CHAPTER 14

Infectious Disorders
A. Septic Arthritis

GEORGE HO, JR., MD

- Septic joints signal the presence of a potentially life-threatening infection. For nongonococcal joint infections, the mortality rate among adults ranges from 10% to greater than 50%.
- The most common pathway to a septic joint is through hematogenous seeding from an extra-articular site of infection, for example, pneumonia, pyelonephritis, or skin infection.
- The causes of adult nongonococcal septic arthritis are Gram-positive cocci (75%–80%) and Gram-negative bacilli (15%–20%). *Staphylococcus aureus* is most common organism in both native and prosthetic joint infections.
- Arthrocentesis and synovial fluid analysis are the cornerstones for the diagnosis of septic arthritis. If the synovial fluid white blood cell (WBC) count is extremely high (e.g., >100,000/mm^3), treatment for presumed septic arthritis should be initiated pending culture result of the fluid.
- Cell count, differential, Gram stain, culture, and examination for crystals are the crucial tests to be performed on synovial fluid. This boils down to the 3 Cs: cell count, culture, and crystals.
- In the setting of nongonococcal septic arthritis, Gram stains of infected synovial fluid are positive only 60% to 80% of the time. Blood cultures are positive in approximately 50% of patients.
- In cases of suspected septic arthritis, antibiotic treatment should begin immediately once proper samples for microbiologic studies have been collected.
- Selection of the initial antibiotic approach is guided by the result of the synovial fluid Gram stain and the organisms most likely to be responsible for the infection, based upon the clinical scenario.

Nongonococcal bacterial infections are the most serious infections affecting the joints. Normal joints, diseased joints, and prosthetic joints are all vulnerable to bacterial infection. The fact that septic joints signal the presence of a potentially life-threatening infection cannot be overemphasized, nor can the importance of early diagnosis and prompt, effective therapy. Mortality rates among adults range from 10% to greater than 50%. Full recovery is possible, but poor outcomes are common among those with preexisting arthritis, especially rheumatoid arthritis (RA). This chapter discusses acute nongonococcal bacterial arthritis in adults. Septic arthritis in children, gonococcal joint infection, and septic bursitis are also briefly discussed.

RISK FACTORS

Independent risk factors for acute nongonococcal septic arthritis are age greater than 80 years, diabetes mellitus, preexisting RA, the presence of a prosthetic joint in the knee or the hip, recent joint surgery, and skin infection (1). Compared to diseased or prosthetic joints, normal joints are very resistant to infection. An important predisposing factor to septic arthritis is an impaired immune system. RA, liver cirrhosis, chronic renal failure, and malignancies are often present among patients with septic arthritis. Hemodialysis patients and intravenous drug abusers are predisposed to bacterial joint infections at axial skeleton sites such as the sternoclavicular joint and the sacroiliac joint. Other susceptible hosts are patients with acquired immunodeficiency syndrome, hemophilia, organ transplantation, or hypogammaglobulinemia (2).

PATHOGENESIS

The most common pathway to a septic joint is bacteremic seeding of the affected joint from an extra-articular site of infection such as pneumonia, pyelonephritis, or skin infection. Direct inoculation of the pathogen into a joint is much less common. A cat bite can introduce

Pasteurella multocida into a finger joint, however, and the piercing of a nail through the sole of a sneaker may lead to a *Pseudomonas aeruginosa* infection of the foot. Septic arthritis resulting from arthrocentesis or joint injection occurs at a rate 0.0002% from such occurrences. Penetrating foreign body injury or any surgery on the joint, including total joint replacement, can result in infection. Attention to technique, environment, and perioperative antibiotic prophylaxis have minimized the rate of early prosthetic joint infections. Late infections, occurring a year or more after joint replacement, result from contamination at the time of the implant surgery or bacterial seeding during transient bacteremia. Patients with this uncommon complication complain of pain in a previously painless total joint replacement. Aseptic loosening of a prosthetic joint must be distinguished from infection causing prosthesis failure, because the infection must be eradicated before undertaking revision arthroplasty.

MICROBIOLOGY

Among nongonococcal causes of acute bacterial arthritis, the Gram-positive cocci are the major pathogens. The causes of adult nongonococcal septic arthritis are Gram-positive cocci (75%–80%) and Gram-negative bacilli (15%–20%). *Staphylococcus aureus* is the most common organism in both native and prosthetic joint infections. *Staphylococcus epidermidis* occurs commonly in prosthetic infections but is rare in native joint infections. Anaerobic infections also occur in this setting. Anaerobic infections and coagulase-negative staphylococci are more common in prosthetic joint infections. In the elderly, the Gram-negative microorganisms may be more common because of the many comorbidities that predispose them to systemic Gram-negative bacillary infections. Underlying joint diseases are also more prevalent among the elderly.

CLINICAL FEATURES

Septic arthritis is more often monoarticular (80%–90%) than polyarticular (10%–20%). The predilection is for a single large joint, typically the knee. Thus, in the evaluation of a patient with an acute monoarthritis, septic arthritis is always a consideration, especially if the patient is febrile, appears toxic, or has an extra-articular site of bacterial infection. In the patient with underlying RA, an acute exacerbation of joint inflammation, whether monoarticular or polyarticular, must raise the suspicion of superimposed infection complicating rheumatoid disease.

TABLE 14A-1. CONDITIONS THAT MAY PRESENT AS PSEUDOSEPTIC ARTHRITIS.

Rheumatoid arthritis
Juvenile rheumatoid arthritis
Gout
Pseudogout
Apatite-related arthropathy
Reiter's syndrome
Psoriatic arthritis
Systemic lupus erythematosus
Sickle cell disease
Dialysis-related amyloidosis
Transient osteoporosis synovitis of the hip
Plant thorn synovitis
Metastatic carcinoma
Pigmented villonodular synovitis
Hemarthrosis
Neuropathic arthropathy

Arthrocentesis and synovial fluid analysis are the cornerstones for the diagnosis of septic arthritis. If the synovial fluid white blood cell (WBC) count is extremely high [e.g., >100,000/mm^3 white blood cells (WBC)], treatment for presumed septic arthritis should be initiated pending culture result of the fluid. Pseudoseptic arthritis—an extremely inflammatory arthritis not due to bacterial infection (Table 14A-1)—can only be diagnosed when one is confident that infectious causes have been excluded (3). In this regard, negative synovial fluid cultures should be corroborated by negative blood cultures and by negative results of tests, such as polymerase chain reaction (PCR), for bacterial DNA in the synovial fluid.

Polyarticular infection occurs more commonly in patients with preexisting arthritis and may portend a less favorable outcome (4). *S. aureus* is again the major pathogen. RA patients with polyarticular septic arthritis had a mortality rate of greater than 50% (5). More than one joint should be aspirated when infection in multiple joints is suspected.

Laboratory Findings

The synovial fluid of septic arthritis typically reflects purulent inflammation, with extremely high WBC counts and a preponderance of polymorphonuclear

cells. Although typically >50,000 WBCs/mm^3 and often >100,000 WBCs/mm^3, the cell count range is wide, depending on the timing or arthrocentesis, pretreatment with antibiotics, and other factors. Gram stains of infected synovial fluid are positive only 60% to 80% of the time. A cell count, a Gram stain, and a wet preparation examination for crystals under polarized microscopy are essential immediate tests after joint aspiration. Culturing the fluid for bacteria and any unusual pathogens under suspicion (e.g., acid-fast bacilli, fungi) is also critical. Blood cultures are positive in approximately 50% of the patients with nongonococcal septic arthritis. In addition to attempts to increase the sensitivity and yield of positive cultures, technological advances, such as PCR assays, can aid in the diagnosis and management of many infectious diseases (6). One shortcoming of PCR assays is their extreme sensitivity and the substantial risk of false-positive results.

The coexistence of crystal-induced inflammation and bacterial infection must not be overlooked. Fever can be due to acute crystal-induced synovitis or acute flare of rheumatoid arthritis without infection. But when fever is present, it must not be attributed to the underlying RA without a diligent search for complicating bacterial infection in the inflamed joint.

THERAPY

Therapeutic approaches to different kinds of joint infections are shown in Table 14A-2. Prompt treatment eradicates the infection with less morbidity and hastens recovery. Once septic arthritis is suspected and the proper samples for microbiologic studies are collected, antibiotic treatment should begin immediately. The choice of which antibiotic agent(s) to use depends on the results of the Gram stain and the organisms most likely to be responsible for the infection based upon the clinical scenario. For hospitalized patients with indwelling vascular catheters or patients on hemodialysis, for example, coverage for Staphylococci and Streptococci may be appropriate, in addition to other organisms. Narrow antibiotic coverage may be appropriate if suspicion for a specific organism is validated by Gram stain (e.g., Gram-positive cocci in clusters or chains). On the other hand, if the Gram-stained smear is inconclusive and there are no clinical clues after searching for an extra-articular source of infection in an elderly debilitated patient, then broad antibiotic coverage (against both Gram-positive cocci and Gram-negative bacilli) should be given initially. In a healthy person who engages in high-risk sexual practice and presents with tenosynovitis and migratory arthritis, initiating monotherapy against gonococcal infection may be appropriate after culturing and Gram staining all portals of possible infection. (The drugs of choice for gonococcal infections—second-generation cephalosporins—have broad antimicrobial activity beyond Gram-negative diplococci.) Once the identity and the sensitivities of the microorganism are known, therapy should continue with the most efficacious agent that has the best safety profile and the lowest cost.

Drainage of the infected joint space must be adequate in order to relieve pain, eradicate the infection, and hasten recovery of lost function. During the initial few days, immobilization of the affected joint and effective analgesic medication helps ensure patient comfort. Physical therapy should be instituted as soon as the patient can tolerate mobilization of the inflamed joint.

Repeated needle aspirations may be adequate in some patients if sterilization of the joint space can be

TABLE 14A-2. EMPIRIC ANTIBIOTIC REGIMENS FOR PATIENTS WITH POTENTIALLY SEPTIC JOINTS.

SYNOVIAL FLUID GRAM-STAIN FINDINGS	INITIAL ANTIBIOTIC REGIMEN
Gram-positive	
Gram-positive cocci in clusters (presumptive *Staphylococcus*)	Nafcillin or oxacillin (aminoglycoside should be added if patient is an injection drug user)
Gram-positive cocci in chains (presumptive *Streptococcus*)	Nafcillin or oxacillin
Gram-negative	
Gram-negative bacilli	Nafcillin or oxacillin/aminoglycoside[a]
Gram-negative diplococci (presumptive gonococcus)[b]	Ceftriaxone or cefotaxime

[a] All patients with prosthetic joints, intravenous line placement, or recent hospitalization are at risk for infection with methicillin-resistant *Staphylococcus* species and should receive vancomycin until culture results are available, regardless of Gram-stain results.

[b] In the absence of definitive Gram-stain results, a reasonable empiric regimen for the adult with possible septic arthritis is the combination of nafcillin or oxacillin with a cephalosporin, such as ceftriaxone or ceftizoxime or cefotaxime. An aminoglycoside should be added in the injection drug user. Vancomycin should be substituted for nafcillin/oxacillin if methicillin-resistant *Staphylococcus* is a possibility.

achieved rapidly. Tidal lavage to wash out the joint and arthroscopic procedures are intermediate steps that may benefit some patients and avoid the morbidity of arthrotomy. Under a variety of circumstances, however, surgical drainage may be necessary. Such circumstances include: (1) if when needle aspiration is technically difficult or does not provide thorough drainage of the joint; (2) if sterilization of the joint fluid is delayed; (3) if the infected joint has is already been damaged by preexisting arthritis; or (4) if infected synovial tissue or bone needs debridement (7). Involving the orthopedic surgeon and the physical therapist early in the course of treatment will facilitate the best choice of drainage procedure and result in the best functional outcome.

The optimal duration of antibiotic treatment has not been studied prospectively. For uncomplicated native joint infections, antibiotic treatment can be as brief as 2 weeks (but more often 4 weeks) if the organism is highly susceptible to the antibiotic selected. This treatment duration is typically more prolonged, between 4 and 6 weeks, for more serious infections in the compromised host. For prosthetic joint infections, the antibiotic course is usually quite protracted. For most cases of infected joint replacement, the prosthesis is removed and antibiotic treatment is continued until the site is sterile before reimplantation is considered. Antibiotic-impregnated cement or beads are sometimes employed in the reimplantation, either during multistaged procedures or during an exchange arthroplasty. On rare occasions, antibiotic treatment is continued indefinitely in the patient in whom the risk of removing the infected prosthesis is deemed too great and the microorganism responsible for the infection can be reasonably suppressed by the use of an oral antibiotic agent.

OUTCOME

Retrospective observations indicate that factors portending a poor outcome include young age, old age, virulent microorganisms, delay in the diagnosis and/or initiation of treatment, presence of underlying joint disease, and infection of particular joints (e.g., the shoulder or hip). But a prospective study confirmed that only old age, preexisting joint diseases such as RA, and the presence of a prosthetic joint constituted poor prognostic factors (8).

Avoiding delays in diagnosis, ensuring adequate decompression to prevent avascular necrosis willingness to consider alternative drainage methods when progress is not evident, and being proactive with rehabilitation are within the control of the clinician. Although evidence-based data are lacking, intuition tells us that these considerations may improve the outcome of those with unfavorable prognostic factors.

PREVENTION

Opportunities to prevent septic arthritis are limited but should be kept in mind in patients with underlying arthritis, especially RA, and or patients with total joint replacements. For most patients who have undergone total joint replacements, antibiotic prophylaxis is not indicated routinely before dental procedures. However, in 2003 the American Dental Association and American Academy of Orthopedic Surgeons modified an earlier advisory statement regarding the use of antibiotic prophylaxis before invasive dental procedures (9). It states that antibiotic prophylaxis is not routinely indicated for most dental patients with total joint replacements. However, all patients with a total joint replacement within 2 years of the implant procedure and some immunocompromised patients with total joint replacements are at high risk for hematogenous infections should be considered for antibiotic prophylaxis before invasive dental procedures. The recommended antibiotic agents are based on an empiric regimen directed against the most common microorganisms responsible for late prosthetic joint infections (*S. epidermidis*).

The issue of the cost effectiveness of antibiotic prophylaxis to prevent late infections in prosthetic joints remains extremely controversial due to the lack of reliable data. No long-term observational studies or prospective trials have been done.

The incidence of late infection of a prosthetic joint as a result of procedure-related bacteremia appears to be extremely low, perhaps between 10 to 100 cases per 100,000 patients with total joint replacement per year. Until future studies provide definitive data on cost effectiveness, the decision regarding the use of antibiotic prophylaxis must be based on the physician's estimation of the potential risks, the possible benefits for individual patients, and discussions between patient and doctor.

Any local or systemic bacterial infections must be treated promptly to minimize the possible spread of the infection to the artificial joint. When confronted with an elective procedure that is likely to lead to transient bacteremia (any degree of bleeding at a site that is not normally sterile), the opportunity for antibiotic prophylaxis should be discussed and the final decision is made in consultation with the patient (Table 14A-3).

TABLE 14A-3. COUNSELING PATIENTS WITH A TOTAL JOINT REPLACEMENT REGARDING ANTIBIOTIC PROPHYLAXIS BEFORE AN INVASIVE PROCEDURE THAT LEADS TO TRANSIENT BACTEREMIA.

(1) You have (this condition, these conditions, or no condition) that may make you more susceptible to infections.

