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Infectious arthritis: clinical features, laboratory findings and treatment

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ABSTRACT

An infection of native joints leads generally to suppurative arthritis, which may be of one joint (monarticular) or several joints (oligoarticular). Bacteria that produce symptoms in multiple joints during bacteraemia, such as *Neisseria gonorrhoeae*, may also induce inflammation in the neighbouring tendon sheaths. Viral infections frequently involve multiple joints and produce inflammation without suppuration. Chronic granulomatous monarticular arthritis may occur because of infection with either mycobacteria or fungi, which must be differentiated from other causes of chronic monarticular arthritis. A sterile arthritis may occur early in infection (as with hepatitis B), or later (as with a post-infectious arthritis). Any patient presenting with an inflamed joint should have infection as a diagnostic possibility and appropriate cultures must be performed.

Keywords Arthritis, bacterial infection, fungal infection, review, viral infection

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PREDISPOSING FACTORS FOR INFECTIOUS ARTHRITIS

The reported incidence of septic arthritis varies from 2–5 cases/100 000 individuals annually in the general population, to 28–38 cases/100 000 individuals annually among patients with rheumatoid arthritis, to 40–68 cases/100 000 individuals annually among patients with joint prostheses [1]. Infectious arthritis usually follows haematogenous inoculation of pathogenic organisms in patients predisposed to infectious arthritis (Table 1). Preceding events include trauma such as an intra-articular injection, intravenous drug use, and behaviour associated with sexually transmitted diseases; predisposing conditions include underlying rheumatoid arthritis or other connective tissue disorders, and immunosuppression, such as that resulting from infection with human immunodeficiency virus (HIV), diabetes mellitus or immunosuppressive therapy [1,2]. Skin infections have been shown to increase the predisposition to joint infection of any individual with an underlying condition such as rheumatoid arthritis [1,3] Post-infectious arthritis can develop after infections with sexually transmitted pathogens such as *Chlamydia*, or enteric infections with *Shigella*, *Salmonella*, *Campylobacter* or *Yersinia*, principally in individuals with the specific histocompatibility antigen HLA-B27 (if the triad of arthritis, conjunctivitis and urethritis is present, this constitutes Reiter's syndrome) [2].

CLINICAL FEATURES

Patients with bacterial arthritis present usually with fever (mild in most cases, with only 30–40% of individuals having a temperature of >39°C), erythema, swelling, tenderness and a decreased range of motion of the affected joint(s). The swelling and joint tenderness can vary from minimal to severe [3]. The knee is the joint affected most commonly in both children and adults with bacterial and mycobacterial arthritis, followed by the hip, shoulder, wrist and ankle [2]. Diagnosis of bacterial infection of the hip and shoulder joints is often delayed, since effusions may be difficult to demonstrate [3].

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Table 1. Risk-factors associated with bacterial arthritis [2,3]

Pre-existing arthritis
Skin infections
Age (> 65 years)
Trauma, including intra-articular injections
Diabetes mellitus
Immunosuppression, e.g., infection with human immunodeficiency virus and immunosuppressive therapy
Intravenous drug abuse
Previous central intravenous catheterisation (sternoclavicular)
Geographical exposure (Lyme's disease, fungi)
Behaviour associated with sexually transmitted diseases

Inter-phalangeal joints of the hand are involved infrequently with bacterial arthritis, but are involved commonly with viral infections; these patients present with a rheumatoid arthritis-like syndrome [4]. Infections of the sacroiliac and sternoclavicular joints have an association with parenteral drug abuse. Sacroiliac joints may also be a site for brucella arthritis, while sternoclavicular septic arthritis can also be a result of infected central lines, with bacteria entering the joint from the adjacent subclavian veins [5–7]. Involvement of multiple joints occurs in up to 10% of patients, particularly among those with rheumatoid arthritis [3]. Viral arthritis tends to involve multiple joints, with most patients having symptoms in the inter-phalangeal joints of the hands and the wrist, and fewer patients having knee, ankle and elbow involvement. Inflammation of multiple tendon sheaths (tenosynovitis) occurs commonly with the disseminated gonococcal syndrome, but may also be seen with other infectious agents such as *Moraxella*, rubella virus and non-tuberculous mycobacteria, and in sporotrichosis [2].

