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Septic Arthritis and Tuberculosis Arthritis

Miriam García-Arias, Silvia Pérez-Esteban and Santos Castañeda*

Rheumatology Unit, La Princesa Universitary Hospital, Madrid, Spain

Abstract

Septic arthritis is an important medical emergency, with high morbidity and mortality. We review the changing epidemiology of infectious arthritis, which incidence seems to be increasing due to several factors. We discuss various different risk factors for development of septic arthritis and examine host factors, bacterial proteins and enzymes described to be essential for the pathogenesis of septic arthritis. Diagnosis of disease should be making by an experienced clinician and it is almost based on clinical symptoms, a detailed history, a careful examination and test results. Treatment of septic arthritis should include prompt removal of purulent synovial fluid and needle aspiration. There is little evidence on which to base the choice and duration of antibiotic therapy, but treatment should be based on the presence of risk factors and the likelihood of the organism involved, patient's age and results of Gram's stain.

Furthermore, we revised joint and bone infections due to tuberculosis and atypical mycobacteria, with a special mention of tuberculosis associated with anti-TNFα and biologic agents.

Keywords: Septic arthritis; Tuberculosis arthritis; Antibiotic therapy; Anti-TNFα; Immunosuppression

Joint and bone infections are uncommon, but are true rheumatologic emergencies given that they cause significant mortality and morbidity. Early diagnosis and prompt and effective treatment are essential for preventing irreversible joint destruction and even death. Despite advances in diagnostic techniques and the emergence of new and potent antibiotics, the incidence of infectious arthritis has increased in recent years, probably due to the aging of the population, immunosuppressant therapies and increasingly resistant pathogens. There is little high-quality evidence on antibiotic therapy for septic arthritis, which may be complicated by the fact that septic arthritis is managed by many physicians who have their own approach to this condition.

Epidemiology

Information concerning the epidemiology of septic arthritis is limited due to several factors. Acute septic arthritis is an uncommon disease, with few reports of series containing more than 50 cases, most of which are from retrospective cohorts [1].

The estimated incidence of acute septic in industrialized countries varies from 2 to 6 cases/100,000 person-years in the general population [2-4]. In particular, the reported incidence of septic arthritis in Western Europe varies from 4 to 10 cases/100,000 person-years [3-5]. Moreover, the incidence increases in populations with low socioeconomic status, as has been demonstrated by studies conducted in both Northern Europe [6] and Australia [4].

Septic arthritis is more prevalent in children and the elderly, and males are more frequently affected than females [1]. In children, the incidence ranges from 5 to 12 cases/100,000 person-years [7], with about one-third of cases occurring in children under 2 years of age. A lower incidence has been reported in children below the age of 3 months [8]. Irreversible loss of joint function develops in 25%-50% of patients and the outcome varies depending on certain variables, such as type of causal agent, age, presence of significant co morbidities, delay in treatment and the joint involved [9].

Mortality due to septic arthritis in hospitalized patients is reported to be around 2%-10% of the total mortality in general hospitals in the USA [9,10].

Several factors have contributed to the increase in the incidence of septic arthritis in recent years, such as increased orthopedic-related infections, an aging population and an increase in the use of immunosuppressive therapy [4].

The exact incidence of osteomyelitis is unknown. In recent years, there was a decline in the incidence of acute osteomyelitis in developed countries [11]. Approximately 50% of pediatric cases occur in the first 5 years of life, and boys are affected twice as often as girls [12]. The incidence of hematogenous vertebral osteomyelitis is 0.5-2.4/100,000 person-years and this incidence increases with age [13].

Microbiology

Many pathogens are capable of causing septic arthritis, and these organisms vary by patient age. *Staphylococcus aureus* is the most frequent organism in all ages and risk groups other than children younger than 2 years, and is isolated in 37%-56% of cases [14,15]. An increase in *methicillin-resistant S. aureus* (MRSA) has recently been reported, especially in intravenous drug abusers, the elderly and in relation to orthopedic procedures [16]. The incidence of MRSA has been reported to account for approximately 25% of septic arthritis cases in a specific urban area [10].

Streptococcus spp. is the next most frequent bacteria involved in adult populations [3,5,16], with *Streptococcus pyogenes* the most commonly isolated streptococcus. *Streptococcus pyogenes* is generally observed in the setting of trauma, autoimmune disorders and chronic skin infections [4,17,18]. Group B streptococci are important agents in the elderly, especially in patients with chronic diseases, such as diabetes,

***Corresponding author:** Dr. Santos Castañeda, Servicio de Reumatología, Hospital Universitario La Princesa, Diego de León 62, 28006 Madrid, Spain, Tel: 915202473; Fax: 914018752; E-mail: scastas@gmail.com

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cirrhosis and neurological disorders [19]. Group C streptococci, Pneumococci and gram-positive bacilli are less frequent. Gram-negative cocci are involved in at least 20% of septic arthritis cases, with *Neisseria gonorrhoeae* and *N. Meningitidis* the two most important gram-negative organisms. *Haemophilus influenzae* is uncommon in the adult population [20]. Gram-negative bacillus such as *Escherichia coli, Proteus mirabilis, Klebsiella* and *Enterobacter* are less common and account for approximately 10%-20% of septic arthritis cases. They usually affect very young populations, the elderly, patients with a previous history of intravenous drug abuse, and immunocompromised patients [21]. Anaerobic microbes rarely cause septic arthritis, but they may be suspected when there is a history of diabetes, joint prosthesis implantation or penetrating trauma [22]. In human immunodeficiency virus (HIV) -infected patients, *S. aureus* is the most common pathogen; however, opportunistic pathogens, such as *S. pneumonia*, mycobacterial species and fungal species, are isolated from approximately 30% of cases [23]. Gram-negative bacillus infections are frequent in intravenous drug users. Moreover, this population is especially susceptible to fungal infections and other unusual agents.

