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Evaluation and Treatment of Acute Arthritis

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Introduction

Patients with acute joint pain present a diagnostic dilemma for many physicians. Classically the joints are hot, swollen, and tender, with reduced range of motion. The differential diagnosis for the painful joint is extensive. (*See Table 1.*) Distinguishing between the various causes can be difficult, especially since there may be more than one cause concomitantly.[1] It is important to promptly diagnose and treat the various etiologies of joint pain, and paramount that septic arthritis be ruled out in all painful joints.

Anatomy and Physiology of the Joint

The parts of a synovial joint are illustrated in Figure 1. The synovium lies within the joint capsule, a connective tissue structure that surrounds the articular surfaces of two or more bones. It is responsible for the production of synovial fluid, which provides nutrition to the avascular articular cartilage and lubricates the cartilage surfaces. The synovium contains numerous immune-modulating cells involved in the recruitment of inflammatory cells that produce arthritis.[2,3] Activation of these cells during inflammatory arthritis causes the synovium to outgrow its vasculature's ability to exchange nutrients and toxins. This leads to a hypoxic and acidotic joint environment and subsequent joint destruction.[3]

The General Approach to the Hot Joint

The history should focus on the onset of symptoms, a comparison to previous joint pain, and concurrent symptoms such as rash or fever. A temporal history of disease progression is important, especially in the setting of polyarticular or migratory joint pain. Inquire into previous joint disease, rheumatic disorders, autoimmune disorders, diabetes, malignancies, history of intravenous drug use, and alcoholism. These factors are associated with various disease processes, including viral, reactive, rheumatoid, crystalloid, and septic arthritis. Ask about sexual exposure, travel, and exposure to tuberculosis and Lyme disease. Some medications can increase the likelihood of crystalloid, rheumatoid, and septic arthritis.

Physical Examination. The physical examination should focus on the affected joint, the general musculoskeletal exam, and a focused physical examination. Examine the affected joint and periarticular area for erythema, swelling, and tenderness to palpation. Compare findings to the contralateral joint. Arthritis typically presents with generalized findings. Focal findings may be indicative of periarticular pathology such as tendinitis or bursitis. Check the

Executive Summary

- Two or more causes of a hot joint may be present at the same time.
- Septic arthritis carries a high morbidity and mortality. Some patients may be afrebrile.
- Arthrocentesis makes the diagnosis of most cases of acute arthritis.
- Patients with rheumatoid arthritis have a higher risk of septic arthritis.

overlying skin for cellulitis, rashes, pustules, wounds, and other lesions suggesting infectious arthritis.

Diagnostic Adjuncts. Although diagnosing the specific cause(s) of acute joint pain is dependent on clinical suspicion, there are a number of diagnostic adjuncts. Remember that there may be more than one disease process affecting a joint, and that septic arthritis must be excluded in all cases of undifferentiated acute joint pain.

The most important tool used in acute arthritis is synovial fluid aspiration. Arthrocentesis is both diagnostic and therapeutic. Removal of joint fluid reduces pain by decreasing intra-articular pressure.[4]

Contraindications to arthrocentesis include superficial infection over the needle insertion site and coagulopathy. Prosthetic joints are a relative contraindication to arthrocentesis.

Arthrocentesis is performed blindly with the use of anatomic landmarks or with the use of ultrasound or fluoroscopy.[5-10] During arthrocentesis, flow of synovial fluid may stop. Potential causes include temporary obstruction by synovial fronds, blockage by fibrin or other debris, loculated synovial fluid collections, or displacement of the needle outside the joint cavity. If flow becomes obstructed, a small amount of fluid can be injected back into the joint to clear any obstruction.[4]

Arthrocentesis is a generally safe procedure. The risk of infection from arthrocentesis is extremely low, at an incidence of 18 per 250,000 intra-articular steroid injections.[11]

Synovial Fluid Analysis. Normal synovial fluid typically is colorless or pale yellow and clear. (*See Table 2.*) It is highly viscous and should be able to form a string stretching approximately 10 cm before surface tension is broken.[12] In cases of inflammatory arthritis, viscosity can be markedly reduced. Cloudy fluid suggests the presence of inflammatory cells, fibrin, crystals, lipids, or amyloid. Bloody fluid is suggestive of trauma, tumors, or hematologic disorders.

