The prevalence of this type of arthritis in patients with rheumatoid arthritis is high, with an average of 25% (ranging from 18% to 35%) [53]. Although *S. aureus* is the most frequently found pathogen in polyarticular infections, *G. streptococci, H. influenzae, S. pneumoniae*, and mixed aerobic and anaerobic bacteria have also been responsible for polyarticular infections.

Taking plain radiographs of infected joints is normal procedure at presentation, and they should be obtained in all such cases, given the possibility, although rare, of associated osteomyelitis or concurrent joint disease. Furthermore, a baseline radiograph is often useful for comparison purposes in cases where the patient's response to therapy is delayed or poor. Radiographs often show nonspecific alterations caused by inflammatory arthritis, including periarticular osteopenia, joint effusion, soft tissue swelling, and joint space loss. Scintigraphy, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can detect effusions and inflammation in joints that are difficult to examine otherwise, especially in hip and sacroiliac joints, and the images thus obtained can be used to determine the extent of the infection [54, 55]. MRI is highly sensitive for early detection of joint fluid and is superior to CT delineation of soft tissue structures. MRI images can show early bone erosion, reveal the presence of soft tissue extension, and help in the arthrocentesis of shoulder, hips, acromioclavicular, sternoclavicular, and sacroiliac joints [56].

Treatment

Treatment of bacterial arthritis must begin immediately after the clinical evaluation has been done and appropriate cultures have been taken. Hospitalization and consultation with an infectious disease specialist are recommended for initial therapy. In patients with infectious arthritis, a good prognosis depends on the intensity of the initial treatment and choosing the correct antibiotics. The most commonly used therapy for this kind of patients consists of parenteral antibiotics during the acute phase of the disease and adequate joint drainage. The initial antibiotic therapy should always be broad spectrum until a particular pathogen is isolated and a specific antibiotic can thus be selected.

The use of antibiotics will depend on the local epidemiology, the clinician experience, and local hospital conditions such as the availability of medicines, especially in developing countries. A suitable antibiotic treatment must account for the geographic variations of organisms and their resistance patterns. Gram stain results and the assessment of the risk factors associated with the disease should guide the therapeutic regimen. Most antibiotics show good penetration into diseased joints. The use of parenteral antibiotics should last approximately 15–21 days, and PO antibiotics should be used afterward for a complete 4-week regime.

The most common therapeutic regimens use third generation cephalosporins with good outcomes, especially when the presence of *S. aureus* or *Streptococci* is highly suspected [57]. B-lactam, aminoglycosides, or quinolones are usually a good choice for gram-negative rods, but recently *N. gonorrhoeae* has shown an increasing resistance against quinolones, and this has led the CDC to discard their use as a viable therapy [58, 59].

Cefixime could be used as oral treatment after a course of intravenous cephalosporins, except against *Chlamydia*, which is resistant to cefixime [47]. Osteomyelitis is a feared outcome in all cases, especially when the infected joint is a cartilaginous one (sternoclavicular or sacroiliac); in those cases, treatment can last up to 6 weeks [60]. Table 3.3 summarizes the empiric antibiotic therapies that have been proposed.

Joint drainage has shown good results when combined with antibiotics, mainly because it improves the circulatory properties of the affected joint, decompresses it, and removes the offending microorganisms and their associated cascade of reactions. Whether arthrocentesis should be preferred over open surgery is still controversial. The known data suggest that arthrocentesis is more effective than open drainage, but the selection of surveyed patients was biased, and ill patients are certainly not good candidates for surgical procedures [37, 61]. There is no consensus about the effect of mobilization in patients suffering bacterial arthritis, but it has been suggested by several authors that early rehabilitation and mobilization yields better outcomes than immobilization,

Table 3.3 Proposals for empiric antibiotic use in bacterial arthritis

Gram stain of synovial fluid	Antibiotic therapy
Gram-positive cocci	Cefazolin 2 g IV q 8 h Cefotaxime 1 g IV q 8 h
Gram-negative cocci	Ceftriaxone 1 g IV q 24 h
Gram-negative rods	Cefepime 2 g IV q 8 h Piperacillin-tazobactam 4.5 g IV q 6 h
MRSA suspicion or risk factors	Vancomycin 1 g IV q 12 h

Modified from Ross [60]

especially with regard to preventing muscle atrophy and joint contractures [62].

Prognosis

Diagnosing and treating an infected joint as soon as possible is the key to a good prognosis. Septic arthritis is a life-threatening emergency with a high mortality (up to 11%). Almost half of the patients with infectious arthritis suffer permanent joint damage. The outcome is closely related to multiple factors, mainly comorbid conditions (e.g., immunocompromised conditions, osteoarthritis, and rheumatoid arthritis, as well as previous joint damage), but also pathogen virulence factors. All clinicians should be aware that an infectious process in a joint can be a potential cause of acute arthritis and should implement proper screening procedures to diagnose and treat it promptly.

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