In the pediatric population, the most common causative organisms involved are methicillin-sensitive *S. aureus, Streptococcus pneumonia* and *Haemophilus influenzae* [24]. However, ever since the H. influenza-type B (Hib) vaccine was introduced into this population, the incidence of *H. influenzae* septic arthritis has decreased in immunized children [25]. *Kingella Kingae* (a normal pathogen of the oropharynx in young children) has replaced *H. influenzae* as the main gram-negative bacteria causing arthritis in children between the ages of 2 months and 5 years, and should be suspected after pharyngeal or oral infections [26]. A significant decrease in pneumococcal septic arthritis was reported after the vaccine was introduced; however, *S. pneumoniae* remains an important causal organism for septic arthritis in children, which is likely due to infection with non-vaccine serotypes [27].

The most frequent organisms affecting infants younger than 2 months of age are *S. aureus, S. agalactiae* and gram-negative enteric bacteria. In children between the ages of 2 months and 5 years, the predominant agents are *S. aureus*, *S. pyogenes, S. pneumoniae* and K. Kingae. Finally, children older than 5 years of age are more likely to have arthritis caused by *S. aureus* and *S. pyogenes* [28].

In hematogenous acute osteomyelitis, the most frequent microorganism involved is *S. aureus*. Other causative agents that can be isolated include coagulase-negative staphylococci, anaerobic Gram-negative bacteria and *Peptostreptococcus spp* [29]. In children, *S. aureus* is the most common microorganism involved and is isolated in 60%-80% of acute hematogenous osteomyelitis cases. Furthermore, as has been described in septic arthritis, methicillin-resistant *S. aureus* are becoming an increasingly common cause. *Group A β-hemolytic streptococci, S. pyogenes* and gram-negative enteric bacteria may cause up to 10% of cases. Post-traumatic osteomyelitis is often a polymicrobial infection and the main agents involved are Staphylococcus and gram positive and negative anaerobic bacilli [29].

Pathogenesis

To develop septic arthritis, pathogens must enter into the synovium. The main routes by which pathogens accumulate in the joints are: a) hematogenously, with consequent lodging of the pathogen in synovial capillaries; b) infected contiguous foci; c) neighboring soft-tissue sepsis and d) direct inoculation due to trauma or an iatrogenic event, such as diagnostic or therapeutic arthrocentesis or joint surgery.

Because synovial tissue has no limiting basement plate, bacterial organisms quickly gain access to the synovial fluid (SF), characteristically creating acute-onset, and purulent joint inflammation [14]. Following the onset of infection, there is marked hyperplasia of the lining cells in the synovial membrane. In addition, the production of host matrix proteins may promote the attachment of bacteria and the progression of the infection [30]. Once the synovial fluid (SF) is colonized, bacteria proliferate rapidly and generate an acute inflammatory response. Under these circumstances, the host produces inflammatory cytokines, such as interleukin 1-β (IL-1β) and interleukin 6 (IL-6), that promote opsonization and activation of the complement system [31]. Phagocytosis of the bacteria by macrophages, synoviocytes and polymorphonuclear cells is stimulated by the production of interleukins and other cytokines, such as TNFα. Progression of the infection generates joint effusion, which increases intra-articular pressure that may result in further cartilage and bone loss.

Osteomyelitis can result from hematogenous spread, direct inoculation and contiguous spread from a local infection. Hematogenous osteomyelitis is the most frequent form and affects the metaphysis of the bone because of bacteria travelling through vascular tunnels and adhering to the bone matrix. Animal models show that bone infection is more likely after local traumatisms [32]. Infection of vertebrae and intervertebral discs is usually hematogenous. Infection occurs via the segmental arterial circulation of the vertebrae and then spreads by extension through the endplate into the disk, which may lead to paravertebral abscess formation [33].

Predisposing Factors

Septic arthritis can affect people at any age; however, elderly patients (especially those over 80 years) and very young children are more frequently affected [2] (Table 1).

