HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Infectious Arthritis

Chapter 135 | Part 5: Infectious Diseases | Part 5 – Infectious Diseases: Bacterial | DETAILED EDITION

KEY CLINICAL POINTS

1. Staphylococcus aureus is the most common cause of nongonococcal bacterial arthritis in adults of all ages.
2. Neisseria gonorrhoeae is the most common cause in young adults and adolescents (<40 years).
3. Synovial fluid cell count >100,000/µL with >90% neutrophils is characteristic of acute bacterial infection.
4. Synovial fluid cell count <30,000–50,000/µL is common in noninfectious inflammatory arthritides.
5. Timely drainage of pus and necrotic debris is required for a favorable outcome to prevent cartilage destruction.
6. Gonococcal arthritis typically presents as a syndrome of arthritis-dermatitis with negative synovial fluid cultures.
7. Lyme arthritis responds to oral doxycycline (100 mg twice daily for 28 days) or amoxicillin.
8. Tuberculous arthritis primarily involves large weight-bearing joints (hips, knees, ankles) and requires 6–9 months of therapy.
9. Prosthetic joint infections often require removal of the prosthesis and delayed reimplantation.
10. Preoperative screening for S. aureus with decolonization is recommended for joint replacement candidates.

FIGURES IN THIS CHAPTER

1. Chronic arthritis caused by Histoplasma capsulatum...
2. Acute septic arthritis of the sternoclavicular...

1. DEFINITION & OVERVIEW

• Infectious arthritis is an inflammation of the joint caused by a pathogen.

• Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures.

• Harrison's defines the evaluation of potentially infected joints as requiring aspiration of synovial fluid or arthrocentesis.

• Infectious arthritis can be classified by acuity (acute vs. subacute/chronic) and distribution (monoarticular vs. polyarticular).

• Acute bacterial infection typically involves a single joint or a few joints.

• Subacute or chronic monoarthritis or oligoarthritis suggests mycobacterial or fungal infection.

• Episodic inflammation is seen in syphilis, Lyme disease, and reactive arthritis following enteric infections and chlamydial urethritis.

• Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute viral hepatitis.

• Viruses often infect multiple joints; however, bacterial infections generally cause mono- or oligoarthritis except in persons with underlying diseases such as rheumatoid arthritis.

1.1 Pathogenesis

• Bacteria enter the joint from the bloodstream, from a contiguous site of infection in bone or soft tissue, or by direct inoculation during surgery, injection, animal or human bite, or trauma.

• In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium.

• Neutrophils and bacteria enter the joint space; later, bacteria acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

• Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells.

• Histologic studies reveal bacteria lining the synovium and cartilage as well as abscesses extending into the synovium, cartilage, and—in severe cases—subchondral bone.

• Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops.

• Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in S. aureus that permit adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

2. EPIDEMIOLOGY

• Patients with rheumatoid arthritis have the highest incidence of infective arthritis (most often secondary to S. aureus) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints.

• Diabetes mellitus, glucocorticoid therapy, hemodialysis, intravenous drug use, and malignancy all carry an increased risk of infection with S. aureus and gram-negative bacilli.

• Tumor necrosis factor inhibitors (e.g., etanercept, infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic bacterial infections and could be associated with septic arthritis in this population.

• Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies.

• Pneumococci, Salmonella species, and H. influenzae cause septic arthritis in persons infected with HIV.

• Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which, while rare, results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly.

• IV drug users acquire staphylococcal and streptococcal infections from their own flora.

• In the United States, a 2012 national outbreak of fungal arthritis (and meningitis) caused by Exserohilum rostratum was linked to intraspinal and intraarticular injection of a contaminated preparation of methylprednisolone acetate.

2.1 Pathogen Distribution by Age Group

• In infants, group B streptococci, gram-negative enteric bacilli, and S. aureus are the most common pathogens.

• Since the advent of the Haemophilus influenzae vaccine, the predominant causes among children <5 years of age have been S. aureus, Streptococcus pyogenes (group A Streptococcus), and (in some centers) Kingella kingae.

• Among young adults and adolescents, N. gonorrhoeae is the most commonly implicated organism.

• S. aureus (including methicillin-resistant S. aureus [MRSA]) accounts for most nongonococcal isolates in adults of all ages.

• Gram-negative bacilli, pneumococci, and β-hemolytic streptococci—particularly groups A and B but also groups C, G, and F—are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses.

• Gram-negative bacilli such as Pseudomonas may occur in immunocompromised patients or intravenous drug users.

• Infections after surgical procedures or penetrating injuries are due most often to S. aureus and occasionally to other gram-positive bacteria or gram-negative bacilli.

• Infections with coagulase-negative staphylococci are unusual except after the implantation of prosthetic joints or arthroscopy.

• Anaerobic organisms, often in association with aerobic or facultative bacteria, are found after human bites and when decubitus ulcers or intraabdominal abscesses spread into adjacent joints.

• Polymicrobial infections complicate traumatic injuries with extensive contamination.

