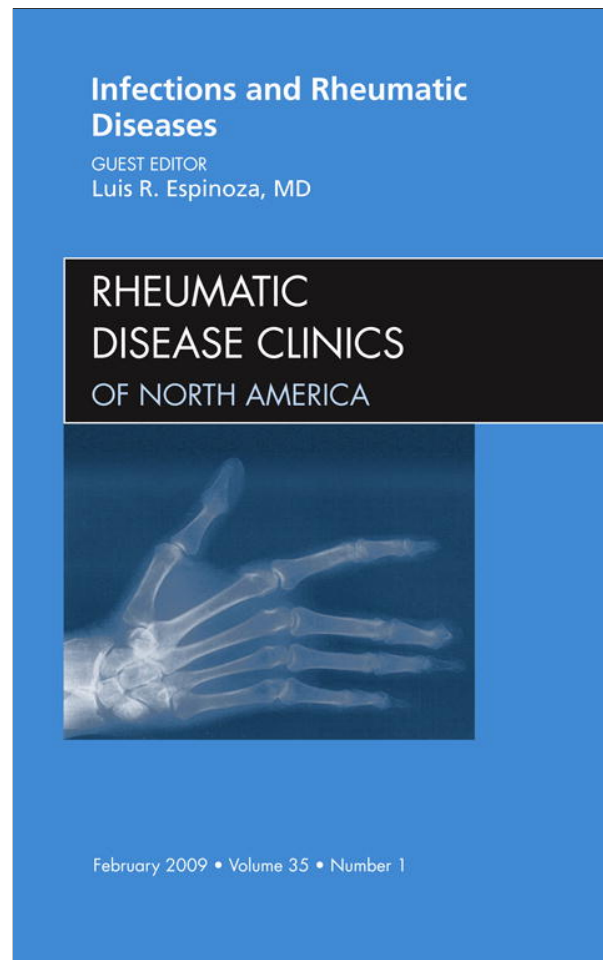


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Gonococcal and Nongonococcal Arthritis

Ignacio García-De La Torre, MD^{a,b,*}, Arnulfo Nava-Zavala, MD, MSc^{a,c}

KEYWORDS

- Gonococcal arthritis • Nongonococcal arthritis
- Bacterial arthritis • Septic arthritis • Infectious arthritis
- Acute arthritis

Acute bacterial arthritis usually is caused by gonococcal or nongonococcal infection of the joints. This term usually refers to most bacterial arthritis caused by bacterial infection, including fungal and mycobacterial infection, and is also known as septic arthritis. This article reviews the risk factors, pathogenesis, clinical manifestations, diagnosis, and treatment of nongonococcal and gonococcal arthritis only. Prosthetic joint infections, fungal, and mycobacterial arthritis are not discussed here because of their unique clinical manifestations.

Nongonococcal and gonococcal arthritis are the most potentially dangerous and destructive forms of acute arthritis. These bacterial infections of the joints are usually curable with treatment, but morbidity and mortality are still significant in patients who have underlying rheumatoid arthritis, patients who have prosthetic joints, elderly patients, and patients who have severe and multiple comorbidities.¹

RISK FACTORS

Experimental evidence suggests that normal joints are resistant to infections compared with diseased joints or prosthetic joints. Recognition of risk factors—systemic, local, and social—is important. Such factors act by increasing the risk for bacteremia or reducing the body's capacity to eliminate organisms from the joint.^{2,3}

Systemic disorders that affect the host's response through an impaired immune system include diabetes mellitus, preexisting rheumatoid arthritis, liver disease, chronic renal failure, malignancies, intravenous drug abuse, hemodialysis, alcoholism, AIDS, hemophilia, organ transplantation, and hypogammaglobulinemia.^{4–8}

^a Department of Immunology and Rheumatology, Hospital General de Occidente, Secretaría de Salud, Justo Sierra 2821, Guadalajara, México, CP 44690

^b Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jalisco, México

^c Unidad de Investigación en Epidemiología Clínica, UMAE, HE, CMO, IMSS, Jalisco, México

* Corresponding author. Department of Immunology and Rheumatology, Hospital General de Occidente, Secretaría de Salud, Justo Sierra 2821, Guadalajara, JAL, México, CP 44690.

E-mail address: igdlt@aol.com (I. García-De La Torre).