Underlying joint diseases, including rheumatoid arthritis (RA), osteoarthritis, crystal-induced arthropathies and other forms of inflammatory arthritides, are predisposing factors for the development of infectious arthritis [2]. Bacteremia is more likely to localize in a joint with pre-existing arthritis, particularly if associated with synovitis. A prospective community-based study of 154 patients with septic arthritis found that 40 percent had pre-existing joint disease, usually either rheumatoid arthritis or osteoarthritis [34]. In particular, patients with RA appear to be especially prone to bacterial arthritis, but the risk may also be increased in patients with gout, pseudogout, osteoarthritis and Charcot's arthropathy [14]. In addition, many of these patients receive immunosuppressive therapy and/or glucocorticoids, which is another important risk factor associated with the development of septic arthritis. Furthermore, the use of classic disease-modifying anti-rheumatic drugs (DMARDs) in RA patients can be an additional risk factor that facilitates infectious arthritis [35]. Since the introduction of anti-TNF agents, unusual cases of septic arthritis caused by bacteria

- Age (> 80 years)
- Pre-existing arthritis (especially, rheumatoid arthritis)
- Immunosuppression, e.g. infection with human immunodeficiency virus, diabetes mellitus, cancer…
- Immunosuppressive therapy
- Trauma and recent joint surgery
- Intra-articular corticosteroid injection
- Intravenous drug abuse
- Skin infections
- Hemodialysis

Table 1: Risk factors associated with septic arthritis.

such as *Roseomonas mucosa*, Salmonella or Listeria have been described [36]. Data from observational registries have suggested an increased incidence of joint infections in patients receiving anti-TNF therapy; however, the incidence does not seem to differ from the risk among patients only treated with classical DMARDs [35].

Patients with other chronic and immunosuppressive diseases, such as diabetes, leukemia, cirrhosis, granulomatous diseases, cancer and hypogammaglobulinemia, also have an increased risk of septic arthritis [37]. Hemodialysis has been reported as an important risk factor for septic arthritis, and the prevalence may be around 500 cases/100,000 patients [38].

Recent joint surgery is also associated with an increased risk of joint infection. Thus, the prevalence of post-arthroscopic septic arthritis has been reported to be around 14 cases/10,000 arthroscopic procedures [39].

Therapeutic intra-articular corticosteroid injection has been considered another important risk factor for infection. The precise risk is difficult to quantify, but has been estimated at around 4 cases/10,000 injections [39]. In addition, skin infections may also facilitate joint infections [2]. Finally, an increased prevalence of musculoskeletal infections has been shown in human immunodeficiency virus (HIV) infected patients [40].

Clinical Features

Acute septic arthritis usually presents with the abrupt onset of a single hot, swollen and very painful joint. Patients with septic arthritis typically present with a 1-2 week history of malaise, erythema, swelling, tenderness and a decreased range of motion of a single joint [30], although these symptoms may not always be present [41]. The onset of fever in most cases is mild, with only 30%-40% of individuals having temperatures >39ºC [41].

Septic arthritis is usually monoarticular. However, the possibility of polyarticular septic arthritis should be carefully considered, especially when patients are a febrile or have an underlying polyarticular joint disease such as RA. Polyarticular disease accounts for around 10%-20% of patients with septic arthritis and usually affects 2-3 joints. It is more likely to occur in patients with significant co morbidities and systemic diseases [42].

Non-gonococcal septic arthritis may affect any joint; however, large joints, such as knees and hips, followed by shoulders, wrists and ankles, are the most frequently affected [43]. Inter-phalangeal joints of the hand are rarely involved in bacterial arthritis, but may be compromised in viral arthritis, and may mimic RA [18].

Atypical joint infections, including those involving the sacroiliac, sternoclavicular and costochondral joints, are seen among parenteral drug users. The sacroiliac joint may also be a site for brucella arthritis, and sternoclavicular septic arthritis can also be a consequence of joint bacterial migration from the adjacent subclavian veins [44-46].

Inflammation of multiple tendon sheaths commonly occurs in disseminated gonococcal syndrome, but may also be seen with other agents such as Moraxella, rubeola virus and sporotrichosis [47].

Septic arthritis in newborns and infants is more deceptive and devastating. The diagnosis may be overlooked because of the absence of classical signs of infection. Clinical manifestations may include vague complaints like irritability, anxiety, failure to thrive, tachycardia and anemia. Systemic symptoms like fever or malaise may be present and refusal to move the affected joint, referred as pseudo paralysis, may be the most significant symptom. The hip is the joint most frequently affected [4]. On physical examination, the infant may flex, abduct and externally rotate the hip to relieve intra-articular pressure on the capsule [48]. In any infant with septicemia, a careful articular examination must be performed. All bones and joints must be explored, with special attention to the hips.

Children usually present with the classical symptoms of infectious arthritis seen in adults and septic arthritis is easier to diagnose in this group than in neonates and infants.

Long bone acute osteomyelitis usually evolves with pain in the affected site and fever. Young infants and toddlers are the most frequently involved, and may present symptoms such as irritability, refusal to bear weight or use an extremity. In infants and neonates, subperiosteal spread may lead to septic arthritis or local symptoms like erythema, warmth, swelling and even spontaneous drainage. Chronic osteomyelitis usually presents with persistent pain and low-grade fever and drainage.

Vertebral osteomyelitis has an insidious onset and patients present local pain and tenderness with fever in less than a half of the cases. The lumbar region of the spine is the most frequently affected (50%-60%), followed by the thoracic and cervical regions. Neurologic deficits due to spinal cord or nerve root compression from paravertebral abscesses can occur in 4%-40% of cases, mainly in the cervical and thoracic regions due to the smaller diameter of the medullary space [49].

Diagnosis

The definitive diagnosis of septic arthritis requires direct identification of bacteria in SF or after culturing the pathogen. The diagnosis is based in most cases on clinical symptoms and from a detailed history, a careful examination and test results [50]. A clinical diagnosis can be difficult to make. It has been suggested that the level of clinical suspicion of an experienced clinician in the diagnosis and management of rheumatic diseases is the "gold standard" for diagnosis of septic arthritis [50].