• Bites and scratches from cats and other animals may introduce Pasteurella multocida or Bartonella henselae into joints either directly or hematogenously.

• Bites from humans may introduce Eikenella corrodens or other components of the oral flora.

• Penetration of a sharp object through a shoe is associated with Pseudomonas aeruginosa arthritis in the foot.

3. ETIOLOGY & PATHOPHYSIOLOGY

• The hematogenous route of infection is the most common route in all age groups, and nearly every bacterial pathogen is capable of causing septic arthritis.

• Bacteria enter the joint from the bloodstream; from a contiguous site of infection in bone or soft tissue; or by direct inoculation during surgery, injection, animal or human bite, or trauma.

• In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium.

• Neutrophils and bacteria enter the joint space; later, bacteria acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

• Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells.

• Histologic studies reveal bacteria lining the synovium and cartilage as well as abscesses extending into the synovium, cartilage, and—in severe cases—subchondral bone.

• Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops.

• Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in S. aureus that permit adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

3.1 Specific Organism Pathogenesis

• Gonococcal arthritis is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx.

• Arthritis due to N. gonorrhoeae is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients.

• True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients.

• Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts.

• Coexistent active pulmonary tuberculosis is unusual.

• Fungal arthritis results from hematogenous seeding or direct extension from bony lesions in persons with disseminated disease.

• Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread.

• Candida infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints.

• Lyme arthritis generally responds well to therapy.

• Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

4. CLINICAL FEATURES

• Patients with acute septic arthritis usually present with joint pain often with limitation of passive and active joint movement, joint swelling, and/or erythema.

• Approximately 90% of patients present with involvement of a single joint—most commonly the knee; less frequently the hip; and still less often the shoulder, wrist, or elbow.

• Small joints of the hands and feet are more likely to be affected after direct inoculation or a bite.

• Among IV drug users, infections of the spine, sacroiliac joints, and sternoclavicular joints are more common than infections of the appendicular skeleton.

• Polyarticular infection is most common among patients with rheumatoid arthritis and may resemble a flare of the underlying disease.

• The most common manifestation of DGI is a syndrome of arthritis-dermatitis.

• Patients present with fever, chills, rash, tenosynovitis, and articular symptoms.

• Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities.

• Migratory arthritis and tenosynovitis of the knees, hands, wrists, feet, and ankles are prominent.

• The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues.

• True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients.

• A single joint such as the hip, knee, ankle, or wrist is usually involved.

• Synovial fluid, which contains >50,000 leukocytes/µL, can be obtained with ease; the gonococcus is evident only occasionally in Gram-stained smears, and cultures of synovial fluid are positive in <40% of

cases.

• Blood cultures are almost always negative.

• Lyme disease due to infection with the spirochete Borrelia burgdorferi causes arthritis in up to 60% of persons who are not treated.

• Intermittent arthralgias and myalgias—but not arthritis—occur within days or weeks of inoculation of the spirochete by the Ixodes tick.

• Later, there are three patterns of joint disease: (1) Fifty percent of untreated persons experience intermittent episodes of monoarthritis or oligoarthritis involving the knee and/or other large joints. The symptoms wax and wane without treatment over months, and each year, 10–20% of patients report loss of joint symptoms.

• (2) Twenty percent of untreated persons develop a pattern of waxing and waning arthralgias.

• (3) Ten percent of untreated patients develop chronic inflammatory synovitis that results in erosive lesions and destruction of the joint.

• Serologic tests for IgG antibodies to B. burgdorferi are positive in >90% of persons with Lyme arthritis, and a NAAT detects Borrelia DNA in synovial fluid in 85% of patients.

• Tuberculous arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and only occasionally involves smaller non-weight-bearing joints.

• Progressive monoarticular swelling and pain develop over months or years, and systemic symptoms are seen in only half of all cases.

• Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts.

• Coexistent active pulmonary tuberculosis is unusual.

• Aspiration of the involved joint yields fluid with an average cell count of 20,000/µL, with ~50% neutrophils.

• Acid-fast staining of the fluid yields positive results in fewer than one-third of cases, and cultures are positive in 80%.

• Culture of synovial tissue taken at biopsy is positive in ~90% of cases and shows granulomatous inflammation in most.

• Fungi are an unusual cause of chronic monoarticular arthritis.

• Granulomatous articular infection with the endemic dimorphic fungi Coccidioides immitis, Blastomyces dermatitidis, and (less commonly) Histoplasma capsulatum results from hematogenous seeding or direct extension from bony lesions in persons with disseminated disease.

• Joint involvement is an unusual complication of sporotrichosis among gardeners and other persons who work with soil or sphagnum moss.

• Articular sporotrichosis is six times more common among men than among women, and alcoholics and other debilitated hosts are at risk for polyarticular infection.

• Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread.

• Candida infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints.

• Unusual cases of arthritis due to Aspergillus species, Cryptococcus neoformans, Pseudallescheria boydii, and the dematiaceous fungi also have resulted from direct inoculation or disseminated hematogenous infection in immunocompromised persons.

