Musculoskeletal Infections and Crystal-Induced Arthropathies

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1. Introduction: Musculoskeletal Infections

Infection may occur in bone, joints, bursae, muscle, or tendon sheaths, although osteomyelitis, infectious arthritis, and bursitis are by far the most common musculoskeletal infections. Varieties of microorganisms including bacteria, viruses, fungi, and parasites may infect joints and other musculoskeletal tissues. Acute bacterial infections most often present as a monoarthritis but trauma and crystal arthritis are much more common causes of acute monoarticular pain and swelling. Most musculoskeletal infections result from hematogenous spread of the organism to the site. *Staphylococcus aureus* (*S aureus*) is the most common cause of musculoskeletal infection. Positive culture in synovial fluid remains the gold standard for the diagnosis of septic arthritis. Other causes of infectious arthritis often require alternative methods for diagnosis including blood and fluid cultures (disseminated gonococcal disease), antibody titers (Lyme arthritis, viral arthritis), synovial biopsy and culture (chronic bacterial and fungal arthritis). The diagnosis of infectious arthritis using the polymerase chain reaction (PCR) to detect bacterial DNA in synovial fluids has not yet reached its potential of routine clinical use.

2. Acute Bacterial Arthritis

Classification

Despite improved antimicrobial therapy, acute bacterial arthritis (septic arthritis) remains a medical emergency and the cause of significant morbidity and mortality.[1,2] Acute bacterial arthritis is usually classified by the type of infecting organism (Table 1). Bacteria commonly infect the synovium through hematogenous spread from a distant site or occasionally directly from penetrating trauma, iatrogenic joint needling, or an adjacent osteomyelitic focus.

Table 1

Septic Arthritis: The Infecting Bacteria

Gram-positive Cocci
Staphylococci: aureus, epidermidis
Streptococci: pyogenes (beta-hemolytic group A), other beta-hemolytic groups (esp. B, G), pneumoniae, viridans group
Gram-negative Cocci
Neisseria gonorrhoeae
Neisseria meningitidis
Other: *Moraxella, Kingella, Branhamella*
Gram-positive Bacilli
Corynebacterium pyogenes
Listeria monocytogenes
Gram-negative Bacilli
Brucella species
Campylobacter species
Chryseobacterium meningosepticum
Escherichia coli
Haemophilus influenzae
Kingella kingae
Klebsiella pneumoniae
Pasteurella multocida
Proteus mirabilis
Pseudomonas aeruginosa

(continued next page)

Table 1 *(continued)*

Septic Arthritis: The Infecting Bacteria

Salmonella species
Serratia marcescens

Anaerobes

Bacteroides fragilis
Clostridium species
Fusobacterium necrophorum
Peptococcus and *Peptostreptococcus* species
Propionibacterium acnes

Spirochetes

Borrelia burgdorferi
Treponema pallidum

Mycoplasma

Mycoplasma hominis
Mycoplasma pneumoniae
Ureaplasma urealyticum

Table 2

Pathogenesis of Arthritis Associated with Infection

Direct Synovial Infection

Hematogenous from a distant focus
Penetrating trauma
Adjacent infection: osteomyelitis, soft tissue abscess
Iatrogenic: postsurgery, post joint needling

Immune Complex Formation

Hepatitis B
Disseminated gonococcal infection
Bacterial endocarditis
? Postinfectious synovitis

Molecular Mimicry

Chronic Lyme arthritis
? Rheumatic fever

Unknown Mechanisms

Reactive arthritis
HIV

Microorganisms may also lead to arthritis by indirect means, such as immune complex formation, molecular mimicry, or unknown mechanisms (Table 2).

Predispositions to septic arthritis include older age (>80 years), serious chronic illness such as diabetes mellitus, cancer and chronic renal failure, rheumatoid arthritis, the presence of a prosthetic joint, intravenous drug use, skin infection and an immunosuppressed state (Table 3). Males and females are equally affected. Polyarticular septic arthritis is not rare, occurring in approximately 15% of cases of septic arthritis, depending on the population studied, with rheumatoid arthritis an important predisposing factor.[3] Polymicrobial infections occasionally occur with penetrating trauma and in patients with joint prostheses.

Table 3

Septic Arthritis: Predisposing Factors

Old age
Comorbidities: cancer, diabetes, chronic renal failure, chronic liver disease, rheumatoid arthritis
Pre-existing joint disease: rheumatoid arthritis, crystal disease, hemophiliac arthropathy
Prosthetic joint
Intravenous drug use
Congenital: hypogammaglobulinemia, complement deficiency
Concomitant infection, eg, skin
Acquired: AIDS, immunosuppressant medication
Immunosuppression

Nongonococcal Septic Arthritis

The most common bacterial causes of acute nongonococcal septic arthritis are shown in Table 4. While *S aureus* is the most common cause of septic arthritis, it generally occurs in joints that were abnormal due to arthritis, trauma, prosthesis, and/or surgery prior to infection, whereas *N gonorrhoeae* is more likely to infect previously intact joints and otherwise healthy individuals. *S aureus* causes the majority of joint infections in the elderly and in patients with rheumatoid arthritis.

Table 4

Common Causes of Nongonococcal Acute Bacterial Arthritis

Staphylococcal aureus	60%
β-hemolytic streptococci	15%
Gram negative bacilli	15%
Streptococcus pneumoniae	5%
Other and polymicrobial	5%

Pathogenesis

When bacteria arrive by the bloodstream, they deposit in the synovial membrane where they are able to incite an inflammatory reaction by a number of mechanisms involving the release of bacterial products: lipopolysaccharide endotoxins from Gram negative organisms; exotoxins from Gram positive organisms; and cell wall fragments or bacterial antigens resulting in immune complex formation. The resultant cellular and humoral proinflammatory events, which have been elucidated in animal models of septic arthritis, include synovial proliferation with phagocytosis of bacteria, early infiltration of CD4+ T cells, and the release of cytokines such as interleukin-1 and tumor necrosis factor-β. These in turn stimulate the release of metalloproteinases, collagen, and stromelysin from synovial cells and chondrocytes, leading to early cartilage loss as a result of proteoglycan breakdown. Cytokine upregulation of adhesion molecules (eg, ICAM-1) results in infiltration of neutrophils with subsynovial micro-abscess formation. The bacteria and inflammatory reaction spill into the joint cavity where bacterial products activate the complement system and phagocytosing neutrophils release lysosomal enzymes; this further enhances the inflammatory reaction and contributes to tissue damage. With ongoing untreated infection, the synovial inflammation is driven forward by these cellular and humoral processes resulting in pannus formation with further erosion of cartilage and bone. The inhibition of these infection-induced inflammatory processes in

experimental *S aureus* arthritis by the concomitant use of nonsteroidal anti-inflammatory drugs or corticosteroids with antibiotics has been shown in animal models to lessen cartilage damage and reduce postinfection synovitis.[4,5] A recent controlled study of septic arthritis in children showed that a short course of intravenous dexamethasone given along with antibiotics resulted in significantly reduced short-term and long-term residual articular dysfunction.[6] An immune-mediated postinfection synovitis that is probably related to the stimulatory effects of the intra-articular bacterial products and the release of neoantigens from cartilage may persist after eradication of the organism by antibiotics.

Clinical Picture

The stereotypical clinical picture of septic arthritis is that of an acutely painful monoarthritis: a red, hot, swollen joint (mainly the knee), associated systemic symptoms of chills and fever, and a high peripheral white cell count. This is seen in about 70% to 80% of patients. However, lack of fever, high peripheral white cell count, and other atypical presentations are common, and depend upon the age and demographics of the patient population, the infecting organism, associated systemic illnesses, and coincident treatment such as the use of nonsteroidal anti-inflammatory agents or inadequate doses of antibiotics.[7] These atypical scenarios will be discussed below. The frequency of involvement of specific joints is given in Figure 1. The differential diagnosis of septic arthritis includes crystal disease, trauma, and acute inflammatory monoarthritis or oligoarthritis, including Reiter's syndrome and juvenile rheumatoid arthritis.

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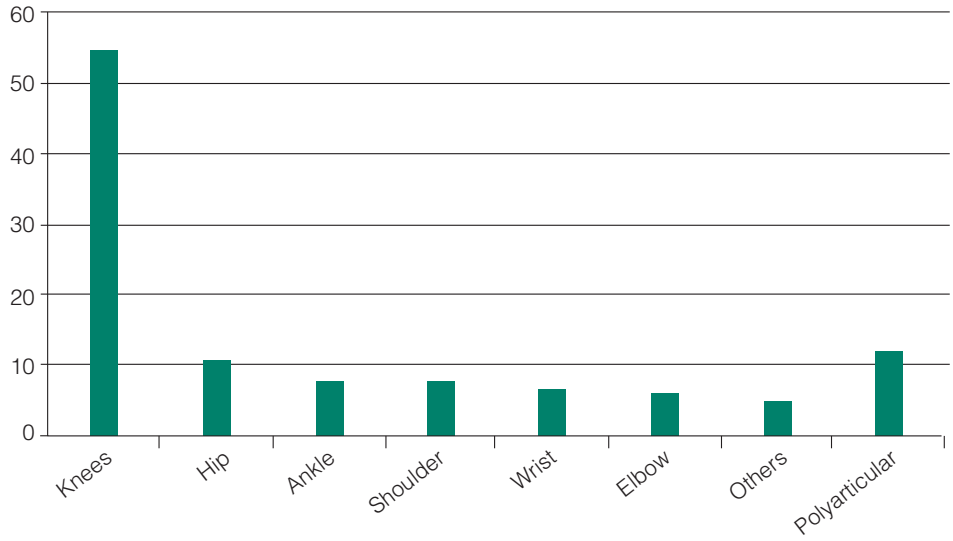
Diagnosis

The definitive diagnostic test is synovial fluid aspiration for Gram stain and culture. Synovial fluid leukocytosis is a helpful but imperfect test. Counts of more than 50,000 white blood cells (WBC)/mm^3 occur in 70% of patients. However, "pseudoseptic" fluids may occasionally be seen with crystal synovitis, rheumatoid arthritis, and spondyloarthropathies. On the other hand, 10% of patients with proven intra-articular infections may have an initial synovial fluid WBC count of less than 25,000/cubic mm.[8] The percentage of neutrophils is usually greater than 90% and often greater than 95%. Synovial fluid lactic acid, produced by bacteria and synovial cells, is elevated in septic arthritis but also in

Figure 1

Septic arthritis: joints involved (%)



other inflammatory arthropathies. A normal synovial fluid lactic acid level virtually excludes septic arthritis.

In nongonococcal septic arthritis, organisms can be seen on Gram stain in 50% to 70% of cases; gram-positive organisms are more frequently visualized than gram negative. Synovial fluid cultures generally yield positive results in over 70% of patients, as do blood cultures in 50% of cases. The use of blood culture bottles (BCB) or isolator tubes (pediatric BCB) may increase the frequency of bacterial isolation.[9] Detection of bacterial antigens by immunological techniques or bacterial DNA by polymerase chain reaction is possible but still remains the purview of research laboratories.[10] Imaging techniques play a limited diagnostic role in routine cases but may be helpful when infectious arthritis occurs in deep-seated sites such the hip, sacroiliac joints, and spine or when a prosthetic joint is present. Radionuclide scanning is very sensitive but not specific; however, three-phase technetium scanning can help localize the process to the underlying bone when there is soft tissue inflammation. Magnetic resonance imaging may be especially helpful in the diagnosis of vertebral osteomyelitis (Figure 2).

Treatment

The principles of treatment are summarized in Table 5. The initial antibiotic regimen will depend upon the clinical setting, but coverage for *S aureus* using beta-lactamase-resistant penicillin, cefazolin, or vancomycin for suspected methicillin-resistant *S aureus* is generally indicated until definitive bacteriologic identification is made. Over 25% of *S aureus* joint infections are methicillin resistant. If a gram-negative organism is suspected, then a third generation cephalosporin should be used. In clinically accessible joints, such as the knee, daily aspiration is preferable to open surgical drainage because of faster recovery of joint mobility. Initial arthroscopic lavage may result in more complete removal of inflammatory products and yield a better outcome, but this has yet to be confirmed. Arthrotomy with surgical drainage is generally indicated in infections of the hip, especially in children, or other joints that are difficult to monitor because of poor accessibility, and for patients who exhibit an inadequate response to antibiotics and repeated joint aspiration within about 7 days.

When the diagnosis is not secure and empirical antibiotic therapy is being employed, nonsteroidal anti-inflammatory drugs should be avoided in the first week in order to assess the clinical response to the antibiotic treatment. Joint immobilization is effective for pain relief, but after the first few days, range of motion exercises should be instituted to avoid contractures. Clinical response with defervescence and reduction in joint pain and erythema should be seen within 2-3 days. Within 5-7 days, synovial fluid WBC should have decreased by 50%, with negative culture. Interestingly, detection of bacterial DNA may persist in the synovial fluid for many weeks after successful eradication of viable organisms.[11] The duration of therapy is empiric but usually 4 weeks or longer is recommended; intravenously for 2 weeks followed by a course of high dose oral antibiotics.

Table 5

Septic Arthritis: Principles of Treatment

Treatment with parenteral antibiotics—initial choice dependent upon clinical situation
Daily aspiration of accessible joints
Arthroscopic lavage or open surgical drainage when required
Monitor clinical response and synovial fluid WBC and culture
Avoid nonsteroidal anti-inflammatory drugs until diagnosis is confirmed
Splint extremity for pain relief but institute range of motion exercises in 2-3 days

Outcome

Patients with rheumatoid arthritis may require more prolonged therapy. Sterile inflammation with joint effusion may persist for many weeks due to a postinfectious synovitis. The prognosis depends upon a number of factors including age, comorbid conditions, the presence of a joint prosthesis, and the duration of

symptoms prior to the institution of treatment. Delay in treatment beyond 7 days leads to incomplete joint recovery in the majority of patients. Prospective studies have shown a high rate of preexisting joint disease and joint prostheses. Outcome is poor in about 33%, and mortality is 10% or higher.[7,12] There is some evidence that pneumococcal septic arthritis has a better prognosis than seen with staphylococcal joint infection.[13]

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI) occurs in about 1% of the 1-3 million cases of gonococcal infections in the United States each year. *Neisseria gonorrhoeae* is a common cause of infectious arthritis, has a characteristic clinical picture, and responds well to antibiotic therapy.