Local factors, such as damage of a specific joint, may be the result of earlier trauma, including acupuncture procedures or recent joint surgery or arthroscopy; also, the presence of arthritis, including osteoarthritis, or a prosthetic joint in the knee or the hip are important predisposing factors for septic arthritis. Age is also important, with newborns and elderly people, especially those older than 80 years of age, being particularly vulnerable.^{9–14} Social factors include occupational exposure to animals with respect to brucellosis,¹⁵ or patients who are inhabitants of regions where this zoonosis remains a public health issue.¹⁶ The risk for tuberculosis is greatly increased in certain racial groups (eg, people from India).¹⁷

Over the past 25 years, however, we have seen a resurgence of tuberculosis in developed countries as a result of mass immigrations from endemic areas of the world; increasing numbers of immunocompromised individuals, including those who have AIDS; increased infection rates in association with drug abuse, homelessness, and therapeutic noncompliance; and the emergence of drug-resistant mycobacteria.¹⁸ In some cases, these risk factors are compounded (eg, patients who have rheumatoid arthritis treated with immunosuppression or steroids are at higher risk for infections). It may also be difficult to distinguish infection from inflammatory synovitis, especially if the patient is receiving steroid therapy.

In a study from The Netherlands, risk factors for bacterial arthritis were identified. In nearly half of the Dutch patients, infections occurred in abnormal joints. More than one quarter of the infected joints in the Dutch study with available clinical information contained prosthetic or osteosynthetic material. All but one of 22 hip infections in Dutch adults involved a prosthesis. About 20% of the Dutch adults had rheumatoid arthritis and accounted for 5 of 16 polyarticular cases. The authors sought clinical factors that might be amenable to future prophylaxis; infected skin lesions, accounting for 38 of 60 adult cases with an identifiable infection source, were considered the most common reason for hematogenous bacterial arthritis in patients who had rheumatoid arthritis (16 of 22 cases). Invasive nonsterile medical interventions distant from the affected joints accounted for 7 cases, all but one in a native joint.^{19,20}

A recent study from Italy²¹ points out that the reported incidence of septic arthritis varies from 2 to 5 cases/100,000 person-years in the general population to 70 cases/100,000 person-years among patients who have rheumatoid arthritis. In fact, individuals who have rheumatoid arthritis are at particular risk for developing septic arthritis. This risk may be due to several reasons: joint disease predisposes to bacterial joint colonization and rheumatoid arthritis itself and its treatment with corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic therapies may decrease the immune function required for protection from pathogens. Steroids and DMARDs seem to affect the leukocyte synovial count; indeed, patients who have rheumatoid arthritis with septic arthritis have a leukocyte count in synovial fluid lower than patients who have septic arthritis without underlying rheumatic diseases. The diagnosis of septic arthritis in patients who have rheumatoid arthritis can be difficult because the development of a hot painful joint is often confused with a relapse of the underlying joint disease leading to delay in diagnosis. **Box 1** lists the most common risk factors that predispose to septic arthritis.

PATHOGENESIS

Septic arthritis is most often a consequence of occult bacteremia that spreads to the joint. Synovium is highly vascular, and contains no limiting basement membrane, making it vulnerable to bacteremic seeding.²² Several microorganisms, such as staphylococci and streptococci, may gain initial access to the bloodstream from their initial

Box 1**Common risk factors in septic arthritis**

Systemic disorders

- Rheumatoid arthritis
- Diabetes mellitus
- Liver diseases
- Alcoholism
- Chronic renal failure
- Malignancies
- Intravenous drug use
- Hemodialysis
- AIDS
- Hemophilia
- Organ transplantation
- Hypogammaglobulinemia
- 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

Data from García-De La Torre I. Advances in the management of septic arthritis. *Rheum Dis Clin North Am* 2003;29(1):61–75.

innocuous location if the integrity of skin and mucosa natural barriers becomes disrupted. Gram-negative septic arthritis probably arises from bacteremia from the gastrointestinal or urinary tracts. Certain bacteria, such as *Neisseria gonorrhoeae*, are particularly likely to infect a joint during a bacteremic episode.²³ Occasionally septic arthritis results from penetrating trauma, such as bite wounds, stepping on nails, or illegal injection drug use. This trauma is the most common means of infection of the small joints of the hands and feet,¹⁹ including also those related to plant thorns and wood splinters injuries.²⁴

Rarely, arthroscopy or therapeutic joint injections with corticosteroids may be complicated by septic arthritis. Also, bacteria may be introduced during joint surgery. Orthopedic surgeons may encounter patients who have joint infections as a result of trauma or surgical procedures. Some examples include penetrating injury or foreign body accidentally introduced into a joint, arthroscopic surgery, open reduction of fractures that involve the joint, and arthroplasties, including total joint replacement.²⁵ Gram-positive organisms are responsible for most cases of septic arthritis. Enteric Gram-negative rods account for 43% of community-acquired bacteremias, but cause only 10% of septic arthritis.^{26,27}