• In the United States, a 2012 national outbreak of fungal arthritis (and meningitis) caused by Exserohilum rostratum was linked to intraspinal and intraarticular injection of a contaminated preparation of

methylprednisolone acetate.

• Painful arthritis often accompanies the fever and rash of several arthropod-borne viral infections, including those caused by Zika, chikungunya, O'nyong-nyong, Ross River, Mayaro, and Barmah Forest viruses.

• Symmetric arthritis involving the hands and wrists may occur during the convalescent phase of infection with lymphocytic choriomeningitis virus.

• Patients infected with an enterovirus frequently report arthralgias, and echovirus has been isolated from patients with acute polyarthritis.

• Several arthritis syndromes are associated with HIV infection.

• An incomplete form of reactive arthritis with painful lower-extremity oligoarthritis may follow an episode of urethritis in HIV-infected persons.

• HIV-associated reactive arthritis appears to be extremely common among persons with the HLA-B27 haplotype, but sacroiliac joint disease is unusual and is seen mostly in the absence of HLA-B27.

• Up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis.

• Painless monoarthropathy and persistent symmetric polyarthropathy occasionally complicate HIV infection.

• Chronic persistent oligoarthritis of the shoulders, wrists, hands, and knees occurs in women infected with human T-lymphotropic virus type 1.

• Synovial thickening, destruction of articular cartilage, and leukemic-appearing atypical lymphocytes in synovial fluid are characteristic, but progression to T cell leukemia is unusual.

• Arthritis due to parasitic infection is rare.

• The guinea worm Dracunculus medinensis may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected.

• Hydatid cysts infect bones in 1–2% of cases of infection with Echinococcus granulosus.

• The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis.

• In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies.

• Monoarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid.

• Reactive arthritis has been attributed to hookworm, Strongyloides, Cryptosporidium, and Giardia infection in case reports, but confirmation is required.

4.1 Clinical Manifestations and Laboratory Findings

• The most common manifestation of DGI is a syndrome of arthritis-dermatitis.

• Patients present with fever, chills, rash, tenosynovitis, and articular symptoms.

• Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities.

• Migratory arthritis and tenosynovitis of the knees, hands, wrists, feet, and ankles are prominent.

• The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues.

• Thus, cultures of synovial fluid are consistently negative, and blood cultures are positive in <45% of patients.

• Synovial fluid may be difficult to obtain from inflamed joints and usually contains only 10,000–20,000 leukocytes/µL.

• True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients.

• A single joint such as the hip, knee, ankle, or wrist is usually involved.

• Synovial fluid, which contains >50,000 leukocytes/μL, can be obtained with ease; the gonococcus is evident only occasionally in Gram-stained smears, and cultures of synovial fluid are positive in <40% of cases.

• Blood cultures are almost always negative.

• Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites.

• NAAT-based urine tests also may be positive.

• Culture requires endocervical (in female patients) or urethral (in male patients) swab specimens.

• Culture is available for detection of rectal, oropharyngeal, and conjunctival gonococcal infection.

• Cultures and Gram-stained smears of skin lesions are occasionally positive.

• All specimens for culture should be plated onto Thayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO2.

• A dramatic alleviation of symptoms within 12–24 h after the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

• Lyme arthritis generally responds well to therapy.

• Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy.

• Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

• The synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/μL, with ~70% neutrophils.

• Stained specimens and cultures of synovial tissue often confirm the diagnosis of fungal arthritis when studies of synovial fluid give negative results.

• Treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen.

• The doses and duration of therapy are the same as for disseminated disease.

• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• Viruses produce arthritis by infecting synovial tissue during systemic infection or by provoking an immunologic reaction that involves synovial joints.

• As many as 50% of women report persistent arthralgias and 10% report frank arthritis within 3 days of the rash that follows natural infection with rubella virus and within 2–6 weeks after receipt of live-virus vaccine.

• Episodes of symmetric inflammation of fingers, wrists, and knees uncommonly recur for >1 year, but a syndrome of chronic fatigue, low-grade fever, headaches, and myalgias can persist for months or years.

• IV immunoglobulin has been helpful in selected cases.

• Self-limited monoarticular or migratory polyarthritis may develop within 2 weeks of the parotitis of mumps; this sequela is more common among men than women.

• Approximately 10% of children and 60% of women develop polyarthritis or polyarthralgia in small joints after infection with parvovirus B19.

• In adults, arthropathy sometimes occurs without fever or rash.

• Pain and stiffness, with less prominent swelling (primarily of the hands but also of the knees, wrists, and ankles), usually resolve within weeks, although a small proportion of patients develop chronic

arthropathy.

• Arthritis due to parasitic infection is rare.

• The guinea worm Dracunculus medinensis may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected.

• Hydatid cysts infect bones in 1–2% of cases of infection with Echinococcus granulosus.

• The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis.

• In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies.

• Monoarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid.

• Reactive arthritis has been attributed to hookworm, Strongyloides, Cryptosporidium, and Giardia infection in case reports, but confirmation is required.