Pathogenesis of DGI

The individual with DGI is usually young and otherwise healthy. However, patients with inherited deficiency of the complement components of the membrane attack complex (C5-C9) are susceptible to Neisserial infections including DGI.[14] Women are affected about 3-4 times more commonly than men. Asymptomatic rather than symptomatic urogenital or other mucosal infection precedes dissemination. In women, DGI tends to occur at the time of menses, during pregnancy or immediately post partum. High-risk sexual practices, including prostitution, are common. Many of the men with DGI are homosexual. Certain strains of *N gonorrhoeae* have virulence factors that are associated with dissemination.[15] The early phase of DGI often consists of a migratory arthralgia/dermatitis/tenosynovitis syndrome, which may resolve spontaneously and is considered to have an immune complex, serum sickness pathogenesis.

Clinical Picture

The clinical presentations of DGI and culture results are shown in Table 6.[16] The bacteremic phase occurs in 65% to 70% of patients with DGI and is characterized by fever, migratory polyarthralgia, tenosynovitis of the wrists, hands, ankles, or feet, and a dermatitis with scattered, usually painless, pustular, vesicopustular, or hemorrhagic macular lesions. Septic monoarthritis occurs in 30% to 40% of patients, involving knees, wrists, and ankles most commonly. With gonococcal arthritis, the synovial fluid is often in the inflammatory range, with WBC counts less than 50,000, rather than frankly purulent. An asymmetric oligoarthritis can occur in about 10% of patients. Cultures of mucosal surfaces (genitourinary, rectal, and oropharynx) for *N gonorrhoeae* yield a higher positivity rate than blood or synovial fluid cultures. Thayer-Martin medium and chocolate agar are the culture media employed. The use of PCR to detect gonococcal DNA or RNA has been studied but is not widely employed.[17]

Treatment

Because of the prevalence of penicillin-resistant strains of *N gonorrhoeae*, a third-generation cephalosporin given parenterally, such as ceftriaxone or cefotaxime, is indicated. Spectinomycin may be used in penicillin-allergic patients. The duration of therapy is empiric but generally 7 days are recommended for the bacteremic phase and 7-14 days for patients with septic arthritis. These latter patients often

Table 6

Disseminated Gonococcal Infection

Clinical Picture	Phase	Culture (% positive)
Fever, polyarthralgia, tenosynovitis, dermatitis	Bacteremic	Blood (10%) Synovial fluid (0%)
Septic arthritis	Arthritic	Synovial fluid (<50%)
Asymptomatic mucosal	During either of above	Mucosal surfaces (80%)

require daily joint aspiration and monitoring similar to nongonococcal septic arthritis. Concurrent treatment for chlamydial infection with oral doxycycline for 7 days is also recommended.

Polyarticular Septic Arthritis

Polyarticular septic arthritis (PASA) accounts for 12% to 20% of patients in reported series of septic arthritis.[1,2] Characteristics of PASA include:

- onset in the elderly (56% greater than 60 years)
- an average of 4 joints involved with knee, elbow, shoulder, and hip predominating
- a high prevalence of concomitant rheumatoid arthritis (52%)
- absence of fever and leukocytosis in 20%
- positive blood (75%) and synovial fluid cultures (92%)
- *S aureus* and *Streptococci* accounting for most cases
- poor prognosis with 32% mortality compared to 4% in patients with monoarticular septic arthritis[2]

3. Prosthetic Joint Infections

The overall infection rate in total joint replacement is approximately 1%, slightly higher for the knee than for the hip.[18] Bacteria can adhere to the inert solid surface of the prosthetic joint, elaborate polysaccharides to form a glycocalyx, and coalesce to form a protective biofilm, which accounts for persistent infection despite antibiotic therapy and normal humoral and cellular immunity.[19] This pathophysiology accounts for the partially suppressive effects of long-term antibiotic therapy with the lack of a durable response and the necessity for removal of the prosthesis to effect a bacteriological cure in most cases. One study has shown that the use of PCR to detect a highly conserved gene encoding bacteria16S ribosomal RNA is more sensitive than microbial culture to distinguish septic from aseptic prosthetic loosening.[20]

Early-onset Prosthetic Infections

Early-onset infections, which account for 70% of all prosthetic infections, occur within the first 3-6 months of joint replacement surgery and are related to intraoperative and perioperative infection. Risk factors for early-onset infections include concomitant systemic illnesses such as rheumatoid arthritis, concomitant nonarticular infections, the duration of surgery and the operative procedures, and postoperative hematoma formation. Giving prophylactic antibiotics just prior to surgery, using antibiotic-impregnated methylmethacrylate cement, and employing clean air systems in operating rooms has substantially reduced these risks. Early-onset infections are most commonly due to *S epidermidis, S aureus*, and polymicrobial organisms. The clinical manifestations are often suggestive of infection with fever and joint pain and associated erythema, induration, and drainage at the incision site. Wound cultures or joint aspiration may yield a microbiological diagnosis.

Late-onset Prosthetic Infections

Late-onset infections are due to bacterial seeding of the prosthesis during hematogenous spread. The most common organisms (with approximate prevalence) are *S aureus* (45%), streptococci (25%), gram-negative bacilli (15%), coagulase-negative staphylococci (10%), and anaerobes (5%). Most patients with late-onset infections have a subacute or chronic course, with joint pain as the predomi-

nant symptom. Radiographs may demonstrate prosthetic loosening but this can commonly occur without infection. More specific radiologic findings for infection are periosteal new bone formation and severe radiolucency at the prosthesis-bone interface. Radionuclide scanning lacks sensitivity and specificity. Joint fluid aspiration and occasionally open synovial tissue or bone biopsy may be needed for definitive microbiological diagnosis of late-onset infection.

Treatment of Prosthetic Joint Infections

Overall cure rates in patients with prosthetic infections using surgical debridement and antibiotics without removal of the prosthesis are only 20% to 30% even in those with early-onset infection. Those with late-onset infections resulting in prosthetic loosening will require surgical removal in addition to antibiotics for cure. Treatment of most patients will require removal of the prosthesis, debridement of the joint, a prolonged course of parenteral antibiotic therapy (6-8 weeks), and subsequent reimplantation of a new prosthesis employing antibiotic-impregnated cement. Even under these conditions, the reinfection rate may be very high (up to 30%). Arthrodesis may be necessary in those patients who are unable to have reimplantation because of mechanical factors in the joint. Initial parenteral antibiotic therapy followed by long-term oral suppressive antibiotic therapy with a cephalosporin or fluoroquinolone may be needed for those unable or unwilling to undergo prosthesis removal. One study suggests that long-term (3-6 months) suppressive treatment with rifampin plus an oral quinolone, of early-onset infection or late-onset infection with recent symptoms and no loosening may result in a high cure rate without prosthesis removal.[21] This strategy may also be tried in frail, elderly patients who cannot or will not undergo surgery. Although perioperative and operative preventive strategies as described previously have been shown to reduce infection rates, there is no scientific evidence that antibiotic prophylaxis is needed for patients with joint prostheses undergoing dental procedures. Oral infections however, should be treated promptly and appropriately.

4. Infections in Children and Geriatric Patients

Children

The clinical presentation of joint infection in very young children (neonates) is often subtle and therefore presents a diagnostic challenge, especially with septic arthritis of the hip, which is the most common joint to be infected. Nonspecific tests such as a very elevated ESR or C-reactive protein provide clues to a serious underlying systemic problem, including infection. The coexistence of osteomyelitis and contiguous septic arthritis is not uncommon in children under 2 years of age because of metaphyseal-epiphyseal interconnecting blood supply. The frequency of *Haemophilus influenza* arthritis has declined with the introduction of the conjugate vaccine in 1990. Infections of the hip, knee and ankle account for 80% of septic arthritis in children, with gram-positive cocci the most common organisms. Infections of the hip require primary surgical decompression and drainage. Penetrating wounds of the feet can cause infectious arthritis or osteomyelitis, occasionally with *Pseudomonas aeruginosa*.

Geriatric Patients

Almost 50% of all adults with nongonococcal septic arthritis are over the age of 60. This likely occurs because of a high frequency of comorbid illnesses, diminished immune function, and preexisting joint disease, including joint prostheses. Furthermore, bacteremia in the postoperative period is a more common cause of septic arthritis in older patients. Like young children, the presence of fever and leukocytosis are insensitive markers of septic arthritis in the elderly, but acute phase reactants (ESR, C-reactive protein) are usually significantly elevated. Morbidity with poor functional outcome and mortality is higher in older patients.

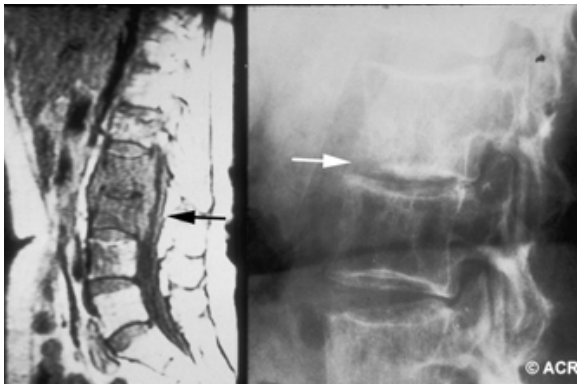
5. Septic Arthritis with Other Conditions

Intravenous Drug Use

Intravenous drug abusers have many risk factors for septic arthritis or osteomyelitis. These may include the development of soft tissue infections and transient bacteremias, and the presence of serious comorbid conditions such as hepatitis, bacterial endocarditis, and HIV infection. Septic arthritis and osteomyelitis in this population may occur at unusual sites with atypical organisms. While involvement of the knees and other medium to large joints is often seen, the fibrocartilaginous joints (sternoclavicular, costochondral, symphysis pubis) and axial skeleton (vertebral osteomyelitis, sacroiliitis) are much more commonly affected than in other patient populations (Figures 2 and 3). Furthermore, after *S aureus,* gram-negative infections *(Pseudomonas aeruginosa, Enterobacter sp., Serratia marcescens)* are the next most common, and may be indolent. Systemic candidiasis with costochondral or sternoclavicular joint infection has been described in addicts using contaminated brown heroin.

Figure 2

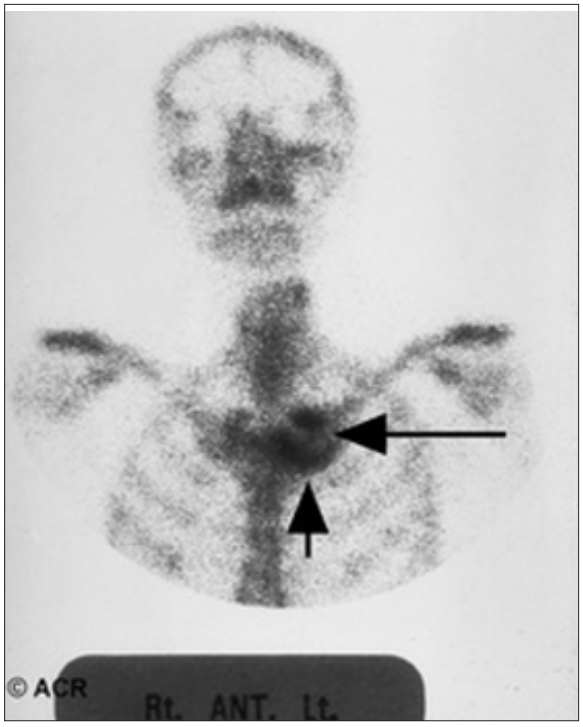
Vertebral osteomyelitis and disk space infection (x-ray and MRI)



The x-ray on the right shows demineralization of the lumbar vertebrae, narrowing of the L2-3 disc space and erosive change in the antero-inferior cortex of L2 (arrow). The MRI on the left (T1-weighted sagittal image) shows decreased intensity (dark) of L2 & L3 and to a lesser degree L1 & L4. There is L2-L3 disk space destruction and inflammation extending into the epidural space (arrow).

Figure 3

Sternoclavicular septic arthritis (technetium radioisotope scan)



There is increased uptake in the medial aspect of the left clavicle (arrow) and the medial aspect of the anterior left first rib (short arrow).

Rheumatoid Arthritis

Patients with longstanding erosive, seropositive rheumatoid arthritis (RA) on corticosteroid therapy are particularly prone to septic arthritis and account for a disproportionately high percentage of cases in many series.[3,5,12] Polyarticular involvement is common. The sources of infection include skin ulcers, ulcerated rheumatoid nodules, and wound infections. Patients may present with subacute worsening of joint complaints mimicking active RA and delaying the diagnosis. Septic arthritis should be considered in any RA patient who develops acutely inflamed monoarthritis or oligoarthritis. Even adequately

treated patients suffer a high recurrence rate of joint sepsis and mortality is significant (20% to 40%), especially with polyarticular infection.

Immunodeficiency

Congenital humoral immunodeficiency is occasionally associated with infectious arthritis involving unusual organisms. Patients with hypogammaglobulinemia are predisposed to acute septic arthritis caused by *Mycoplasma* and *Ureaplasma*. Patients with deficiency of the late complement components (C5-C9) can get joint infections with *Neisseria species*. Patients with acquired cellular immunodeficiency either related to infection (AIDS) or immunosuppressant drugs, may get acute septic arthritis or chronic tuberculous or fungal arthritis.

Other

Patients with chronic renal failure, especially those on hemodialysis, are at high risk for septic arthritis, mainly due to *S aureus*. This predisposition is multifactorial and related to recurrent vascular invasion, abnormalities in immune function, and high rates of nasal colonization with *S aureus*. Simultaneous crystal arthropathy, gout, pseudogout, and septic arthritis are unusual but have been described.[22] To complicate matters, both gout and pseudogout can cause a pseudoseptic arthritis with fever, leukocytosis, and synovial fluid WBC count greater than 50,000/mm^3. Osteoarticular brucellosis occurs in about 30% of *Brucella melitensis* infections with sacroiliitis, peripheral arthritis, spondylitis, and osteomyelitis being the major complications. Culture or a rise in antibody titer establishes diagnosis and brucellosis is treated with doxycycline and rifampin, generally for 6 weeks. The prognosis of arthritis is excellent but patients with spondylitis may require more prolonged therapy.