This finding likely relates to the superior ability of Gram-positive organisms to bind connective tissue and extracellular matrix proteins. *Staphylococcus aureus*, the most common cause of septic arthritis, produces several surface adhesions that bind extracellular matrix proteins, known as “microbial surface components recognizing adhesive matrix molecules.” Staphylococcal strains defective in microbial surface components recognizing adhesive matrix molecules are less arthritogenic in animal models.²⁸

Joint damage in septic arthritis results from bacterial invasion, host inflammation, and tissue ischemia. Bacterial enzymes and toxins are directly injurious to cartilage. Cartilage may suffer “innocent bystander” damage, as host neutrophils release active oxygen species and lysosomal proteases. Cytokines activate host matrix metalloproteinases, leading to autodigestion of cartilage. Ischemic injury also plays a role. Cartilage is avascular and highly dependent on diffusion of oxygen and nutrients from the synovium. As purulent exudates accumulate, joint pressure increases and synovial blood flow is tamponaded, resulting in cartilage anoxia.²⁹ Under these conditions, cartilage degradation accelerates and inhibition of cartilage synthesis and irreversible bone loss occur,²³ as evidenced in the specific case of hip joint septic arthritis in which delayed presentation beyond 3 weeks predicts higher joint damage, leading to a need for excision arthroplasty.³⁰

CLINICAL FEATURES

Bacterial arthritis generally presents with characteristic signs and symptoms that can easily lead to a diagnosis of either gonococcal or nongonococcal arthritis. Acute infectious arthritis is most commonly monoarticular but it can overlap with other causes of polyarthritis and could also be the presentation form of any polyarticular disease. The differential diagnosis in patients who have monoarthritis should be made with two other main conditions, trauma and crystal-induced arthropathies.³¹

In a typical case nongonococcal arthritis presents in a patient who has a short history of high fever, leukocytosis, and with involvement of a single hot, swollen, and exquisitely painful joint, especially large joints, more than 50% affecting the knee.³² Approximately 20% of nongonococcal arthritis is polyarticular and affects two to three large joints, although this is a characteristic presentation mainly in patients who have chronic degenerative diseases, such as rheumatoid arthritis and osteoarthritis.^{22,31}

The clinical and laboratory diagnosis of a nongonococcal bacterial arthritis is often difficult, however. Some clinical manifestations, such as high-grade fever, are only present in 58% of the cases,⁴ but low-grade fever may be present in approximately 90% of the patients; leukocytosis is found in only 50% of patients.³³ In patients who have rheumatoid arthritis or in those taking corticosteroids or immunosuppressive drugs the joint pain may be masked, a situation that may delay the diagnosis.

Gonococcal infection is by far the most common cause of monoarthritis in young sexually active adults, with a female/male ratio of 3:1. This difference might be

because women usually have a more asymptomatic clinical picture and present more often with untreated genitourinary tract infections.^{34–36} There is a characteristic triad of clinical components: migratory polyarthralgia, dermatologic lesions usually presenting as macules and papules, and tenosynovitis often affecting multiple joints simultaneously (particularly wrists, fingers, ankles, and toes), as well as systemic inflammatory symptoms.^{37,38}

There are usually two forms of presentation of this form of infectious arthritis, one being the classic triad defined above and the other an asymmetric polyarticular or monoarticular disease, present in less than 50% of patients, with knees, ankles, and wrists being the most commonly affected joints. Tenosynovitis usually affects wrists, ankles, and other small joints and usually is painful. The dermatologic features usually exhibit nonpainful macules or papules in arms or legs, although there is no specific localization described.³⁷

A recent exposure to sexual encounters should raise suspicion of this type of arthritis and even though a positive Gram stain of synovial fluid is present in less than 50% of these patients, simultaneous cultures of cervix, urethra, and rectus should be obtained to augment the positive result, especially searching for the presence of *N gonorrhoea*.³⁷ A summary of the distinguishing clinical characteristics between gonococcal and nongonococcal arthritis is shown in **Table 1**.

DIAGNOSIS

The diagnosis of bacterial arthritis has not changed substantially in the last decade. The mainstay of diagnosis continues to be culture and isolation of the pathogen itself, but it is of great importance to differentiate between the two major types of infectious arthritis. It is well recognized that gonococcal arthritis is an important cause of septic arthritis and its differentiation from nongonococcal arthritis is exceedingly important because of prognostic and disability factors.

To achieve an accurate diagnosis, a combination of clinical and laboratory data and radiologic imaging studies plays an important role. In this case clinical and laboratory data represent almost 100% of final diagnoses (**Box 2**).