Laboratory features

In a systematic review of the literature, it was concluded that there is limited evidence to suggest that any clinical or laboratory feature is specifically significant for septic arthritis. Blood tests show increases in ESR, CRP and white-cell count (WBC). However, the absence of elevated acute phase reactants does not exclude the diagnosis of septic arthritis, but they should always be measured because they are useful for monitoring treatment response [6,17]. Li et al. [51] demonstrated that a high WBC count in the joint fluid (jWBC) increases the likelihood of a diagnosis of septic arthritis. WBC counts higher than 11,000/mm^3, ESR over 20 mm/h and jWBC >50,000/mm^3 have a sensitivity for joint infection of 75%, 75% and 50%, and corresponding specificities of 55%, 11% and 88%, respectively. The overall sensitivity of the three tests together is 100%, but the specificity is low (24%) [51]. In a recent study, Hugle et al. [52] demonstrated that serum procalcitonin could be used to differentiate between septic and non-septic arthritis, but its accuracy has not been established [52]. To date, there is no test with sufficient sensitivity, specificity and predictive values to allow its use in routine clinical practice.

Blood culture

Blood cultures must be obtained before starting antibiotic treatment to optimize the possibility of isolating the causative bacteria. Blood

cultures are reported to be positive in 50%-70% of patients with non-gonococcal arthritis [14].

Synovial fluid

Aspiration of SF from a swollen joint is mandatory for establishing the correct diagnosis. In septic arthritis, SF usually has a turbid appearance with a WBC >50,000/mm^3. However, other non-bacterial inflammatory diseases, such as acute microcrystalline arthritis and reactive arthritis, may have similar WBCs. In a study conducted by Coutlakis et al. [53] in 2002, infectious arthritis was diagnosed in 77% of patients with synovial jWBC >100,000/mm^3, in 47% of patients with jWBC between 50,000-100,000/mm^3 and in 5% of patients with jWBC <50,000/mm^3. Eighty-one percent of patients with jWBC ranging from 15,000 to 50,000 had a diagnosis of RA or crystal-induced synovitis [53]. SF glucose is often depressed (<40 mg/dl or less than half the serum glucose concentration), and lactic acid and lactate dehydrogenase levels are raised; however, these findings may be seen in other inflammatory diseases, and thus lack discriminative power [9].

The presence or absence of crystals should always be examined by polarizing microscopy. Evidence of crystals, however, does not preclude the possibility of concomitant septic arthritis [54].

SF should be cultured for aerobic and anaerobic bacteria, mycobacteria and fungus, especially in immunocompromised patients. Gram staining of SF is important for the diagnosis of septic arthritis, and may help differentiate between gram-positive and gram-negative bacteria, which are essential for selecting antibiotic therapy. SF cultures are positive in 67% of non-gonococcal arthritis cases, whereas Gram staining reveals positive results in only 50% cases [14]. Cultures can be negative after initiating antibiotic treatment. However, injecting the aspirated joint fluid into blood culture bottles may increase the diagnostic yield compared to conventional agar culture [55]. Among patients with negative cultures by conventional methods, one third of those not receiving antibiotics and 50% of those receiving antibiotics had positive cultures with this approach [55].

New techniques have emerged for the detection of bacteria in biological fluids. DNA-based techniques, hybridization probes, PCR-based techniques and protein detection by mass-spectroscopy provide quick results. Detection of microorganisms by PCR shows promising results. However, the risk of contamination, the presence of background DNA, the lack of a gold standard and the fact that PCR techniques detect DNA instead of living pathogens makes the interpretation difficult [56]. PCR assays have not been demonstrated to have any advantage over bacterial culture in staphylococcal or streptococcal infections [57], but are useful for identifying *K. kingae*, anaerobic bacteria and *Streptococcus spp*. [58].

Imaging studies

Conventional radiography should always be the first imaging technique used, although the results are usually normal at presentation and generally lack sensitivity and specificity. Osteopenia is usually the first radiological manifestation. As the infection progresses, diffuse joint space narrowing may evolve. In osteomyelitis, the initial finding is also osteopenia, followed by cortical destruction and periosteal new bone formation. Sub acute and chronic osteomyelitis have different imaging characteristics than marginal sclerosis and osteopenia, which indicate areas of healing. The most specific finding of chronic osteomyelitis is a sequestrum, a fragment of dead bone surrounded by inflammatory tissue, which radiographically appears as a focal area of sclerotic bone within an area of lucency [59].

Ultrasonography is useful for detecting fluid effusions as small as 1 to 2 ml and for examining otherwise inaccessible joints such as the hip [60]. An ultrasonographic characteristic of a septic joint is the presence of effusions with echoes inside. Ultrasonography is a noninvasive and inexpensive technique that allows guided diagnostic arthrocentesis to be performed in patients with suspected septic arthritis when joints are not easily accessible or the amount of fluid is small. However, it is not useful in osseous infections because ultrasound is unable to pass through bone [61].

CT is better for visualizing local edema, bone erosions, osteitic foci and sclerosis [62].