(2) The procedure that you are about to undergo may cause these kinds of bacteria to enter your bloodstream briefly. This normally results in no problems. (Brushing your teeth or moving your bowels may result in a small number of bacteria entering your bloodstream briefly in a similar manner.)

(3) Taking this antibiotic drug beforehand may reduce the likelihood of the bacteria causing problems in the replaced joint. But there is no proof or guarantee that this preventive step is 100% effective.

(4) The antibiotic medication is not very expensive. But taking it is associated with a slight risk of unpredictable side effects, similar to ones that what you may encounter with taking other medications (skin rash, nausea, vomiting, joint pain).

(5) The risk of total joint replacement infection as the result of the procedure is very small (estimated to be between 1 in 10,000 and 1 in 10,000), and taking an antibiotic beforehand may reduce the risk even further, but it will not reduce the chance to zero.

(6) If the artificial joint becomes infected, it usually means that it has to be removed and the infection has to be treated until it is cured, and then another total joint replacement procedure can be considered.

(7) In my opinion (recommend one of the three choices): a, b, or c
- (a) You most likely do not need to take an antibiotic before this procedure.
- (b) Even though taking an antibiotic before your procedure is associated with a small risk, I believe that assuming this small risk would be worthwhile in your case because of the significant implications of a joint infection and the possibility (however small) that such an infection might occur.
- (c) I believe that taking the antibiotic beforehand is worthwhile in your case.

I would be happy to review any of these points with you again before you make your decision.

SEPTIC ARTHRITIS IN CHILDREN

Septic arthritis in children is monoarticular more than 90% of the time. Knee and hip joints account for about two thirds of all cases. Children less than 2 years old are more susceptible to septic arthritis than older children. Signs of joint disease in the neonate and infant may be minimal or absent. After *S. aureus*, group B streptococcus and Gram-negative microorganisms are important pathogens in the neonate and young infant. *Candida* and Gram-negative bacilli are usually acquired in the hospital or in another health care setting.

With the decline in *H. influenzae* septic arthritis in children less than 5 years old, microorganisms such as *Kingella kingae* account for a greater percentage of patients. Gonococcal infection must always be considered in the sexually active adolescent with migratory arthritis and pustular skin lesions.

Septic arthritis and osteomyelitis can coexist or complicate each other in the very young child because the metaphyseal and epiphyseal blood vessels communicate and the metaphyses of some long bones are within the joint capsule. Avascular necrosis of the femoral head is unique to septic arthritis of the hip in children. Early surgical decompression to reduce the high intra-articular pressure will restore blood flow to the femoral head. The outcome of treatment of septic arthritis in children is more favorable than in adults. Leg length discrepancy, limitation of joint mobility, and secondary degenerative joint disease are late sequelae in 25% of cases.

GONOCOCCAL JOINT DISEASE

Migratory arthritis and tenosynovitis with or without skin lesions in a sexually active adult should raise the suspicion of disseminated gonococcal infection (DGI). Joint infections caused by *Neisseria gonorrhoeae* differ from nongonococcal disease. In contrast to patients with nongonococcal arthritis, who are often elderly or have serious underlying illnesses, individuals with gonococcal (GC) arthritis are typically young, healthy adults. Women are more susceptible to DGI than men. Positive GC cultures at extra-articular sites, for example, genitourinary tract, rectum, and throat, can help confirm the diagnosis because the synovial fluid Gram stain and culture are typically negative.

Prompt response to antibiotic therapy is the rule and residual problems in the affected joint are uncommon. Resistance to penicillin is on the rise and it is wise to use a third-generation cephalosporin as the initial treatment for DGI.

SEPTIC BURSITIS

The bursae throughout the body facilitate joint mobility and many are located in close proximity to the synovial joints. The superficial bursae are more susceptible to bacterial infection than the deep bursae (10). The most common sites of septic bursitis are the olecranon

and the prepatellar bursa. The pathogenesis of septic bursitis is the direct extension of a superficial skin infection into the adjacent bursa. Some of the activities that cause trauma to the superficial bursae are carpet laying, mining, plumbing, roofing, gardening, wrestling, gymnastics, and hemodialysis. *S. aureus* is the most common pathogen, responsible for greater than 80% of all cases.

Extensive cellulitis surrounding the bursa and distal edema on the affected limb are common. A careful search for skin lesions as the portal of bacteria invasion is often rewarding. A bursal effusion or fluctuance of the bursal sac on physical examination should lead to aspiration of the content.

The bursal fluid is usually inflammatory and the Gram stain is positive for Gram-positive cocci. A bactericidal antistaphylococcal agent is the initial drug of choice. In mild infections, an oral agent will suffice with outpatient follow-up and adequate drainage. If the infection is severe and the patient appears toxic, admission to the hospital for parenteral antibiotic treatment is advisable. In draining the bursa, a large bore needle is necessary when the content is thick or contains particulate matter. Surgical drainage or bursectomy is rarely necessary. The outcome of treatment of septic bursitis of the superficial bursae is usually excellent.

REFERENCES

1. Kaandorp CJE, Van Schaardenburg D, Krijnen P, et al. Risk factors for septic arthritis in patients with joint disease: a prospective study. Arthritis Rheum 1995;38: 1819–1825.
2. Franz A, Webster AD, Furr PM, et al. Mycoplasmal arthritis in patients with primary immunoglobulin deficiency: clinical features and outcome in 18 patients. Br J Rheumatol 1997;36:661–668.
3. Ho G Jr. Pseudoseptic arthritis. R I Med 1994;77:7–9.
4. Dubost J, Fis I, Denis P, et al. Polyarticular septic arthritis. Medicine 1993;72:296–310.
5. Epstein JH, Zimmermann B, Ho G Jr. Polyarticular septic arthritis. J Rheumatol 1986;13:1105–1107.
6. Post JC, Ehrlich GD. The impact of the polymerase chain reaction in clinical medicine. JAMA 2000;283: 1544–1546.
7. Ho G Jr. How best to drain an infected joint: will we ever know for certain? J Rheumatol 1993;20:2001–2003.
8. Kaandorp CJE, Krijnen P, Moens HJB, et al. The outcome of bacterial arthritis: a prospective community-based study. Arthritis Rheum 1997;40:884–892.
9. American Dental Association/American Academy of Orthopaedic Surgeons. Advisory statement: antibiotic prophylaxis for dental patients with total joint replacements. J Am Dent Assoc 2003;134:895–899.
10. Zimmermann B III, Mikolich DJ, Ho G Jr. Septic bursitis. Semin Arthritis Rheum 1995;24:391–410.

CHAPTER 14

Infectious Disorders
B. Viral Arthritis

LEONARD H. CALABRESE, DO

- Three general patterns of virus-associated illness are observed in rheumatic disease: acute, self-limited illness; chronic infection; and latent infection, with potential for reactivation.
- Parvovirus B19 can cause a polyarticular, small-joint arthritis that mimics rheumatoid arthritis (RA).
- The "slapped cheek" rash characteristic of parvovirus B19 infections in children is seen rarely in adults.
- In contrast to RA, the duration of joint symptoms in B19 infections almost never persists beyond 1 month, and the joint disease is never erosive.
- Rubella infections are associated with fever, constitutional symptoms, cervical and posterior occipital lymphadenopathy, and a characteristic maculopapular rash.
- Hepatitis C can be associated with a variety of rheumatic complaints, none of which are associated ultimately with joint erosions: A nonerosive, nonprogressive arthritis associated with tenosynovitis and joint symptoms out of proportion to physical findings; intermittent mono- and oligoarticular arthritis; and symmetrical polyarthritis involving small joints and resembling RA.
- The majority of patients with hepatitis C virus infections are rheumatoid factor positive, often in high titer. This frequently leads to diagnostic confusion.
- Acute hepatitis B infections are associated with the sudden onset of an inflammatory polyarthritis and often with an urticarial or maculopapular rash.
- The arthritis of hepatitis B generally precedes the onset of jaundice by days to weeks, then subsides once jaundice begins.
- Human immunodeficiency virus (HIV) infection should be considered in individuals who present with features of reactive arthritis, psoriatic arthritis, or unusual inflammatory joint complaints.

The potential relationships between many viral infections and rheumatic syndromes are confounded by the ubiquity of viral agents, and by the fact that all individuals are afflicted intermittently by viral infections of some kind. Three patterns of viral illness are useful when considering the possibility of a virus-associated rheumatic disease:

- **Acute but self-limited illness.** The pathogen produces a short-lived infection and survives by moving on to the next host. Many respiratory viruses, e.g., parvovirus B19 and rubella, fit this pattern.
- **Chronic infection**. The viral agents establish ongoing infections following the primary stage in all or only some of the patients whom they infect. Examples of viruses known to lead to chronic infections include hepatitis B (HBV), hepatitis C (HCV), and the human immunodeficiency virus (HIV).
- **Latent infection, with potential for re-activation**. In this pattern, typified by herpesviruses such as *Varicella zoster*, the primary infection may be either apparent or subclinical.

This chapter focuses on viral pathogens associated with the first two of these clinical disease patterns, as the acute (but self-limited) and chronic infection patterns are most likely to cause articular complaints. Table 14B-1 provides a full list of viral infections known to produce clinically significant forms of arthritis (1).

PARVOVIRUS B19

Parvovirus B19, a small DNA virus, is the cause of fifth disease, also known as erythema infectiosum, which is principally a disease of childhood. In addition, B19 can cause a polyarticular, small-joint arthritis that mimics rheumatoid arthritis (RA). B19 occurs in outbreaks and is spread by respiratory secretions. The secondary transmission rate to adults is about 50%. Up to 50% of healthy adults are positive for anti-B19 IgG antibodies but negative for IgM directed against this virus, indicating previous exposure to this agent and (in most cases) asymptomatic infection at some point in the past. Seronegative individuals in contact with school-aged

TABLE 14B-1. COMMON VIRAL INFECTIONS WITH PROMINENT JOINT INVOLVEMENT.

PATHOGEN	MOST CHARACTERISTIC ARTICULAR MANIFESTATIONS
Parvovirus B19	Rheumatoid arthritis–like illness lasting days to weeks after infection
Rubella virus	Morbilliform rash and self-limited polyarthritis following natural infection or vaccination
Hepatitis C virus	Chronic polyarthralgias or polyarthritis; mimic of rheumatoid arthritis
Hepatitis B virus	Acute polyarthritis in prodromal phase of hepatitis; chronic polyarthritis with systemic vasculitis
Human immunodeficiency virus (HIV)	Changing patterns of rheumatic morbidity in modern era of HIV therapy

children or with an actively infected individual are at highest risk. Eliciting a history of such contacts is essential in the evaluation of patients with an acute polyarthritis (2).

Articular symptoms in adult B19 infection generally include the acute onset of polyarthralgias or, less commonly, polyarthritis. Although the ultimate pattern of joint involvement is similar to classic RA, the arthritis of B19 infection may start in one or a few joints and spread with an additive pattern. For the purposes of diagnosis in adults, unfortunately, the striking "slapped cheek" rash so often evident in children is seen rarely. The median duration of joint symptoms is about 10 days, but pain and stiffness may persist for longer and may recur (3). In contrast to RA, however, the duration of joint symptoms almost never persists beyond 1 month in B19 infections, and the joint disease is never erosive.

Most patients with parvovirus B19 arthropathy lack rheumatoid factor, although occasional patients have been noted to have positive rheumatoid factors, antinuclear antibodies (ANAs), anti-DNA, and other autoantibodies. Other rheumatic syndromes have also been described including a lupus-like syndrome, vasculitis, and cytopenias.

The diagnosis of B19-associated arthritis depends on a high degree of clinical suspicion, often driven by the critical medical history of exposure to sick children, the appropriate clinical picture, and the detection of anti-B19 IgM antibodies. The presence of anti-B19 IgG is insufficient, as this merely indicates past infection. The detection of B19 DNA in serum by polymerase chain reaction (PCR) can also secure the diagnosis, but this is rarely necessary. The essential elements of treatment are recognizing the self-limited nature of the condition and not confusing it with RA. Treatment is generally symptomatic, though in rare cases of chronic arthritis following acute B19 infection the administration of intravenous immunoglobulin has been reported to efficacious (3).

RUBELLA

Rubella, a small RNA virus, is spread by airborne droplets. Two or three weeks after the infection, rubella produces an exanthemous illness characterized by fever, constitutional symptoms, cervical and posterior occipital lymphadenopathy, and a characteristic maculopapular rash. Before the widespread application of vaccines, rubella occurred in epidemic patterns every 6 to 9 years. Since the introduction of aggressive immunization programs, the rates of new infections have become a mere fraction of those previously seen. Thus, many clinicians overlook rubella in the differential diagnosis of acute arthritis (1).

In the course of natural infection with rubella, symmetrical arthralgias or arthritis associated with morning stiffness may mimic RA. A more migratory pattern of joint involvement may occur, as well. Periarthritis, tenosynovitis, and carpal tunnel syndrome have also been reported. The articular phase of the illness is self-limited and generally lasts less than 2 weeks (4). Antirubella IgM antibodies appear within a few weeks of infection and persist for 4 to 6 months; thus their detection in the appropriate clinical setting is diagnostic.

Rubella can be prevented by vaccination. Postvaccination rheumatic symptomatology, however, including arthralgias, arthritis, myalgias, and paresthesias, have lessened overall enthusiasm for universal vaccination. The vaccine is a live attenuated virus that has undergone modification in recent years in the interest of diminishing arthritogenicity. Despite these modifications, adult immunization is associated with arthropathy in about 15% of individuals. These generally occur 2 weeks after immunization and last less than a week. Children undergoing immunization may develop a peculiar lumbar radiculoneuropathy that produces popliteal pain, dubbed "catcher's crouch," upon arising in the morning. This may occur 1 to 2 months following immunization and generally resolves without therapy. Rubella arthritis is managed conservatively with analgesics and nonsteroidal anti-inflammatory agents.

HEPATITIS C VIRUS

Hepatitis C virus is the major cause of post-transfusion and community acquired non-A, non-B chronic hepatitis. The natural history of HCV is generally one of a

subclinical infection followed by chronicity in 70% to 80% of individuals. The incidence of HCV is 150,000 new cases each year in the United States, resulting in 93,000 cases of chronic hepatitis C. Hepatitis C, currently estimated to infect 3.5 million people nationwide, is transmitted predominantly by parenteral routes. Most patients never develop progressive liver disease, but in about 20% of cases cirrhosis or hepatocellular carcinoma ensues over two to three decades. HCV is associated with a wide variety of extrahepatic manifestations, many of which are rheumatic and immunologically driven (Table 14B-2) (5).

Articular disease manifested by painful joints is common in the setting of HCV infection. Remarkably little is known or agreed upon with regard to the articular manifestations of HCV: their clinical features, pathogenesis, natural history, or optimal therapy. Data on the prevalence of articular symptoms in HCV infection vary markedly among studies, probably due to major differences in design (e.g., reliance upon questionnaires as opposed to detailed physical examinations). Whereas studies utilizing physical examination suggest arthritis as a complication of HCV in less than 5% of patients, those employing questionnaire methodology describe joint complaints in up to 30% of infected individuals (1).

Whether HCV is associated with a distinct form of inflammatory joint disease is still unsettled, though a growing number of observational reports suggest it is. One syndrome recently described depicts a nonerosive, nonprogressive arthritis associated with tenosynovitis and joint symptoms out of proportion to physical findings. Others have found an RA-like picture, as well as an intermittent mono- and oligoarticular arthritis, all without erosive changes. On physical examination, joint tenderness is common but frank synovitis less so. Joint effusions are distinctly rare.