Acute septic bursitis is caused usually by *Staphylococcus aureus*, commonly following local trauma (77%) [8]. The olecranon and pre-patellar bursae are the usual sites.

LABORATORY FINDINGS

Patients with bacterial arthritis have an elevated erythrocyte sedimentation rate, elevation of the peripheral blood leukocyte count, and a synovial leukocyte count of $>50\,000/mm^3$, with >75% polymorphonuclear leukocytes. However, these findings are not specific for bacterial arthritis [2,3]. Furthermore, synovial fluid leukocyte counts of $<28\,000$ cells/mm^3 occur in infected patients who have malignancy, are receiving corticosteroids, or are intravenous drug abusers, although the percentage of segmented neutrophils is >90% [9]. Protein levels and a low synovial fluid glucose level are neither sensitive nor specific for bacterial arthritis. Leukocyte counts in patients with bacterial bursitis are $>1000/mm^3$.

Smears of joint fluid stained for bacteria are positive in only one-third of cases with bacterial arthritis, while blood cultures are positive in up to 60% of adults, and joint cultures are positive in 90% of cases [2,3,10]. Other sites to be cultured, if appropriate, include skin lesions and spinal fluid in a patient with central nervous system features; pharyngeal, rectal, cervical or urethral areas should be cultured for gonococci if disseminated gonococcal infection (DGI) is suspected. PCR technology for the detection of bacterial DNA within the synovial fluid and synovial tissue can be used to detect *Yersinia* spp., *Chlamydia* spp., *Mycoplasma hominis*, *Ureaplasma* spp., *Borrelia burgdorferi* and *Neisseria gonorrheae* [3]. Cultures of synovial tissue obtained by needle biopsy or open biopsy produce higher yields for mycobacterial and fungal infection than do those of synovial fluid.

RADIOLOGICAL AND IMAGING EVALUATION

The most frequent radiographic abnormalities observed in association with bacterial arthritis are related to soft-tissue, including distension of the joint capsule evidenced by the 'fat pad' sign [11]. In mycobacterial infection, minimal joint space narrowing occurs with marginal erosions and extensive demineralisation (Phemister's triad) [12].

Sonography, computed tomography and magnetic resonance imaging are more sensitive than radiographs for detecting joint effusions, but are rarely needed. Magnetic resonance imaging may be helpful in cases of extra-articular infection [11]. Injection of contrast (arthrography) into joint spaces has been used to demonstrate hip and shoulder effusions, but has been replaced by magnetic resonance imaging. Radionuclide imaging with three-phase bone scan is useful for detecting bacterial sacroiliitis, but bone and gallium scans are otherwise of little use [11].

ACUTE BACTERIAL ARTHRITIS

In infants aged <1 month, group B streptococci, Gram-negative bacilli and *S. aureus* are causative organisms. *S. aureus* is the most frequent organism causing bacterial arthritis in children aged

>2 years, and is the causative organism in the vast majority of cases of suppurative arthritis in adults [2,3]. *Staphylococcus epidermidis* is isolated frequently from patients with prosthetic joint infections [3]. *N. gonorrhoeae* was once the predominant cause of bacterial arthritis in young, sexually active adults, but is seen much less frequently today.

Although group A β-haemolytic streptococci are most common, the non-group A streptococci (groups B, C and G) are also recognised as significant pathogens, particularly group B streptococci with diabetic patients [10]. *Streptococcus pneumoniae* occurs as a rare cause of suppurative arthritis in patients with bacteraemia who do not necessarily have pneumonia [13].

Infectious arthritis caused by Gram-negative bacilli is seen in patients with co-morbid conditions, such as intravenous drug abuse, as well as in hospitalised patients with underlying chronic arthritis [2,14]. In the past, *Pseudomonas aeruginosa* was seen commonly in intravenous drug abusers, but is nowadays less common [2,3,14]. *Kingella kingae* has been recognised increasingly as a cause of early childhood (aged < 2 years) osteoarticular infections [15]. Arthritis has also been reported recently with *Arcanobacterium haemolyticum*, an organism associated especially with pharyngitis and tonsillitis in young individuals [16].