A definite diagnosis of bacterial arthritis can be established only by visualizing bacteria on a Gram-stained smear or by culturing bacteria from the synovial fluid. Gram stain and culture of synovial fluid should be routinely obtained in any case of

Characteristics	Gonococcal	Nongonococcal
Patient profile	Sexually active young adults, mainly women	Newborns or adults with chronic disease (diabetes, RA, OA)
Presentation	Migratory polyarthritits dermatitis, tenosynovitis	Single joint involvement
Pattern of joint involvement	Polyarticular ~50%	Oligoarticular ~90%
Culture positivity	Less than 50%	Nearly 90%
Prognosis	Good with adequate antibiotic therapy	Usually bad prognosis, requiring joint drainage in most cases

Abbreviations: OA, osteoarthritis; RA, rheumatoid arthritis.

Data from Goldberg DL. Septic arthritis. *Lancet* 1998;351:197–202.

Box 2**Clinical and laboratory data suggestive of infectious arthritis***Key clinical data*

Recent onset of fever, general malaise

Arthralgia and synovitis (mono/polyarticular)

Risk factors for infectious arthritis

Joint fluid characteristics

More than 50,000 cells/mL

More than 90% polymorphonuclear cells

Positive Gram stain and culture

Low glucose and high lactate

Data from Shirliff ME, Mader JT. Acute septic arthritis. Clin Microbiol Rev 2002;15:527–44.

undiagnosed arthritis. Gram staining of synovial fluid, however, lacks sensitivity for the diagnosis of septic arthritis. Gram stains are positive in 71% of Gram-positive septic arthritis,⁴ 40% to 50% of cases of Gram-negative septic arthritis,³⁹ and less than 25% of cases of gonococcal septic arthritis.²³ Usually, synovial fluid cultures are positive in 70% to 90% of cases of nongonococcal bacterial arthritis.^{23,40} Blood cultures are positive in 40% to 50% of cases of bacterial arthritis and are the only method of identifying the pathogen in about 10% of cases. Sometimes, an infection in an extra-articular site suggests a clue to the etiologic agent infecting the joint, as in the case of bacterial arthritis in association with pneumococcal pneumonia, or a urinary tract infection caused by *Escherichia coli*.

In cases of a gonococcal infection, the culture for *N gonorrhoeae* is almost always negative in skin lesions and is positive in less than 50% of synovial fluids and less than one third of blood cultures. This negativity may be the result of the difficulty in growing this organism in vitro. The tenosynovitis and dermatitis associated with disseminated gonococcal infection may not yield viable organisms; however, it can be easily recovered from the genitourinary tract. Patients who have the clinical features of gonococcal arthritis should have synovial, skin, urethral, or cervical cultures, and rectal cultures submitted on Thayer-Martin media. Approximately 50% of patients who have gonococcal arthritis have positive cultures from one of the last three mucosal sites.⁴¹ If associated urethritis is simultaneously present, a Gram stain of the urethral exudate should be obtained and examined for the presence of the Gram-negative diplococci characteristic of *N gonorrhoeae* infection. Culture and Gram stain of specimens obtained from skin lesions or tendon sheaths are often negative. Polymerase chain reaction techniques can detect gonococcal DNA in the synovial fluid of some culture-negative cases of suspected gonococcal arthritis, but the technique is not standardized and is not widely available.^{42,43}

The organisms causing nongonococcal septic arthritis in adults are 75% to 80% Gram-positive cocci and 15% to 20% Gram-negative bacilli.⁴ *Staphylococcus aureus* is the most common organism in native and prosthetic joint infections. The next most common group of Gram-positive aerobes is the streptococci, including *Streptococcus pneumoniae*. *Streptococcus pyogenes* is followed by groups B, G, C, and F in frequency. Patients who have immunosuppression, diabetes mellitus, malignancy, and severe genitourinary or gastrointestinal infections usually present non-group A

streptococcal disease.⁴⁴ Group B streptococcal arthritis in adults is rare; however, it can be a serious infection in patients who have diabetes and also in those who have prosthetic hip infections.⁴⁵ Infections with Gram-negative bacilli usually occur in patients who have a history of intravenous drug abuse, in immunocompromised patients, and in very old patients.⁴⁶ The most common Gram-negative organisms are *E coli* and *Pseudomonas aeruginosa*.

Infections caused by anaerobes occur in 5% to 7% of septic arthritis.^{19,40} Common anaerobes include *Bacteroides*, *Propionibacterium acnes*, and various anaerobic Gram-positive cocci. Foul-smelling synovial fluid or air in the joint space should raise the suspicion of anaerobic infection, and appropriate cultures should be obtained and held for at least 2 weeks. This type of infection is most frequent in patients who have wound infections or joint arthroplasty and in immunocompromised hosts.