Obtain a Gram stain and cultures of the synovial fluid if septic arthritis is suspected. If there is sufficient fluid, obtain a cell count. An elevated polymorphonuclear leukocyte (PMN) count suggests an inflammatory and/or infectious process. Examine the synovial fluid for crystals. Monosodium urate crystals (MSU) are strongly birefringent and are easily identified under a polarized microscope.

Re-evaluation in Undiagnosed Cases. If there is low suspicion for septic arthritis and the initial evaluation is not diagnostic, arrange for follow up in 2-5 days for re-evaluation as an outpatient. At that time, serum testing, radiographs, and synovial fluid analysis should be repeated and other imaging modalities considered.[13]

Case 1. A 76-year-old male with diabetes and rheumatoid arthritis presents with a 2-day history of increasing right knee pain, especially with weight bearing. He denies trauma.

On physical examination, he is afebrile. There is a healing non-infected abrasion over the anterior tibial surface. The right knee joint is warm, diffusely tender, and slightly swollen with an appreciable effusion. The complete blood cell count (CBC) is normal, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are slightly elevated. The right knee X-ray shows chronic arthritic changes. Arthrocentesis yields 10 cc of cloudy fluid. The synovial white blood cell count is 76,000 with 90% polymorphonuclear cells. The Gram stain is negative, and the cultures are pending.

Septic Arthritis

Epidemiology. In the general population, the annual incidence of septic arthritis ranges from 2-5 per 100,000 persons.[14,15] The rate is 10-30 times higher in patients with rheumatoid arthritis or prosthetic joints.[12,14] It is estimated that 8-27% of patients who present to the emergency department with acute arthritis eventually will be diagnosed with septic arthritis.[16] Even with timely diagnosis, hospitalization, and antibiotic therapy, the mortality rate is estimated at 7-25%.[5,12,16-18] The mortality rate can approach 50% in patients with *Staphylococcus aureus*-associated septic arthritis.[5] One-third to one-half of survivors suffer permanent loss of joint function.[5,11]

Pathophysiology. Bacteria invade the synovial space via hematogenous spread or direct invasion. Bacterial invasion of synovial space leads to joint destruction through pathogen-mediated inflammation, host response-mediated inflammation, and tissue ischemia. Bacterial enzymes and toxins directly damage cartilage. Host-mediated cytokines activate proteolytic enzymes that autodigest cartilage and bone. Vascular congestion and local inflammation contribute to development of a purulent effusion. This growing effusion eventually leads to elevated joint pressure that tamponades synovial blood flow and causes cartilage anoxia.[19] Septic arthritis can lead to joint destruction in as few as 10 days

and can progress to systemic sepsis.[20]

Gram-positive organisms are the most common pathogens in non-gonococcal septic arthritis (70-80% of cases). Staphylococcus is the most common organism, followed by streptococcus.[11,16-18,21,22] Most infections occur from disruptions to skin or mucosal barriers.[19] Community-acquired methicillin resistant *Staphylococcus aureus* (CaMRSA) associated septic arthritis is increasing in incidence and, in some regions, is the predominant organism.[22,23] Patients with prosthetic hardware are also at risk for coagulase negative staphylococci infection.

Gram-negative infection accounts for 15-20% of non-gonococcal septic arthritis cases, most often *H. influenza*, *E. coli*, and *P. aeruginosa*.[11,21] Gram-negative bacteria usually originate from the gastrointestinal or genitourinary system.[19] It more commonly affects elderly and immunocompromised patients.[22]

Anaerobes, fungi, tuberculosis, and brucellosis are rare causes of septic arthritis. They are more common in immunocompromised patients or in specific at-risk populations.[20,24] Anaerobic bacteria joint infections generally occur in the setting of penetrating trauma.[22,25] Brucellosis-associated septic arthritis is rare and typically occurs in patients with a history of occupational exposure.[20,24]