Gonococcal arthritis is caused by organisms belonging to the protein 1-A serotype, which are more resistant to serum than strains causing urethritis [10]. This syndrome, which is now diagnosed less commonly, manifests as one of two forms: a polyarticular syndrome with systemic symptoms such as fever, skin lesions and positive blood cultures (DGI), or a monarticular suppurative infection with recovery of the organism from joint fluid. *N. gonorrhoeae* can be recovered from cultures of the genital, rectal and pharyngeal areas.

Other microorganisms that can be present in cases of skin rash and arthritis include *Haemophilus influenzae*, *Moraxella osloensis*, *Streptobacillus moniliformis* and *Neisseria meningitidis* [10]. Patients with meningococcaemia and DGI syndrome have been reported to have many more skin lesions (>100) than those with gonococcal DGI; some patients also present 5–10 days after the onset of the infection with sterile joint effusions in multiple joints which resolve quite rapidly [2].

Specific epidemiological associations for infectious arthritis are summarised in Table 2. Septic arthritis following bites can be caused by the various microorganisms listed in Table 2. Obligate anaerobic bacteria are obtained rarely from joint fluid, particularly prosthetic joints. An acute septic arthritis occurs with *Mycoplasma hominis* and *Ureaplasma urealyticum* in post-partum women and immunocompromised (hypogammaglobulinaemic) individuals [3].

Table 2. Epidemiological associations with infectious arthritis [2]

Epidemiological association	Organism
Female during menstrual cycle or pregnancy; multiple skin lesions (> 100)	*Neisseria gonorrhoeae* *Neisseria meningitidis*
Human bite	*Eikenella corrodens*, *Fusobacterium nucleatum*
Cat or dog bite	*Pasteurella multocida*
Rat bite	*Streptobacillus moniliformis*
Tick exposure	*Borrelia burgdorferi* (Lyme disease)
Ingestion of unpasteurised dairy products, e.g., goat milk in Mexico	*Brucella* spp.
Intravenous drug abuse	*Pseudomonas aeruginosa*
Immunocompromised patients	Gram-negative bacilli
Post-partum women and hypogammaglobulinaemia	*Mycoplasma hominis*
Trauma in aquatic environment	*Mycobacterium marinum*

CHRONIC ARTHRITIS

A polyarthritis of large and small joints has been reported in the later stages of syphilis [17]. Chronic monarticular arthritis with a granulomatous reaction can result from infection with the mycobacterial or fungal organisms listed in Table 3. Patients with *Mycobacterium tuberculosis* infections present principally with pain in a single weight-bearing joint, such as the knee, with concurrent pulmonary tuberculosis in 23% of cases and immunosuppression in 19% of cases [18]. Patients with tuberculosis, as well as those with syphilis, should have an HIV test performed because of the common association between these infections. Non-tuberculous mycobacteria, including *Mycobacterium kansasii*, *Mycobacterium marinum* and members of the *Mycobacterium avium–intracellulare* complex, have a propensity to involve the wrist and hands and to cause flexor tenosynovitis, carpal tunnel syndrome and, rarely, olecranon bursitis [2]. In such a patient with chronic monarticular arthritis, synovial tissue should be cultured for mycobacteria, including incubation at 30°C, as *Mycobacterium marinum* grows better at this temperature. Patients with lepromatous leprosy and erythema nodosum leprosum may have a

Table 3. Geographical and other associations with different forms of chronic monarticular arthritis [10,19]