6. Lyme Disease

Lyme disease (LD) is the most common vector-borne (Ixodes tick) infection in the United States with 15,000 new cases reported annually.[23,24] It has focal endemicity with moderate to very high frequencies along the eastern seaboard (northeast to mid-Atlantic), in parts of Michigan, Wisconsin, Minnesota, and Northern California. This illness has protean manifestations and will be described under the following categories:

- Infectious features
- Rheumatic features
- Diagnosis, treatment, and prevention
- Autoimmunity
- Lyme-related somatic syndrome

Infectious Features

LD is caused by infection with the spirochete *Borrelia burgdorferi* (Bb). The clinical picture of LD can be classified in stages: early (localized or disseminated) and late. Early LD occurs most frequently from spring through early fall when nymphal and adult ticks are abundant and feeding. Early localized disease is characterized by an expanding, often asymptomatic, erythematous rash—erythema migrans (EM)—starting at the site of the tick bite. It is often accompanied by fever (usually less than 102°F) and a viral-like syndrome characterized by arthralgia and myalgia, occasionally sore throat, but generally without rhinorrhea. These constitutional features may occur without EM, but in highly endemic areas, EM is the most commonly presenting early feature of LD, approaching 80% to 90%. Early disseminated LD, related to hematogenous spread of Bb, is characterized predominately by involvement of any of 3 organ systems–skin, nervous system, heart–and includes disseminated EM lesions, facial palsy, meningitis, radiculoneuropathy, and rarely heart block of any degree. About 20% of patients who present with EM have a disseminated rash. Facial palsy may be isolated or accompanied by subtle or flagrant meningitis and may occasionally be bilateral. Early LD may remit spontaneously, but if untreated, over 50% of patients develop late features: mainly arthritis (see below) or neurological involvement (peripheral neuropathy, encephalopathy).

Coinfection with *Babesia microti,* an intraerythrocytic microorganism, or with the agent of human granulocytic ehrlichiosis (HGE), *Anaplasma phagocytophilum*, a rickettsia-like organism, may occur with LD since all 3 microorganisms use the Ixodes tick as vector.[25] However, in areas highly endemic for LD, Bb is found three to five times more commonly in ticks than the HGE agent, reflecting the relative frequencies of the clinical illnesses. Babesia parasitemia may be silent but can be fatal in splenectomized individuals. HGE often presents with an acute illness with high fever, arthralgia, and myalgia. Leukopenia, thrombocytopenia, and high transaminases, which are not features of LD, occur quite commonly with HGE. HGE may be particularly severe and even fatal in the elderly but is responsive to doxycycline therapy. Thus the rare fatalities attributed to Lyme disease may have been related to coinfection or isolated HGE infection. Diagnosis of both babesiosis and HGE is best performed by specific PCR assays although antibody testing and thick blood smear for the organisms in red cells or granulocytes respectively have also been utilized.

Rheumatic Features

The articular features of LD are shown in Table 7.[26] With early LD, arthralgia and myalgia are common. Over 50% of patients with untreated or incompletely treated LD develop arthritis. Initially, this is an intermittent migratory asymmetric mono- or oligoarthritis, appearing within weeks to months after infection. Recurrent joint inflammation may continue over many months, eventually becoming persistent in 10% of patients, with large effusions and even Baker's cysts, usually in one or both knee joints. The differential diagnosis includes juvenile rheumatoid arthritis (children and adolescents), spondyloarthropathy such as Reiter's syndrome, other causes of bacterial arthritis, and crystal arthritis. The synovial fluid is inflammatory and tests for LD are positive (see below) so the diagnosis is generally not difficult, especially if a patient lives in or has traveled to an endemic area. Arthritis which persists after antibiotic treatment may be related to slow resolution of the inflammatory response, rarely lack of response to antibiotics with persistent infection or intrasynovial autoimmunity, and is described below. Generalized arthralgia and myalgia may occur and persist despite adequate courses of antibiotics and is known as post-LD syndrome.

Table 7

Lyme Disease: Rheumatic Features

Stage	Rheumatic Feature
Early infectious	Arthralgia/myalgia
Late infectious	Intermittent arthritis Chronic mono- or oligoarthritis
Late "autoimmune" (postantibiotics)	Chronic monoarthritis
Late somatic (postantibiotics)	Arthralgia/myalgia

Diagnosis, Treatment, and Prevention

Diagnosis

The presence of an EM rash on a patient in an endemic area is characteristic enough that other tests are not needed and treatment may be instituted. It should be noted, however, that patients can present with a flu-like syndrome without EM, "summer flu." Culture of Bb from skin lesions, blood (during dissemination), and spinal fluid has been reported; however, the organism is slow growing and this technique is relatively insensitive, making it impractical for routine diagnosis. Similarly, the results of molecular tests for borrelial DNA sequences by PCR have proven disappointing for use in routine diagnosis because of relative insensitivity, technical difficulty and lack of specificity (often because of faulty technique). Interestingly, the "PCR test" has great sensitivity (85%) in the synovial fluids of patients with untreated Lyme arthritis, despite uniformly negative synovial fluid cultures.

Testing for antiborrelial antibodies, although an indirect diagnostic technique, is the mainstay of laboratory diagnosis for early and late LD.[27] A two-step approach has been recommended: a screening enzyme-linked immunosorbent assay (ELISA) followed, in equivocal and positive cases, by a more specific Western blot test. IgM Western blot testing, which suffers from significant false positivity rates,

is recommended within the first 4 weeks of infection when true positive results are more likely to occur. IgG Western blot testing, which has a very high specificity, can be performed at any time during the course of illness but is much more likely to be positive with disseminated or late stage LD. Misinterpretation of IgM Western blots, that is, considering a positive blot done months to years after the start of symptoms as indicating borrelial infection, is one of the more common diagnostic errors. Virtually all patients with Lyme arthritis are IgG Western blot positive, making it an excellent diagnostic test for patients in a Lyme endemic area who present with an oligoarthritis or monoarthritis. However, antibodies to Bb, once present, may persist in serum for many years, reducing the value of serological tests alone in distinguishing active from past infection. Although antibody titers generally decline over months and years, technical variability from laboratory to laboratory or even in the same laboratory at different time periods render serial antibody testing inadequate as a measure of response to treatment. A newer antibody test has been approved for diagnosis that utilizes an antigenic sequence (C6) of a borrelial-expressed protein (VlsE). This C6 ELISA assay has been found to be as sensitive and specific as the 2-step approach for the diagnosis of early and late LD and is not influenced by prior vaccination for LD.[28] The role of other laboratory tests for LD diagnosis such as urine PCR, or Bb immune complex assay, has not been confirmed. The Lyme urine antigen test (LUAT) is unreliable.[29]

Treatment

Early localized LD (EM) is generally treated with 2-4 weeks of doxycycline 100 mg bid or amoxicillin 500 mg tid (in children). Doxycycline is also active against HGE. Patients with early disseminated or late disease are usually treated with oral or parenteral antibiotics depending on the severity of illness and the organ system involved. In general, neurological involvement is treated with intravenous ceftriaxone, 2 g daily for 3-4 weeks. Isolated facial palsy may be treated with oral antibiotics. Carditis may be treated with intravenous antibiotics, initially followed by oral antibiotics when the heart block reverses. Lyme arthritis may be treated with oral antibiotics for 28 days, followed, if there is no response, by another course of antibiotics, oral or intravenous. There is no scientific evidence that more prolonged courses of antibiotics alter the course of Lyme disease infection.

Prevention

Prevention of LD by the use of antibiotics for asymptomatic individuals with Ixodes tick bites is not recommended, except possibly if the tick is engorged, a sign of feeding for more than 24-48 hours. Otherwise, the incidence of developing either symptomatic LD or asymptomatic seroconversion is very low, equaling the risk of developing a side effect from the antibiotic therapy. A recent study has shown that a single dose of doxycycline given within 72 hours of a tick bite is effective prophylaxis.[30] LD vaccine, which utilizes a single recombinant protein, outer surface protein A (OspA), has been proven safe and 70% to 80% effective in clinical trials; however, this vaccine was withdrawn from the market.[31] Appropriate protective clothing and inspection of the entire body for ticks remain the mainstays of prevention in endemic areas.

Autoimmunity

About 10% of patients with Lyme arthritis have chronic persistent synovitis (generally of a knee) despite one or more adequate courses of antibiotics. The synovial fluid and tissue are negative for Bb DNA by PCR, even if they had been positive prior to antibiotic treatment. Antibodies to Bb are present in high titer (strongly positive IgG Western blot) with antibodies to OspA being especially prominent at this stage although unusual in earlier LD. T cells isolated from blood and synovial fluid from these patients also show heightened responses to OspA. Synovial fluid T cells, either polyclonal or OspA-specific, are of the Th1 (proinflammatory) type. Patients with chronic antibiotic resistant Lyme arthritis also have a higher frequency of the HLA DR4 haplotype and especially those alleles that contain the rheumatoid arthritis shared epitope (eg, DRB1*0401, 0404, 0101). Synovial fluid T cells from antibiotic resistant Lyme arthritis respond to a few immunodominant OspA epitope peptides; one of these peptides shows sequence homology to human LFA-1, the ligand for ICAM-1.[32] Thus, it is possible that the heightened T-cell response to OspA seen in patients with Lyme arthritis results in an autoimmune reaction in those HLA DR4 positive individuals because of molecular mimicry between an OspA epitope presented by DRB1*0401 and human LFA-1 (Figure 4). The approach to treatment of these patients is anti-inflammatory therapy and

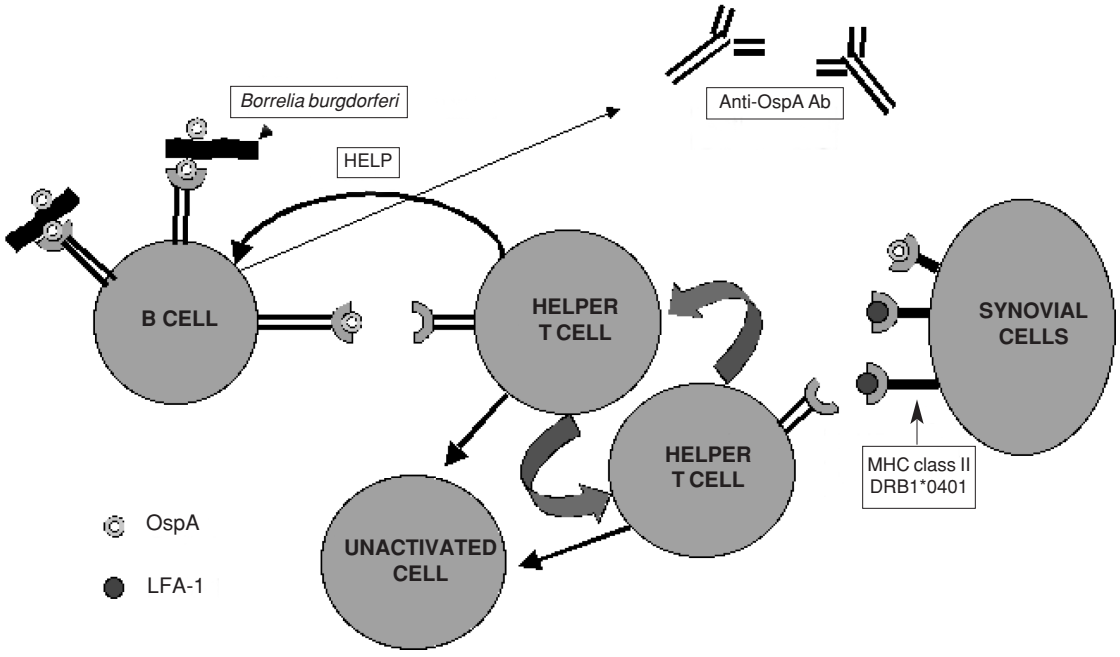
on occasion, arthroscopic synovectomy. A recent study, however, suggests that this cross reactivity of T cells from LD patients, while present, does not correlate with a specific clinical syndrome.[33]

Lyme-related Somatic Syndrome

A small percentage of patients have persistent or recurrent arthralgia, myalgia, and fatigue following LD, despite adequate courses of antibiotics. This is often called post-Lyme disease syndrome or Lyme induced fibromyalgia (FM).[34] Associated symptoms are common, including memory and concentration difficulties, neuropathic pains, headache, and unrefreshing sleep. Patients may feel better during antibiotic therapy but the effect is not durable and relapse is the rule when antibiotics are discontinued. The symptoms wax and wane but the overall course is chronic. Objective findings are not present except for soft tissue tender points. Not all patients fulfill ACR criteria for FM but all patients have an FM-like somatic syndrome. There has been controversy as to whether this condition is related to chronic borrelial infection and therefore a form of chronic Lyme disease. However, a recent study was unable to find evidence for borrelial infection in these patients and they showed no response to 3 months of antibiotic treatment compared to placebo-treated patients.[35] Thus the treatment of these patients is supportive and symptomatic and includes nighttime amitriptyline or cyclobenzaprine, antidepressant therapy when needed, exercise programs, and coping strategies.

Figure 4

Autoimmunity in Lyme arthritis: molecular mimicry



Borrelia burgdorferi within the joint space triggers an inflammatory reaction and a cellular and humoral immune response to OspA peptides. Those patients with susceptible DR4 alleles, including DRB1*0401, present an OspA peptide which has sequence homology to LFA-1. The synovial inflammatory response has caused upregulation of LFA-1 on lymphocytes and antigen presenting cells (including synovial cells). Thus OspA primed helper T cells now react with presented LFA-1 peptides leading to recruitment of previously unactivated T cells and perpetuation of the synovial inflammation in the absence of *B burgdorferi.*

7. Acute Bacterial Infections of Other Musculoskeletal Structures

Osteomyelitis

Osteomyelitis is an infection in bone characterized by progressive inflammatory destruction and relative resistance to medical therapy.[35,36] Bacteria gain access to bone either through hematogenous seeding, contiguous spread of infection, or direct trauma (compound fractures). Otherwise healthy children are more frequently affected than adults with osteomyelitis after bacteremia, and it most commonly involves the metaphysis of the femur, tibia, and humerus. In adults, especially intravenous drug abusers and the elderly, hematogenous infection may involve the axial skeleton: vertebrae, sacrum and sacroiliac joints, symphysis pubis, clavicle, and sternoclavicular joints. Diabetic patients with peripheral vascular insufficiency or foot ulcers, and often both, are especially susceptible to osteomyelitis of the bones of the feet. Prosthetic joint infections as described above involve bone and joints.