Factors that impair normal joint function put specific joints at increased risk for septic arthritis. (*See Table 3.*) These factors include prior joint trauma, the presence of arthritic changes, and the presence of joint prosthesis.[19] It is estimated that 46% of bacterial arthritis cases occur in joints with pre-existing joint damage.[20] Systemic disorders that increase the risk for septic arthritis include diabetes, pre-existing rheumatoid arthritis, liver disease, chronic kidney disease, malignancy, intravenous drug use, hemodialysis, alcoholism, organ transplant, hemophilia, hypogammaglobulinemia, and acquired immune deficiency syndrome (AIDS).[19,21,26] Extremes of age (newborns and those older than 80 years), diabetes, and HIV infection increase the risk of infection[19] and also increase the risk of death from septic arthritis.[17]

Table 1: Differential Diagnosis of Monoarticular Arthritis[16,29]

Septic arthritis	Osteomyelitis
Nongonococcal	Paget's disease involving joint
Gonococcal	Osteochondritis dissecans
Mycobacterial	Osteogenic sarcoma
Fungal	Synovial metastasis
Crystal arthritis	Synovioma
Gout	Systemic lupus erythematosus
Pseudogout	Amyloidosis
Hydroxyapatite	Intermittent hydrarthrosis
Rheumatoid arthritis	Pancreatic fat necrosis
Osteoarthritis	Gaucher's disease
Intra-articular injury	Behçet's disease
Fracture	Family Mediterranean fever
Loose body	Hemogobinopathies: Sickle cell
Meniscal tear	Plant thorn synovitis
Osteonecrosis	Pigmented villonodular synovitis
Hemarthrosis	Transient synovitis of the hip
Lyme disease	

Figure 1: Anatomy of Synovial Joint (Knee)

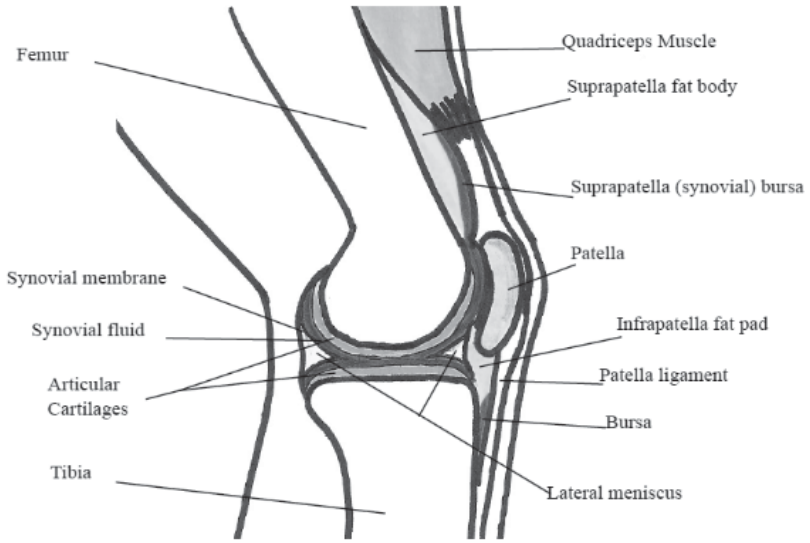


Illustration courtesy of Pim Jetanalin, MD.

Clinical Presentation. The septic joint typically is acutely hot, painful, and swollen, with reduced range of motion. Patients typically present early, but a later presentation may be seen with prosthesis infection or low-virulence organisms like tuberculosis.[18,25] It is monoarticular in 80-90% of cases.[19-21,24,25] The most commonly affected joints are the knee (50%), hip, and shoulder.[6,11,19,20,22] In pediatric patients, the hip is the most common site.[27] Septic arthritis in fibrocartilaginous joints of the skeleton such as sternoclavicular, sacroiliac, and intervertebral disk spaces is strongly associated with intravenous drug abusers.[28]

The absence of fever does not

Table 2: General Characteristics of Synovial Fluid[12,20]

Characteristic	Normal	Non-inflammatory	Rheumatoid Arthritis	Crystal Arthritis	Septic Arthritis	Hemorrhagic
Color	Transparent	Transparent	Translucent or purulent	Translucent or purulent	Translucent or purulent	Bloody
Viscocity	High	High	Low	Low	Variable	Variable (low)
Gram stain	Negative	Negative	Negative	Negative	Positive	Negative
Culture	Negative	Negative	Negative	Negative	Positive	Negative
jWBC count (cells/mm^3)	< 180	200-2000	2000-50,000	2000-50,000	> 50,000	200-2000
Neutrophil %	< 25%	< 25%	> 50%	> 50%	> 75%	50-75%
Crystals	Negative	Negative (occasional CPPD and hydroxy-apatite crystals)	Negative	Positive	Negative except in case of concomitant crystal arthritis	Negative