One of the most frequent challenges in the HCV-infected population is differentiating true RA from the polyarthritis of HCV infection. The differential diagnosis is complicated by the fact that HCV-infected individuals have a high prevalence of rheumatoid factor (RF; 50%–60%) activity as well as other laboratory manifestations of autoimmunity (Table 14B-3). The high proportion of HCV-infected patients who are positive for RF is explained in part by the high prevalence of cryoglobulins among HCV-infected individuals. (The IgM component of mixed cryoglobulinemia has RF activity; i.e., reacts with the Fc portion of the IgG component; see Chapter 21E.)

TABLE 14B-2. AUTOIMMUNE CONDITIONS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION.

Cryoglobulinemic vasculitis
Autoantibody production
Autoimmune cytopenias
Membranoproliferative glomerulonephritis
Sicca-like syndrome
Arthralgias and arthritis

TABLE 14B-3. ESTIMATED PREVALENCE OF SEROLOGIC ABNORMALITIES IN PATIENTS WITH HEPATITIS C VIRUS INFECTION.

SEROLOGIC FINDING	PREVALENCE
Rheumatoid factor	50%–60%
Cryoglobulins	30%–40%
Antinuclear antibody	10%–40%
Monoclonal gammopathy	10%–15%
Antithyroid antibodies	5%–10%
Antiphospholipid antibodies	20%
Antismooth muscle antibody	7%–20%
Antineutrophil cytoplasmic antibody (ANCA)*	10%

SOURCE: Adapted from Vassilopoulos D, Calabrese LH. Curr Rheumatol Rep 2003;5:200–204, with permission of *Current Rheumatology Reports*.
*ANCA is hepatitis C virus infection is not directed against proteinase or myeloperoxidase.

Although the presence of RF does not correlate with articular symptoms, it has led to much confusion in differentiating articular syndromes in HCV infection from true RA. Antibodies to CCP are of higher diagnostic sensitivity than is RF for the diagnosis of RA (6). RA patients also tend to have much more in the way of objective joint changes (i.e., frank synovitis) than patients with HCV infection, in whom arthralgias are more common. Finally, HCV-associated joint disease is not associated with erosive changes. Evidence of joint destruction or bone erosions invoke other diagnoses.

The management of HCV-associated articular manifestations remains problematic. A recent uncontrolled study of interferon-based therapy suggested that HCV-related articular manifestations may respond to aggressive antiviral therapy, but controlled trials and better clinical definitions of disease and response are needed (7). Given the potential for exacerbation of the underlying hepatic disease, all therapies must be administered with caution.

HEPATITIS B INFECTION

Hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA virus. HBV is transmitted by both parenteral and sexual routes. With an estimated

one third of the world's population having histories of HBV infection (self-limited in the majority of cases) and 5% to 10% remaining chronically infected, HBV is the most common viral illness worldwide. HBV can cause cirrhosis and hepatocellular carcinoma, as well as a variety of extrahepatic manifestations (8).

Acute HBV infection is associated with an inflammatory polyarthritis that is clinically important to recognize, for it may mimic the onset of classic RA. Often associated with the articular phase of this infection is an urticarial or maculopapular rash. The arthritis, usually sudden in onset, involves the wrists, knees, and ankles as well as the small joints of the hands in a symmetrical fashion. The arthritis generally occurs in the prodromal phase of viremia and subsides after the appearance of jaundice, which it precedes by days to weeks.

The pathogenesis of this illness is believed to be secondary to immune complex deposition in small blood vessels. No specific therapy is required for the arthritis other than supportive care because the condition is self-limited. The condition should be suspected in any patient with the acute onset of polyarthritis, and heightened when risk factors for HBV acquisition are evident.

The vast majority of patients with HBV-associated arthritis have some liver enzyme abnormalities at the time of arthritis onset. The presence of IgM directed against HBV surface antigen or the detection of HBV DNA in serum is diagnostic. Recognizing the underlying etiology (and avoiding inappropriate therapy for other joint disorders) is critical (1). Persistent polyarthritis lasting more than a few weeks should raise the suspicion for transformation to a systemic vasculitic state (i.e., polyarteritis nodosa; see Chapter 21B).

HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus (HIV-1), a lentivirus, is the etiologic agent of acquired immunodeficiency syndrome (AIDS). HIV disease has been reported in virtually every part of the world and is a major global public health problem. By the end of this decade, there will be 100 million individuals infected with HIV. HIV disease is a chronic illness with a mean life expectancy after infection of approximately 10 years. The virus preferentially infects CD4 lymphocytes and through a variety of mechanisms leads to progressive CD4 lymphocyte depletion, progressive immunodeficiency, and opportunistic infection or malignancy. In recent years, the introduction of combination antiretroviral therapy (highly active antiretroviral therapy; HAART) has dramatically changed the natural history of the disease for those individuals with access to drugs. For many of these patients, HIV disease has become—rather than an invariably fatal disease—a chronic illness, albeit one that is complex in management.

In the pre-HAART era, severe cases of reactive arthritis and psoriatic arthritis were observed in the HIV population. In addition, atypical forms of joint inflammation not fitting any particular pattern, often referred to as HIV-associated arthritis, were also described. Although relatively uncommon, these conditions were often clinically dramatic and at times difficult to manage (9).

Today, these entities should be considered in individuals with documented HIV infection or risk factors for HIV infection who develop features of reactive arthritis, psoriatic arthritis, or unusual inflammatory joint complaints. Clues to the presence of these conditions in HIV include the propensity for overlapping features (e.g., clinical features of reactive arthritis in the presence of psoriasis vulgaris) and a sparing of the axial spine.

Acquiring precise data on incidence of these forms of arthritis has been problematic, with multiple studies using different methodologies yielding disparate results (9). Since the introduction of HAART in 1997, these syndromes have been reported with diminishing frequency in Western countries but in sub-Saharan Africa, where access to such therapies is unfortunately rare, these disorders are widely seen (1,10).

With the changing patterns of overall morbidity in HIV disease have come changing patterns of rheumatic complications, including the descriptions of an *immune reconstitution syndrome* following the institution of HAART (10). In this disorder, following initiation of HAART in patients with advanced forms of immunodeficiency, the new onset or exacerbation of previously mild or unrecognized autoimmune disease such as sarcoidosis, RA, systemic lupus erythematosus, or autoimmune thyroid disease may be seen weeks to months later. A similar syndrome is well recognized to occur with immune reconstitution to occult infections with organisms such as mycobacteria, fungi, viruses, bacteria, and parasites. In general, most immune reconstitution syndromes are self-limited, but their recognition is vital to plan an appropriate course for management. HAART need not be interrupted or discontinued. Immunosuppressive therapy can be employed as necessary in individuals with the immune reconstitution syndrome, although aiming for the minimal effective doses in controlling inflammation is obviously desirable.

OTHER FORMS OF VIRAL ARTHRITIS

Articular symptoms consisting of polyarthralgias are observed commonly in the course of many common viral syndromes that are rarely diagnosed in clinical

practice and are so self-limited that they rarely receive rheumatologic attention. A variety of far less common viral infections can also be associated with arthritis, including the alphaviruses such as Chikungunya, O'nyong-nyong and Igbo viruses, and Ross River, Sinbis, and Mayaro viruses, which are found worldwide, especially in Asia and the Pacific, South America, and Scandinavia. All of these agents should be considered in the differential diagnosis of unusual forms of arthritis with or without fever and other constitutional symptoms given the appropriate epidemiologic history (10). Infection with HTLV-1, an endemic retrovirus in the Pacific and Caribbean now increasingly seen in intravenous drug users in the United States, is also associated with a number of rheumatic syndromes, including an illness that resembles RA in its presentation (10).

REFERENCES

1. Calabrese LH, Naides SJ. Viral arthritis. Infect Dis Clin North Am 2005;19:963–980.
2. Young NS, Brown KE. Parvovirus B19. N Engl J Med 2004;350:586–597.
3. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumor necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. Ann Rheum Dis 2004;63(Suppl 2):ii18–ii24.
4. Smith CA, Petty RE, Tingle AJ. Rubella virus and arthritis. Rheum Dis Clin North Am 1987;13:265–274.
5. Vassilopoulos D, Calabrese LH. Rheumatic manifestations of hepatitis C infection. Curr Rheumatol Rep 2003; 5:200–204.
6. Sene D, Ghillani-Dalbin P, Limal N, et al. Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjogren's syndrome. Ann Rheum Dis 2006;65:394–397.
7. Zuckerman E, Keren D, Rozenbaum M, et al. Hepatitis C virus-related arthritis: characteristics and response to therapy with interferon alpha. Clin Exp Rheumatol 2000; 18:579–584.
8. Lai CL, Ratziu V, Yuen MF, Poynard T. Viral hepatitis B. Lancet 2003;362:2089–2094.
9. Vassilopoulos D, Calabrese L. Rheumatic aspects of human immunodeficiency virus infection and other immunodeficiency states. In: Hochberg M, Silman A, Smolen J, Weinblatt M, Weisman M, eds. Rheumatology. 4th ed. St. Louis: Mosby; 2006:26.1–26.9.
10. Calabrese L, Kirchner E, Shrestha R. Rheumatic complications of human immunodeficiency virus (HIV) infection in the era of highly active antiretroviral therapy (HAART): emergence of a new syndrome of immune reconstitution and changing patterns of disease. Semin Arthritis Rheum 2005;35:166–174.

CHAPTER 14

Infectious Disorders
C. Lyme Disease

LINDA K. BOCKENSTEDT, MD

- Lyme disease is a tick-borne zoonosis caused by spirochetes of the genus *Borrelia burgdorferi sensu lato*.
- The majority of Lyme disease cases are localized to endemic foci in the United States, Europe, and Asia.
- In the United States, more than 90% of cases occur in only nine states: New York, Connecticut, New Jersey, Pennsylvania, Massachusetts, Maryland, Rhode Island, Wisconsin, and Minnesota.
- *B. burgdorferi* species are transmitted by hard-shelled ticks of the *Ixodes* complex, for example, *Ixodes scapularis* in the northeastern and north central United States.
- Upon infecting humans, *B. burgdorferi* replicates in the skin and then disseminates via the bloodstream to other organs, leading to extracutaneous disease manifestations.
- Seventy to eighty percent of Lyme disease patients develop a characteristic skin rash, erythema migrans (EM), at the site of tick feeding. The rash usually appears within days to weeks of the tick bite (range, 3–30 days).
- The hallmark of disseminated Lyme disease is the appearance of multiple EM lesions. These arise in about 50% of untreated patients with early localized disease. Secondary lesions are similar to the primary lesion, although are generally smaller in size and can appear anywhere on the body.
- Fever, malaise, myalgias, and arthralgias generally accompany dissemination of the *Borrelia* infection.
- Cardiac involvement in Lyme disease occurs in 4% to 10% of untreated patients, usually as varying degrees of atrioventricular heart block.
- Acute peripheral nervous system disease may take several forms in Lyme disease: cranial nerve palsies (unilateral or bilateral seventh nerve palsy is the most common neurological manifestation), sensorimotor radiculopathies, and mononeuritis multiplex.
- Late manifestations of Lyme disease may occur in the joints, nervous system, and skin. At this stage, joint involvement usually presents as an intermittent, oligoarticular arthritis. The knee is most commonly affected.

Lyme disease is a tick-borne zoonosis caused by spirochetes of the genus *Borrelia burgdorferi sensu lato* (1). The disease was first recognized in 1976 with evaluation of a clustering of children with presumed juvenile rheumatoid arthritis in the area around Lyme, Connecticut. The onset of arthritis was often heralded by a characteristic skin rash, erythema migrans (EM), which had been linked previously to the bite of *Ixodes ricinus* ticks in Europe and the subsequent appearance of neurologic abnormalities (Bannworth's syndrome). With time, it became apparent that arthritis was one manifestation of a multisystem disorder that involved the skin, heart, joints, and nervous system. In 1981, Willy Burgdorfer isolated the causative agent that bears his name, *Borrelia burgdorferi,* from *Ixodes scapularis* ticks collected on Long Island. The subsequent demonstration of antibodies to *B. burgdorferi* in the sera of patients with Lyme disease along with the eventual culture of the organism from tissues and body fluids confirmed the spirochetal etiology of the disorder.

EPIDEMIOLOGY

Lyme disease is widespread, with the majority of cases localized to specific endemic foci in the United States, Europe, and Asia (2). In each of these locations, *B. burgdorferi* species are transmitted by hard-shelled ticks of the *Ixodes* complex: *Ixodes scapularis* in the northeastern and north central United States, *I. pacificus* along the United States west coast, *I. ricinus* in Europe, and *I. persulcatus* in Asia. The *B. burgdorferi* species transmitted by *Ixodes* ticks differs among continents, with exclusively *B. burgdorferi sensu stricto* in North America, and *B. burgdorferi sensu stricto, B. afzelii*, and *B. garinii* in Europe and Asia. Although

similar in genetic make-up, these Borrelia species are not identical and disease manifestations resulting from infection can vary across species. Arthritis is more common after *B. burgdorferi sensu stricto* infection. Neurologic disease is associated more strongly with *B. garinii*, and chronic skin disease with *B. afzelii* (see below).

Lyme disease is the most common vector-borne disease in the United States, with 19,804 cases reported in 2004 to the Centers for Disease Control (CDC) (3). The incidence of Lyme disease parallels the prevalence of infected ticks, with more than 90% of cases originating from just nine states: New York, Connecticut, New Jersey, Pennsylvania, Massachusetts, Maryland, Rhode Island, Wisconsin, and Minnesota. The seasonal variation of Lyme disease relates to the 2-year life cycle and feeding patterns of *Ixodes* ticks. In the northeast, larval ticks first acquire *B. burgdorferi* by feeding on small rodent reservoir hosts (especially the white-footed mouse), then molt into nymphs, the predominant vector for human disease. The peak incidence of Lyme disease occurs during the late spring and summer, when nymphal ticks feed, as adult ticks prefer to feed on white-tailed deer. Transovarial transmission of *B. burgdorferi* from infected adult female tick to egg does not occur, so a competent reservoir host, such as the white-footed mouse, is required to maintain *B. burgdorferi* in nature. This may explain the paucity of cases of Lyme disease in warmer climates, where larvae preferentially feed on noncompetent reservoirs such as lizards. Although the primary reservoir for *B. burgdorferi* is mammals, the organism can also survive in birds.

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease largely reflect the biology of *B. burgdorferi* as it replicates in the skin and then disseminates via the bloodstream to other internal sites where disease can be seen. Typically signs and symptoms appear in overlapping stages as early localized disease, early disseminated infection, or late disease (1,4).