Diagnosis

A microbiological diagnosis is critical for appropriate therapy; needle biopsy or open surgical biopsy is generally required. The predominate organism is *S aureus*, but the clinical situation often dictates other likely organisms, such as *Pseudomonas* in intravenous drug abusers, streptococci or anaerobic bacteria in the diabetic foot, Salmonella or *Streptococcus pneumoniae* in sickle cell disease, opportunistic infections and *Mycobacterium tuberculosis (M tuberculosis)* in immunocompromised patients. Imaging helps to anatomically localize the infection and to aid in diagnosis. Plain radiographs may be normal, but may also show cortical destruction and periosteal new bone formation, a relatively specific finding. Technetium bone scanning is sensitive for an inflammatory process, but not specific for infection. Computed tomography (CT) scanning can identify the extent of bone edema, inflammation, and destruction; the presence of necrotic bone (sequestra); and the surrounding soft tissue involvement. Magnetic resonance imaging (MRI) is best for detection of spinal infection.

Treatment

Acute osteomyelitis, especially when caused by hematogenous spread and when treated early, may be cured with parenteral antibiotics alone. The principles of therapy are to employ the appropriate parenteral antibiotics in adults for 4-6 weeks. For *S aureus* infections, there is some evidence that a higher cure rate is obtained when rifampin is added to standard anti-staphylococcal regimens. Children may be treated with a shorter course of parenteral antibiotics, followed by several weeks of oral therapy. Chronic osteomyelitis, by definition, is refractory to medical treatment and usually requires surgical debridement and removal of necrotic bone, in addition to appropriate antibiotic therapy. Therapy with fluoroquinolones, with or without rifampin, given for some months, has been used to suppress the symptoms and signs of chronic refractory osteomyelitis, as in the diabetic foot.

Septic Bursitis and Tenosynovitis

Septic Bursitis

Septic bursitis is a common clinical problem.[38] The vast majority of cases are post-traumatic, with direct penetration of skin bacteria. Diabetes, alcoholism, and systemic corticosteroid therapy are risk factors. Involvement of the olecranon and prepatellar bursae account for the majority of the cases. An overlying tissue inflammation or cellulitis is common. In distinction from septic arthritis of the elbow or knee, passive extension is full and pain free. Bursal fluid WBC counts are elevated, although lower on average than synovial fluid counts in septic arthritis, and the bursal fluid is not usually purulent. *S aureus* is the most common cause of septic bursitis with streptococci second in frequency and together they account for over 90% of cases. The major differential diagnosis is acute gouty bursitis. Uncomplicated olecranon bursitis, with little overlying cellulitis, in an otherwise healthy individual may be treated with a course of oral antibiotics (eg, dicloxacillin or cephalexin) and close follow up, including repeat bursal aspirations. Treatment should continue until the bursal fluid is sterile, usually 7-10 days. Older and immunocompromised patients, patients with accompanying cellulitis or systemic symptoms, and those with prepatellar septic bursitis are best treated initially with parenteral antibiotics; the duration of therapy

should be about 2 weeks. Occasionally septic bursitis may require surgical drainage. An occasional sequela of septic bursitis is a chronically inflamed aseptic bursa, which is cured by bursectomy.[9]

Acute Infectious Tenosynovitis

Acute digital flexor tenosynovitis is a true emergency since delay in treatment will result in tendon necrosis. Patients almost always have a history of a cut or puncture wound on the palmar side of a finger or a chronic hand condition with skin ulceration, such as scleroderma. *S aureus* and *Streptococcus pyogenes* are the most likely causes. Patients with an acutely inflamed digital tendon sheath should be referred immediately to a hand surgeon for appropriate drainage and irrigation as well as antibiotic therapy. If there is any question about the diagnosis, ultrasonography may be a useful imaging technique.[39]

Pyomyositis

Pyomyositis is an acute bacterial infection of muscle, usually caused by *S aureus*. Although common in the tropics, it was rarely described in temperate climates until the advent of HIV/AIDS.[40] *S aureus* is by far the most common cause, and infection is seeded in muscle through hematogenous spread. Patients present with fever, constitutional symptoms, and localized muscle pain. The muscle is tender and indurated, not fluctuant. One or a few muscle groups may be involved, most commonly the quadriceps femoris. Blood cultures are rarely positive but cultures of the muscle aspirate usually reveal the infecting organism. The creatine phosphokinase levels may be normal or slightly elevated and local asymmetric muscle pain, not weakness, is the main clinical feature. Therefore, pyomyositis is easily distinguishable from inflammatory muscle diseases. Radiographs are normal and diagnosis is made by ultrasound that may show a fluid collection, or more definitively by CT scan or MRI, which may show intramuscular inflammation and abscess formation. Treatment requires parenteral antibiotics and drainage of the abscess, if present.

8. Osteoarticular Tuberculosis

With the advent of HIV, the incidence of tuberculosis (TB) and the frequency of extrapulmonary TB have risen dramatically. Skeletal TB occurs in approximately 1% to 3% of cases. Osseous infection with *M tuberculosis* typically occurs during hematogenous spread, either with primary infection or after many years with late reactivation. Spinal osteomyelitis with seeding to the vertebral bodies is the most common skeletal manifestation of TB. Joint involvement may occur secondary to hematogenous spread or from a contiguous focus of tuberculous osteomyelitis. The clinical syndromes associated with osteoarticular TB are shown in Table 8. Although pulmonary involvement (abnormal chest x-ray) is found in only 30% of patients with skeletal TB, the tuberculin skin test is positive in almost all immunocompetent patients. Treatment of osteoarticular TB is by combination chemotherapy, usually for 12-18 months.[41] The widespread use of tumor necrosis factor antagonists in RA and Crohn's disease has resulted in reactivation of tuberculosis in a predisposed population.[42] Interestingly, the majority of these patients have disseminated tuberculosis and some have developed osteoarticular disease. Therefore, patients with RA on these medications who develop atypical spinal or musculoskeletal pains have to be thoroughly investigated.

Table 8

Osteoarticular Tuberculosis: Clinical Syndromes

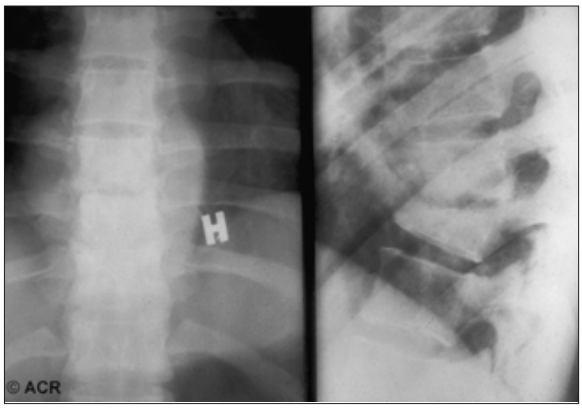
Spondylitis (Pott's disease)
Tuberculous arthritis
Extraspinal osteomyelitis
Tenosynovitis
Poncet's disease

Spondylitis (Pott's Disease)

Spine involvement accounts for 50% of all osteoarticular TB.[43] It commonly begins in the anterior portion of a vertebral body in the thoracic or lumbar spine. The inflammation and caseation necrosis lead to destruction of the vertebral end plates, contiguous disc involvement with narrowing, and vertebral collapse (Figure 5). Infection often extends to one or two adjoining discs and vertebrae eventually leading to kyphosis. Soft tissue extension with abscess formation may occur resulting in pressure on neurological structures and, if left untreated, cord compression with paraplegia can be the outcome.

Figure 5

Pott's disease: thoracic spine



An anterioposterior x-ray of the thoracic spine shows a paravertebral soft tissue mass. The lateral view on the right shows bone destruction of adjacent vertebral margins and severe loss of intervertebral space leading to a gibbus deformity.

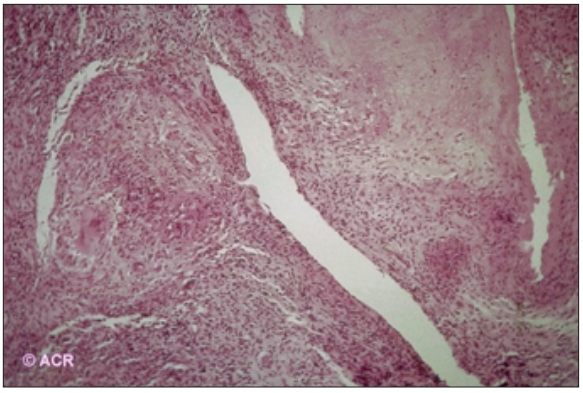
Tuberculous sacroiliitis can also occur. The cardinal symptom is the subacute onset of back pain, gradually increasing over weeks to months. Constitutional symptoms of fever and weight loss are present in less than half the patients, although the ESR is usually elevated. Radiographs usually are abnormal but CT scanning or MRI better defines the vertebral, disc, and soft tissue involvement. The diagnosis is best made by bone biopsy for histology and culture.

Tuberculous Arthritis

Patients usually present with an indolent monoarthritis of a weight-bearing joint, occasionally with mild constitutional features.[41] Radiographic changes may show mild joint space and marginal erosions but often only para-articular osteopenia. Adjacent osteomyelitis may be present. While the synovial fluid is inflammatory and TB cultures may be positive, the diagnosis is best made by synovial biopsy where histology shows a granulomatous synovitis and acid fast stains and culture are more likely to be positive (Figure 6). Prosthetic joint infections with *M tuberculosis* can rarely occur.[44]

Figure 6

Tuberculous synovitis



The synovium is thickened with caseation necrosis in the upper right, dense lymphocytic infiltration and granulomatous inflammation with Langerhan's giant cells.

Other Mycobacterial Syndromes

Tuberculous osteomyelitis generally involves the long bones in adults and may be multifocal, especially in immunocompromised patients. Dactylitis of the metacarpals and phalanges due to TB has been described mainly in children. Tenosynovitis of the wrists and hands can mimic other infectious as well as noninfectious causes of tendinitis. Flexor or extensor tendinitis, with or without arthritis, is found. Diagnosis is often delayed. Treatment consists of combination chemotherapy and surgical debridement, generally with a good result. Poncet's disease is a "reactive" polyarthritis, mainly in the hands and feet, in the setting of active TB that resolves with antituberculous therapy.[45] Articular infections with atypical mycobacteria, especially *M marinum, M kansasii, M avium intracellulare*, may occur with a predominance of arthritis and tendinitis in the hands and wrists. Carpal tunnel syndrome may occur. Definitive diagnosis is often delayed and treatment usually requires combination chemotherapy and surgical debridement.

9. Fungal Arthritis

Fungal musculoskeletal infections, especially osteomyelitis and arthritis, often create diagnostic difficulties because of a lack of clinical suspicion. Candidal organisms can cause arthritis by a number of mechanisms and in a number of settings, including hematogenous spread in intravenous drug abusers or in seriously ill, immunosuppressed, hospitalized patients with indwelling vascular lines, direct intra-articular inoculation, and infection of prosthetic joints. Acute monoarthritis, especially of the knee, can be seen with *Candida* whereas most other fungal infections cause an indolent chronic monoarthritis and sometimes oligoarthritis. Treatment with ketoconazole or fluconazole is effective for *Candida albicans*.

General characteristics of arthritis caused by other fungi including coccidioidomycosis, sporotrichosis, blastomycosis, cryptococcosis, and histoplasmosis:

- Related to geographic distribution or occupation
- Lung and skin involvement common
- May have an initial self-limited polyarthritis
- Chronic monoarthritis, mainly of the knee (occasionally oligoarthritis)
- Diagnosis best made by staining and culture of synovial tissue
- Treatment with systemic antifungal agents and surgical debridement

10. Viral Arthritis

Although arthralgia commonly accompanies many viral infections, arthritis is a well-recognized feature of but a few viral illnesses.[46] Table 9 lists the viruses that may be associated with arthritis, some commonly, and others rarely. The mechanism of the arthritis accompanying viral infections is direct invasion for a few, immune complex formation for many, and unknown for some. The arthritis often occurs during the viral prodrome, at the time of the rash. Viral arthritis is generally characterized by the sudden onset of symmetrical small and medium joint pain and stiffness with or without joint swelling (rheumatoid arthritis-like), lymphocytic/monocytic joint fluids, and a self-limited, non-destructive course.

Parvovirus B19

Parvovirus, a single-stranded DNA virus, is the cause of erythema infectiosum (fifth disease) in children and a rheumatoid-like polyarthritis in adults.[47] It presents clinically with acute and occa-

Table 9

Viral Infections Associated with Arthritis

Virus	Mechanism	Frequency of Arthritis
Parvovirus B19	?IM	C
Rubella	DI	C
Alphaviruses (arboviruses)	?IM	C
Chikungunya		
O'nyong-nyong		
Ross River (epidemic polyarthritis)		
Other		
Hepatitis Viruses		
Hepatitis A	?	U
Hepatitis B	IM	C
Hepatitis C	IM	U
Retroviruses		
HTLV-1	DI	U
HIV	?	C
Other		
Mumps	?	U
Echoviruses	?DI	U
Varicella-Zoster	?DI	U
Epstein-Barr	?DI	U
Adenovirus	?	U

UDI = direct invasion-culture of virus from synovium or detection of viral DNA/RNA by PCR
IM = immune mediated - viral antigen/antibody in serum and/or synovial fluid
C = common
U = uncommon

sionally persistent joint pain, morning stiffness, and occasional swelling most often involving the hands, wrists, and knees. Although symptoms resolve within 1-2 weeks in most patients, in up to 10% it persists for weeks to many months, often waxing and waning and mimicking seronegative rheumatoid arthritis. To complicate matters even more, some patients in the acute phase develop low titers of rheumatoid factor. However, pannus formation, with resulting erosive damage, and rheumatoid nodules are not features of parvoviral arthritis. Adults usually lack the characteristic "slapped cheek" rash seen in children. Serological testing for anti-viral antibodies supports diagnosis. IgG antibodies are evidence of past infection and are highly prevalent (more than 50% of the population). IgM antibodies point to recent infection and usually remain positive for 1-2 months. Treatment with nonsteroidal antiinflammatory drugs or low doses of corticosteroids (in chronic cases) provides symptomatic relief. The pathogenesis of parvoviral arthritis is uncertain. Although viral DNA has been found in the synovial fluid of affected individuals, it has also been found in other arthropathies including RA and osteoarthritis. Viremia clears prior to the onset of clinical disease, suggesting that direct infection may not be the cause of the arthritis. Interestingly, an increased prevalence of HLA DR4 has been reported in patients with chronic arthritis (>2 months duration) supporting an immune-mediated pathogenesis.