Table 3: Risk Factors for Septic Arthritis[16,34]

Systemic Risk Factors
- Rheumatoid arthritis
- Liver disease
- Malignancy
- Intravenous drug use
- Diabetes
- Hemodialysis
- Alcoholism
- Immunosuppression
- Hemophilia
- Hypogammaglobulinemia

Local Risk Factors
- Prior joint trauma
- Prior arthritic joint changes
- Prosthetic joint
- Prior arthroscopic procedure

Other Risk Factors
- Extremes of age
- Socioeconomic status
- Occupational risk factors

rule out septic arthritis.[16,19] The presence of fever, rigors, and diaphoresis is neither specific nor sensitive.[6,11,16,18-20,22,26] In children, septic arthritis usually is accompanied by fever, malaise, poor appetite, irritability, and progressive reluctance to use the affected limb.[28] Geriatric and immunocompromised patients are often afebrile.

The most sensitive indicators of septic arthritis are joint pain (85%) and swelling (75%). These findings, though sensitive, are not specific; they are found in other inflammatory joint processes.[16,18] Disproportionate pain, loss of function, erythema, or systemic symptoms should increase suspicion for septic arthritis in patients with arthritic disease.[20]

Diagnostic Tests. Normal ESR and CRP levels have a negative predictive value, but they do not rule out septic arthritis.[1,5,7,20,29,30] ESR and CRP are useful for monitoring response to treatment in confirmed cases of septic arthritis.[22] Blood cultures identify the offending organism in 50-70% of non-gonococcal septic arthritis cases.[11]

Plain radiographs provide no benefit in diagnosing septic arthritis but may be useful in looking for underlying joint damage or concurrent osteomyelitis.[11,22,31] Magnetic resonance imaging (MRI) and scintigraphy can distinguish septic arthritis from non-inflammatory arthritis, but do not differentiate between septic, rheumatoid, and crystalloid arthritis.[16,22] Reserve scintigraphy for suspected cases of synovial fistulas and MRI for cases concerning for concomitant osteomyelitis.[10,22]

Arthrocentesis is necessary in all suspected cases of septic arthritis. Although needle aspiration through overlying cellulitis is a contraindication, some advocate going through infected skin when necessary.[16] When arthrocentesis does not yield adequate fluid, a small amount of sterile saline can be used to irrigate the joint space in order to collect fluid for Gram stain and culture.[12] Cloudy or purulent aspirate is suggestive of septic arthritis.[4,21] It is also important to remember that the presence of crystals does not exclude the diagnosis of septic arthritis.[1] Synovial protein, glucose, lactate, and serologic markers can increase suspicion for septic arthritis, but do not discriminate between other causes of inflammatory arthritis.[22,25,32-34]

An elevated joint white blood cell count (jWBC) and a predominance of polymorphonuclear cells are the most useful indicators of septic arthritis.[15,32] A markedly elevated jWBC (> 50,000/mL) is highly suggestive of septic arthritis (88% specificity). However, a jWBC less than 50,000/mL does not rule out septic arthritis (sensitivity 61%). Treatment is indicated when there is high clinical suspicion for septic arthritis and an elevated jWBC (>

Table 4: Empiric Antibiotic Regimens for Patients with Potentially Septic Joints[21,28]

Synovial Fluid Gram Stain	Antibiotic Coverage	Dose
Gram-positive cocci in clusters (presumed Staphylococcus)	Nafcillin/oxacillin Cefazolin	2 g IV q 4 hrs 1-2 g IV q 8 hrs
Gram-positive cocci in clusters (presumed MRSA)	Vancomycin Clindamycin Linezolid	1 g IV q 12 hrs 900 mg IV q 8 hrs 600 mg IV q 12 hrs
Gram-positive cocci in chains (presumed Steptococcus)	Nafcillin Penicillin Cefazolin	2 g IV q 4 hrs 2 million U IV q 4 hrs 1-2 g IV q 8 hrs
Gram-negative diplocci (presumed Gonococcus)	Ceftriaxone Cefotaxime	2 g IV q 24 hrs 1 g IV q 8 hrs
Gram-negative bacilli	Nafcillin/oxacillin *plus* gentamicin	2 g IV q 4 hrs 7 mg/kg IV q 24 hrs