5. DIFFERENTIAL DIAGNOSIS

• Table 135-1 lists the differential diagnosis of arthritis syndromes categorized by acuity and distribution.

• Acute monarticular arthritis includes Staphylococcus aureus, Streptococcus pneumoniae, β-Hemolytic streptococci, Gram-negative bacilli, Neisseria gonorrhoeae, Candida spp., Crystal-induced arthritis, Fracture, Hemarthrosis, Foreign body, Osteoarthritis, Ischemic necrosis, Monoarticular rheumatoid arthritis.

• Chronic monarticular arthritis includes Mycobacterium tuberculosis, Nontuberculous mycobacteria, Borrelia burgdorferi, Treponema pallidum, Candida spp., Sporothrix schenckii, Coccidioides immitis, Blastomyces dermatitidis, Aspergillus spp., Cryptococcus neoformans, Nocardia spp., Brucella spp., Legg-Calvé-Perthes disease, Osteoarthritis.

• Polyarticular arthritis includes Neisseria meningitidis, N. gonorrhoeae, Nongonococcal bacterial arthritis, Bacterial endocarditis, Candida spp., Poncet's disease (tuberculous rheumatism), Hepatitis B virus, Parvovirus B19, HIV, Human T-lymphotropic virus type 1, Rubella virus, Arthropod-borne viruses, Sickle cell disease flare, Reactive arthritis, Serum sickness, Acute rheumatic fever, Inflammatory bowel disease, Systemic lupus erythematosus, Rheumatoid arthritis/Still's disease, Other vasculitides, Sarcoidosis.

5.1 Distinguishing Features

• Acute bacterial infection typically involves a single joint or a few joints.

• Subacute or chronic monoarthritis or oligoarthritis suggests mycobacterial or fungal infection.

• Episodic inflammation is seen in syphilis, Lyme disease, and the reactive arthritis that follows enteric infections and chlamydial urethritis.

• Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute viral hepatitis.

• Viruses often infect multiple joints; however, bacterial infections generally cause mono- or oligoarthritis except in persons with underlying diseases such as rheumatoid arthritis.

6. INVESTIGATIONS & DIAGNOSIS

• Aspiration of synovial fluid or arthrocentesis—an essential element in the evaluation of potentially infected joints—can be performed without difficulty in most cases by the insertion of a large-bore needle into the site of maximal fluctuance or tenderness or by the route of easiest access.

• Ultrasonography or computed tomography (CT) may be used to guide aspiration of difficult-to-localize effusions of the hip and, occasionally, the shoulder and other joints.

• Normal synovial fluid contains <180 cells (predominantly mononuclear cells) per microliter.

• Synovial cell counts averaging 100,000/µL (range, 25,000–250,000/µL), with >90% neutrophils, are characteristic of acute bacterial infections.

• Crystal-induced, rheumatoid, and other noninfectious inflammatory arthritides usually are associated with <30,000–50,000 cells/µL.

• Cell counts of 10,000–30,000/µL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections.

• Definitive diagnosis of an infectious process relies on identification of the pathogen in stained smears of synovial fluid, isolation of the pathogen from cultures of synovial fluid and blood, or detection of microbial nucleic acids and proteins by nucleic acid amplification tests (NAATs) and immunologic techniques.

• Gram stain is positive in about 30−50% of cases.

• Synovial fluid culture is positive in >60% of nongonococcal bacterial arthritis cases.

• Matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry is helpful in patients who have negative culture and high suspicion of infectious arthritis.

• Sonication of explanted prosthetic joints (placement of the material into liquid and then immersion in an ultrasound bath) increases the yield of organism detection, especially in the case of prior antibiotic use within 14 days.

• Specimens of peripheral blood and synovial fluid should be obtained before antibiotics are administered.

• Blood cultures are positive in up to 50–70% of S. aureus infections but are less frequently positive in infections due to other organisms.

• The synovial fluid is turbid, serosanguineous, or frankly purulent.

• Gram-stained smears confirm the presence of large numbers of neutrophils.

• Levels of total protein and lactate dehydrogenase in synovial fluid are elevated.

• The glucose level is depressed; however, these findings are not specific for infection, and measurement of these levels is not necessary for diagnosis.

• The synovial fluid should be examined for crystals because gout and pseudogout can resemble septic arthritis clinically, and infection and crystal-induced disease occasionally occur together.

• Organisms are seen on synovial fluid smears in nearly three-quarters of infections with S. aureus and streptococci and in 30–50% of infections due to gram-negative and other bacteria.

• Cultures of synovial fluid are positive in >90% of cases.

• Inoculation of synovial fluid into bottles containing liquid media for blood cultures increases the yield of a culture, especially if the pathogen is a fastidious organism or the patient is taking an antibiotic, but should be interpreted in the context of the Gram's stain result.

• Pathogen nucleic acid amplification based assays (NAAT) or MALDI-TOF mass spectrometry, when available, can be useful for the diagnosis of partially treated or culture-negative arthritis.

• Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein tend to be elevated in septic arthritis but are nonspecific.

• Serum procalcitonin elevation is only ~50% sensitive but should not be used to rule out infectious arthritis.

• Synovial fluid procalcitonin might be useful, although data are limited.

• Plain radiographs show evidence of soft tissue swelling, joint space widening, and displacement of tissue planes by the distended capsule.

• Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis.

• Ultrasound is useful for detecting effusions in the hip.

• CT or MRI can demonstrate infections of the sacroiliac joint, the sternoclavicular joint, and the spine very well.

• NAAT assays are extremely sensitive in detecting gonococcal DNA in synovial fluid, but they are not FDA approved for this purpose.

• A dramatic alleviation of symptoms within 12–24 h after the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

• All specimens for culture should be plated onto Thayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO2.

6.1 Diagnostic Criteria and Thresholds

• Synovial cell counts averaging 100,000/µL (range, 25,000–250,000/µL), with >90% neutrophils, are characteristic of acute bacterial infections.

• Synovial cell counts of 10,000–30,000/µL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections.

• Synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/µL, with ~70% neutrophils.

• Synovial fluid in true gonococcal septic arthritis contains >50,000 leukocytes/µL.

• Synovial fluid in DGI syndrome usually contains only 10,000–20,000 leukocytes/µL.

• Cultures of synovial fluid are positive in >60% of nongonococcal bacterial arthritis cases.

• Cultures of synovial fluid are positive in >90% of cases (general bacterial).

• Cultures of synovial fluid are positive in <40% of cases (gonococcal).

• Cultures of synovial fluid are consistently negative (gonococcal arthritis syndrome).

• Blood cultures are positive in up to 50–70% of S. aureus infections.

• Blood cultures are positive in <45% of patients (gonococcal).

• Blood cultures are almost always negative (gonococcal).

• Serologic tests for IgG antibodies to B. burgdorferi are positive in >90% of persons with Lyme arthritis.

• NAAT detects Borrelia DNA in synovial fluid in 85% of patients.

• Acid-fast staining of the fluid yields positive results in fewer than one-third of cases (TB).

• Cultures are positive in 80% (TB).

• Culture of synovial tissue taken at biopsy is positive in ~90% of cases (TB).

7. MANAGEMENT & TREATMENT

• Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity.

• Once samples of blood and synovial fluid have been obtained for culture, empiric antibiotics should be directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient's age and risk factors.

• Initial therapy should consist of IV-administered bactericidal agents; direct instillation of antibiotics into the joint is not necessary to achieve adequate levels in synovial and fluid and tissue.

• If there are gram-positive cocci on the smear, IV vancomycin (15−20 mg/kg/dose) every 8–12 h should be started empirically.

• If methicillin-resistant S. aureus is an unlikely pathogen (e.g., when it is not widespread in the community), cefazolin (2 g every 8 h), oxacillin (2 g every 4 h), or nafcillin (2 g every 4 h) should be given.

• If initial Gram's stain shows gram-negative bacilli, the risk for P. aeruginosa infection should be evaluated.

• If the patient does not have risk factors for P. aeruginosa infection, an IV third-generation cephalosporin such as cefotaxime (2 g every 8 h) or ceftriaxone (2 g every 24 h) provides adequate empirical coverage for most community-acquired infections.

• In addition, if the patient has a higher risk for P. aeruginosa infection, then anti-pseudomonal coverage such as cefepime (2 g every 8−12 h) or ceftazidime (2 g every 8 h) should be given.

• Double coverage of Pseudomonas with cephalosporin and ciprofloxacin or aminoglycoside can be considered empirically in severely ill patients or in the setting of highly resistant Pseudomonas infection incidence.

• Definitive therapy is based on the identity and antibiotic susceptibility of the bacteria isolated in culture.

• Infections due to staphylococci are treated with cefazolin, oxacillin, nafcillin, or vancomycin for 4 weeks.

• In patients without evidence of endocarditis, IV antibiotics can be used for 7–14 days of treatment followed by oral antibiotics to complete the treatment course.

• Pneumococcal and streptococcal infections due to penicillin-susceptible organisms respond to 2 weeks of therapy with penicillin G (2 million units IV every 4 h).

• Infections caused by H. influenzae and by strains of Streptococcus pneumoniae that are resistant to penicillin are treated with cefotaxime or ceftriaxone for 2 weeks.

• Most enteric gram-negative infections can be cured in 3–4 weeks by a second- or third-generation cephalosporin given IV or by a fluoroquinolone such as levofloxacin (500 mg IV or PO every 24 h).

• P. aeruginosa infection should be treated for at least 2 weeks with antipseudomonal cephalosporin such as ceftazidime (2 g IV every 8 h), cefepime (2 g every 8–12 h).

• If tolerated, this regimen is continued for an additional 2 weeks.

• Gonococcal arthritis initial treatment consists of ceftriaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms.