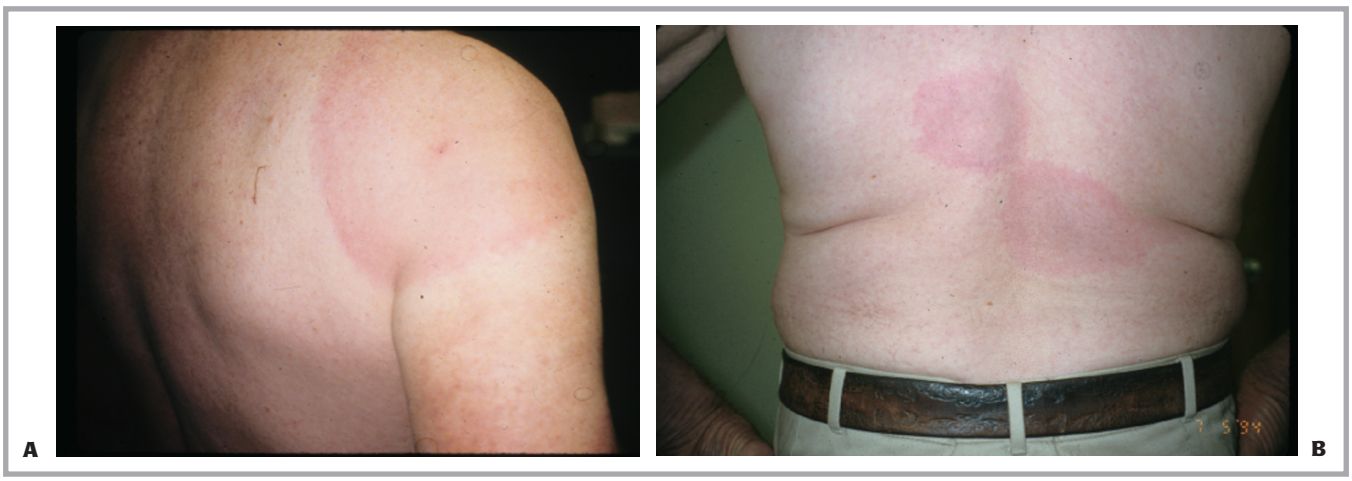
Early Localized Disease

Within days to weeks of the tick bite (range, 3–30 days), 70% to 80% of infected individuals develop a characteristic skin rash, erythema migrans (EM), at the site of tick feeding [Figure 14C-1(A)]. As ticks preferentially feed in skin folds or where clothing grips the skin, common sites are the axilla, popliteal fossa, groin, and abdomen. EM typically begins as a single painless erythematous macule or papule that expands rapidly (2–3 cm/day), with some lesions more than 70 cm in diameter (most, however, are on the order of 5 cm). These features distinguish EM from reactions to the tick bite itself, which usually begins within hours and is associated with significant pruritis.

Although classically reported as a bull's eye rash, EM more commonly appears as an expanding macular lesion, occasionally with a vesicular or necrotic center. It is unusual for EM to produce local symptoms other than tingling and burning or occasionally mild pruritis.

FIGURE 14C-1

(A) Erythema migrans rash with central clearing on the shoulder of a patient. Note the central hyperpigmentation at prior tick bite site (punctum). *Borrelia burgdorferi* was isolated from a biopsy culture performed at the periphery of the lesion. (B) Multiple erythema migrans lesions on the back of a patient whose primary lesion is depicted in (A). Note absence of central papule or postinflammatory skin change. (From Nadelman RE, Wormser GP, Am J Med 1995;98:16S, with permission from Excerpta Medica, Inc.)



EM can be associated with systemic viral-like symptoms including malaise, fever, headache, stiff neck, myalgia, and arthralgia. These latter symptoms without EM can be the presenting manifestation in up to 18% of patients, and can be distinguished from other viral syndromes by the absence of upper respiratory or gastrointestinal involvement. Histopathology of EM lesions reveals mononuclear and lymphoplasmacytic infiltrates.

Erythema migrans must be distinguished from another EM-like rash associated with the bite of the lone star tick, *Amblyomma americanum*, found in the southeastern and south-central states. Patients with Southern tick-associated rash illness (STARI) develop a bull's eye rash but are seronegative for Lyme disease (5). A noncultivable spirochete, *Borrelia lonestari,* has been identified in *A. americanum* ticks, and one patient has been described in whom *B. lonestari* DNA was detected in a skin biopsy of the rash and in the biting tick.

Another recognized but rare skin manifestation seen in European Lyme disease is borrelial lymphocytoma, which typically presents on the earlobe or nipple as a solitary bluish-red nodule. It arises with EM or somewhat later, but may persist for months or more than a year, in contrast with EM, which usually disappears without specific therapy within weeks.

Early Disseminated Infection

Weeks to months after the onset of infection, spirochetes can disseminate to internal organs, with disease primarily seen in the skin, joints, heart, and nervous system. The hallmark of disseminated Lyme disease is the appearance of multiple EM lesions [Figure 14C-1(B)], which arise in about 50% of untreated patients with early localized disease. Secondary lesions are similar to the primary lesion, although are generally smaller in size and can appear anywhere on the body. Patients generally are ill during this phase, with fever, malaise, myalgias, and arthralgias.

Musculoskeletal involvement in Lyme disease is common at all stages of infection, but inflammatory arthritis appears in <10% of infected individuals and is considered a manifestation of late disease (see below). Fleeting migratory pains in muscles, joints, and periarticular structures, lasting only hours to days, can be seen in both early localized infection as well as in acute disseminated disease. Although myalgia is a common symptom, true myositis with elevation in muscle enzymes and abnormalities on muscle biopsy is rare.

Cardiac involvement in Lyme disease occurs in 4% to 10% of untreated patients, and typically manifests as varying degrees of atrioventricular heart block. Electrophysiology studies have demonstrated that conduction system disease occurs most commonly above the bundle of His and involves the atrioventricular node, but can involve multiple levels. Although myopericarditis can rarely occur, acute valvular disease and congestive heart failure are not found in Lyme carditis, distinguishing *B. burgdorferi* infection from acute rheumatic fever or viral myopericarditis. Lyme carditis resolves without specific therapy, but in some cases temporary pacemakers are required.

Lyme disease can affect both the peripheral and the central nervous systems. Neurologic involvement, once seen in 10% to 15% of untreated patients, has declined with earlier recognition and treatment of Lyme disease. Acute peripheral nervous system disease results in cranial nerve palsies, sensorimotor radiculopathies, and mononeuritis multiplex. Unilateral or bilateral seventh nerve palsy is the most common neurological manifestation in the United States. Even in endemic areas, however, Lyme disease accounts for only about 25% of cases of seventh nerve palsies arising during the periods of nymphal tick feeding (spring/summer). Acute central nervous system involvement presents as a lymphocytic meningitis and rarely encephalomyelitis, the latter more commonly seen in Europe. Cerebrospinal fluid examination of patients with isolated seventh nerve palsy can reveal an asymptomatic lymphocytic pleocytosis, but given the favorable outcome with oral antibiotic regimens that penetrate the central nervous system (CNS), performance of lumbar puncture is not generally recommended in the absence of suggestive signs and symptoms of meningitis or encephalomyelitis.

Disseminated *B. burgdorferi* infection can result in abnormalities in other organ systems, including the eye (keratitis), the liver (hepatitis), the spleen (necrosis), and subcutaneous tissue (panniculitis). Disease in these organ systems is rare and generally associated with more classic manifestations of Lyme disease. Routine screening for Lyme disease in the absence of other suggestive signs of *B. burgdorferi* infection in this setting is unwarranted.

Late Disease

A minority of patients develops late manifestations of Lyme disease, principally confined to the joints, nervous system, and the skin. At this stage, joint involvement may present as an intermittent, oligoarticular arthritis. The knee is most commonly affected, followed by the shoulder, the elbow, the temporomandibular joint, and the wrist. Joint effusions can be quite large (50–100 cc in the knee) but not particularly painful. Synovial fluid is inflammatory; cell counts average 25,000/mm^3, with a neutrophil predominance. Periarticular symptoms such as bursitis and tendonitis can also be seen. Patients with Lyme arthritis can experience recurrent attacks of joint inflammation with the frequency and duration of attacks

diminishing with time. Lyme arthritis can mimic other causes of mono- or pauciarticular arthritis, including the seronegative spondyloarthropathies and juvenile rheumatoid arthritis. Low back pain and spinal involvement is rare in Lyme disease, however. Less than 10% of patients with recurrent Lyme arthritis evolve a pattern of chronic unremitting synovitis involving a single joint, especially the knee. In these individuals, the spirochete DNA can no longer be detected by polymerase chain reaction (PCR) of joint fluid and synovial specimens, and further treatment with antibiotics does not alter the time to resolution, which generally occurs within 5 years.

Late neurologic manifestations of Lyme disease include encephalomyelitis, peripheral neuropathy, and encephalopathy. Encephalomyelitis is primarily seen in Europe and presents as a slowly progressive, unifocal or multifocal disease involving the white matter. A lymphocytic pleocytosis, elevated protein, and normal glucose are characteristic cerebrospinal fluid (CSF) features. Magnetic resonance imaging of the brain reveals contrast-enhancing areas of inflammation with increased signal on T2 imaging. The peripheral neuropathy of late Lyme disease presents with intermittent paresthesias in a stocking-glove distribution, occasionally associated with radicular pain. Reduced vibratory sensation can be found on physical examination, and electrophysiology studies are consistent with mononeuritis multiplex. Late encephalopathy presents with mild impairment in cognitive function and memory testing that is demonstrable on neuropsychology testing. CSF examination in this rare manifestation of Lyme disease is generally normal. Brain imaging is either normal or reveals minor, nonspecific abnormalities.

In Europe, *B. afzelii* infection can result in a chronic skin lesion, *acrodermatitis chronica atrophicans*. This skin lesion first appears as an erythematous hyperpigmented lesion that evolves to a chronic stage of hypopigmentation and atrophic, cellophane-like skin. *Acrodermatitis chronica atrophicans* responds to antibiotics if treated during the inflammatory phase. Because *B. afzelii* is not found in North America, *acrodermatitis chronic atrophicans* is not a manifestation of Lyme disease acquired on that continent.

PATHOGENESIS

Lyme disease begins when spirochetes are transmitted to humans serving as incidental bloodmeal hosts for infected ticks. *B. burgdorferi* resides in the midgut of unfed ticks and migrates to the salivary glands during the first 24 hours of tick feeding. During this period, spirochetes bind host plasminogen to disseminate within the tick, downregulate outer surface protein (Osp) A, a midgut adhesin, and upregulate Osp C, a protein required for mammalian infection. The immunomodulatory properties of *Ixodes* tick saliva promote the initial survival of spirochetes within the mammal. As an extracellular pathogen, spirochetes evade host defense mechanisms through several features, including (1) inhibition of complement through *erp* and *CRASP* gene products that bind factor H and factor H-like protein I and (2) by defeating antibody-mediated clearance through antigenic variation, especially of the *vlsE* gene. *B. burgdorferi* also expresses proteins that promote establishment of infection in the extracellular matrix and dissemination through the vasculature. These include the fibronectin-binding protein BBK32, decorin-binding proteins A and B, the integrin-binding protein p66, and the glycosaminoglycan-binding protein Bgp.

A characteristic feature of Lyme disease is that symptoms can be severe despite a paucity of organisms in tissues; much of the pathology is believed to be due to the host immune response to spirochete components. Highly inflammatory *B. burgdorferi* lipoproteins activate innate immune cells through the Toll-like receptor (TLR) family of pattern recognition receptors, principally TLR2/1 and TLR2/6 heterodimers. TLR stimulation results in a cascade of immune events, including production of inflammatory cytokines and chemokines, upregulation of adhesion molecules on endothelial cells, and priming of the adaptive T- and B-cell response. Macrophages expressing TLRs readily ingest and kill *B. burgdorferi*, but human polymorphonuclear leukocytes (PMNs) require opsonization of spirochetes for efficient phagocytosis. PMNs produce the zinc-binding protein calprotectin, which inhibits *B. burgdorferi* growth in vitro at concentrations of calprotectin found within inflamed joints.

Humoral immunity is a key host defense against *B. burgdorferi* infection. Antibodies that arise in the absence of T-cell help are sufficient to resolve inflammation and prevent challenge infection in the mouse model of Lyme borreliosis. Sera from patients with late Lyme disease contain protective antibodies. Immune complexes, found in the serum of patients with Lyme disease, are concentrated in the joints of those with Lyme arthritis. Analysis of plasma cells derived from the synovium of patients with treatment-resistant Lyme arthritis reveals evidence of expansion of the antibody a response, but the driving antigens have not been identified.

B. burgdorferi infection primes both CD4+ and CD8+ T cells and the predominance of T-helper 1–type responses correlates with more severe arthritis. The synovium of Lyme arthritis patients resembles rheumatoid synovium, with mononuclear cell infiltration and pseudolymphoid follicles formed by T cells, B cells, and plasma cells. There is an association between T- and B-cell responses to Osp A and the development of chronic antibiotic-resistant Lyme arthritis (6).

HLADRB1*0401, 0101 and related alleles are more commonly found in patients with this form of arthritis, and it has been proposed that in these individuals, Osp A immune responses are perpetuated through molecular mimicry with host proteins after *B. burgdorferi* has been cleared. Although an Osp A T-cell epitope reactive with a human LFA-1 peptide has been identified, available evidence points away from this self-peptide as a driving force for persistent inflammation. Because even treatment-resistant Lyme arthritis subsides with time (within 5 years), the immune responses detected may be appropriate and directed toward eliminating persisting antigens rather than viable organisms. Prolonged arthritis may also be due to the persistence of an abnormal immune regulatory state after the pathogen and its inflammatory products have been eliminated.

The pathogenesis of neurologic disease is more enigmatic. Peripheral neuropathy has been associated with a vasculopathy resembling endarteritis obliterans, which may secondarily lead to nerve ischemia, mononeuritis multiplex, and other manifestations of nerve dysfunction. Patients with Lyme disease rarely develop persistent neurologic abnormalities, most notably subtle cognitive changes with radicular pain or distal paresthesias. These symptoms are not responsive to antibiotics and may represent sequelae from irreversible tissue injury.

DIAGNOSIS

The diagnosis of Lyme disease should be suspected in individuals who have an appropriate clinical history and a reasonable risk of exposure to *B. burgdorferi*–infected ticks (7). The hallmark skin lesion EM is a diagnostic criterion for early Lyme disease and is sufficiently distinctive to warrant treatment without further testing. In contrast, other manifestations require supporting laboratory evidence to secure the diagnosis. Although culture is a gold standard for many bacterial infections, *B. burgdorferi* is only rarely detected by this method from diseased sites, the exception being the leading margin of EM lesions. Routine laboratory tests are nonspecific, with occasional elevation in the white blood cell count, erythrocyte sedimentation rate, and mild abnormalities of liver function tests. As noted above, analysis of synovial fluid from patients with Lyme arthritis reveals an inflammatory infiltrate (cell counts ranging from 3,000–100,000/mm^3; mean, ~25,000/mm^3) and the synovial histopathology is indistinguishable from that of rheumatoid arthritis or reactive arthritis. CSF examination in patients with CNS disease reveals lymphocytic pleocytosis, but oligoclonal bands are not present.