Note:
1. All patients with prosthetic joints, intravenous line placement, recent hospitalization, or known carriers are at risk for infection with MRSA species. They should be empirically treated until culture and sensitivities return, regardless of gram stain results.
2. In the absence of definitive gram-stain results, a reasonable empiric regimen for the adult with possible septic arthritis is the combination of nafcillin or oxacillin with a cephalosporin, such as ceftriaxone or cefotaxime. An aminoglycoside should be added in the injection drug user.

20,000/mL).[13,35-37]

Definitive diagnosis is confirmed by either Gram stain or culture. Unfortunately, Gram stain is positive in only half of all septic arthritis cases.[6,25] Therefore, empiric antibiotics should be started in all suspected cases.[20] Cultures will confirm the diagnosis. Polymerase chain reaction (PCR) testing is a potential new adjunct for diagnosing septic arthritis, and it may be useful when antibiotics are started before synovial fluid was obtained.[38] It can identify borrelia, gonorrhea, and other species typically difficult to culture.[25]

Treatment. Patients with septic arthritis should be hospitalized and orthopedics consulted, especially in cases of suspected prosthesis infection.[11,20] With early and aggressive treatment, 50% of patients with *S. aureus*-associated septic arthritis recover without residual joint damage.[11] (*Table 4 summarizes current antibiotic therapy.*)[11,22,24,25] Patients who are elderly, immunosuppressed, or intravenous drug abusers should be placed on broad-spectrum antibiotics to cover both gram-positive and gram-negative organisms.[11,21,22] Young, healthy, sexually active patients with low suspicion for non-gonococcal arthritis should be treated for gonorrhea (see next section).

There are no data on the optimal duration of antibiotic treatment. IV antibiotics are continued for up to two weeks or until clinical improvement, followed by appropriate oral antibiotics for an additional 2-6 weeks.[20,22] Clinical improvement and inflammatory markers such as ESR and CRP are useful in guiding duration of antibiotic therapy.[22]

Drainage of the infected joint is recommended to decrease joint damage caused by pathogens, host inflammation, and elevated intra-articular pressure. Drainage can be performed through serial needle aspirations or surgery.[24,25] There is no demonstrated superiority of one treatment over the other;[22] however, arthroscopic or open joint drainage is indicated when serial aspirations do not yield satisfactory results and in cases of complicated fluid collections or osteomyelitis.[20] In addition to antibiotic therapy and joint drainage, treat underlying comorbidities and discontinue immunosuppressants.[11,20]

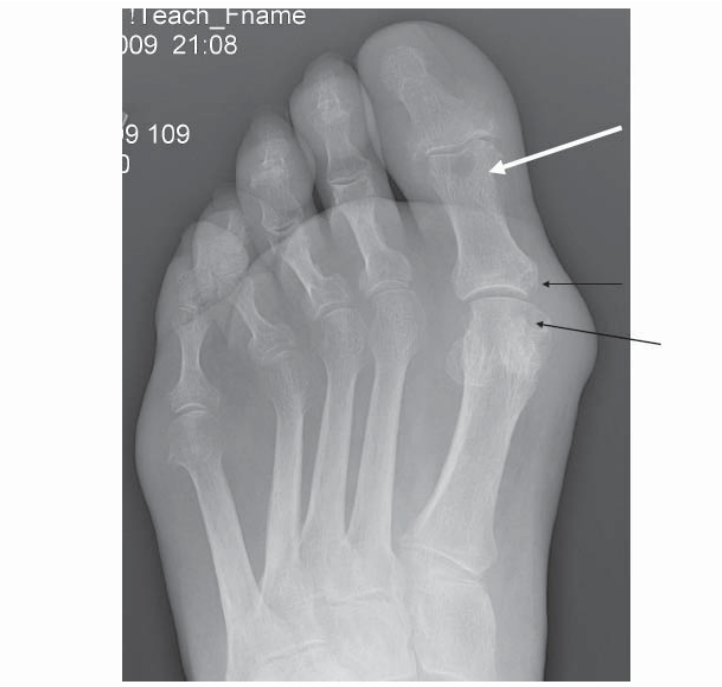
Gonococcal Arthritis

Gonococcal arthritis is the most common cause of non-traumatic monoarthritis in young sexually active persons.[27] It is estimated that 3% of patients with untreated gonorrhea infections develop gonococcal arthritis.[11] Infected women tend to have a more asymptomatic gonococcal infections than males and are therefore more likely to present with untreated infections.[19] There is a 3:1 female-to-male predominance.[7,19]