• Once local and systemic signs are clearly resolving, a 7-day course of antibiotics may be completed with daily IM ceftriaxone given at 500 mg daily (or 1g for those weighing over 150 kg).

• An oral fluoroquinolone such as ciprofloxacin (500 mg twice daily) may be used if the organism is known to be susceptible.

• If penicillin-susceptible organisms are isolated, amoxicillin (500 mg four times daily) may be used.

• Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment.

• Arthroscopic lavage or arthrotomy is rarely required.

• The Centers for Disease Control recommends that when chlamydial infection has not been excluded, treatment with PO doxycycline 100 mg twice daily for 7 days should be given.

• Sexual partners should be offered testing and presumptive treatment for gonorrhea and chlamydial infection.

• Lyme arthritis generally responds well to therapy.

• A regimen of oral doxycycline (100 mg twice daily for 28 days), oral amoxicillin (500 mg three times daily for 28 days), or parenteral ceftriaxone (2 g/d for 2–4 weeks) is recommended.

• Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy.

• Tuberculous arthritis therapy is the same as that for tuberculous pulmonary disease, requiring the administration of multiple agents for 6–9 months.

• Therapy is more prolonged in immunosuppressed individuals, such as those infected with HIV.

• Fungal arthritis treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen.

• The doses and duration of therapy are the same as for disseminated disease.

• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• Reactive polyarthritis develops several weeks after ~1% of cases of nongonococcal urethritis and 2% of enteric infections, particularly those due to Yersinia enterocolitica, Shigella flexneri, Campylobacter jejuni, Clostridioides difficile, and Salmonella species.

• Only a minority of these patients have the other findings of classic reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash.

• Studies have identified microbial DNA or antigen in synovial fluid or blood, but the pathogenesis of this condition is poorly understood.

• The arthritis may occur several days or weeks after the infection and can be associated with dactylitis, enthesitis, or extraarticular involvement such as conjunctivitis.

• Reactive arthritis is most common among young men (except after Yersinia infection) and has been linked to the HLA-B27 locus as a potential genetic predisposing factor.

• Patients report painful, asymmetric oligoarthritis that affects mainly the knees, ankles, and feet.

• Low back pain is common, and radiographic evidence of sacroiliitis is found in patients with long-standing disease.

• Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis.

• Anti-inflammatory agents help relieve symptoms, but the role of prolonged antibiotic therapy in eliminating microbial antigen from the synovium is controversial.

• Migratory polyarthritis and fever constitute the usual presentation of acute rheumatic fever in adults (Chap. 371).

• This presentation is distinct from that of poststreptococcal reactive arthritis, which also follows infections with group A Streptococcus but is not migratory, lasts beyond the typical 3-week maximum of acute rheumatic fever, and responds poorly to aspirin.

• Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved.

• In most cases, the prosthesis must be removed and replaced to cure the infection.

• Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame.

• In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation.

• Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis.

• In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be drained vigorously by open arthrotomy or arthroscopically, preferably with polyethylene liner exchange, to have a more successful outcome.

• In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, lifelong suppression of the infection with antibiotics may be a reasonable goal.

• A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and another antibiotic (e.g., a quinolone, an antistaphylococcal penicillin, or vancomycin) is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration.

• This approach is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase.

7.1 Gonococcal Arthritis Treatment

• Initial treatment consists of ceftriaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms.

• Once local and systemic signs are clearly resolving, a 7-day course of antibiotics may be completed with daily IM ceftriaxone given at 500 mg daily (or 1g for those weighing over 150 kg).

• An oral fluoroquinolone such as ciprofloxacin (500 mg twice daily) may be used if the organism is known to be susceptible.

• If penicillin-susceptible organisms are isolated, amoxicillin (500 mg four times daily) may be used.

• Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment.

• Arthroscopic lavage or arthrotomy is rarely required.

• The Centers for Disease Control recommends that when chlamydial infection has not been excluded, treatment with PO doxycycline 100 mg twice daily for 7 days should be given.

• Sexual partners should be offered testing and presumptive treatment for gonorrhea and chlamydial infection.

7.2 Prosthetic Joint Infections Treatment

• Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved.

• In most cases, the prosthesis must be removed and replaced to cure the infection.

• Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame.

• In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation.

• Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis.

• In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be drained vigorously by open arthrotomy or arthroscopically, preferably with polyethylene liner exchange, to have a more successful outcome.

• In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, lifelong suppression of the infection with antibiotics may be a reasonable goal.

• A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and another antibiotic (e.g., a quinolone, an antistaphylococcal penicillin, or vancomycin) is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration.

• This approach is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase.

8. PROGNOSIS & COMPLICATIONS

• Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity.

• Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis.

• Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis.

• Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• Infection complicates 0.5–2% of total joint replacements.

• Prosthetic joint infection occurs more often in knee arthroplasty compared with hip arthroplasty.

• The majority of infections are acquired intraoperatively or immediately postoperatively as a result of wound breakdown or infection; less commonly, these joint infections develop later after joint replacement and are the result of hematogenous spread or direct inoculation.