Serologic tests are the mainstay of diagnosis because they provide evidence of *B. burgdorferi* exposure. A two-tiered approach is recommended, using an enzyme-linked immunosorbent assay (ELISA) to measure serum IgM and IgG reactivity to *B. burgdorferi* as a screening tool, followed by immunoblot (Western blot) to confirm specificity (Table 14C-1). IgM reactivity usually appears within 2 to 3 weeks of infection and should be used to support a diagnosis of Lyme disease in patients with signs and symptoms present for less than 4 weeks. IgG responses are detectable after 1 month of illness and should be positive in patients with a clinical history of longer duration; IgG reactivity alone should not be used for diagnosis in these individuals. A persistently positive IgM response without IgG seroconversion is consistent with a false-positive test. Both rheumatoid factor and antinuclear antibodies can give rise to positive Lyme serology by ELISA. An IgM and IgG immunoblot of *B. burgdorferi* antigens separated by molecular weight should be used to confirm antibody specificities for all positive or equivocal ELISA samples, but should not be routinely performed on negative ELISA samples. Patients with Lyme disease may test negative within the first 1 to 2 weeks of infection. A synthetic C6 peptide ELISA, which measures antibodies to a constant region of the VlsE protein, may be useful in the early diagnosis of Lyme disease. The high specificity (99%) and sensitivity (74% in acute Lyme disease to 100% in late Lyme disease) of this assay are particularly helpful when patients present with only viral-like symptoms in the absence of EM. In the case of Lyme meningitis, intrathecal antibodies to *B. burgdorferi* can be detected. Evidence of an elevated CSF to serum IgG ratio is supportive of CNS infection. Positive serologic tests must be interpreted in the clinical setting; the rate of seropositivity in asymptomatic individuals may be as high as 4% in endemic areas. The vast majority of patients with disseminated infection are seropositive; in those with initially negative or equivocal tests, a follow-up convalescent titer 2 weeks after the first sample will often be positive, even with antibiotic therapy. Once positive, IgM and

TABLE 14C-1. CRITERIA FOR WESTERN BLOT INTERPRETATION IN THE SEROLOGIC CONFIRMATION OF LYME DISEASE.

ISOTYPE TESTED	CRITERIA FOR POSITIVE TEST
IgM	Two of the following three bands are present: 23 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla)
IgG	Five out of 10 bands are present: 18 kDA, 21 kDa, 28 kDa, 39 kDa, 41 kDa, 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa

SOURCE: Adapted from Centers for Disease Control and Prevention, Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease, MMWR 1995; 44:590–591.

IgG antibody titers may remain elevated for months to years after treatment and should not be used to monitor response to therapy.

Other methods for detecting *B. burgdorferi* infection include PCR amplification of spirochete DNA targets from tissues and body fluids. This technique has been used with variable success to detect *B. burgdorferi* DNA in synovial fluid and CSF specimens from patients with Lyme disease. Up to 85% of synovial fluid specimens may test positive, whereas *B. burgdorferi* DNA could be detected in less than 40% of CSF specimens from patients with Lyme meningitis. Other tests, such as a urine antigen test and blood microscopy for borrelia have not been validated.

Imaging modalities for CNS disease can provide supporting evidence of neurologic abnormalities, but no imaging findings are diagnostic of CNS Lyme disease. Magnetic resonance imaging of the brain is generally normal, but 25% of patients with encephalopathy may have white matter lesions. Absence of oligoclonal bands in the CSF helps distinguish patients with CNS Lyme disease from those with multiple sclerosis, in whom oligoclonal bands are typically present and serologic tests for Lyme disease are negative.

TREATMENT AND PROGNOSIS

Recommendations for treatment of Lyme disease, recently revised, are summarized in Table 14C-2 (8). Doxycycline, amoxicillin, and cefuroxime axetil are effective therapies for early localized or early disseminated Lyme disease in the absence of neurologic manifestations or high degree atrioventricular block. Doxycycline is the preferred antibiotic because it is also effective against another tick-borne pathogen, *Anaplasma phagocytophilum*, which causes human granulocytic anaplasmosis. Macrolides are not as effective as the other antimicrobials and should not be used as first-line therapy. First generation cephalosporins are ineffective. Most manifestations of Lyme disease can be managed with oral therapy, the exceptions being any neurologic involvement other than isolated cranial nerve palsy, cardiac disease with advance atrioventricular block, and recurrent arthritis after oral therapy.

In general, the response to therapy correlates with duration of signs and symptoms, with late manifestations requiring weeks to months for improvement or resolution. Antibiotic therapy may not hasten the resolution of cranial nerve palsies or carditis, which resolve without therapy, but patients should be treated to avoid other complications from Lyme disease. Individuals with early Lyme disease who present with more severe viral-like symptoms or who have persistent fever after 48 hours of antibiotic therapy should be evaluated for evidence of co-infection with *A. phagocytophilum* or *Babesia microti*, particularly if there is associated unexplained leucopenia, thrombocytopenia, or anemia. Patients with Lyme arthritis who fail to respond completely to oral therapy should receive a second course of either oral or intravenous therapy. If arthritis persists and PCR analysis of synovial tissue or fluid is negative for *B. burgdorferi* DNA, then treatment with nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections, or disease-modifying antirheumatic drug (DMARD) therapy with plaquenil may be considered. Synovectomy for chronic Lyme arthritis can be curative. Individuals with late neurologic abnormalities may not respond completely to antibiotic therapy because of irreversible tissue injury. Re-treatment of this subgroup of patients is not generally recommended unless there is objective evidence of relapse or progression of disease. Serologies and intrathecal antibody production are not useful to assess response to therapy as successfully treated patients may have positive tests that persist for years.

Treatment of Lyme disease in pregnancy follows the same recommendations as for the nonpregnant state except that doxycycline should be avoided. While maternal–fetal transmission of *B. burgdorferi* can occur, there is no evidence that *B. burgdorferi* infection results in fetal abnormalities or demise in cases where the mother has received recommended antibiotic therapy. *B. burgdorferi* infection cannot be transmitted by ingestion of breast milk.

About 10% of patients may experience a Jarisch–Herxheimer reaction within 24 to 48 hours of initiation of antibiotic therapy. This condition is self-limited; supportive care with reassurance and nonsteroidal anti-inflammatory agents may help relieve symptoms. Most patients with Lyme disease respond to the recommended courses of antibiotics without significant objective sequelae, but a minority may complain of persistent fatigue, musculoskeletal pain, and cognitive dysfunction. Objective findings are generally lacking. In a study of these individuals with a previously well-documented history of Lyme disease, an extended course of antibiotics (30 days of intravenous ceftriaxone followed by 60 days of oral doxycycline) had no effect on symptoms when compared to a placebo group (9). The conclusion regarding these subjective complaints is that Lyme disease may result in a post-Lyme syndrome similar to fibromyalgia or chronic fatigue syndrome. There are, however, numerous reports of patients with chronic subjective complaints in whom serologic tests are negative yet who receive extended courses of antibiotics for Lyme disease (10). Many of these individuals report a partial response rate to therapy, which may be a placebo effect or due to anti-inflammatory properties of the antibiotics themselves that are unrelated to antimicrobial actions. When evaluated at academic medical

TABLE 14C-2. RECOMMENDED TREATMENT OF LYME DISEASE.[a,b]

MANIFESTATION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE	DURATION (RANGE)
Erythema migrans (Recommended)	Doxycycline[c]	100 mg po b.i.d.	<8 years, not recommended ≥8 years, 4 mg/kg/day in two divided doses (max 100 mg/dose)	14 days (10–21 days)
	Amoxicillin	500 mg po t.i.d.	50 mg/kg/day in three divided doses	14 days (10–21 days)
	Cefuroxime axetil	500 mg po b.i.d.	30 mg/kg/day in two divided doses	14 days (10–21 days)
Erythema migrans (Alternative)[d]	Azithromycin	500 mg po q.i.d.	10 mg/kg q.i.d. (max 500 mg/day)	7–10 days
	Clarithromycin	500 mg po b.i.d	7.5 mg/kg b.i.d.	14–21 days
	Erythromycin	500 mg po q.i.d.	12.5 mg/kg q.i.d. (max 500 mg/dose)	14–21 days
Acute neurologic disease				
Cranial nerve palsy[e]	Same as oral regimens for erythema migrans			14 days (10–21 days)
Meningitis or radiculopathy[f]	Ceftriaxone	2 g IV q.i.d.	50–75 mg/kg IV q.i.d. in single dose (max 2 g/day)	14 days (10–28 days)
(Alternative IV)	Cefotaxime	2 g IV q8h	150–20 mg/kg/d IV in three to four divided doses (max 6 g/day)	
	Penicillin G	18–24 million units	200,000–400,000 U/kg/day divided q4h (max 18–24 million U/day)	
Cardiac disease[g]	Same as for erythema migrans *or* IV regimen as for neurologic disease			14 days (10–21 days) 14 days (10–21 days)
Late disease				
Arthritis without neurologic	Same as for erythema migrans			28 days (28 days)
Recurrent arthritis after oral regimen	Repeat oral regimen *or* IV regimen as for neurologic disease			14 days (14–28 days)
Central or peripheral nervous system disease	IV regimen as for acute neurologic disease			14 days (14–28 days)

SOURCE: Adapted from Wormser GP, et al., Clin Infect Dis 2006;43:1089–1134, by permission of *Clinical Infectious Diseases*.

[a,b] Complete response to treatment may be delayed beyond the treatment period, regardless of the clinical manifestation, and relapse may recur. Patients with objective signs of relapse may need a second course of treatment.

[c] Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

[d] Due to their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

[e] Patients without clinical evidence of meningitis may be treated with an oral regimen. The recommendation is based on experience with seventh cranial nerve palsy. Whether oral therapy would be as effective for patients with other cranial neuropathies is unknown; the decision between oral and parenteral therapy should be individualized.

[f] For nonpregnant adult patients intolerant of beta-lactam agents, doxycycline 200–400 mg/day orally (or IV if unable to take oral medications) in two divded doses may be adequate. For children ≥8 years of age, the dosage of doxycycline for this indication is 4–8 mg/kg/day in two divided doses (maximum daily dosage of 200–400 mg).

[g] A parenteral antibiotic regimen is recommended at the start of therapy for patients who have been hospitalized for cardiac monitoring; an oral regiment may be substituted to complete a course of therapy or to treat outpatients. A temporary pacemaker may be required for patients with advanced heart block.

centers, the majority of such patients do not have objective evidence of *B. burgdorferi* exposure or infection. Some have other treatable diseases.

PREVENTION

The most effective strategy to prevent Lyme disease is to limit potential exposure to infected ticks through environmental and personal protective measures. Eliminating brushy areas and spraying properties with insecticides can reduce the local tick population. For individuals in endemic areas, wearing protective clothing, topical application of DEET-containing insect repellents, and daily personal surveillance to remove ticks can reduce the risk of infection. For individuals bitten by *Ixodes* ticks that have been attached for ≥36 hours, a single 200 mg dose of doxycycline (or 4 mg/kg for children ≥8 years of age) is effective at preventing Lyme disease, but no data are available regarding other tick-borne diseases. This therapy is not recommended unless the tick was acquired in an area where the tick infection rate is ≥20%. A recombinant Osp A–based Lyme disease vaccine received US Food and Drug Administration approval and was briefly available for prevention of Lyme disease. Although phase I to III

studies demonstrated that the vaccine was safe and 80% effective at preventing Lyme disease after three doses, it was withdrawn in part because of public concern for potential vaccine-related side effects, especially Osp A–associated arthritis.

REFERENCES

1. Steere AC, Coburn J, Glickstein L. The emergence of Lyme disease. J Clin Invest 2004;113:1093–1101.
2. Dennis DT, Hayes EB. Epidemiology of Lyme borreliosis. In: Kahl O, Gray JS, Lane RS, Stanek G, eds. Lyme borreliosis: biology, epidemiology and control. Oxford: CABI Publishing; 2002:251–280.
3. Lyme disease statistics. Centers for Disease Control Web site. Available at: http://www.cdc.gov/ncidod/dvbid/lyme/ld_statistics.htm.
4. Bockenstedt LK. Lyme disease. In: Imboden JB, Hellmann DB, Stone JH, eds. Current diagnosis and treatment in rheumatology. 2nd ed. New York: McGraw-Hill. 2007:372–382.
5. James AM, Liveris D, Wormser GP, et al. *Borrelia lonestari* infection after a bite by an *Amblyomma americanum* tick. J Infect Dis 2001;183:1810–1814.
6. Steere AC, Falk B, Drouin EE, et al. Binding of outer surface protein A and human lymphocyte function-associated antigen 1 peptides to HLA-DR molecules associated with antibiotic treatment-resistant Lyme arthritis. Arthritis Rheum 2003;48:534–550.
7. Aquero-Rosenfeld ME, Wang G, Schwartz I, et al. Diagnosis of Lyme borreliosis. Clin Microbiol Rev 2005; 18:484–509.
8. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1089–1134.
9. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345:85–92.
10. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 2005;34:1340–1345.

CHAPTER 14

Infectious Disorders
D. Mycobacterial, Fungal, and Parasitic Arthritis

STEVEN R. YTTERBERG, MD

- Osteoarticular involvement occurs in about 5% of patients with tuberculosis (TB), with estimated percentage ranging from about 2% of all TB cases in the United States to more than 6% in developing countries.
- Pott's disease (spinal tuberculosis) is the most common form of osteoarticular infection with *Mycobacterium tuberculosis*.
- Articular TB is usually due to reactivation of a hematogenously seeded focus and need not be associated with active disease elsewhere; it can also spread from adjacent osteomyelitis.
- Lengthy delays in diagnosis—on the order of 3 to 4 years—are reported.
- Poncet's disease is a form of reactive arthritis occurring during active TB.
- *Mycobacterium marinum* infection is often associated with such aquatic exposures as fish tank water, fish hook lacerations, skin punctures by fish spines, and cuts from boat motor propellers.
- The syndrome of erythema nodosum leprosum, manifested as crops of subcutaneous nodules, fever, and arthralgia or arthritis, occurs in patients with lepromatous leprosy.
- *Valley fever* (or *desert rheumatism*) are terms used for an immune complex–mediated syndrome associated with cocciodiomycosis infection. This syndrome, which is self-limited, is characterized by joint complaints, fever, rash, erythema nodosum, erythema multiforme, eosinophilia, and hilar adenopathy.
- Sporotrichosis, which usually presents as a painful erythematous nodule at the site of a skin wound. Inoculation of the organism *Sporothrix schenckii* into the skin through gardening or landscape exposures to soil or plant material is the mode of pathogenesis (the classic exposure is to a rose thorn).

Mycobacteria, fungi, and parasites are unusual causes of musculoskeletal infections. Infections with these organisms are seen with growing frequency in the United States, however, for two major reasons: (1) increasing numbers of persons who are immunosuppressed because of the presence of debilitating diseases, medical therapy, advanced age, or human immunodeficiency virus (HIV) infection; and (2) greater immigration from developing countries endemic for these infections. These agents should be considered in patients with chronic monoarticular arthritis, but they may present with other manifestations, including osteomyelitis, spondylitis, tendonitis, and erythema nodosum (Table 14D-1). Definitive diagnosis usually depends on identification of the responsible organism in pus, synovial fluid, or tissue. Some agents, however, may cause inflammatory disease without direct infection, resembling reactive arthritis.

MYCOBACTERIA

Mycobacterium Tuberculosis

Infection with *M. tuberculosis*, usually acquired by inhalation, begins as nonspecific pneumonitis, followed by lymphatic and hematogenous spread to upper lobes of the lung and other organs. In immunocompetent hosts, infection is limited by cellular immunity. Reactivation may occur during a period of diminished host immunity, with multiplication of bacilli in dormant foci, and spread via lymphatics or blood. Osteoarticular involvement occurs in about 5% of patients with tuberculosis (TB), with estimated percentages ranging from about 2% of all TB cases in the United States to more than 6% in developing countries (1). In children, bone infection typically occurs via hematogenous seeding during primary pulmonary infection. In contrast, in adults,

TABLE 14D-1. TYPICAL PRESENTATIONS OF OSTEOARTICULAR INFECTIONS CAUSED BY MYCOBACTERIA AND FUNGI.