MRI provides better resolution than radiography or CT for detecting joint effusion and for differentiating between bone and soft tissue infections. MRI with intravenously administered gadolinium contrast has a sensitivity of almost 100%, with a specificity of over 75% [63]. MRI findings include joint effusion, cartilage and bone destruction, soft tissue abscesses, bone edema and cortical interruption. Acute and chronic osteomyelitis can be differentiated with MRI. Acute infections do not show a sharp zone of transition between normal and abnormal bone marrow and do not have cortical thickening or sequestrum. As with other imaging techniques, MRI is unable to differentiate between infective and other inflammatory arthritides [64].

Radionuclide scans are useful for locating areas of inflammation. Leukocytes labeled with ^{99m}Tc sulfur colloid accumulate in areas where osteoblasts are active and where there is increased vascularity [65]. The results are considered positive for infection if an uptake of sulfur colloid is observed in the area of interest. Ga-citrate and 111In-chloride scans are more sensitive and specific than ^{99m} Tc, but it is difficult to distinguish between bone, joint and soft tissue inflammation with these techniques [66].

Prognosis

Mortality from septic arthritis seems to be around 11% for monoarticular arthritis [67]. Irreversible loss of joint function is close to 40% [5,9]. Delay between the onset of disease and the start of treatment, advanced age, underlying joint diseases and the presence of synthetic material within the joint are conditions associated with poor prognosis. Delaying treatment for as little as 7 days results in poor outcomes [20]. Underlying joint diseases are also associated with a poor prognosis because symptoms of septic arthritis can frequently be mistaken for those of the preexisting joint disease [41]. Patients with polyarticular septic non-gonococcal arthritis have a poor prognosis with a mortality rate of 30% [41] (Table 2).

Management

The mainstay of treatment should be the prompt removal of purulent material and early treatment with antibiotics [68].

No randomized controlled studies have evaluated antibiotic regimens for bacterial arthritis. The initial choice of antimicrobial treat-

- Delayed diagnosis
- Delayed treatment
- Advanced age
- Underlying comorbidities
- Underlying joint diseases
- Prosthetic joint
- Virulent organisms
- Immunosuppression

Table 2: Poor prognosis factors.

ment should be based on clinical presentation, patient history, likely organisms involved and the Gram staining results [40,49]. Because the most frequent pathogens are *S. aureus* and streptococci, the empiric antibiotic treatment (before bacterial identification) should be effective against these organisms. If necessary, the initial antibiotic treatment should be modified or adjusted based on culture and antibiotic sensitivity results. There have been no controlled trials examining the duration of antibiotic therapy in infectious arthritis, and treatment recommendations are based on clinical case series and cannot be generalized for all patients. The usual course of therapy for non-gonococcal and non-complicated arthritis, such as streptococci or gram-negative cocci, is 2-3 weeks, with 3-4 weeks for staphylococci. Antimicrobial therapy should be maintained for at least 4 weeks for pneumococci and gram-negative bacilli [40].

Intra-articular antibiotics are not recommended because effective parenteral or oral therapy produces optimal levels of antimicrobial agents in joint fluid. Moreover, direct instillation of antibiotics into a joint may cause an inflammatory response.

Successful management of septic arthritis also includes prompt removal of purulent material from the joint space. No randomized controlled studies have evaluated joint drainage procedures in adults for bacterial arthritis, and recommendations are based on small retrospective studies and are dependent on the joint affected and the time from onset of infection to evaluation. It has been suggested that needle aspiration is preferable compared to surgical treatment as an initial mode of drainage, although in a study performed by Goldenberg et al. [68], both methods achieved similar results. Moreover, needle aspiration during the first 7 days of treatment has been demonstrated to be a successful treatment. Decreased SF volume and a lower jWBC with a smaller percentage of polymorphonuclear leukocytes indicate that the treatment was effective [68]. When needle aspiration is incomplete and the effusion persists beyond 7 days, arthroscopy or open drainage needs to be performed. For knee, shoulder and wrist infections, arthroscopy is often preferred because of easier irrigation and better visualization of the joint [69]. For hip infections, initial open surgical drainage may be necessary. Although arthrotomy has been considered standard treatment, a retrospective study involving six patients with septic hips found that arthroscopic treatment with large-volume irrigation was effective [70]. Arthrotomy should be performed in clinical situations when urgent decompression is required due to neuropathy or compromised blood supply, when conservative drainage techniques have failed, when the joint is seriously damaged by preexisting articular disease and when septic arthritis is complicated by underlying osteomyelitis [30].

During the acute phase of infection, optimal positioning of the affected joint is essential to prevent deformities and contractures. Splints may be useful for maintaining the joint in its proper functional position, and isotonic exercise must be initiated to prevent muscular atrophy. After the acute phase, early physical therapy and mobilization of the affected joint are imperative for optimal recovery [18,71].

Some experimental studies have suggested that glucocorticoids in conjunction with antibiotic treatment may be a more effective treatment than antibiotics alone [72,20]. Nonetheless, the use of corticosteroids in a patient with a serious infection should be carefully considered.

In animal experimental models, the combination of bisphosphonates with intraperitoneal corticosteroids and antibiotics reduces inflammation and bone and cartilage destruction [73,74]. Other potential therapies using interleukin 10 or interleukin 12 in combination with antibiotics have been investigated in animal experimental models [75,76].