• The presentation may be acute, with fever, pain, and local signs of inflammation, especially in infections due to S. aureus, pyogenic streptococci, and gram-negative bacilli.

• Alternatively, infection may persist for months or years without causing constitutional symptoms when less virulent organisms—such as coagulase-negative staphylococci, Cutibacterium (formerly Propionibacterium) species, enterococci, or diphtheroids—are involved.

• Such indolent infections or usually are acquired during joint implantation and are discovered during joint replacement and are the result of hematogenous spread or direct inoculation.

8.1 Long-term Follow-up

• Most patients recover within 6 months.

• Prolonged recurrent disease is more common in cases that follow chlamydial urethritis.

• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, lifelong suppression of the infection with antibiotics may be a reasonable goal.

9. SPECIAL CONSIDERATIONS

• Patients with rheumatoid arthritis have the highest incidence of infective arthritis (most often secondary to S. aureus) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints.

• Diabetes mellitus, glucocorticoid therapy, hemodialysis, intravenous drug use, and malignancy all carry an increased risk of infection with S. aureus and gram-negative bacilli.

• Tumor necrosis factor inhibitors (e.g., etanercept, infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic bacterial infections and could be associated with septic arthritis in this population.

• Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies.

• Pneumococci, Salmonella species, and H. influenzae cause septic arthritis in persons infected with HIV.

• Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which, while rare, results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly.

• IV drug users acquire staphylococcal and streptococcal infections from their own flora.

• In the United States, a 2012 national outbreak of fungal arthritis (and meningitis) caused by Exserohilum rostratum was linked to intraspinal and intraarticular injection of a contaminated preparation of methylprednisolone acetate.

• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, lifelong suppression of the infection with antibiotics may be a reasonable goal.

• A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and another antibiotic (e.g., a quinolone, an antistaphylococcal penicillin, or vancomycin) is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration.

• This approach is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase.

9.1 Prevention

• To avoid the disastrous consequences of infection, candidates for joint replacement should be selected with care.

• All modifiable risk factors should be identified and minimized preoperatively to improve the surgical outcome and prevent surgical site infection.

• Preoperative screening for S. aureus with decolonization should be considered.

• Rates of infection are particularly high among patients with rheumatoid arthritis, persons who have undergone previous surgery on the joint, and persons with medical conditions requiring immunosuppressive therapy.

• Perioperative antibiotic prophylaxis, usually with cefazolin, and measures to decrease intraoperative contamination, such as laminar flow, have lowered the rates of perioperative infection to <1% in many centers.

• After implantation, measures should be taken to prevent extraarticular infections that might give rise to hematogenous spread to the prosthesis.

• The effectiveness of prophylactic antibiotics is controversial.

10. KEY PEARLS & CLINICAL TRAPS

• Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures.

• Synovial cell counts averaging 100,000/µL (range, 25,000–250,000/µL), with >90% neutrophils, are characteristic of acute bacterial infections.

• Synovial cell counts of 10,000–30,000/µL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections.

• Timely drainage of pus and necrotic debris from the infected joint is required for a favorable outcome.

• Needle aspiration of readily accessible joints such as the knee may be adequate if loculations or particulate matter in the joint does not prevent its thorough decompression.

• Arthroscopic drainage and lavage may be employed initially or within several days if repeated needle aspiration fails to relieve symptoms, decrease the volume of the effusion and the synovial white cell count, and clear bacteria from smears and cultures.

• In some cases, arthrotomy is necessary to remove loculations and debride infected synovium, cartilage, or bone.

• Septic arthritis of the hip is best managed with arthrotomy, particularly in young children, in whom infection threatens the viability of the femoral head.

• Septic joints do not require immobilization except for pain control before symptoms are alleviated by treatment.

• Weight bearing should be avoided until signs of inflammation have subsided, but frequent passive motion of the joint is indicated to maintain full mobility.

• Although some clinical studies suggest that adjunctive use of glucocorticoids showed some benefit in children with septic arthritis, they are not widely used in clinical practice.

• Gonococcal arthritis is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx.

• True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients.

• Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites.

• NAAT-based urine tests also may be positive.

• Lyme arthritis generally responds well to therapy.

• Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy.

• Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

• Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts.

• Coexistent active pulmonary tuberculosis is unusual.

• Fungi are an unusual cause of chronic monoarticular arthritis.

• Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread.

• Candida infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints.

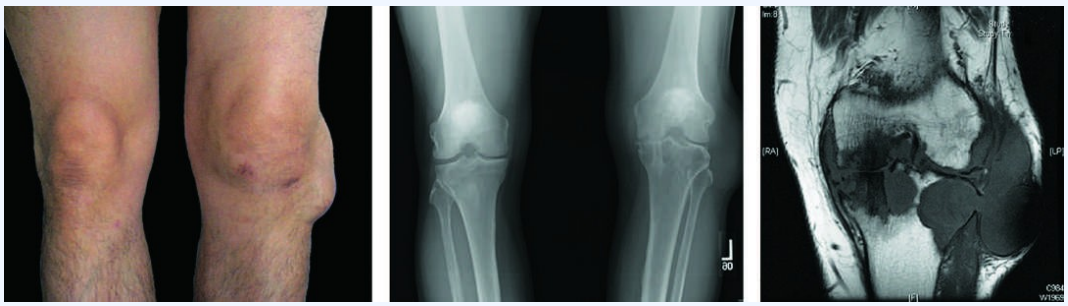
• In fungal prosthetic joint infection, the removal of all prosthetic joint material is highly recommended.