Mycobacteria	
Tuberculosis	Spondylitis (Pott's disease) Monarticular arthritis of large weight-bearing joints Osteomyelitis and dactylitis Bursitis and tenosynovitis Reactive arthritis (Poncet's disease)
BCG treatment	Migratory arthritis or arthralgia
Atypical mycobacteria	Arthritis or tendonitis of hand or wrist Multifocal bone, joint, or tendon infection
Leprosy	Polyarthritis with erythema nodosum leprosum Destructive arthritis of small bones and joints of hands and feet Neuropathic arthritis of wrists or ankles
Fungi	
Candidiasis	Polyarthritis with osteomyelitis in seriously ill infants Monarticular arthritis of knee in seriously ill patients past infancy
Coccidioidomycosis	Polyarthritis with erythema nodosum Monarticular arthritis of knee Osteomyelitis
Sporotrichosis	Monarticular arthritis of knee, wrist, or hand Polyarthritis with disseminated cutaneous lesions
Blastomycosis	Osteomyelitis Spondylitis Monarticular arthritis of weight-bearing joints with lung and cutaneous lesions
Cryptococcosis	Osseous infection Spondylitis Rare monarticular arthritis
Histoplasmosis	Polyarthritis with erythema nodosum

ABBREVIATION: BCG, Bacillus Calmette-Guerin.

bone infection usually occurs from either a quiescent pulmonary focus or an extrapulmonary site. Tuberculin skin tests are positive in most patients with osteoarticular TB, but chest radiographs are often normal. The definitive diagnosis is made by the demonstration of *M. tuberculosis* in tissue or synovial fluid.

The classic presentation of osteoarticular infection is spinal TB, or Pott's disease. Infections at peripheral sites, especially weight-bearing joints, tendons, bursae, or bones, also occur. Reactive arthritis (Poncet's disease) has been reported (see below).

Spinal Tuberculosis

Pott's disease is the most common form of osteoarticular infection with *M. tuberculosis* (2). Thoracic vertebrae are involved most frequently, followed by lumbar, and, less commonly, cervical and sacral vertebrae. In regions endemic for TB, spinal TB is primarily a disease of children and young adults. In the United States and Europe, most cases are in adults, occurring by reactivation of dormant foci (3).

Infection characteristically begins in the anterior portion of the vertebral bodies, with subsequent disc involvement, disc space narrowing, destruction of vertebral end plates, and collapse of the anterior portion of the vertebral body, causing the characteristic gibbus deformity (Figure 14D-1) (1,4). Infection often extends to adjoining discs or vertebrae, or to distant sites. Localized soft tissue inflammation, for example, paravertebral or psoas abscesses or sinus tracts may ensue, accompanied by neurologic injury.

Spinal TB can mimic vertebral osteomyelitis (spondylodiskitis) caused by pyogenic bacteria, but usually has a longer duration of symptoms. Fever is less common in Pott's disease (5). Back pain and tenderness are present in most patients. Neurologic manifestations from compression of spinal cord or roots occur in 12% to 50% of patients. Active pulmonary TB may be absent, but there is often evidence of past disease.

Radiographs typically show disc space narrowing with vertebral collapse and paraspinous abscess (4). Computerized tomography (CT) can define the bony anatomy and paraspinal masses. Magnetic resonance imaging (MRI) can reveal the extent of inflammation and impingement of neural structures. The differential diagnosis is broad, including other infections, neoplasm, and sarcoidosis; bacteriologic confirmation is required. Diagnosis is best made by CT-guided or open biopsy.

Therapy is complicated by the increase in drug-resistant TB. Six to nine months of combination chemotherapy including rifampin is recommended (6). The role of surgery is not clearly defined. Indications for surgery have included the presence of motor deficits, spinal deformity, a nondiagnostic needle biopsy, and noncompliance with or lack of response to medical therapy. However myelopathy and functional impairment can resolve with chemotherapy alone (6). Although adjunctive glucocorticoids are recommended for some extrapulmonary manifestations of TB, such treatment is not recommended for musculoskeletal involvement (6).

Tuberculous Arthritis

Tuberculous arthritis occurs mainly as monoarticular arthritis affecting a hip or knee, but may involve other joints (1,7,8). Most patients are middle-aged or older, often with underlying medical disorders. The onset is

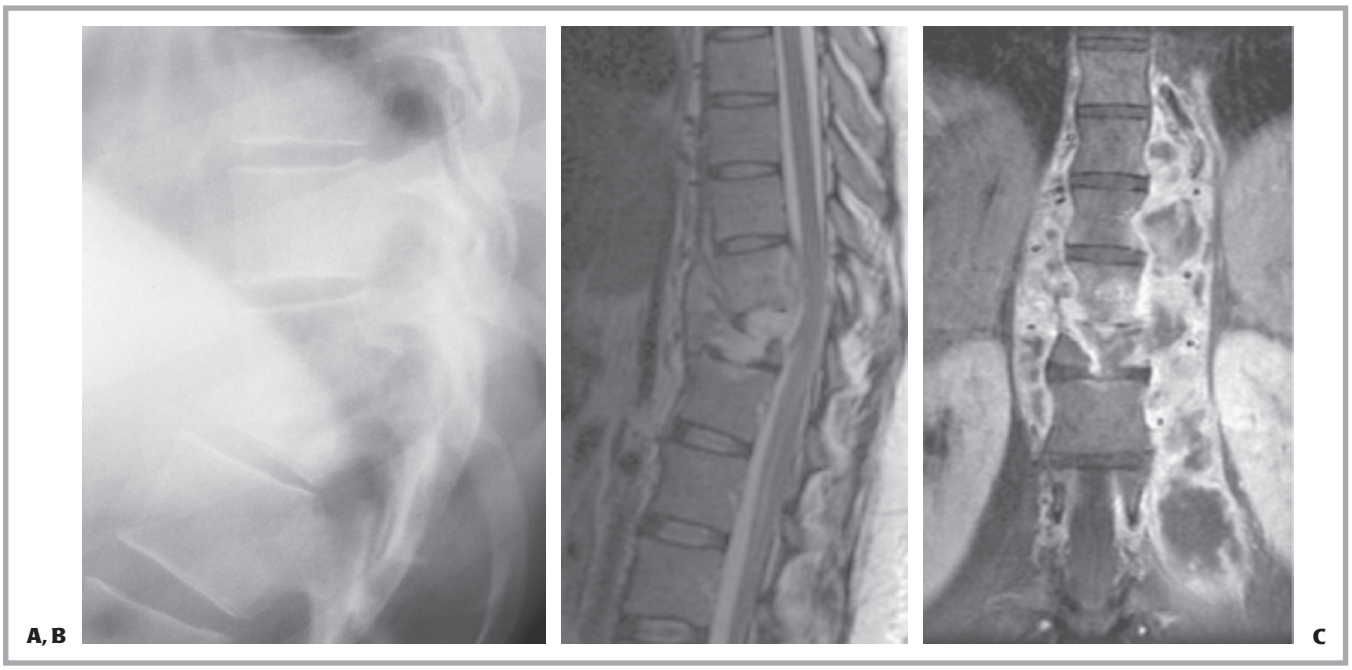


FIGURE 14D-1

Tuberculous spondylitis (Pott's disease). (A) A lateral radiograph of the thoracic spine shows destruction of adjacent vertebral endplates of the T10 and T11 vertebrae with disc space narrowing and vertebral collapse, resulting in a gibbus deformity. (B) A lateral T2 weighted magnetic resonance imgaing (MRI) scan of the thoracic spine in the same patient demonstrates inflammation in the area of collapse and extension anteriorly. (C) An anterioposterior T2 weighted MRI image of the thoracic spine of the same patient demonstrates a multilocular soft tissue mass extending above and below the area of vertebral collapse. (Courtesy of Dr. Timothy Maus, Mayo Clinic, Rochester, MN.)

typically insidious. Joint pain and swelling are usually present, but signs of inflammation may be limited. Lengthy delays in diagnosis—on the order of 3 to 4 years—are reported. Articular TB is usually due to reactivation of a hematogenously seeded focus and need not be associated with active disease elsewhere; it can also spread from adjacent osteomyelitis. Tuberculous osteomyelitis can occur without joint involvement. In adults, a single lesion is most common, usually involving the metaphysis of a long bone. In children, the hands and feet may be involved, causing tuberculous dactylitis.

Characteristic radiographic findings of tuberculous arthritis are juxta-articular osteoporosis, marginal erosions, and gradual joint space narrowing (Phemister's triad). Similar changes can occur in other forms of infection or rheumatoid arthritis. Compared with pyogenic joint infections, however, joint space is preserved early in TB arthritis. Additional radiographic findings that may be present include soft tissue swelling, subchondral cysts, bony sclerosis, periostitis, and calcifications.

The synovial fluid white blood cell count is generally elevated, usually with a predominance of neutrophils but occasionally of lymphocytes (9). The glucose in the synovial fluid is usually low. Synovial fluid acid-fast smears are positive in about 20% of cases, and culture is positive in up to 80%. The diagnosis of tuberculous arthritis is best made by histologic and microbiologic examination of synovium. Synovial cultures are positive in over 90% of cases. Histology may demonstrate caseating or noncaseating granulomas.

Tuberculous arthritis usually responds to combination chemotherapy (1,6,8). Surgery may be needed for synovectomy, debridement, joint stabilization, or removal of infected prostheses.

Poncet's Disease

Poncet's disease is a form of reactive arthritis occurring during active TB (10). Polyarticular arthritis typically involves the hands and feet. Joint fluid and tissue samples are sterile. Symptoms abate with antituberculous treatment.

Mycobacterium Bovis and Bacillus Calmette-Guerin

Mycobacterium bovis infection is now rare, but musculoskeletal symptoms have been related to attenuated *M. bovis* as a component of Bacillus Calmette-Guerin

(BCG) (11). Intravesicular BCG instillation for bladder cancer has been associated with fever, malaise, and migratory polyarticular arthralgia or arthritis in a minority of patients. Symptoms worsen with repeated treatments and can be prevented by isoniazid. Considerable debate exists within the literature about whether the inflammation is an immune-mediated response, or whether it represents a manifestation of active BCG infection. Some musculoskeletal complications of this therapy, for example, monoarticular arthritis accompanied by the isolation of *M. bovis* from joints, are clearly related to active infection. Reactive arthritis and Sjögren's syndrome have also been reported.

Atypical Mycobacteria

Musculoskeletal involvement with atypical (nontuberculous) mycobacteria can mimic TB and include bone, joint, tendon, and bursal infection. Infections are indolent, with insidious onset. The peak age incidence is 40 to 69 years, with a male-to-female ratio of 3:1 (12). The majority of infections are caused by *M. marinum, M. kansasii,* and *M. avium* complex. Various other mycobacterial species are identified in the remaining cases. A history of prior trauma, surgery, or intra-articular injection is usual, but occasionally hematogenous seeding occurs. Glucocorticoid use and underlying arthritis are additional risk factors. *M. marinum* infection is often associated with such aquatic exposures as fish tank water, fish hook lacerations, skin punctures by fish spines, and cuts from boat motor propellers.

Any joint, bursa, or tendon sheath may be infected, but the hands are most frequently involved, followed by the wrists and knees. Polyarticular involvement occurs in less than one fourth of patients. The most common presentation is joint swelling, followed by joint pain and limited motion. Carpal tunnel syndrome may arise from synovitis involving the flexor tendons of the wrist. A slowly healing cutaneous wound may be present. Constitutional symptoms, such as fever, chills, weight loss, and malaise are infrequent.

Radiographs of affected joints are often normal. If abnormalities are present, they are usually soft tissue swelling, effusion, bony erosion, or joint destruction. A pattern of preservation of the central joint space with marginal erosion containing sclerotic borders of adjacent bone has been described.

Synovial fluid may be noninflammatory or markedly inflammatory. Pathology typically demonstrates noncaseating granulomas, but the absence of granulomas does not exclude the diagnosis. Diagnosis is made by demonstration of mycobacteria in synovial fluid or tissue. Negative cultures do not rule out infection, as these organisms can be difficult to cultivate.

Treatment of atypical mycobacterial joint infections involves a combination of antituberculous therapy and surgery. Most strains of nontuberculous mycobacteria are resistant to antituberculous drugs to some degree. Combination chemotherapy is required for most.

Mycobacterium Leprae

Leprosy can cause several forms of arthritis (13,14). Erythema nodosum leprosum occurs in patients with lepromatous leprosy. Manifestations include crops of subcutaneous nodules, fever, and arthralgias or arthritis. The joint symptoms usually are mediated by an immunologic mechanism, but septic arthritis with *M. leprae* in synovial fluid occurs infrequently. Chronic erosive arthritis of large and small joints resembling rheumatoid arthritis, which improves with treatment of the leprosy, is also described. In late stages of leprosy, Charcot joints may develop due to sensory neuropathy and repeated trauma.

FUNGI

Most fungal musculoskeletal infections have an insidious onset, an indolent course, and generally mild inflammation. Other than positive cultures, laboratory findings are nonspecific.

Candida

Candida species are commensal organisms in humans. They are the most common cause of opportunistic infection among fungi, but rarely cause joint infection (15). Fungi, most commonly *Candida albicans*, cause only 1% of infected prosthetic joints (16). Arthritis can arise from direct inoculation or hematogenous spread of organisms (16,17). Intra-articular inoculation may occur during joint surgery or arthrocentesis. Infection is typically indolent, monarticular, and chronic. Symptoms may not develop until 2 years after surgery. Loosening of prosthetic components is seen radiographically. When related to arthrocentesis, infection is usually caused by species other than *C. albicans*.

Hematogenous spread of *C. albicans* to joints can occur during disseminated candidiasis. Disseminated candidiasis is associated with drug abuse; among non–drug abusers, it is seen in seriously ill patients receiving intensive medical care, notably hospitalized infants. In infants, *Candida* arthritis is usually polyarticular and associated with local osteomyelitis. Older patients with disseminated candidiasis typically have a serious illness treated with antibiotics, chemotherapy, and/or immunosuppressive agents. The clinical course may be acute, with marked synovitis, or milder and more indolent. Arthritis is monarticular in about 75% of cases. Septic bursitis may occur.

The diagnosis is made by culture of synovial fluid or tissue. Treatment with systemic or intra-articular amphotericin B has been successful. 5-Fluorocytosine may be helpful as an adjunct to amphotericin B, but should not

be used alone because of resistance. Ketoconazole and fluconazole have been successful in treating candidal infection, but the *Candida* species causing infection must be identified, as some nonalbicans species are resistant (18). Treatment of infected prosthetic joints usually requires removal of the prosthesis and debridement.

Coccidioidomycosis

Coccidioidomycosis is caused by *Coccidioides immitis*, a soil fungus endemic in semi-arid areas of the southwestern United States, Central America, and South America. Osteoarticular involvement can occur during primary or disseminated infection.

Primary infection is often asymptomatic, but about 40% of patients develop self-limited symptoms that range from flulike complaints to pneumonia. *Valley fever* or *desert rheumatism* are terms used for a self-limited, immune complex–mediated syndrome of arthralgias or arthritis that can occur during primary infection. Fever, rash, erythema nodosum, erythema multiforme, eosinophilia, and hilar adenopathy may occur. The arthritis, usually polyarticular and migratory, resolves within 4 weeks without treatment (15).