Rubella Virus

Rubella virus infection is commonly associated with arthralgia and arthritis, especially in adult women.[48] Joint symptoms usually begin within one week of the German measles rash as an abrupt symmetrical polyarthralgia or polyarthritis syndrome with stiffness involving the hands, wrists, knees, and ankles. Periarthritis, tenosynovitis, and carpal tunnel syndrome may be seen. In most patients, these symptoms resolve within a few weeks. In some patients, however, chronic and recurrent arthritis may occur for months to years. In the past, there was a high incidence of an arthralgia/arthritis syndrome following rubella vaccination, but using a less arthritogenic strain of the live attenuated virus has reduced the frequency of this complication. The presence of IgM antirubella antibodies or a rise in IgG antibodies (paired acute and convalescent sera) supports the diagnosis of rubella-associated arthritis. Direct infection of the synovium is likely the cause of rubella arthropathy since the virus has been cultured from synovial tissue.

Alphaviruses (Arboviruses)

The alphaviruses are mosquito-borne viruses that can cause epidemics of febrile polyarthritis in Africa, Asia, Australia, and New Zealand (Ross River virus), Northern Europe, and South America. Patients typically develop fever, arthritis, and a morbilliform rash. The onset of the arthritis may be abrupt (chikungunya, o'nyong-nyong) or gradual. Typically, the hands, feet, and medium size joints of the upper and lower extremities are involved. The acute disease usually resolves within 10 days but it may recur or persist for months. Viral isolation or serological studies can confirm the diagnosis.

Hepatitis Viruses

Hepatitis A

Arthralgia occasionally occurs with hepatitis A infection but arthritis is very rare. The mechanism is unknown.

Hepatitis B (HBV)

HBV, in about 30% of acutely infected patients, causes a serum-like illness in the preicteric phase of hepatitis, characterized by urticaria and arthritis. The arthritis is usually sudden in onset, symmetric, and additive. Pain, stiffness, and swelling of the hands and knees are common. Joint symptoms usually last from 1-3 weeks, occasionally persisting after the onset of jaundice. Soluble antigen-antibody complexes of HbsAg and HbsAb can be detected in both serum and synovial fluid.[49] Decreases in serum complement levels may be found, supporting an immune complex-mediated pathogenesis. Patients with chronic HBV infection, including those who develop a polyarteritis nodosa-like syndrome, may have recurrent arthralgia or arthritis. The joint disease is self-limited but the liver disease may require interferon therapy.

Hepatitis C
Hepatitis C infection is common and often asymptomatic. Arthritis is unusual except in those patients who develop circulating immune complex disease where the triad of arthritis, vasculitic purpura, and cryoglobulinemia are common. Interferon treatment may be required to control the clinical features of the cryoglobulinemic syndrome.

Retroviruses

Human T Lymphotrophic Virus Type I (HTLV-1)
HTLV-1 is endemic in Japan, where it has been associated with a number of clinical syndromes including myelopathy and adult T-cell leukemia/lymphoma. HTLV-1 has also been associated with acute and chronic oligoarthritis accompanied by a nodular skin rash. Direct infection is likely since these patients have antibodies to HTLV; type C viral particles are seen in the skin lesions and the synovium has atypical synovial cells with lobulated nuclei.

Human Immunodeficiency Virus (HIV)
Rheumatic features accompanying HIV and AIDS are protean (Table 10).[50] Nonspecific joint and muscle pains are common in AIDS patients, as part of acute HIV, a superimposed infectious process, or a chronic functional somatic syndrome such as fibromyalgia. Three defined articular syndromes are associated with HIV: 1) a severe, intermittent, and short-lived (hours) oligoarticular joint pain syndrome; 2) a lower extremity oligoarthritis; 3) an arthrocutaneous syndrome with enthesopathy, but usually without sacroiliitis or spinal involvement, resembling Reiter's syndrome or psoriatic arthritis.[51] Patients with this Reiter's-like presentation almost always have frank AIDS. HLA-B27 is present in 65% to 75% of these patients, a frequency similar to Reiter's syndrome without AIDS. The pathogenesis of this arthrocutaneous syndrome is not known. It is similar to the spondyloarthropathies in patients without AIDS and may have a similar pathogenesis since MHC Class I (HLA-B27) and CD8+ cells rather than CD4+ cells seem important in both. Another cause of musculoskeletal pain and inflammation in AIDS patients is opportunistic infection in joints, bone, and muscle including bacterial arthritis, pyomyositis, and osteoarticular TB. Treatment of the idiopathic arthralgias and arthritis of AIDS with nonsteroidal antiinflammatory drugs may suffice. However, the painful oligoarticular syndrome often requires narcotic analgesia. The oligoarthritis and arthrocutaneous syndrome may require more potent antirheumatic treatment including intra-articular corticosteroids, low-dose oral corticosteroids, sulfasalazine, or hydroxychloroquine. Aggressive antiretroviral treatment theoretically has greatly reduced the frequency of the articular syndromes and other rheumatic complications of HIV. Although immunosuppressive therapy, including methotrexate, could lead to worsening of the immune function in these patients, it has been used successfully in patients controlled on antiretroviral drugs. Other rheumatic features in HIV/AIDS are shown in Table 10.

Table 10

Rheumatic Features of HIV/AIDS

Arthralgia	Acute HIV infection Superimposed opportunistic infection Chronic somatic syndrome Acute painful oligoarticular syndrome
Arthritis	Oligoarthritis – lower extremity Arthrocutaneous syndrome +/- Enthesopathy (Reiter's, psoriatic-like) Infectious arthritis
Myositis	HIV-related AZT-induced Pyomyositis
Sjögren's syndrome	Diffuse infiltrative lymphocyte syndrome (DILS)
Vasculitis	Leukocytoclastic vasculitis Polyarteritis type vasculitis
Autoantibody production	ANA, anticardiolipin antibody

Other Viral Illnesses

Adults with mumps virus infection may occasionally develop a migratory polyarthritis affecting large joints beginning 1-3 weeks after infection and subsiding after 2 weeks without joint damage. The pathogenesis of this syndrome is unknown. Enterovirus (coxsackie and echovirus) infections are common but are uncommonly associated with arthritis. A self-limited polyarthritis involving large and small joints is seen, usually at the peak of the viral clinical illness. Although the pathogenesis is not proven, echovirus has been isolated from the joints. Varicella-zoster infection, both chickenpox and zoster, may rarely be associated with an inflammatory arthritis. An acute monoarthritis has been described with chickenpox and virus has been isolated from the joint. Patients with zoster may have severe nerve root pain mimicking joint disease. Epstein-Barr virus infection (infectious mononucleosis) frequently causes arthralgia but rarely arthritis. A large joint monoarthritis is typical, and recently viral DNA was detected in synovial fluid lymphocytes.[52] A patient has been described with an acute polyarthritis associated with hantavirus infection (hemorrhagic fever with renal syndrome).[53] Diagnosis in most cases of viral arthritis is made by the typical clinical picture, serological testing for viral antibodies when needed, and synovial fluid analysis to rule out other causes of inflammatory arthritis (bacterial infection, crystal disease).

11. Poststreptococcal Reactive Arthritis and Rheumatic Fever

Although certainly not musculoskeletal infections, poststreptococcal reactive arthritis (PSRA) and rheumatic fever (RF), similar if not identical entities which cause an inflammatory arthritis, deserve mention because of their clear association with hemolytic group A streptococcal pharyngeal infections.[54-56] While they are diseases of young children with peak incidence from 4-9 years, they can also occur in adolescents and young adults, when the arthritis is more prominent and less migratory. PSRA patients may not fulfill the Jones criteria for RF (Table 11), but some clearly do. The arthritis of PSRA tends to be like that of adults with RF—more persistent (additive), recurrent, involvement of small as well as large joints and poor response to salicylates and NSAIDs. In RF, typically 6-16 joints may be inflamed, each for one week or so, the synovial fluid is inflammatory and the x-rays are usually normal. This clinical picture can be altered by NSAIDs or corticosteroids. Subcutaneous nodules when present are firm, painless and often directly on the olecranon and are associated with rheumatic carditis. Erythema marginatum is an evanescent, non-pruritic pink rash with a sharp outer edge. It occurs early and may persist or recur after the arthritis has settled. It also is associated with rheumatic carditis. Of course, rheumatoid factor, ANA, and complement levels are normal. The key element in the diagnosis is strong evidence of a preceding (by 2-4 weeks, shorter with PSRA) streptococcal pharyngitis as other sites of infection and other organisms are not associated with PSRA or RF. A rise in antibody titer to streptolysin O (ASO) is the most reliable test (positive in 80%) but other antibodies may be positive such as anti-DNAase or anti-DNAase B and antihyaluronidase. These tests are more reliable than throat culture that is associated with false positive and false negative results. Acute phase reactants may be helpful in monitoring disease activity. The etiology of RF is unknown but is likely some combination of host (genetic) factors and immunological factors leading to molecular mimicry. Antibodies to streptococcal M protein and myosin cross react. Treatment is trimodal—symptomatic relief with anti-inflammatory drugs, treatment of the streptococcus with penicillin and prevention of future infections with continuous penicillin until young adulthood.

Table 11

Jones Criteria for Rheumatic Fever

Evidence of a preceding streptococcal infection PLUS 2 major criteria OR 1 major and 2 minor

Major

- Carditis
- Polyarthritis – migratory
- Chorea (Sydenham)
- Erythema marginatum
- Subcutaneous nodules

Minor

- Fever
- Arthralgia
- Previous RF or rheumatic heart disease

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Crystal-Induced Arthropathies

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Contents

1. Introduction: Crystal-Induced Arthropathies

The crystal-induced arthropathies are a collection of clinical syndromes characterized by crystalline deposition in articular and periarticular tissues. These diseases may encompass both acute and chronic presentations as well as involve any number of joints. The inflammatory response to crystals, both in and around affected joints, is dependent upon the complex interplay of a host of issues including local tissue damage, associated diseases, genetic factors, lifestyle, and provocative stimuli. In addition to pain and systemic manifestations, these diseases can result in joint damage as well as pose significant diagnostic dilemmas for the clinician. Moreover, the common presentation of crystal-induced arthropathies in a monoarticular fashion dictates that a careful, systematic evaluation be undertaken in order to distinguish crystal-induced arthritis from other important conditions including infection, trauma, tumor, degenerative arthritides, foreign-body synovitis, and the monoarticular presentation of a systemic disorder.[1] Finally, the fact that crystals can be seen within and around joints, yet in the absence of inflammation or damage highlights the need for further research into the etiopathogenesis of clinically relevant syndromes. The discovery of a variety of familial calcium crystal diseases such as fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, and Albright hereditary osteodystrophy should help illuminate the mechanisms involved in these pathologic processes.

2. Overview of Implicated Crystals

The main species of crystals found in synovial fluids of arthritis patients include monosodium urate (MSU), calcium pyrophosphate, and apatite crystals (Table 1). These may also be found within bursal fluid and deposited in soft tissues. Less commonly noted species include calcium oxalate, amyloid, aluminum, cystine, xanthine, hypoxanthine, cholesterol and liquid lipid crystals. Proteins such as cryoglobulins can crystallize in blood vessels and tissues. Because these various unusual crystals may have manifestations that can be confused with the more common syndromes of gout and calcium pyrophosphate deposition disease (CPPD), it is important to understand the relationship between crystals and their associated metabolic and pseudovasculitic syndromes (Table 1).

Crystal Identification

Not all crystals can be identified using compensated polarizing microscopy (Figure 1). However, in the cases of gout and CPPD, the type of birefringence is distinguishing. Monosodium urate crystals are

Table 1

Crystal Species and Associated Clinical Disorder

Crystal	Clinical Disorder
Monosodium urate	Gout
Calcium pyrophosphate	Pseudogout
Hydroxyapatite	Calcific periarthritis
Calcium oxalate	Primary and secondary oxalate gout
Crystalline lipids	Cholesterol emboli syndrome
Crystallized proteins	Cryoglobulinemia
Cystine crystals	Cystinosis

strongly birefringent and are seen as yellow when the crystal in question is parallel to the axis of slow vibration on the first order color compensator (negatively birefringent). In contrast, calcium pyrophosphate crystals are positively birefringent, and hence yellow in appearance, when perpendicular to the compensator. Moreover, such crystals are only weakly birefringent.[1] Liquid lipid crystals may display intense birefringence in the pattern of a Maltese cross. Calcium hydroxyapatite crystals do not manifest birefringence under polarized light. Other methods available for the identification of crystals include electron microscopy, infrared spectroscopy, elemental analysis, atomic force microscopy, and x-ray powder diffraction. Special stains such as Alizarin red S can suggest the presence of basic calcium phosphate crystals or aluminum containing particles.