Next, we will make a special mention to Chlamydia-induced arthritis, although it belongs to the group known as reactive arthritis (ReA).

Chlamydia-Induced Reactive Arthritis

Reactive arthritis (ReA) is a sterile synovitis caused by an extraarticular infection. ReA belongs to the group of spondyloarthritides (SpA), which are grouped together because of their common clinical features. There are two main types of ReA: post-chlamydial and post-enteric arthritis. The mayor chlamydial species that causes ReA is Chlamydia trachomatis (Ct). Furthermore, Ct is felt to be the most common cause of reactive arthritis nowadays [77].

Epidemiology

The prevalence of ReA is estimated to be 30-40 cases per 100,000 adults, and the annual incidence for Chlamydia-induced arthritis is estimated to be 4.6/100,000 person-years [78].

Pathophysiology

All chlamydial species are obligate intracellular bacterial parasites of eukaryotic cells.

The sites of primary infection are the epithelial surfaces of the urogenital tract and the ocular conjunctivae [79]. At the sites of primary infection, Ct can cause acute disease or be asymptomatic. The chlamydial developmental life cycle is biphasic [80]. In the first phase, the infectious extracellular form of the organism attaches to the appropriate host cell and is brought in a membrane-bound vesicle into the host cell cytoplasm, forming the reticulate body. The reticulate body undergoes several rounds of division reorganizing back into elementary bodies, which are then released from the host cell to cause further infection. This development cycle takes around 48 hours to complete. Chlamydia in the normal developmental life cycle are rather easily detected with traditional culture techniques. After this acute infection, these organisms have the ability to disseminate from their site of primary infection and establish long-term residence at distant anatomic locations [81]. It is at these sites that the organism enters into an unusual biological state referred to as "persistence state" [81]. In this persistent state, a block in gene expression impedes completion of the developmental life cycle and the organisms exhibit aberrant morphological and transcriptional factors. These persistent Chlamydia cannot be detected with traditional culture techniques, but are readily detectable by electron microscope (EM) or polymerase chain reaction (PCR).

Clinical features

Chlamydia-induced ReA combine four syndromes: peripheral arthritis, enthesopathy, pelvis axial syndrome, and extra musculoskeletal manifestations such as conjunctivitis, keratoderma blenorrhagicum, and urethritis or erythema nodosum. The typical picture of arthritis is an asymmetric oligoarthritis, often affecting the lower extremities. However, about 50% of patients have arthritis in the upper limbs, and some have polyarthritis in the small joints [82]. Swelling at the heels is the most characteristic symptom of enthesitis. Patients can also develop dactylitis.

Diagnosis

The test of choice is examination of the first portion of the morning urine by nucleic acid amplification [83] because it is more convenient

and comparable with urogenital swab. Evidence of Chlamydia by PCR in the joint is diagnostic, but the methods from synovial samples are not validated.

The use of serology (complement fixation, microimmunofluorescence, enzyme immunoassay) is useful in upper genital tract infections and seroepidemiologic studies but not in lower urinary tract infections. In addition, the tests are hampered by the serologic cross-reactivity between Ct and C. Pneumoniae and by the persistence of antibodies, which prevents distinction between past and present infection [83].

Treatment

Management of extra-articular infection: A therapy resulting in the eradication of bacteria should cure the disease. Since urogenital tract infection with Ct is a venereal disease, its treatment is indicated irrespective of the presence of arthritis. Azithromycin (1 g orally as a single dose) or doxycycline (100 mg twice a day for 7 days) should be used [84]. The patient's sexual partner should be treated simultaneously to prevent reinfection.

Whether long-term antibiotics are useful in patients with chronic reactive arthritis is especially important in Chlamydia-induced arthritis. Carter et al. [85] evaluated two different regimens of treatment in a trial involving 42 patients with Chlamydia-related ReA of at least six months duration. These patients also showed positive testing for Ct by a special PCR in blood or synovial tissue. Patients were randomly assigned to receive six months treatment with rifampicin plus either doxycycline or azithromycin or to receive placebo. The composite endpoint for improvement was reached significantly more often by the patients receiving combination antibiotics (63% versus 20%). However, this study have some limitations such as the small number of patients in each group and the fact that the study was limited to patients with evidence of persistent Chlamydial infection by special PCR using peripheral blood or synovial samples, and not routine urine samples. Further studies with larger numbers of patients are required to confirm these findings.

Management of ReA: Joint involvement. Non-steroidal anti-inflammatory drugs (NSAID) are effective in the therapy of arthritis. DMARDs are indicated for persisting symptoms, erosive joint disease, or recurrent flares. Sulfasalazine started during the first 3 months of ReA can induce clinical remission more rapidly compared with placebo [86]. Intra-articular use of glucocorticoids is usually of benefit in patients with monoarticular or oligoarticular disease.

Axial involvement: The cornerstone of the therapy of axial involvement is physical therapy and NSAIDs.

Enthesitis: Therapy of enthesitis consists of NSAIDs, physical therapy and orthoses. In the case of multiple enthesitis and elevated acute-phase reactants, treatment with sulphasalazine is recommended. Enthesopathy also responses to local corticosteroid injections.