Organism	Association
Bacteria	
Brucella spp.	Worldwide; unpasteurised milk products
Tropheryma whipplei	Whipple's disease
Treponema pallidum	Syphilis
Mycobacteria and *Nocardia*	
Mycobacterium tuberculosis	Worldwide
Mycobacterium kansasii	Worldwide
Mycobacterium marinum	Aquatic
Mycobacterium avium–intracellulare complex	Worldwide
Mycobacterium fortuitum	Soil
Mycobacterium haemophilum	Immunocompromised
Mycobacterium leprae	Worldwide
Nocardia asteroides	Worldwide
Fungi	
Sporothrix schenckii	Warm, moist soil
Coccidioides immitis	Southwestern USA, Mexico
Blastomyces dermatitidis	North America
Paracoccidioides brasiliensis	South America
Candida albicans	Worldwide
Pseudallescheria boydii	Tropical

Table 4. Common associations of viruses causing arthritis [4]

Common causes of viral arthritis	
Adult females with tenosynovitis	Rubella
Adult females with erythema infectiosum exposure	Parvovirus B19
Adult females with aseptic meningitis	Lymphocytic choriomeningitis virus
Adult males	Mumps
Pre-icteric phase of serum hepatitis	Hepatitis B
Arthropod-borne viruses	
East Africa, India	Chikungunya
East Africa	O'nyong-nyong
Sweden	Ockelbo agent
Australia	Ross River agent
	Barmah Forest virus

symmetrical polyarthritis of the wrist, metacarpals and other small joints of the hands; juxta-articular erosions can be seen in the carpal bones [10].

Chronic arthritis of single or multiple joints can be caused by infection with a number of fungi (Table 3) [19]. *Sporothrix schenckii* affects the knee, wrist or elbow with tenosynovitis. In endemic areas of the Americas, a chronic arthritis of the knee occurs in non-white, immunocompromised men, caused by *Coccidioides immitis* [10]. Joint infection occurs rarely in patients with blastomycosis in North America (an infection that spreads from osteomyelitis) or with *Paracoccidioides* infection in South America (involving joints of the long bones in rural workers).

With *Candida* spp., infections of the joints present with an acute onset resulting from haematogenous spread, with polymorphonuclear leukocytes in synovial fluid; rarely, the fungus may be introduced during intra-articular corticosteroid injection [2]. *Pseudallescheria boydii* bursitis or arthritis in rural tropical areas occurs following penetrating trauma of the knee or elbow. Penetrating trauma also precedes a chronic bursitis with *Scedosporium inflatum* or dematiaceous fungi such as *Exophiala jeanselmei* [2,10].

VIRAL ARTHRITIS

Arthritis is a reasonably frequent event resulting from infection with rubella or mumps virus (Table 4) [4]. A polyarthritis can develop in adult women with rubella, lymphocytic choriomeningitis or parvovirus B19 infection [10]. With rubella, the joint symptoms occur in conjunction with the rash and involve primarily the small joints of the hand. Rubella vaccine given to post-pubertal females can also induce joint symptoms. In late winter and spring, a symmetrical arthritis in adults can be seen in women with erythema infectiosum exposure ('fifth disease' in children), which is an infection caused by parvovirus B19. Lymphocytic choriomeningitis, caused by an arenavirus, has also been reported to cause arthritis in laboratory personnel. In men, arthritis in multiple large and small joints has been associated with mumps [4]. Arthritis develops in up to 20% of patients with hepatitis B infection, in association with urticaria, between 2 days and 6 weeks before the onset of jaundice. This arthritis is symmetrical, with a predilection for the hands, followed by the knees and ankles. Symptoms usually disappear with the onset of jaundice. Patients infected with hepatitis C who are in a mixed cryoglobulinaemic state, present occasionally with arthritis; a positive rheumatoid factor may present a diagnostic dilemma. A number of arthropod-borne alphaviruses of the togavirus family can also cause arthritis (Table 4).

Infrequently, patients infected with human T-lymphotropic virus type 1 have a chronic persistent oligoarthritis. This is a proliferative synovitis involving large joints, with atypical lymphocytes in synovial fluid and pro-viral DNA within tissue cells [10]. Infection with HIV-1 can produce arthralgias of multiple joints and, rarely, monarticular arthritis. Thus, HIV infection may mimic connective tissue disorders, such as Sjogren's disorder, and myositis with arthritis. HIV-infected patients also have a propensity to develop septic arthritis.