Characteristics of the Inflammatory Response to Crystals

Crystals are capable of stimulating the release of inflammatory mediators from cells such as phagocytes and synoviocytes via non-specific activation of signal transduction pathways. Among the soluble mediators released can be found arachidonic acid metabolites, interleukins (IL-1, IL-6, IL-8), and tumor necrosis factor-α (TNF-α). Proteolytic release of chemotactic factors and enhancement of endothelial-neutrophil adhesion are mechanisms whereby granulocyte influx is supported. This in turn is a key event in the initiation of clinically apparent inflammation such as synovitis. Venous uptake of soluble inflammatory mediators such as IL-1, IL-6, IL-8, and TNF-α, likely accounts for systemic clinical manifestations including fever and the rise in acute phase reactants. Transforming growth factor-β (TGF-β) has been implicated in limiting the duration of inflammation by virtue of an inhibiting effect upon white cells.[2]

Figure 1

Components of a polarizing microscope

Analyzer: 90° orientation to the polarizer	A polarizer	
First order red compensator	In the light path between the polarizer and the analyzer	Depending upon orientation to the polarizer, a monosodium urate crystal will be either blue or yellow
Crystal	Wet prep placed between polarizing plates	Elongation is the process of orienting the crystal's long axis parallel to the orienting line of the compensator
Polarizer	Orients light into parallel planes	
Light source	White light	

Gout

Etiology

Gout is the prototypical crystal-induced arthropathy. It represents a diverse group of diseases that can be characterized by arthritis, tophi, kidney stones, and nephropathy. It is in fact a metabolic disorder due to a defect in the handling of uric acid. Predictive factors for gout include increasing uric acid levels, alcohol consumption, diuretics, and body mass index. Epidemiological studies associate hyperuricemia with renal impairment, lipoprotein abnormalities, body mass, and alcohol. The worldwide incidence and prevalence of gout is increasing.[29]

The prevalence of gout in the United States is estimated at 8.4 per 1000 persons (all ages). About 10% of patients are overproducers of uric acid. In general, this clinical state can be seen in the setting of increased nucleic acid turnover such as in myeloproliferative disease and, possibly, psoriasis. Rarely, overproduction is seen in the situation of inherited disorders of purine nucleotide synthesis such as in HGPRT (hypoxanthine-guanine phosphoribosyltransferase) deficiency or in PRPP (5-phosphoribosyl-1-pyrophosphate) synthetase superactivity (Table 2). The vast majority of patients have disease characterized by uric acid underexcretion. Underexcretion can be distinguished from overproduction by measuring the 24-hour urine uric acid excretion. On a normal diet, excess excretion is defined as 800 mg or more. On a purine-restricted diet, overexcretion may be defined as greater than 600 mg/24 hours.[3]

A renal tubular defect may play a role in some patients with underexcretor physiology. Any disease that predisposes to renal insufficiency may contribute to gout (Table 3). Diabetes mellitus and hypertension can be associated with decreased uric acid excretion. Organic acids can compete for renal tubular secretion as can be seen in ethanol intoxication with lactic acidosis or starvation diet with ketosis. Pharmaceutical agents can impair renal tubular handling of uric acid and the list of such agents notably includes diuretics, cyclosporine, and low-dose salicylates.

A combination of overproduction and underexcretion of uric acid likely accounts for many cases of gout. A noteworthy example involves alcohol consumption. In this situation both mechanisms of disease physiology are in play because alcohol intake accelerates urate production while alcohol-induced lactic acidemia blocks uric acid excretion. Beer is particularly injurious to gouty physiology owing to the presence of guanosine, which is an intermediary in the nucleic acid catabolism pathway. Over a period of years, untreated hyperuricemia leads to an increase in the total body burden of uric acid. Collec-

Table 2

Conditions Associated with Urate Overproduction

HGPRT deficiency
PRPP synthetase superactivity
Myeloproliferative/lymphoproliferative disease
Hemolysis
Psoriasis
Paget's disease
Glycogen storage diseases (myogenic hyperuricemia)
Ethanol
Fructose-1-phosphate aldolase deficiency

Table 3

Conditions Associated with Uric Acid Underexcretion

Lactic acidosis
Ketoacidosis
Renal insufficiency
Diuretics
Cyclosporine
Low-dose aspirin
Hypertension
Lead nephropathy

tions of noninflammatory crystalline material, called tophi, can be found in soft tissues. Shedding of microtophi and intra-articular precipitation of crystals are two mechanisms whereby an acute attack of inflammation is initiated.

Diet and Gout

There is an increased risk of gout associated with obesity. A gain of more than 30 pounds since age 21 more than doubles the relative risk for gout in men. Similarly, a reduction in weight is associated with a reduction in gout risk (in both men and women). NHANES III data suggests that high intake of meat and fish is associated with higher levels of serum uric acid. In contrast, a uricosuric effect has been implicated for (low fat) dairy-based protein intake.

Consumption of alcohol may contribute to both increased uric acid production and reduced uric acid excretion. Alcohol stimulates degradation of ATP to AMP, which in turn is converted to uric acid. Ketoacidosis appears to activate urate transporter-1 (URAT1), thereby driving enhanced reabsorption of urate by the proximal tubular cells of the kidney. NHANES III data, however, implicates only beer and liquor consumption with higher serum uric acid levels. Wine may have a protective effect against hyperuricemia.[28]

Purine Metabolism

Metabolism of purine nucleotides provides the substrate for the chemical reactions that ultimately produce uric acid. The sources of purine nucleotides can be exogenous (dietary) or endogenous (de novo synthesis). Oxidative catabolism of degradation products derived from these purine nucleotides results in the generation of uric acid (Figures 2 and 3). The final such catalytic pathways involve the enzyme xanthine oxidase whereby xanthine is ultimately converted to uric acid (Figure 3). Enzymatic deficiencies, such as in Lesch-Nyhan syndrome (HGPRT deficiency), can result in enhanced purine de novo synthesis with ultimate overproduction of uric acid. Excessive enzymatic activity, such as with PRPP synthetase superactivity, augments PRPP availability and thereby drives uric acid production. These two enzymes (HGPRT and PRPP synthetase) are X-linked. Xanthine oxidase inhibitors, such as allopurinol, exert profound antihyperuricemic effect.

Uric Acid Homeostasis

Hyperuricemia should not be thought of as a disease but rather a risk factor for gout. Generally speaking, men have higher serum levels of uric acid. The relative protected status enjoyed by women may reflect the uricosuric effect of estrogen. After menopause, this gender discrepancy in serum uric acid levels regresses. Although humans possess the gene for uricase, this gene is inactive. Hence humans, as opposed to many animals, must rely upon alternate pathways for the elimination of uric acid. The antioxidant properties of uric acid have been proposed as a "teleological" explanation for this "acquired" state of phenotypic uricase deficiency. One pathway of elimination of uric acid involves bacterial oxidation in the gut. However, this is a relatively minor pathway. The major pathway of elimination of uric acid is renal excretion. Plasma urate is filtered, reabsorbed, and ultimately secreted by the proximal tubules of the kidney. Initially, 95% of the filtered load of plasma urate is reabsorbed by the proximal tubules. The anion exchangers responsible for this reabsorption remain incompletely characterized.[4] At physiologic pH, the majority of uric acid is in the form of urate. But in the lower pH environment of the urinary tract,

Figure 2

The biochemical pathway for the synthesis of purine nucleotides

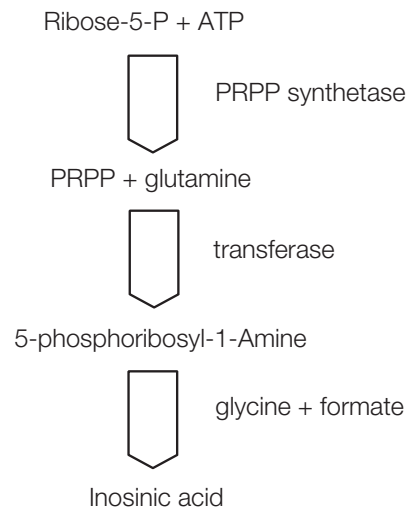
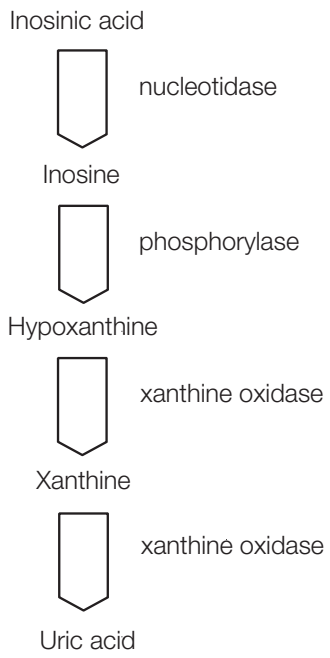


Figure 3

The biochemical pathway for the synthesis of purine nucleotides



relatively insoluble uric acid is formed which in turn may precipitate crystals. The annual incidence of gout rises in concert with the serum level of uric acid.

Pathology

Needle-shaped crystals may be seen within the synovial membrane. It should be noted, however, that the presence of crystals alone does not necessarily reflect clinical disease activity. During active disease, a surrounding foreign-body granulomatous reaction including giant cells and mononuclear cells may be observed histologically. Both special stains (DeGolantha) and polarizing microscopy can be used to identify crystals in tissue prepared in alcohol-fixed or frozen specimens.

Uric acid crystals may be seen within the synovial fluid of both active and inactive gouty joints.[5] The finding of intracellular negatively birefringent crystals is particularly compelling for a diagnosis of acute gout. Because synovial fluid leukocyte counts may approach 100,000/mm^3, it is necessary to perform appropriate microbiological studies in order to establish the absence of infection (especially since the coexistence of gouty arthritis and septic arthritis has been described). Hence, it is important to remember that synovial fluid analysis should always extend beyond polarizing microscopy to include cell count, culture, and Gram staining. Of note is the fact that intracellular uric acid crystals may also be identified on Gram stain specimens.

Animal models of monosodium urate crystal-induced inflammation suggest that crystal shedding and subsequent interaction with phagocytic synoviocytes activates complement and Hageman factor. Mast cells and endothelial cells in turn support leukocyte migration and local vasodilation. Early monocyte migration into the joint is followed by polymorphonuclear leukocyte infiltration. Pro-inflammatory cytokines such as interleukin-8 appear to be important in initiating the synovitis of acute gout.[4] Finally, monosodium urate monohydrate crystals directly interact with other cells in the synovial environment such as neutrophils and monocytes. For example, monosodium urate monohydrate crystals can cause cell activation and prostaglandin synthesis.[6]

Laboratory Analysis

The determination of serum uric acid level is predictive of gout. Above a level of 9 mg/dL, the annual incidence of gouty arthritis exceeds 5%. At a serum level of 13 mg/dL, the annual incidence of renal stone formation is 50%. Serial monitoring of the serum uric acid is particularly helpful for assessing the effectiveness of antihyperuricemic therapy. Although identifying the overexcretor patient is best accomplished through measurement of a 24-hour urine collection, a spot urine uric acid multiplied by the plasma creatinine and normalized to the spot urine creatinine yields a value that correlates weakly with the 24-hour data.[3] A value above 0.6 suggests that a 24-hour collection measurement should be obtained. A spot urine sample that is collected for these purposes should be a midmorning specimen following a light, low-purine, low-fructose breakfast.

Bone and joint damage due to chronic gout can be imaged radiologically. The destructive features of gout may resemble the erosive disease of rheumatoid

arthritis (RA). Some differences that can help distinguish between these two inflammatory arthropathies include the "bland" appearance of RA erosions due to periarticular osteopenia and the tendency of gouty erosions to develop in a location somewhat removed from the synovial reflection off of bone resulting in an "overhanging edge." In addition, the pattern of joint involvement in gouty arthritis is typically characterized as asymmetric.

Clinical Presentation

The classic presentation of clinical gout is that of acute, intermittent attacks of intense joint inflammation. Common precipitating factors include trauma, surgery, alcohol, and certain drugs (diuretics, low dose aspirin). Nucleating factors likely play a role in microtophi formation. Rapid fluxes (up or down) in synovial fluid urate concentration is another important condition toward the initiation of crystal formation. Initial twinges of discomfort rapidly develop into warmth, redness, and swelling.[7] Intensity peaks within 12 hours and the time to resolution may be as long as 2 weeks, even in untreated cases. Attacks most frequently involve the metatarsophalangeal (MTP) joint (called podagra) but polyarticular presentations as well as involvement of other joints are not uncommon. Systemic symptoms of an attack include fever and chills. Subcutaneous tophi are a sign of an increased total body burden of urate and may be seen over extensor surfaces including the digits and olecranon bursae. They may also be found on the helix of the ear or the Achilles' tendon. During the intercritical period patients may be asymptomatic with no demonstrable joint abnormality (especially early in the disease). Renal stones occur in up to 25% of patients.

Treatment of Gout

Overview

Treatment for acute gouty arthritis must be distinguished from long-term management issues. As a general principle, intervention for the acute event is most effective when provided early into the development of symptoms. Acute management is directed at rapid relief of pain and inflammation, whereas long-term management seeks to reduce the frequency and severity of attacks as well as to reduce the risk for joint damage and kidney stones, and where necessary, resolve tophi (Table 4).

Table 4

Management of Gout

Acute Therapy	Chronic Therapy
Nonsteroidals	Nonsteroidals
Colchicine	Colchicine
Corticosteroids	Uricosurics
	Xanthine oxidase inhibitors

Acute Gout

Intervention for the acute attack largely relies upon judicious use of nonsteroidal anti-inflammatory agents (NSAIDs), colchicine, and corticosteroids. Traditionally, indomethacin has been employed to ameliorate an acute gout attack. However, many other NSAIDs may be equally effective, especially when higher dosing is employed during the first 24-48 hours of an attack. Limited comparative data are available in this regard. Particular caution must be exercised when considering NSAID therapy for individuals with reduced creatinine clearance, gastropathy, or congestive heart failure (in general this applies to intravascularly depleted states). Elderly patients are at increased risk for adverse effects from NSAIDs. The use of colchicine to treat acute gouty arthritis is limited by toxicity and in clinical practice is less commonly a first-line therapy. Colchicine forms a tubulin-colchicine dimer that inhibits microtubule assembly.[8] Physiologic effects of colchicine include inhibition of neutrophil phagocytosis, interference with lysosomal transport, and reduction of neutrophil mobility. Colchicine also diminishes the production of crystal-induced chemotactic factor and IL-6. Care with regard to colchicine dosing is especially important for individuals with renal or hepatic impairment or for those on concomitant P-450 inhibitors. The major route of elimination of colchicine is renal. Therefore dosages should be halved in individuals with reduced creatinine clearance. Patients with liver disease are at increased risk for toxicity due to the enterohepatic circulation of colchicine. Common manifestations of acute colchicine toxicity include abdominal cramps and diarrhea. Other less common toxicities include marrow suppression and neuromuscular disease.[3] Although the effectiveness of colchicine exceeds 90% when given within the first 24 hours of an attack, this response rate for initiation of therapy quickly dissipates by the third day into an attack. Corticosteroids have efficacy when provided orally, parenterally, or intra-articularly.[9] Concurrent diabetes mellitus complicates the management of gout. Even intra-articular deposition of corticosteroids may adversely impact glycemic control. Nevertheless, the case for intervention with corticosteroid therapy is particularly compelling when colchicine and NSAIDs are relatively contraindicated, such as in the situation of renal insufficiency.