Tuberculosis Arthritis

Musculoskeletal involvement with tuberculosis is relatively uncommon, representing approximately 1% to 3% of all cases [87]. Osteoarticular lesions usually result from hematogenous spread of a primary infection.

Epidemiology

Tuberculosis remains one of the leading causes of morbidity and mortality worldwide. In 2006, there were 9.2 million new cases of tuberculosis, among them approximately 709,000 (8%) occurred in HIV-positive individuals [88].

In 2007, the rate of tuberculosis in foreign-born persons in the United States was 10 times higher than in the native population. The non-Hispanic black population had the largest number of cases [88]. A similar increase in the incidence of bone and joint tuberculosis is occurring in some European countries due to the migration of certain groups from Africa with a high incidence of tuberculosis [89].

Bone and joint infection may account for approximately 9% of cases of extra pulmonary tuberculosis and, overall, for almost 2% of all cases of tuberculosis [87]. Musculoskeletal tuberculosis involves the spine in approximately one-half of patients. Sites more frequently affected are peripheral joints, followed by extra spinal tuberculosis osteomyelitis [89].

Pathophysiology

M. tuberculosis infection occurs through inhalation of aerosolized bacteria, ingestion or direct inoculation from infected individuals. Particles less than 5 μm can carry 1 to 5 bacilli, which is enough to infect an immunocompromised individual. Infection depends on the number of organisms that survive phagocytosis and their ability to escape host defenses, such as alveolar macrophages and delayed hypersensitivity responses. Mycobacteria multiply intracellularly using Toll-like receptor-2; complement, mannose and cholesterol-related receptors and CD14, leading to a burst of pneumocytes. Microorganisms invading regional lymphatic nodes initiate the development of protective immunity that is mainly mediated by CD4+ lymphocytes with help from CD8+ cytotoxic lymphocytes and B cells.

Cytokines play a key role in protecting against tuberculosis and in granuloma formation. Particularly, TNFα recruits macrophages, leading to granuloma formation and maintenance.

Musculoskeletal features

As previously described, musculoskeletal infection accounts for 1% to 3% of all forms of tuberculosis. Tuberculosis bone and joint involvement (9%) is reported to be the fifth most common extra pulmonary location, following lymphatic (27%), pleural (21%), genitourinary (16%), and miliary (10%) locations [90].

Spinal tuberculosis: Tuberculosis spondylitis, also named Pott's disease, represents approximately half of all cases of musculoskeletal tuberculosis. The vertebral column is affected in approximately 50% of all cases of skeletal tuberculosis and results from hematogenous spread of a primary infection. The thoracic spine is involved in 50% of spinal tuberculosis, whereas the lumbar and cervical regions of the spine are each involved in 25% of cases [91]. Clinical presentation may include back pain, which becomes more severe over several weeks to months. Constitutional symptoms, such as general malaise, low-grade fever, weight loss and night sweats are present in less than 40% of patients [92]. In the early stages, infection involves the anterior vertebral endplates, resulting in herniation of the intervertebral disc into the vertebral bodies with loss of vertebral height. Kyphosis is a late finding, and its combination with scoliosis produces a gibbus deformity. The most feared complication of spinal tuberculosis, occurring in 10% to 47% of patients, is neurologic compromise due to spinal deformity or epidural abscess formation [92].

Peripheral joint arthritis: Tuberculosis arthritis can affect any joint, but the peripheral joints most commonly involved are the hips (15%), knees (15%) and ribs (5%) [90]. In endemic areas, children and

young adults are the most frequently affected; in non-endemic areas, non-white males in their 40s and 50s are the most commonly affected. Typical symptoms consist of slowly progressive joint pain, swelling and loss of function that progresses over weeks to months, rather than days. Constitutional symptoms, fever, and weight loss occur in about 30% of cases [93]. A single joint is usually involved, but multiple lesions can occur.

Diagnosis

In areas where tuberculosis is endemic, clinical and radiographic findings may be sufficient to make the diagnosis. In other areas, the diagnosis may be suspected with the appropriate clinical history, including questions about country of origin, previous exposure to tuberculosis and prior positive tuberculin skin test. Patients with risk factors for tuberculosis, such as immunocompromised individuals, the elderly, and patients taking corticosteroids and/or immunosuppressive and biological agents deserve special attention and should undergo microbiologic or histologic studies.

Laboratory abnormalities, such as elevated ESR and CRP, are non-specific. The gold standard in the diagnosis of tuberculosis is the direct identification of *M. tuberculosis* by microbiologic or histologic techniques.

Over 90% of immunocompetent patients with skeletal tuberculosis have positive tuberculin skin test (TST) [94]. However, skin tests may be negative in a small percentage of immunocompetent patients and a larger percentage of immunosuppressed patients; thus, a negative skin test does not exclude tuberculosis. Furthermore, it has little value in endemic regions and widespread BCG vaccination.

Culture is a sensitive test (80%). *M. tuberculosis* grows slowly, taking 3 to 6 weeks in solid media (Lowenstein-Jensen or Middlebrook agar) incubated at 37ºC. Whenever possible, the diagnosis of tuberculosis should be confirmed by microscopy and culture of infected material [90].