ANTIMICROBIAL THERAPY

Empirical antimicrobial therapy to cover most pathogens causing bacterial arthritis would normally be prescribed after obtaining blood cultures and withdrawing synovial fluid for culture, Gram's stain, leukocyte counts and chemical tests. The choice of drug depends on the Gram's stain result and the patient's age and history of sexual activity. Previously, cefuroxime 100 mg/kg per day for children, divided into three daily doses, and 1.5 g every 8 h for adults could be used to cover both *S. aureus* and streptococci [10]. Since more community-acquired infections in the USA and elsewhere are now caused by methicillin-resistant *S. aureus*, recommendations for treatment of infections in such patients, and in those with prosthetic joints, would include vancomycin 1 g every 12 h [20]. Ceftriaxone is a reasonable initial choice for sexually active adults, particularly if they present with DGI syndrome. Therapy should be changed to the optimal and least expensive agent as soon as culture and susceptibility results become available.

The usual course of therapy for suppurative arthritis lasts 2 weeks for *H. influenzae*, streptococci or Gram-negative cocci, 3 weeks for staphylococci, and 4 weeks for pneumococci or Gram-negative bacilli [10,13]. The DGI gonococcal arthritis–dermatitis syndrome is treated with parenteral antibiotics for 2 days after clinical improvement is noted, followed by oral therapy to complete treatment for 7–10 days. Gonococcal septic arthritis requires treatment with parenteral antibiotics for 2 weeks. Mycobacterial infections are treated with four drugs for 2 months; for tuberculosis, treatment can then be switched to isoniazid and rifampicin (if the organisms are susceptible) for a total of 9–12 months [18]. For non-mycobacterial organisms, clarithromycin 500 mg twice-daily may be used in addition. Most fungal infections are responsive to either amphotericin B or lipid complex, or oral itraconazole. The Sanford Guide to Antimicrobial Therapy 2005 [21] provides an up-to-date source of information concerning therapy for specific mycobacterial or fungal infections. Approaches to the special case of prosthetic joint infections have been summarised recently by Shirtliff and Mader [22].

OTHER THERAPEUTIC MODALITIES AND COURSE OF THE ILLNESS

Most individuals with suppurative arthritis respond adequately to appropriate antimicrobial agents after an initial joint aspiration for diagnosis. Repeated needle aspiration for recurrent joint effusions and arthroscopic drainage have both been used with success during the first 5–7 days of treatment, especially if the volume of synovial fluid, the cell count and the percentage of polymorphonuclear leukocytes decrease with each aspiration [3]. Visualisation of joint tissue, lysis of adhesions, drainage of pockets and debridement of necrotic material are possible with arthroscopy [23]. Surgical drainage is required for joints that are not easily accessible for needle aspiration, such as the hip and shoulder, if there is evidence of soft-tissue extension of infection or if the clinical response to antimicrobial therapy is inadequate [3]. Treatment with systemic antimicrobial agents should be continued for up to 1 week after open drainage, and the wound should be allowed to close by secondary closure. Surgical drainage of bacterial bursitis is indicated if there is no clinical response within 7 days [8].

It is not necessary to immobilise the infected joint, although weight-bearing should be avoided until signs of inflammation and pain have disappeared [3]. Joint contractures are a risk early in the course of suppurative arthritis, and an active and passive range of motion exercises may be needed. The joint should be maintained in the functional position, and passive motion may be initiated once the symptoms of pain have subsided. As the inflammation diminishes, active exercises can be started, and weight-bearing can be permitted when all signs of inflammation have disappeared.

The prognosis following infection in the elderly, those with infections of the hip and those with underlying joint disease is poor (Table 5) [2,3,10]. However, most patients with septic arthritis immediately following arthroscopy

Table 5. Predictors of poor outcome with bacterial arthritis

Age >60 years
Pre-existing rheumatoid arthritis
More than four joints affected
Infection in hip and shoulder
Duration of symptoms before treatment of >1 week
Persistently positive culture after 7 days of appropriate therapy

experience few sequelae [24]. Infectious causes of chronic monarticular arthritis are associated occasionally with substantial residuals, even after maximal therapy [19].

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