Polyarticular septic arthritis is much less common than monoarticular infection.³¹ Many of the patients have one or more comorbidities, and some have been intravenous drug abusers. The occurrence of this type of arthritis in patients who have rheumatoid arthritis is high and averages 25% (range 18%–35%).⁴⁷ Although *Staphylococcus aureus* is the most common pathogen, group G streptococci, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or mixed aerobic and anaerobic bacteria have been responsible for polyarticular infections.

Plain radiographs of the infected joint are usually normal at presentation but should be obtained in all patients because associated osteomyelitis or concurrent joint disease may rarely be present. In addition, a baseline radiograph is often useful for comparison purposes should the response to therapy be delayed or poor. Radiographs often show nonspecific changes of inflammatory arthritis, including periarticular osteopenia, joint effusion, soft tissue swelling, and joint space loss. Scintigraphy, ultrasound, CT, or MRI can detect effusions and inflammation in joints that are difficult to examine, especially in the hip and sacroiliac joints, and can provide useful images to delineate the extent of the infection.^{48,49} MRI is highly sensitive in early detection of joint fluid and is superior to CT delineation of soft tissue structures. These images can show early bone erosion; reveal soft tissue extension; and facilitate arthrocentesis of joints, such as shoulders, hips, acromioclavicular, sternoclavicular, and sacroiliac joints.⁵⁰

TREATMENT

Treatment of bacterial arthritis must begin immediately after the clinical evaluation is complete and appropriate cultures have been taken. The acuity with which a clinician decides to initiate treatment and the correct choice of antibiotic in a patient who has infectious arthritis determines a good prognosis. The mainstay of therapy in these patients is parenteral antibiotic in the acute phase of the disease and adequate joint drainage. Initial antibiotic therapy should always be broad spectrum until a definite pathogen is isolated and thus a specific antibiotic chosen.

Many proposals have been made on the use of antibiotics but this is something that always depends on local epidemiology, clinician experience, local hospital conditions, and availability of therapy, especially in developing countries. Gram stain and risk factors should guide therapeutic regimens. Most antibiotics show a good penetration into diseased joints and the duration of parenteral antibiotics should be approximately 15 to 21 days and afterward continue with oral antibiotics for a complete 4-week regimen.

The most frequently used regimens use third-generation cephalosporins with good effective outcomes, especially if there is a high suspicion for *Staphylococcus aureus* or

Table 2 Proposal 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

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

Data from Ross JJ. Septic arthritis. *Infect Dis Clin N Am* 2005;19:799–817.

streptococci.⁵¹ The use of B-lactam and aminoglycosides or quinolones for Gram-negative rods is usually a good choice, but recently the use of quinolones has shown an increased resistance from *N gonorrhoeae* and this has made the Centers for Disease Control discard its use as a viable therapy.^{52,53}

The use of oral cefixime should continue after a course of intravenous antibiotic with other cephalosporins for the suggested time, always ensuring that *Chlamydia* is not the offending pathogen because of the lack of effectiveness against it.⁴¹ In all cases, osteomyelitis is a feared outcome, especially in those patients who have involvement of a cartilaginous joint (sternoclavicular and sacroiliac), so therapy in those cases might need to have a duration of up to 6 weeks.⁵⁴ **Table 2** summarizes empiric antibiotic regimens.

Joint drainage has shown good results when combined with antibiotics, especially because it has the advantage of improving vascularization in the joint; it decompresses the joint, and it removes the organism and its offending cascade of inflammatory reactions. Whether to use arthrocentesis or open surgery is still debatable, but available data suggest that arthrocentesis is more effective than open drainage; patient selection might be biased and critically ill patients are not good candidates for surgical procedures, having worse mortality outcomes than arthrocentesis.^{32,55} There is no consensus about joint immobilization in patients who have bacterial arthritis but it is generally suggested by several authors that early rehabilitation and joint mobilization provide better outcomes than immobilization, especially in the prevention of muscle atrophy and joint contractures.⁵⁶

PROGNOSIS

The ability to diagnose and treat an infected joint as soon as possible is the key for a good prognosis. Mortality occurs in approximately 10% of patients and permanent joint damage affects almost half of the patients affected with infectious arthritis. Outcome is closely related to multiple factors, especially comorbid conditions (eg, immunocompromised state, presence of underlying osteoarthritis and rheumatoid arthritis, and previous joint damage and pathogen virulence factors). All clinicians should be aware of the presence of an infectious process as a potential cause of acute arthritis to do an adequate screening to diagnose and treat it promptly.

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