SF aspiration and/or synovial biopsy are important diagnosis tools. SF is often non-hemorrhagic, turbid and xanthochromic. The WBC count is moderately elevated and ranges between 10,000 and 20,000 cells/ml with a predominance of polymorphonuclear leukocytes.

The polymerase chain reaction (PCR) or Gen-probe are promising techniques, and imaging techniques are also useful tools for confirming the diagnosis.

Spinal tuberculosis: There are no skeletal radiographic findings pathognomonic of tuberculosis. In the earlier stages, radiological findings include resorption of dense margins of the endplates and demineralization, narrowing or obliteration of the disc space. In the later stages, a lytic progressive destruction of the anterior vertebral body leads to vertebral collapse and kyphosis.

CT is helpful in revealing small abnormalities and paravertebral abscesses. MRI has a higher soft tissue definition than CT and is more specific for delineated swelling [95].

Peripheral joint arthritis: Plain radiography may show joint and soft tissue swelling with effusion in early stages. Late-stage findings may reveal periarticular osteopenia and the Phemister's triad (peripheral osseous erosions, articular destruction with narrowing of the joint space and juxta-articular osteoporosis). Other imaging techniques such as CT, MRI and scintigraphy are useful for establishing the diagnosis.

Treatment

The mainstay of treatment of musculoskeletal tuberculosis is still three or four-drug antimicrobial therapy based on current guidelines. First-line drugs include 8 weeks of oral daily treatment with isoniazid, 5 mg/kg or 300 mg; rifampicin, 10 mg/kg or 600 mg; pyrazinamide, 15 to 30 mg/kg and ethambutol, 5 to 15 mg/kg; or streptomycin, 15 mg/kg or 1 g intramuscularly. Patients should then undergo 28 to 36 weeks of treatment with isoniazid plus rifampicin for 5 days per week to complete 9 to 12 months of treatment. Moreover, pyridoxine, 25 to 50 mg daily, may be added to daily regimens that include isoniazid. Patients generally recover full joint function if adequate chemotherapy is initiated in the early stage of the disease [90].

Indications for surgical treatment vary depending on the site of infection. In tuberculosis spondylitis, indications for surgery include marked neurological defect, large abscess with obstructive symptoms, and progressive neurological defect, kyphosis or instability despite adequate antimicrobial therapy [96]. Generally, the best results are obtained with anterior decompression and arthrodesis. Postoperatively, a prolonged course of antimicrobial therapy is required to prevent reactivation of the infection, although the optimal duration of treatment is uncertain [96].

Tuberculosis associated with anti-TNFα and biologic agents

Active tuberculosis that, in most instances, is the result of reactivation of latent TB infection has been associated with treatment with tumor necrosis factor (TNF) antagonists. The estimated incidence of tuberculosis in patients with RA treated with anti-TNFα was 472/100,000 in 2000 and 172/100,000 in 2002 [90]. Various recommendations for targeting patients with latent TB infection have been proposed by scientific organizations, health authorities, and other experts worldwide to decrease the risk of active TB. Guidelines for preventing tuberculosis infection during anti-TNFα treatment include treatment with INH for 9 months in patients with a TST result of 5 mm and/or chest radiography finding suggestive of previous tuberculosis.

Atypical Mycobacteria Infections

Atypical mycobacteria infections are more common in immunosuppressed individuals, patients with pre-existing diseases, including HIV infection and cancer, and patients taking glucocorticoids.

Microbiology

M. leprae and other atypical mycobacteria can produce musculoskeletal infections. Osteoarticular lesions usually derive from hematogenous spread or percutaneous inoculation. *M. avium-intracellulare, M. cheloni, M. fortuitum, M. haemophilum, M. marinum* and *M. kansasii* are the most common agents involved in musculoskeletal infections [90].

Clinical manifestations

Clinical features vary depending on the causative microorganism. The clinical manifestations of M. leprae range from non-sensitive or hypo pigmented skin spots to severe neuropathic and osteoarticular damage. Well-recognized musculoskeletal features of leprosy are neuropathic or Charcot joints, septic arthritis and acute polyarthritis [90]. Clinical manifestations of other mycobacteria include malaise, low-grade fever, weight loss and local pain. Bone and joint features due to these mycobacteria can include tenosynovitis, soft tissue abscess and osteomyelitis.

Diagnosis

As occurs with other types of infectious arthritis, laboratory findings such as an elevated ESR and CPR are non-specific. SF is frequently a transudate. Definitive diagnosis requires histopathological or bacteriological demonstration of mycobacteria from tissue samples, and/or biopsies from soft tissue lesions [90]. Plain radiographs may reveal lytic areas with erosions, sclerosis and osteoporosis.

Management

Most of the atypical mycobacteria are resistant to anti-tuberculostatic drugs and require longer duration of therapy. Dapsone (100 mg daily) and rifampicin (600 mg daily) for 12 months are recommended for the treatment of the paucibacillary form. Multibacillary infection requires dapsone (100 mg daily), rifampicin (600 mg daily) and clofazimine (50 mg daily) for 2 years [97].

Treatment of M. avium-intracellulare, M. chelonei, M. fortuitum includes macrolides, ethambutol, and a third drug to be chosen from rifampicin, ciprofloxacin, amikacin, cefoxitin, clofazimine and/or tetracycline. Duration of treatment is not definite and varies from 12 to 18 months [90].

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