Chronic pulmonary infection occurs in about 2% of patients and disseminated disease is seen in about 0.2%. Arthritis and osteomyelitis can occur during disseminated infection. The most frequent articular manifestation is chronic arthritis of one knee. Nodular cutaneous lesions and draining sinuses may be present (19). Radiographs show lytic lesions and bony erosions. Delay in diagnosis averages over 4 years. Osteomyelitis occurs in 10% to 20% of patients with disseminated disease, most often involving ends of long bones, the skull, vertebrae, and ribs.

Synovial fluid samples rarely yield *C. immitis*. The diagnosis is best made by demonstration of organisms in tissue. Treatment involves surgical drainage of pus, debridement, or synovectomy, and chemotherapy with amphotericin B. Early infections have been treated with azole antifungal agents, but infection may recur after stopping therapy (15,18). Intra-articular amphotericin B has been reported to be useful.

Sporotrichosis

Sporotrichosis, caused by *Sporothrix schenckii*, is usually limited to cutaneous disease, presenting as a painful erythematous nodule at the site of a skin wound. Inoculation of the organism into the skin through gardening or landscape exposures to soil or plant material is the mode of pathogenesis (the classic exposure is to a rose thorn). Infection is spread by lymphatic drainage or local extension.

Extracutaneous disease primarily affects musculoskeletal structures, causing arthritis, tenosynovitis, osteitis, or granulomatous myositis (19). Cutaneous findings are present in most patients with musculoskeletal disease. The arthritis, usually chronic, may be monoarticular or polyarticular, involving the knees, wrists, small joints of the hands, ankles, and elbows. Disseminated sporotrichosis is rare, usually occurring in immunosuppressed or systemically ill patients. Most patients with disseminated sporotrichosis have bone or joint involvement or both. Radiographs show lytic lesions with minimal periostitis.

Synovial pathology demonstrates chronic, noncaseating granulomatous inflammation. Diagnosis is based on culture of organisms from joint fluid or tissue. Amphotericin B with or without surgical debridement is often curative, but prolonged treatment may be necessary (15,18). Azole antifungal agents and intra-articular amphotericin B have been reported to be effective.

Blastomycosis

Blastomyces dermatitidis is endemic in the Ohio and Mississippi River valleys and in the mid-Atlantic portion of the United States. Primary pulmonary infection occurs after inhalation of infectious spores; other sites are seeded by hematogenous or lymphatic spread. Skeletal infection occurs in up to 60% of patients (19). Osteomyelitis is most common, involving vertebrae, ribs, tibiae, and skull. Vertebral infection mimics TB. Arthritis is typically monoarticular but can be polyarticular (15). Patients with blastomycosis usually have constitutional symptoms and their arthritis tends to be acute in onset, characteristics that lead generally to quicker diagnoses compared with other fungal causes of arthritis. A knee is most frequently involved, followed by an ankle or elbow. Articular disease may arise from hematogenous spread or from extension from nearby osteomyelitis.

Stains of synovial fluid may reveal organisms, but definitive diagnosis requires culture. Blastomycosis can be treated with amphotericin B, ketoconazole, or itraconazole. Surgery may be required for patients who fail treatment with these drugs.

Cryptococcosis

Inhalation of *Cryptococcus neoformans* can cause clinically silent or overt pulmonary infection. Hematogenous spread may seed other organs, notably the central nervous system. Most clinically apparent disseminated cases occur in immunosuppressed patients. Osseous infection occurs in 5% to 10% with dissemination, involving the long bones, vertebrae, ribs, tarsals, and carpals with a subacute or chronic course (19). Vertebral infection may mimic TB. Radiographs show lytic lesions with little periosteal reaction. Cryptococcal arthritis is infrequent, usually due to direct extension of adjacent osteomyelitis (15,19). The diagnosis is made by

demonstration of organisms in synovial fluid or tissue. Treatment is usually with amphotericin B, with or without 5-fluorocytosine. Fluconazole may be sufficient for immunocompetent hosts.

Histoplasmosis

Histoplasmosis, caused by *Histoplasma capsulatum,* is endemic in the Mississippi and Ohio River valleys of the United States. Most infections are subclinical and self-limited. During primary infection, acute self-limited migratory polyarthritis or arthralgias may occur, with or without erythema nodosum or erythema multiforme. Arthritis in these cases is immunologically mediated (15,19). Dissemination occurs in less than 0.1%, usually in elderly or immunosuppressed patients (19). Arthritis, osteomyelitis, tenosynovitis, and carpal tunnel syndrome are rarely described in disseminated histoplasmosis. Diagnosis is based on the culture of *H. capsulatum* from tissue or histologic demonstration of organisms. Successful treatment has been accomplished with amphotericin B, itraconazole, and fluconazole, but surgical debridement may be required.

Other Fungal and Related Organisms

A variety of other fungi have been reported rarely as causes of infectious arthritis (19). Invasive *Aspergillus* infection can involve a variety of organs, most often the lungs and sinuses. Direct extension of infection can result in osteomyelitis of vertebrae, ribs, or skull. Vertebral involvement can mimic Pott's disease. Articular involvement is rare (15,19). Paracoccidioidomycosis is caused by *Paracoccidioides brasiliensis*, endemic to South America. The organism may disseminate and cause osteomyelitis with extension to joints (14).

Maduromycosis, or mycetoma, is a chronic infection of skin, subcutaneous tissue, and bone, most often involving the foot (14). Maduromycosis is caused by a variety of organisms, including true fungi and actinomyces (which are actually bacteria). Infection begins with subcutaneous inoculation of organisms and local extension, with eventual development of granule-draining sinus tracts.

PARASITES

Parasites are organisms that live on or in a host organism and derive their nourishment from the host. Some parasites may persist in the host for extended periods. Parasites can be grouped as protozoa, helminths, and arthropods. Immune responses induced by parasitic infections can cause tissue injury and musculoskeletal manifestations, including hypersensitivity reactions and immune complex deposition. Such manifestations are usually benign and often resolve with treatment of the underlying infestation. Arthralgia is more common than arthritis, but the frequency of joint involvement is not clearly known (20).

Among protozoa, *Giardia lamblia* has been reported as a cause of acute-onset, mild, recurrent seronegative arthritis, similar to reactive arthritis. Other protozoa associated with arthralgia and arthritis include *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Toxoplasma gondii*.

Several helminths have been associated with joint symptoms (20). Dracunculosis can produce arthralgia, as well as acute or chronic monarticular arthritis due to joint invasion or death of the worm in situ near a joint. Among patients with filariasis, monoarticular arthritis, often involving knee or ankle may occur. Reactive arthritis and sacroiliitis have been described with *Strongyloides stercoralis* and schistosomiasis. *Echinococcus granulosus*, which causes hydatid cysts, can lead to cystic infection of bone and pathologic fractures.

REFERENCES

1. Leonard MKJ, Blumberg HM. Musculoskeletal tuberculosis. In: Schlossberg D, ed. Tuberculosis & nontuberculous mycobacterial infections. 5th ed. New York: McGraw-Hill; 2006:242–263.
2. Martini M, Ouahes M. Bone and joint tuberculosis: a review of 652 cases. Orthopedics 1988;11:861–866.
3. Cormican L, Hammal R, Messenger J, Milburn HJ. Current difficulties in the diagnosis and management of spinal tuberculosis. Postgrad Med J 2006;82:46–51.
4. Ridley N, Shaikh MI, Remedios D, Mitchell R. Radiology of skeletal tuberculosis. Orthopedics 1998;21:1213–1220.
5. Perronne C, Saba J, Behloul Z, et al. Pyogenic and tuberculous spondylodiskitis (vertebral osteomyelitis) in 80 adult patients. Clin Infect Dis 1994;19:746–750.
6. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167:603–662.
7. Garrido G, Gomez-Reino JJ, Fernandez-Dapica P, Palenque E, Prieto S. A review of peripheral tuberculous arthritis. Semin Arthritis Rheum 1988;18:142–149.
8. Malaviya AN, Kotwal PP. Arthritis associated with tuberculosis. Best Pract Res Clin Rheumatol 2003;17:319–343.
9. Allali F, Mahfoud-Filali S, Hajjaj-Hassouni N. Lymphocytic joint fluid in tuberculous arthritis. A review of 30 cases. Joint Bone Spine 2005;72:319–21.
10. Dall L, Long L, Stanford J. Poncet's disease: tuberculous rheumatism. Rev Infect Dis 1989;11:105–107.
11. Tinazzi E, Ficarra V, Simeoni S, Artibani W, Lunardi C. Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. Rheumatol Int 2006;26:481–488.
12. Yangco BC, Espinoza CG, Germain BF. Nontuberculous mycobacterial joint infections. In: Espinosa L, Goldenberg

D, Arnett F, Alarcon G, eds. Infections in the rheumatic diseases. Orlando: Grune & Stratton; 1988:139–157.
13. Gibson T, Ahsan Q, Hussein K. Arthritis of leprosy. Br J Rheumatol 1994;33:963–966.
14. McGill PE. Geographically specific infections and arthritis, including rheumatic syndromes associated with certain fungi and parasites, Brucella species and Mycobacterium leprae. Best Pract Res Clin Rheumatol 2003;17:289–307.
15. Kohli R, Hadley S. Fungal arthritis and osteomyelitis. Infect Dis Clin North Am 2005;19:831–851.
16. Silveira LH, Cuellar ML, Citera G, Cabrera GE, Scopelitis E, Espinoza LR. Candida arthritis. Rheum Dis Clin North Am 1993;19:427–437.
17. Cuende E, Barbadillo C, Isasi C, Trujillo A, Andreu JL. Candida arthritis in adult patients who are not intravenous drug addicts: report of three cases and review of the literature. Semin Arthritis Rheum 1993;22:224–241.
18. Perez-Gomez A, Prieto A, Torresano M, et al. Role of the new azoles in the treatment of fungal osteoarticular infections. Semin Arthritis Rheum 1998;27:226–244.
19. Cuellar ML, Silveira LH, Citera G, Cabrera GE, Valle R. Other fungal arthritides. Rheum Dis Clin North Am 1993;19:439–455.
20. Peng SL. Rheumatic manifestations of parasitic diseases. Semin Arthritis Rheum 2002;31:228–247.

CHAPTER 14

Infectious Disorders
E. Rheumatic Fever

STANFORD SHULMAN, MD
PREETI JAGGI, MD

- Acute rheumatic fever (ARF) is most frequent among 5 to 15 year olds, with a declining incidence in adults.
- It is extremely rare in children under age 3, prompting some speculation that more than one group A streptococcal (GAS) respiratory tract infection is needed before a host develops the immune mechanisms required to develop ARF.
- With the exception of chorea, the latent period between the inciting GAS infection and symptoms of ARF is approximately 3 weeks.

EPIDEMIOLOGY

The global prevalence of ARF has been estimated to be approximately 15.6 million cases, with 282,000 new cases per year and 233,000 deaths (mostly from chronic rheumatic heart disease) per year (1). It is estimated that the annual incidence of ARF among children aged 5 to 14 years is highest in sub-Saharan Africa (5.7 cases per 1000), the Pacific and indigenous populations of Australia and New Zealand (2.2 cases per 1000), and south central Asia (2.2 cases per 1000) (1). Rates in the United States and most of Western Europe are much lower, <1 case per 100,000.

CLINICAL FINDINGS

Diagnostic Criteria

The diagnostic criteria for ARF are based on T. Duckett Jones' proposed guidelines, derived from clinical observation of hundreds of patients with ARF. The guidelines were originally proposed in 1944 and have been revised several times, the last being in 1992 (2). The current Jones criteria are shown in Table 14E-1, and it is of note that they apply only to first attacks of ARF. Exceptions to these criteria include patients presenting with pure chorea or with indolent carditis; in these patients the antistreptococcal antibody levels usually have returned to normal by the time the patient presents, and no other rheumatic symptoms may be present.

Major Clinical Criteria

Arthritis occurs in approximately 75% of patients with ARF. The arthritis is characteristically migratory, which is in contrast to poststreptococcal reactive arthritis. Left untreated, the affected joint becomes inflamed and then resolves spontaneously, but the migrating pattern of polyarthritis persists for 1 to 4 weeks. The arthritis mainly affects larger joints, including knees, ankles, wrists, and elbows, but can also less frequently affect the smaller joints of the hands and feet; the axial skeleton is rarely involved. Inflamed joints are often red, hot, swollen, and exquisitely tender, and classically even minimal contact with the affected joint can cause exquisite pain. Another characteristic strongly suggestive of the arthritis of ARF is a dramatic response to salicylates, so much so that a lack of response to salicylate therapy within 48 hours should prompt the clinician to doubt the diagnosis of ARF and to explore other diagnoses.

Carditis occurs in approximately 50% to 60% of ARF cases and accounts for significant morbidity and even mortality. When rheumatic fever affects the heart, it usually involves the endocardium, myocardium, and pericardium to varying degrees. Endocarditis is the hallmark, and this is manifested by mitral and/or aortic valvulitis; the tricuspid and pulmonary valves are rarely affected. In resultant chronic rheumatic heart disease, valvular regurgitation can evolve to valvular stenosis. The revised Jones criteria for ARF require auscultation of a new valvular murmur in order to meet the criterion of carditis; echocardiographic findings of valvular

TABLE 14E-1. MODIFIED JONES' CRITERIA FOR DIAGNOSIS OF ACUTE RHEUMATIC FEVER.[a]

Major criteria
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules
Minor criteria
Fever
Arthralgia
Elevated acute phase reactant (C-reactive protein or erythrocyte sedimentation rate)
Prolonged PR interval on electrocardiogram
Supporting evidence of antecedent Group A streptococcal infection
Positive throat culture or rapid antigen test
Elevated or rising streptococcal antibody titer

[a] Diagnosis requires two major criteria or one major and two minor criteria, plus supporting evidence of antecedent group A streptococcal infection.

regurgitation without a murmur do not fulfill this criterion. Myocarditis manifests as tachycardia that is disproportionate to the degree of fever and is best assessed during sleep. Pericarditis is the least common finding in rheumatic carditis. It usually manifests as a pericardial effusion and/or friction rub. Myocarditis and/or pericarditis in the absence of valvular involvement is very unlikely to be due to ARF, and in this circumstance, other diagnoses should be explored.

Sydenham chorea (St. Vitus dance) is the manifestation of central nervous system involvement in ARF and occurs in 10% to 15% of patients. It is usually a later manifestation of ARF, occurring several months after the inciting streptococcal infection. Cross-reactive immune responses that affect the basal ganglia neurons are thought to be the etiology. The characteristic features of chorea are purposeless involuntary movements (but not stereotyped like a tic), incoordination, difficulty with handwriting, facial grimacing, and emotional lability. In one recent pediatric series, hemichorea was seen in 29% of patients (3). Chorea is a self-limited illness, and full recovery takes several months. Rarely, symptoms can occur over years and are exacerbated by stress, pregnancy, oral contraceptives, and intercurrent illnesses.

Erythema marginatum occurs in fewer than 2% of patients. It is characteristically an erythematous, serpiginous macular rash with pale central clearing. The rash usually occurs on the trunk and extremities and characteristically spares the face. The rash waxes and wanes, may be transient and is exacerbated by warmth.