• In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, lifelong suppression of the infection with antibiotics may be a reasonable goal.

• A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and another antibiotic (e.g., a quinolone, an antistaphylococcal penicillin, or vancomycin) is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration.

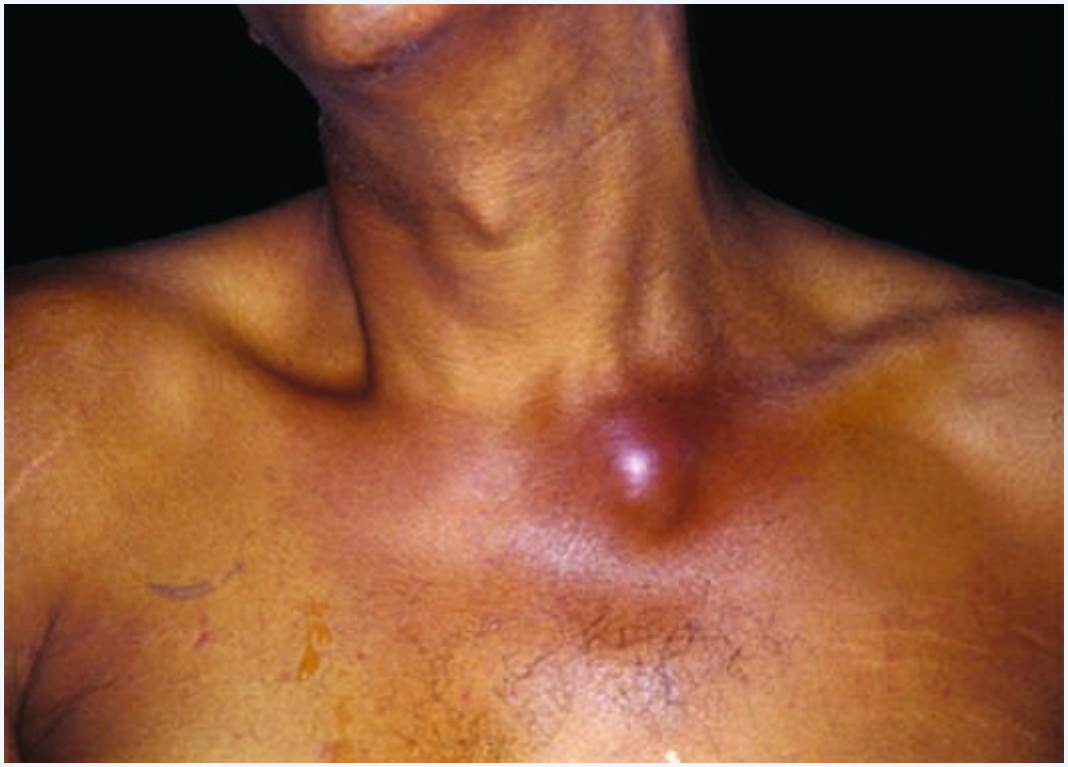
• This approach is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 135-2 Chronic arthritis caused by Histoplasma capsulatum in the left knee. A. A and difficulty walking for several years. He had undergone arthroscopy for a meniscal tear glucocorticoid injections. The patient developed significant deformity of the knee over multiple abnormalities, including severe medial femorotibial joint-space narrowing, a large suprapatellar joint effusion, and a large soft tissue mass projecting laterally over nature of the lateral knee abnormality. Synovial biopsies demonstrated chronic All clinical cystic lesions and the effusion resolved after 1 year of treatment with (Courtesy of the late Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; — Figure 135-1: Clinical photograph of acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with fever and lower neck pain. Physical examination revealed jaundice and a painful swollen area over the left sternoclavicular joint. Blood cultures grew group B Streptococcus.



Harrison's 22e · Figure 2

FIGURE 135-1 Acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with a new onset of fever and lower neck pain. He had no history of IV drug use or previous catheter placement. Jaundice and a painful swollen area over his left sternoclavicular joint were evident on physical examination. Cultures of blood drawn at admission grew group B Streptococcus. The patient recovered after treatment with IV penicillin. (Courtesy of the late Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.) — Figure 135-2: Chronic arthritis caused by Histoplasma capsulatum in the left knee. X-ray shows severe medial femorotibial joint-space narrowing, subchondral cysts, and a large soft tissue mass. MRI defines the cystic nature of the lateral knee abnormality. Synovial biopsy demonstrated chronic inflammation with giant cells, and cultures grew H. capsulatum after 3 weeks of incubation.