Prophylaxis

Lifestyle issues play a role in the management of gout in some individuals. Weight loss and avoidance of alcohol-containing products may be beneficial. A low-purine diet generally yields only modest results. Recently, dietary measures to overcome insulin resistance have been advocated as a possible mechanism to reduce the serum uric acid levels. Hyperinsulinism is associated with hyperuricemia owing to decreased uric acid clearance.[4] Blood pressure and lipid management should be carefully reviewed in all patients with gout. Some evidence suggests that the angiotensin receptor blocker, losartan, may have a hypouricemic effect, possibly by way of uricosuric activity. Similarly, fenofibrate has been shown to reduce serum uric acid levels. Future avenues of intervention may include administering uricase associated with polyethylene glycol-204 or gene therapy with hematopoietic prostaglandin D synthetase.[10]

In certain instances, prophylaxis with daily use of colchicine (up to 1.2 mg daily), NSAIDs, or a combination of the two, can be effective. But in the situations of sustained hyperuricemia, chronic tophaceous gout, destructive arthropathy, or nephrolithiasis, then uric acid lowering therapy is indicated. In general, such individuals will be characterized by a genetically-directed overproduction of uric acid, a significant impairment of excretion of uric acid, or both. The mainstay of drug therapy centers on uricosurics and xanthine oxidase inhibitors (Table 5). Uricosuric agents include probenecid and sulfinpyrazone. Uricourics increase urinary urate excretion until a new steady state is achieved at a lower serum uric acid level. Their side effects include rash

Table 5

Indications for Xanthine Oxidase Inhibitor Therapy

Urate overproduction
Tophus formation and erosive arthropathy
Nephrolithiasis
Excessive cell turnover (eg, myeloproliferative disorder, hemolysis, psoriasis)

and gastrointestinal disturbance but in general are relatively safe. The potential risk of uricosuric intervention also includes the formation of uric acid crystals in the urinary collection system. Maintaining a high and alkaline urine output may help reduce this risk.[8] The uricosuric effect of probenecid declines with the glomerular filtration rate (GFR) and therefore will be of little use when the GFR drops below 50 cc/min. Salicylates may also reduce the uricosuric effect of probenecid. It should be kept in mind that probenecid may inhibit excretion of other drugs including penicillin and indomethacin. In contrast, probenecid enhances the excretion of allopurinol and its use may therefore dictate increased dosing of allopurinol. In turn, allopurinol increases the biological half-life of probenecid, thereby potentiating uric acid elimination.

Allopurinol is a hypoxanthine analogue that inhibits xanthine oxidase.[8] In this manner, purine biosynthesis is inhibited in favor of production of purine nucleotides. The major metabolite of allopurinol is oxypurinol whose long half-life is further prolonged in the presence of renal insufficiency. Therefore dosage adjustment is required when the GFR is 60 cc/min or less. Allopurinol dosing recommendations start at 50 mg daily in patients with renal disease and ultimately not to exceed 100 mg daily for a GFR of 30 cc/min, 200 mg daily for a GFR of 60 cc/min.[11] Additionally, dosage adjustment of concomitantly used medications may be required. In particular, drugs that would normally be inactivated by xanthine oxidase can have increased toxicity during concomitant allopurinol therapy. Two examples of such medications include azathioprine and mercaptopurine. Side effects of allopurinol therapy include rash, nausea, diarrhea, and headache. Some 2% of allopurinol-treated individuals develop hypersensitivity reactions, of which 20% are characterized as severe.[3] Severe allopurinol hypersensitivity syndrome is manifested as an exfoliative dermatitis that may be fatal. Individuals at increased risk for such reactions include those with renal insufficiency and those on diuretic therapy. Rare adverse experiences with allopurinol include marrow suppression and hepatitis. Maximal uric acid lowering is seen by the third week of introducing or increasing the dosage of allopurinol. Most patients can be controlled with a daily dose of 300 mg or less. Resolution of tophi typically takes months to years of allopurinol therapy. Discontinuing allopurinol allows serum uric acid levels to increase to pretreatment levels.

Febuxostat is a nonpurine inhibitor of xanthine oxidase. It is an analogue inhibitor that is orally administered. It is metabolized in the liver and hence may have utility in patients with renal insufficiency. Its use is associated with sustained lowering of serum uric acid, reduction of gout flares, and reduction of tophus area. In one study, rashes and abnormal liver function tests lead to increased rates of withdrawal as compared with allopurinol.[26,27]

Finally, no matter which uric acid lowering therapy is used, none should be initiated during an acute attack because the attack may worsen in terms of severity or duration. Dosage adjustments of uric acid lowering therapy should be guided by serial monitoring of serum uric acid levels. For purposes of prevention, a serum level less than seven mg % is often desirable while even lower serum levels are recommended for tophaceous disease. The subsaturating level for serum uric acid is <6.0 mg/dL. Failure to achieve this target in allopurinol users is associated with a 75% increased risk of flare as compared to successful suppression of serum uric acid.[25]

Pseudogout

Etiology

The manifestations of calcium pyrophosphate dihydrate (CPPD) crystal deposition are protean and may include the inflammatory clinical syndrome termed pseudogout. When calcium-containing crystals are present in cartilage this is termed chondrocalcinosis. CPPD deposition is associated with aging and degenerative arthritides and suspected to be associated with various endocrinopathies, the most notable of which is hyperparathyroidism (Table 6). Metabolic syndromes such as hemochromatosis have been associated with pseudogout, and this disorder in particular may be of significance in the differential diagnosis of the younger patient (under age 55) presenting with chondrocalcinosis.[12] Finally, familial CPPD deposition diseases are a rare, but well-established phenomenon.[13] Mutations in the ANKH gene (involved in cellular transport of PPi) can be demonstrated in patients with CPPD and chondrocalcinosis.[31]

Table 6

Clinical Associations with Chondrocalcinosis

Hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Wilson's disease
Degenerative arthritis
Aging

Overproduction of inorganic pyrophosphate, a component of CPPD, is associated with crystal formation. Shedding of preformed articular crystalline deposits and the intracellular dissolution of calcium-containing crystals with subsequent release of calcium play a role in the initiation and maintenance of the inflammatory process. Calcium-containing crystals appear to activate neutrophils much in the same manner as MSU crystals. Moreover, calcium crystals appear to induce IL-8 expression in monocytes. IL-8, in turn, is a chemoattractant and acts to promote the release of proteases.

CPPD Crystal Physiology

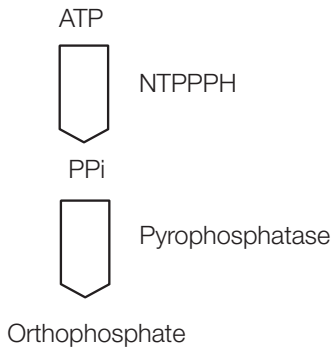
Inorganic pyrophosphate (PPi) is formed from nucleoside triphosphate substrates by nucleoside triphosphate pyrophosphohydrolase (NTPPPH). This enzyme can be found in articular cartilage and its action hydrolyzes ATP to PPi (Figure 4). PPi is the anionic component of CPPD crystals. PPi in turn is metabolized to orthophosphate by pyrophosphatases such as alkaline phosphatase thereby controlling the intra- and extracellular levels of PPi. Overproduction of PPi can be caused by ascorbate as well as excess activity of transforming growth factor-β (TGF-β). Specifically, TGF-β upregulates expression of NTPPPH.[14] Despite the presence of increased levels of synovial fluid PPi, plasma levels and urinary excretion of PPi are not elevated. This suggests a local (articular) process resulting in excess articular anion production. Probenecid, insulin-like growth factor, tissue-nonspecific alkaline phosphatase, and IL-1 inhibit the formation of PPi. When the correct mix of solute excess, nucleating factors, and growth promoting factors assert themselves, CPPD crystals may form. Magnesium and proteoglycan can inhibit crystal formation.

Pathology

Synovial fluid and crystal characteristics such as crystal load, size, protein coating, and intrinsic crystalline structural composition, have all been implicated as important in generating the inflammatory response.[15] Other synovial fluid factors such as inflammatory cytokines, tumor necrosis factor-β, and G-CSF are important as well. CPPD-induced membranolysis, crystal-induced superoxide release, and signaling events caused by contact between calcium-containing crystals and the cellular component of joints are all current topics of investigation.[15] The nature of the tissue matrix interface with the site of NTPPPH activity is also likely of clinical relevance and may help explain why CPPD is more commonly observed in the setting of osteoarthritis since the cartilage tissue is abnormal to begin with. Fibroblasts and mononuclear synovial lining cells ingest CPPD crystals.

Figure 4

Inorganic pyrophosphate (PPi) biochemistry



Laboratory Analysis

Undercompensated polarizing microscopy, CPPD crystals are typically rhomboid or rectangularly shaped and demonstrate weakly positive birefringence. Crystals may be intracellular. Synovial fluid cell counts are predominately polymorphonuclear and may range upwards of 80,000/mm^3. Histological demonstration of CPPD crystals within tissue samples is difficult due to the decalcification that occurs in turn due to the acidic nature of hematoxylin.[14]

The radiographic finding of chondrocalcinosis is most commonly seen in the menisci and hyaline cartilage of the knees, the intervertebral disks, and the fibrocartilage of the wrists and symphysis pubis. Osteo-arthritic change is also frequently seen radiographically. As compared to control subjects without CPPD, significant associations have been found between CPPD deposition and trapezioscaphoid arthropathy as well as 1st carpometacarpal arthropathy. Other areas of association include disease of the capitolunate, scaphoid-trapeziod, lunate-hamate, and radiolunate junctures. Earlier detection of cartilage calcification may be feasible through the use of cross-sectional imaging modalities including computed tomography, magnetic resonance imaging, and ultrasonography.[16]

Clinical Presentation

Acute pseudogout may be indistinguishable in clinical appearance from gout except for a predilection for larger joint involvement (Table 7). Abrupt onset of self-limited attacks may individually last for up to two weeks. Rarely, a mix of MSU and CPPD crystals may be seen within the same synovial fluid specimen. Similarly, the possibility of coexistent joint infection dictates that appropriate microbiological studies be performed upon new, atypical, or persistent cases of pseudogout arthritis. Major illness, surgery, joint lavage, and trauma are all precipitating factors. Cases of acute pseudogout have been described following hyaluronic acid injection therapy for osteoarthritis.[17] Case reports also exist implicating both granulocyte colony-stimulating factor (G-CSF) and pamidronate in precipitating CPPD crystal disease.[18] Monoarticular and polyarticular presentations are possible. A small percentage of patients follow a pseudo-rheumatoid pattern with stiffness, fatigue, and persistent, symmetric, synovial inflammation. Systemic features of acute and chronic pyrophosphate arthropathy may include fever, elevated acute phase reactants, and leukocytosis, thereby mimicking a septic process.

Table 7

Differential Diagnosis of CPPD Deposition Disease

Gout and other crystal-induced arthropathies
Septic arthritis
Rheumatoid arthritis
Polymyalgia rheumatica
Malignancy
Seronegative spondyloarthropathies
Palindromic rheumatism
Hemochromatosis
Lyme arthritis (in endemic regions)

Treatment of Pseudogout

Nonsteroidal anti-inflammatory agents are the mainstays of management for CPPD-related diseases. Colchicine may reduce the severity or frequency of attacks and hence may be of benefit both for the acute presentation as well as for prevention of episodic disease. Therefore disease responsiveness to colchicine is not post hoc evidence of a diagnosis of gout. Corticosteroids are frequently beneficial and may be particularly useful as an intra-articular intervention for a monoarticular presentation of pseudogout. Incidental and anecdotal reports of therapeutic benefit from hydroxychloroquine, methotrexate, oral magnesium, or arthroscopic irrigation should be considered experimental and may be applicable only to limited or special populations.[14]

Apatite Arthropathy

Partially carbonate-substituted hydroxyapatite is an example of a basic calcium phosphate crystal. Other examples of basic calcium phosphate crystals include octacalcium phosphate, tricalcium phosphate, and magnesium whitlockite.[19] Such crystals may deposit in cartilage and periarticular structures

and may or may not be symptomatic. The most commonly recognized site of clinical involvement is in tendons near the shoulder joints. Besides this type of acute periarthritis, basic calcium phosphate crystals can be associated with frozen shoulder, acute articular inflammation, large joint destructive arthropathy (eg, Milwaukee shoulder), and calcinosis cutis. The end result of an acute calcific periarthritis of the shoulder may be a frozen shoulder.

Intra-articular basic calcium phosphate crystals remain a poorly understood phenomenon. Large effusions are commonly associated with the Milwaukee shoulder syndrome. Such effusions are often bloody with cell counts that are predominately mononuclear (see below). Basic calcium phosphate crystals are also associated with osteoarthritis. In particular, the presence of basic calcium phosphate crystals correlates with the severity of osteoarthritis.[19] Under compensated polarizing microscopy analysis, these crystals do not demonstrate birefringence. They may be seen on light microscopy alone when aggregated together to form coin-like clumps. Staining with Alizaren red S or von Kossa are inexpensive techniques that may suggest the presence of basic calcium phosphate crystals. However, these stains are limited by false-positive results.