Subcutaneous nodules occur in fewer than 1% of cases of ARF, most often in those with severe carditis. The nodules are firm, nontender, and are usually less than 2 cm in diameter. They are typically located over bony prominences or tendon sheaths. Nodules usually resolve spontaneously without permanent sequelae.

Minor Clinical Criteria

The fever in ARF is usually greater than 39.0°C. It is usually present at the onset of illness and resolves over several weeks, even without treatment. Arthralgia may fulfill a minor criterion in the revised Jones' criteria, but only in the absence of polyarthritis. Arthralgia may be migratory, and pain may be severe, even without objective signs of arthritis.

DIAGNOSTIC TESTS

Approximately one third of patients presenting with ARF have no history of a recent symptomatic pharyngeal infection, and, therefore, it is necessary to find laboratory evidence of a recent streptococcal infection. This can be done either by (a) obtaining history of a throat culture or a GAS rapid antigen test positive for GAS from a throat swab, or by (b) documenting an elevated or rising serum antistreptococcal antibody titer. It is important for the clinician to recognize that normal values of antistreptococcal antibodies in the general population vary by patient age, geographic location, and season of the year, with highest values observed in 10 to 12 year olds and at the end of the streptococcal season (late spring) (4). The use of normal ranges established for adults for interpretation of pediatric values is misleading.

The antistreptolysin O (ASO) titer is the most commonly used streptococcal antibody test to establish a recent streptococcal infection. An ASO titer of 240 Todd units or higher in adults or in excess of 320 Todd units in children is considered modestly elevated. ASO titers above 500 Todd units are uncommon in healthy individuals and therefore more reliably serve as evidence of a recent streptococcal infection (4).

Because ASO titers can be normal in approximately 20% of ARF patients, other streptococcal antibody tests are useful to help establish a recent GAS infection; these include antideoxyribonuclease B (anti-DNase B), antistreptokinase, and antihyaluronidase. If all antistreptococcal antibody titers are normal on initial presentation and ARF remains a clinical concern, it is highly advisable to repeat these tests a few weeks later to see if the antibody titers have risen because a single low antistreptococcal antibody titer does not exclude the diagnosis of ARF.

SPECIAL TESTS

Synovial fluid analysis of the arthritis of ARF reveals a sterile inflammatory fluid typically with 10,000 to 100,000 white blood cells/mm^3 (with a predominance of neutrophils), normal glucose level, and a protein concentration of approximately 4g/dL.

The nonclinical (laboratory) minor criteria of the revised Jones' criteria include an increased PR interval on electrocardiogram (which does not per se indicate carditis) and elevated acute phase reactants (C-reactive protein and/or erythrocyte sedimentation rate). Acute phase reactants are almost always greatly elevated in ARF patients presenting with polyarthritis or acute carditis, but are often normal in patients presenting with chorea alone.

DIFFERENTIAL DIAGNOSIS

Other than ARF, the most frequently encountered diseases in the differential for acute polyarticular arthritis include juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), serum sickness, and gonococcal arthritis. Choreiform movements can occur in SLE, neoplasms involving the basal ganglia, Wilson's disease, and Huntington's disease. Chorea can occasionally be encountered in pregnancy (chorea gravidarum).

PATHOGENESIS

The pathogenesis of ARF is not completely understood, but it appears to involve immune responses to GAS antigens that then cross-react with human tissue through molecular mimicry (Figure 14E-1). Only a small percentage of individuals with untreated GAS pharyngitis go on to develop ARF. ARF is not considered a sequela of cutaneous GAS infection (5). Recent evidence supports the conclusion that ARF has declined markedly in the United States over the past four decades because of a decline in rheumatogenic types of GAS causing pharyngitis (6).

Host genetic factors appear to influence the susceptibility to ARF. Observational studies in the 19th century recognized familial tendencies to develop ARF, and in the early 1940s, studies showed familial clustering of the disease, with greatest risk occurring in children if both parents had rheumatic heart disease (7). Genetic susceptibility to develop ARF has been characterized as autosomal recessive or autosomal dominant with variable penetrance and has been linked with human leukocyte antigen (HLA) types. Significant increases in the frequency of DRB1*0701, DR6, and DQB1*0201 confer susceptibility to ARF in several international studies (8). However, monozygotic twins usually do not both develop ARF, clearly indicating that there are also important environmental factors involved in the pathogenesis of the disease (9).

TREATMENT

Treatment of ARF requires anti-inflammatory treatment, prevention of future streptococcal infections, and symptomatic care (Table 14E-2). Upon diagnosis, a dose of intramuscular benzathine penicillin or 10 days of oral penicillin or erythromycin (for penicillin-allergic patients) is recommended regardless of streptococcal

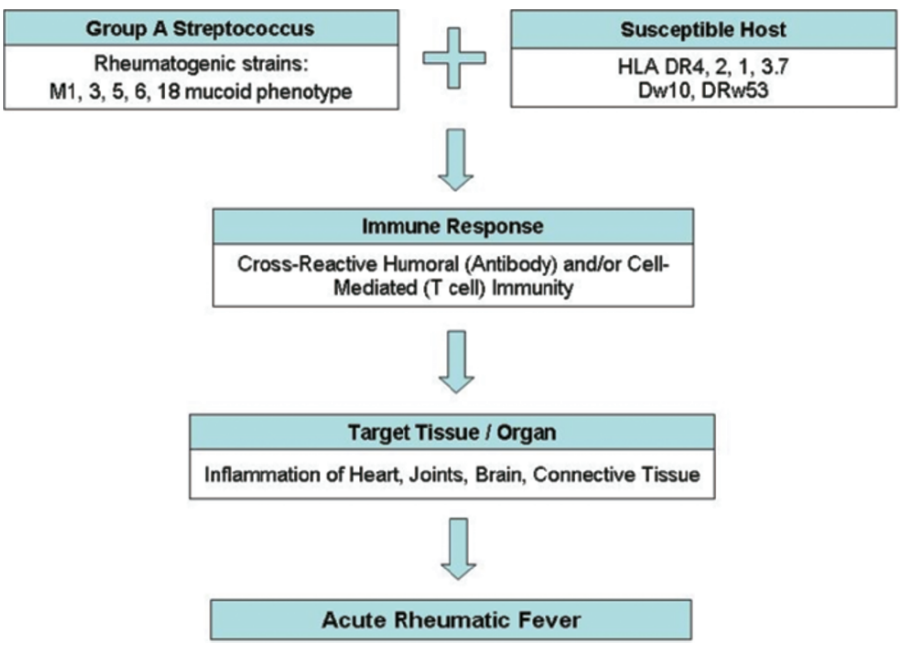


FIGURE 14E-1

Pathogenesis of acute rheumatic fever (proposed).

TABLE 14E-2. TREATMENT OF ACUTE RHEUMATIC FEVER.

CONDITION	ANTI-INFLAMMATORY TREATMENT
Mild or no carditis	Aspirin 50–100 mg/kg/day in four divided doses for 2–4 weeks, then taper over 4–6 weeks
Moderate or severe carditis	Prednisone 2 mg/kg/day in two doses for 2–4 weeks, then taper over about 4 weeks, with addition of aspirin when prednisone is ≤ 0.5 mg/kg/day.
Primary antistreptococcal therapy	1.2 million units of benzathine penicillin G IM or oral penicillin or erythromycin for 10 days
Prophylaxis of GAS infection	1.2 million units benzathine penicillin G IM q.i.d. 4 weeks or sulfadiazine 500 mg po q.i.d. (≤ 27 kg) or 1.0 g po q.i.d. (≥ 27 kg) or penicillin V 250 mg po b.i.d
Medications to control cardiac symptoms (if needed)	Diuretic, angiotension-converting enzyme inhibitor, and/or cautious use of digoxin
Medications to control chorea (if needed)	Haloperidol or phenobarbitol
Infective endocarditis prophylaxis	As recommended by the American Heart Association

throat culture results. Anti-inflammatory treatment includes oral salicylates (50–100 mg/kg/day) in four daily doses. This is continued for 2 to 4 weeks, then is gradually tapered over 4 to 6 weeks. Corticosteroid treatment should be reserved for those patients with congestive heart failure or at least moderate cardiomegaly on chest radiograph. Corticosteroids are tapered slowly over about 6 weeks; during the taper of corticosteroids, salicylates are added. Supportive care for cardiac dysfunction includes diuretics, antihypertensives, or digoxin. For patients with Sydenham chorea, haloperidol or phenobarbital may be of some benefit.

Prevention of GAS infection is of utmost importance to prevent recurrent attacks of ARF that can be associated with increased severity of cardiac disease or with development of cardiac disease not previously present. All patients with ARF should receive antimicrobial prophylaxis with intramuscular benzathine penicillin G every 4 weeks or twice daily oral penicillin, or once daily sulfadiazine if penicillin allergic, or erythromycin if penicillin and sulfa allergic. The recommendations for the duration of secondary prophylaxis of streptococcal infection are based upon likelihood of recurrence and years since last ARF episode. The current American Heart Association recommendations for duration of antimicrobial prophylaxis of ARF are listed in Table 14E-3 (10). In addition, patients with rheumatic heart disease should receive infective endocarditis prophylaxis as recommended by the American Heart Association.

TABLE 14E-3. RECOMMENDATIONS OF DURATION OF ANTIMICROBIAL PROPHYLAXIS IN PATIENTS WITH ACUTE RHEUMATIC FEVER.

CONDITION	TREATMENT DURATION
Patients with rheumatic fever with carditis and residual heart disease	At least 10 years since last episode and at least until age 40, sometimes lifelong prophylaxis
Rheumatic fever with carditis but no residual heart disease (no valvar disease)	10 years or well into adulthood, whichever is longer
Rheumatic fever without carditis	5 years or until age 21 years, whichever is longer

PROGNOSIS

The only long-term manifestation of ARF is that of rheumatic heart disease, and the prognosis of patients with ARF is generally attributable to the degree of cardiac involvement, to consequences of infective endocarditis, and to the risk of recurrent ARF secondary to recurrence of GAS pharyngitis. Patients presenting only with chorea or polyarthritis may develop rheumatic heart disease if they develop recurrent ARF, thus emphasizing the importance of prophylactic antibiotics.

POSTSTREPTOCOCCAL REACTIVE ARTHRITIS

General Considerations

Those patients who do not fulfill the diagnostic criteria for ARF but who develop arthritis after a streptococcal infection are deemed to have poststreptococcal reactive arthritis (PSRA). This arthritis is predominantly associated with GAS infections but has also been reported after infection with group C and G streptococci. There

appears to be a bimodal age distribution of PSRA, with peak incidence at ages 8 to 14 years and 21 to 37 years. In Caucasians, PSRA is associated with the class II HLA antigen DRB1*01 (11,12).

Clinical Findings

The arthritis of PSRA is generally acute and nonmigratory and predominantly affects the large joints of the lower limbs, occasionally causing tenosynovitis. It may be mono- or polyarticular, and symmetrical or asymmetrical. The axial skeleton is affected in about 20% of patients. During the antecedent GAS infection, fever with or without a scarlatiniform rash may be present, but they are not usually when arthritis has manifested. The interval between the inciting streptococcal infection and the onset of arthritis (onset usually 3–14 days after infection) is generally shorter than that of ARF. The symptoms of PSRA resolve slowly over a few weeks to several months (mean of 2 months). Characteristically, PSRA patients have a gradual response to nonsteriodal anti-inflammatory drug (NSAID) therapy in contrast to ARF patients, who typically have a dramatic and prompt response to NSAIDs (11,13,14). Recurrences have been reported after subsequent streptococcal pharyngitis episodes. The most concerning possible sequela is that of late-onset carditis; in the original description of PSRA, this occurred in 4 of 13 (31%) patients with PSRA who did not meet the criteria for and did not have a clinical history of ARF; these patients developed evidence of cardiac disease 1 to 18 years after their original diagnosis. Substantially lower rates of development of late carditis have been observed in more recent series. Other possible extra-articular manifestations of PSRA include glomerulonephritis (which is very rare with ARF) and uveitis in the minority of patients.

Diagnostic Criteria

The diagnostic criteria for PSRA are not clearly defined, but the criteria proposed by Ayoub and colleagues (15) are detailed in Table 14E-4.

TABLE 14E-4. PROPOSED DIAGNOSTIC CRITERIA FOR DIAGNOSIS OF POSTSTREPTOCOCCAL REACTIVE ARTHRITIS.

A.	Characteristics of arthritis 1. Acute in onset, symmetric or asymmetric, usually nonmigratory 2. Persistent or recurrent symptoms 3. Lack of a dramatic response to nonsteroidal anti-inflammatory drugs
B.	Evidence of an antecedent group A streptococcal infection (previous positive throat culture or rapid antigen test positive for GAS, or elevated or rising antistreptolysin O and/or anti-DNase B titers)
C.	Does not fill the modified Jones criteria for acute rheumatic fever

Treatment

Patients with PSRA generally respond much less dramatically to aspirin or other NSAIDs than do those with classic ARF, but these agents can be used to treat this form of arthritis. Some experts recommend both a baseline echocardiogram and a follow-up echocardiogram 1 to 2 years later because of the concern of occult carditis. The American Heart Association (AHA) currently recommends that patients with PSRA should be followed while receiving antistreptococcal prophylaxis for 1 to 2 years to assess for evidence of cardiac involvement, and that prophylaxis should be discontinued after 1 to 2 years if no evidence of carditis is found. Penicillin is recommended as first-line therapy, and erythromycin is appropriate for penicillin-allergic patients. Some experts suggest that the same prophylaxis recommendations for ARF patients also should apply to those with PSRA because the time of onset of documented carditis can be widely variable, but this recommendation has not been endorsed by the AHA or other organizations.

REFERENCES

1. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685–694.
2. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 1992;268:2069–2073.
3. Zomorrodi A, Wald ER. Sydenham's chorea in western Pennsylvania. Pediatrics 2006;117:e675–e679.
4. Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. Pediatrics 1998;101:86–88.
5. Stollerman GH. Rheumatic fever in the 21st century. Clin Infect Dis 2001;33:806–814.
6. Shulman ST, Stollerman G, Beall B, Dale JB, Tanz RR. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. Clin Infect Dis 2006;42:441–447.
7. Wilson M, Schweitzer, MG, Lubschez R. The familial epidemiology of rheumatic fever. J Pediatr 1943;22: 461–491.
8. Guedez Y, Kotby A, El-Demellawy M, et al. HLA class II associations with rheumatic heart disease are more evident and consistent among clinically homogeneous patients. Circulation 1999;99:2784–2790.

9. Taranta A TS, Metrakos JD. Rheumatic fever in monozyogotic and dizygotic twins. Circulation 1959;20:778–792.
10. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. Pediatrics 1995;96:758–764.
11. Mackie SL, Keat A. Poststreptococcal reactive arthritis: what is it and how do we know? Rheumatology (Oxford) 2004;43:949–954.
12. Ahmed S, Ayoub EM, Scornik JC, Wang CY, She JX. Poststreptococcal reactive arthritis: clinical characteristics and association with HLA-DR alleles. Arthritis Rheum 1998;41:1096–1102.
13. Herold BC, Shulman ST. Poststreptococcal arthritis. Pediatr Infect Dis J 1988;7:681–682.
14. Shulman ST, Ayoub EM. Poststreptococcal reactive arthritis. Curr Opin Rheumatol 2002;14:562–565.
15. Ayoub EM, Ahmed S. Update on complications of group A streptococcal infections. Curr Probl Pediatr 1997;27: 90–101.