The pathophysiology of basic calcium phosphate crystals is far from being fully elucidated and mixtures of different types of crystals are frequently reported in the same tissue. Presumably factors such as supersaturation of tissue fluids, trauma, hypovascularity, and the interplay with natural inhibitors of crystal formation, are important in the generation of these crystals. Evidence for their pathogenic role is accumulating. Basic research suggests that such crystals can induce matrix metalloproteinase production, mitogenesis, proteolytic enzyme secretion, and induce cycloxygenases, as well as downregulate the synthesis of tissue inhibitor of matrix metalloproteinases.[19] Of interest is the finding that while high levels of extracellular PPi contributes to CPPD, extracellular PPi also inhibits in vivo hydroxyapatite formation, thereby suggesting that narrow regulation of extracellular PPi levels is necessary for joint health.[20]

Management of these syndromes traditionally relies upon nonsteroidal anti-inflammatory agents, but colchicine and corticosteroids (especially as intra-articular injection) have been employed. Care must be exercised if intra-articular injection is contemplated owing to the possibility of dislodging crystals and increasing the risk for future attacks. Improvement in calcific periarthritis has been reported following EDTA treatment. Nondurable improvement in symptomatic calcific tendonitis of the shoulder has been reported following six weeks of ultrasound therapy as compared to sham treatment.[21] Therapies targeting the known cellular effects of basic calcium phosphate crystals may someday be utilized. For example, basic calcium phosphate crystals upregulate both cytokines and nitric oxide, agents known to mediate features of degenerative arthritis.[30]

Milwaukee Shoulder Syndrome

A large joint (commonly the shoulder or the knee), destructive arthropathy is associated with basic calcium phosphate crystals. The Milwaukee shoulder syndrome (also termed "apatite-associated destructive arthritis" and "cuff tear arthropathy") is predominately a disease in older women or in patients with glenohumeral instability and can be characterized by limited flexibility, pain, and swelling (Table 8). A large, bloody effusion may be present. Rupture of the effusion is a known potential complication. Radiographic investigation will demonstrate bone resorption and calcific deposits. A protracted course with residual deficit is common. Management may be difficult. Analgesics, anti-inflammatory agents, and nerve blocks have been employed.

Table 8

Clinical Syndromes Associated with Basic Calcium Phosphate Crystals

Calcific periarthritis
Acute and chronic synovitis
Osteoarthritis
Milwaukee shoulder
Calcinosis cutis

Cholesterol and Liquid Lipid Crystals

The clinical significance of plate-like cholesterol crystals within the synovial fluid is often discounted as merely reflecting an epiphenomenon of chronic arthropathy such as rheumatoid arthritis or osteoarthritis. This conclusion is supported by the lack of evidence for phagocytosis of such crystals by inflammatory cells.[22] Cholesterol crystals are commonly observed in chronic olecranon bursitis. Bone and joint trauma may also result in the finding of cholesterol crystals within synovial fluid. The microscopic appearance of birefringent liquid lipid spherules seen in joint fluid aspirates has been likened to that of a "Maltese cross."[23] When cholesterol crystals have been implicated in the pathogenesis of monoarticular synovitis, neutrophils were the predominant cell type on synovial fluid analysis. Cholesterol crystals take on greater clinical significance in the cholesterol crystal embolization syndrome. This syndrome may be precipitated by endovascular instrumentation and by anticoagulation. It may be characterized by calf pain, blue toes, leg ulcers, gastrointestinal bleeding, renal impairment, and eosinophilia. Because of these manifestations, cholesterol emboli syndrome has been termed pseudovasculitis. Factors implicated in the generation of cholesterol crystals include increased cholesterol synthesis, bleeding, and the promoting effect of lipid complexes with albumin.

Cryoglobulin Crystals

Immunoglobulins may crystallize. Temperature-dependent, reversible crystallization is a characteristic of cryoglobulins. These crystals can be detected in serum, and rarely, in synovial fluid. They may be comprised of monoclonal or mixed cryoglobulins and may be seen in autoimmune, neoplastic, and chronic infectious (such as hepatitis C) disorders. Monoclonal cryoglobulins tend to be associated with lymphoproliferative disorders or multiple myeloma. Mixed cryoglobulins are associated with connective tissue diseases, viral hepatitis, infective endocarditis, and chronic parasitic syndromes. Mixed cryoglobulins often contain IgM molecules with rheumatoid factor activity. Cryoglobulins may cause some symptoms by virtue of hyperviscosity. Cryoglobulinemia must be considered in the differential diagnosis of Raynaud's phenomenon. Other features may include arthritis, glomerulonephritis, palpable purpura, livido reticularis, and ischemic acral ulcers. Resolution of the inciting chronic infection may lead to resolution of cryoglobulin generation.

Oxalate Gout

Inborn errors of glyoxylate metabolism may lead to hyperoxaluria. These rare syndromes present with nephrolithiasis, renal failure, and systemic oxalosis. Systemic oxalosis may be characterized by bone pain, compression fracture, arthritis, and vascular calcification or insufficiency. Oxalate deposits may lead to peripheral neuropathy, aseptic meningitis, and cerebral edema with necrosis.[23] Liver biopsy is required to establish the diagnosis. Secondary oxalosis is seen in situations of excess dietary intake coupled with decreased excretion. Increased oxalate absorption is seen in inflammatory bowel disease. Oxalate formation is enhanced by intake of its metabolic precursor, ascorbic acid. Secondary oxalosis may also complicate renal failure. Oxalate crystals may induce a granulomatous response. Synovial fluid oxalate crystals are pleomorphic and brightly birefringent. They stain with Alizarin red S and hence may be confused with apatite crystals.

Special Situations

Corticosteroids may be poorly miscible in the aqueous solutions used for intra-articular administration. Steroid crystal-induced inflammation is a reaction that may be seen within hours of instrumenting a joint. Such crystals are pleomorphic and may demonstrate both positive and negative birefringence. Foreign bodies may be seen on synovial fluid analysis, including plant thorn material and fiberglass. Children, farmers, construction workers, gardeners, and swimmers are most commonly affected. In general, foreign body synovitis will be heralded by a painful penetrating injury followed by an asymptomatic hiatus.[24] Foreign body synovitis due to sea urchin spines may be associated with lymphadenopathy and fevers.[24] Finally, in vitro contamination of synovial fluid specimens may include glass fragments, glove powder, and lens paper fibrils.

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5. Questions

Musculoskeletal Infections

1. A 50-year-old women with a 15-year history of erosive rheumatoid arthritis presents with increasing pain and swelling of the both shoulders, R wrist and L knee over the past 4 weeks. For the previous 3 years the arthritis had been reasonably well controlled on methotrexate 15 mg po weekly. The only other medications she was taking were folic acid 1 mg daily, prednisone 2.5 mg daily, and propranolol 25 mg daily for mild hypertension. She has taken naproxen 500 mg bid for up to 7 days intermittently for joint flares but has not needed any for 6 months.

   She denies fever or chills or significant morning stiffness. The pain has increased in the involved joints over the past 2 weeks so that now she has difficulty using her R upper extremity and bearing weight on her L leg. She started naproxen 500 mg two days ago and the pain is slightly improved.

   On examination she is afebrile. BP 130/80, pulse 100. She is uncomfortable moving around. General physical examination is unremarkable. She has evidence of prior joint damage secondary to rheumatoid synovitis with ulnar deviation and swan neck deformities of both hands and plantar subluxation of the metatarsal heads of both feet. L and R shoulders revealed some soft tissue swelling and tenderness over the glenohumeral line. There was painful reduction of abduction and external rotation. The R wrist was swollen dorsally and was moderately tender. The L knee was painful to flexion with a moderate intraarticular effusion. There was a rheumatoid nodule in the R olecranon bursa.

   Lab studies reveal:

   Hbg 12.5g/dL, WBC 4,000/mm^3 with 70% neutrophils, platelet count 400,000/mm8.5 pt ESR 90; Rheumatoid factor pending.

   Aspiration of the L knee yields 20 cc of cloudy yellow synovial fluid, WBC 60,000 with 92% neutrophils. Gram stain and crystals are negative.

   The most appropriate course of action is:

   A. Increase the prednisone to 10 mg/day and begin etanercept 25 mg SC twice weekly

   B. Give 40 mg DepoMedrol IM® and increase the methotrexate to 20 mg po weekly

   C. Admit her to the hospital, perform blood cultures and begin intravenous antibiotics

   D. Have her continue on the naproxen and see how she responds over the subsequent week

   E. Have her return for intra-articular corticosteroid injections into the shoulders, wrist and knee

2. A 65-year-old urban homeless man has chronic monoarthritis of the R knee (6 months), weight loss, normal chest x-ray. X-ray reveals a small tibial erosion at the joint edge. The most likely diagnosis is:

   A. Reactive arthritis

   B. Rheumatoid arthritis

   C. Lyme disease

   D. HIV-related arthritis

   E. Tuberculous arthritis

3. Which of the following is NOT considered a rheumatic feature associated with Lyme disease?

   A. Chronic polyarthritis

   B. Intermittent oligoarthritis

   C. Acute monoarthritis

   D. Chronic monoarthritis

   E. Chronic polyarthralgia

4. Acute oligoarthritis or polyarthritis can be a feature of the following infections EXCEPT:

A. Hepatitis B

B. EBV

C. Hantavirus

D. Histoplasmosis

E. HTLV-1

5. Which of the following details about prosthetic joint infections is correct?

A. Synovial fluid culture is more sensitive for the diagnosis than detection of bacterial nucleic acids by PCR

B. Rheumatoid arthritis is not a risk factor

C. *S epidermidis* is the commonest cause of late infections

D. Addition of rifampin to a quinolone or other antibiotic therapy may increase the cure rate

E. Removal of a loosened prosthesis is rarely needed

Answers

1. C.
The major differential diagnosis here is a flare of rheumatoid arthritis (RA) or polyarticular septic arthritis, likely due to *S aureus*. Despite the lack of fever and the low WBC (probably secondary to methotrexate), septic arthritis is of great concern when one or a few joints flare in a patient with destructive RA who has been previously stable. Furthermore, RA is a common predisposing cause of polyarticular septic arthritis. The clue is the synovial fluid analysis, which reveals a WBC higher than one usually finds in RA and a neutrophil percentage highly suggestive of joint infection, especially in the absence of crystals.

2. E.
While all the possibilities can be associated with a monoarthritis for 6 months, the demographics provide the real clue to the diagnosis here. TB is a high risk in this population and tuberculous arthritis patients usually have positive PPD tests but normal chest x-rays. Definitive diagnosis is usually made by synovial biopsy and culture.

3. A.
Chronic polyarthritis is very rare in Lyme disease. The classical clinical picture is an intermittent oligoarthritis followed in untreated patients by an acute monoarthritis, which in some patients can become chronic. Chronic polyarthralgia is a feature of post-Lyme disease syndrome.

4. B.
EBV is rarely associated with arthritis although a few cases of monoarthritis have been described.

5. D.

Crystal-Induced Arthropathies

1. A 42-year-old patient with Type I diabetes mellitus is six months status post renal transplantation. Among other medications, he is taking cyclosporine and diuretics. His serum creatinine is 2.4. In order to control frequent attacks of gout, he has been placed on colchicine at a dose of 0.6 mg daily. He is now complaining of proximal weakness. Physical examination demonstrates diminished deep tendon reflexes. A muscle biopsy reveals a vacuolated myopathy. Treatment recommendations should include which of the following?:

A. Discontinue the colchicine

B. Reduce the cyclosporine dose by at least 50%

C. Implement high dose prednisone (1 mg / Kg) daily

D. Initiate monthly intravenous immunoglobulin therapy

2. Alcohol promotes hyperuricemia by which of the following mechanisms?

A. The higher purine content in some alcoholic beverages

B. Accelerated hepatic breakdown of ATP

C. Hyperlactic acidemia

D. All of the above

E. None of the above

3. Calcium pyrophosphate dihydrate deposition is associated with:

A. Overproduction of inorganic pyrophosphate (PPi) by chondrocytes

B. Aging

C. Severe radiographic joint degeneration

D. All of the above

E. None of the above

4. True statements about apatite crystal identification include all of the following EXCEPT:

A. Combinations of apatite and pyrophosphate crystals are not infrequently seen together

B. X-ray powder diffraction can identify the crystals

C. Alizarin red S staining is the gold standard test for identification of crystals

D. Plain or polarized microscopy may reveal globular clumps resembling shiny coins

5. True statements important to lipid liquid crystals physiology include all of the following EXCEPT:

A. Lipid liquid crystals have the appearance of a Maltese cross on polarizing microscopy

B. Lipid liquid crystals do not take up Sudan black stain

C. Lipid liquid crystals may be seen after trauma

D. Starch from gloves may appear as angular or elongated Maltese cross-like particles

Answers

1. A.
Transplant recipients have multiple risk factors for gout. Gout has been reported in up to 13% of renal transplant recipients. Such patients may also be at increased risk for colchicine-induced myoneuropathy as described here. The reasons for this are likely many, but probably includes the fact that cyclosporine may cause intrarenal vasoconstriction and thereby reduce GFR.

2. D.
Alcohol consumption, diuretics, and obesity are independent predictors of gout among hyperuricemic subjects. Alcohol both has the capability to increase uric acid production and inhibit its excretion. Organic acids such as lactic acid will block uric acid excretion.

3. D.
CPPD is the most common of the calcium crystal arthritides. Excess PPi production is necessary for CPPD crystal formation. PPi elaboration is stimulated by TGF-β, retinoic acid, thyroid hormone, and ascorbate. It is inhibited by IL-1 and IGF-I. Chondrocalcinosis in the Framingham study demonstrated a radiographic prevalence rate of 27% in those over the age of 85. The strongest association between OA and CPPD is that between severe radiographic degeneration and CPPD. It may be that the heterogeneity of OA in general explains the conflicting study results in this regard.

4. C.
Plain microscopy is a nonspecific method for identification of apatite crystals. Alizarin red S staining is a calcium stain that can only be considered a screening test. With this technique, both false positive and false negative findings have been reported. Electron microscopy with chemical analysis or electron diffraction may identify the crystals. Apatite may contain mixtures of basic calcium salts.

5. B.
Lipid spherules will stain with Sudan black. Starch can cause a crystal-like artifact similar to lipid liquid crystals. Moreover, some glove powders contain calcium phosphates that will stain with Alizarin red S. Intracellular lipid liquid crystals have been reported and neutral lipid may be seen after trauma, or in the case of lymphatic obstruction, pancreatic disease, or hyperlipoproteinemia.