Gonococcal arthritis presents as a migratory polyarthralgia that affects the knees, ankles, and wrists.[25] It is often associated with fever, tender tenosynovitis, painless vesicles, pustules, macules, and/or papules on the extremities.[11,19,32] However, 30-40% of the time it presents solely as a monoarticular arthritis.[19]

The diagnosis of gonococcal arthritis rests largely on clinical suspicion. Consider obtaining oropharyngeal, genital, and anorectal cultures in addition to blood cultures based on the clinical history and exam. Up to 80% of suspected cases

Figure 2: Gouty Arthritis



A radiographic study of the left foot in a 77-year-old male with gouty arthritis shows hallux valgus deformity of the great toe, "overhanging" edge (white arrow), and erosions at the base of the proximal phalanx and the first metatarsal head. Courtesy of Bassett Healthcare.

of gonococcal septic arthritis will be identified by peripheral culture.[21] PCR also may aid in confirming the diagnosis of gonococcal arthritis. With early and aggressive treatment, 95% of patients with gonococcal arthritis recover without any residual joint damage.[11]

Case 1 Revisit. The patient's history, elevated jWBC, ESR, CRP, and WBC suggest septic arthritis. The patient is started on IV antibiotics and admitted to orthopedics.

Case 2. A 56-year-old male with a history of gout and chronic kidney disease presents with left elbow pain that has worsened over the last 24 hours. He reports the pain is typical of his previous gout attacks. He denies fever, chills, or rigors.

On physical examination, he appears well and is afebrile. The left elbow reveals a gouty tophus. The joint is slightly red, tender, warm to touch, and has a palpable effusion. Pain is elicited with both passive and active movement.

The patient receives analgesia. The CBC is normal; ESR and CRP are slightly elevated. X-rays of the left elbow show no fracture but reveal joint destruction consistent with chronic gouty arthritis. Arthrocentesis yields synovial fluid that appears thick and white, with a jWBC of 36,000, 70% polymorphonuclear cells. The Gram stain is negative, and the cultures are sent. Polarized microscopy shows needle-shaped crystals and strongly negative birefrigence.

Gout

Epidemiology. Gout is an inflammatory arthritis caused by deposition of sodium urate crystals in joints. It afflicts more than 2.1 million Americans.[39] The prevalence is greater in men than women, affecting 0.7-1.4% of men and 0.5-0.6% of women. Its prevalence is greatest over age 65, with 4.4-5.2% of men and 1.8-2.0% of women affected.[11] The overwhelming majority of women (90%) are post-menopausal at the time of their first gout attack.[40]

Pathophysiology. An elevated uric acid level is a prerequisite to developing gout.[41] High levels of uric acid form uric acid salts that are deposited in the joint synovium.[11] The crystals activate inflammatory mediators that stimulate the migration of neutrophils into the synovial spaces and the release of proteolytic enzymes that damage the joint.[11] Gout crystal-protein complexes, known as tophi, deposit outside the synovium in tendons, cartilage, ligaments, bones, and bursae. They commonly deposit in the ears, nose, feet, fingers, knees, and around or in the olecranon and prepatellar bursae.

A gout flare can last from several hours to weeks. A typical flare is self-limited to 2-3 weeks.[11,42] Untreated, most patients will have improvement in joint pain by day 5, and improvement of swelling by day 7. If left untreated, most patients will develop recurrent acute arthritis that eventually will lead to chronic arthritis. Without the use of urate-lowering agents, 20-40% of patients will develop chronic tophaceous gouty arthritis.[11]

Risk factors for gout include high alcohol intake, hyperlipidemia, obesity, renal disease, lymphoproliferative, and myeloproliferative disorders, and family history of gout.[11,43] Various medications have been implicated in the development of gout, including diuretics, low-dose aspirin, cyclosporins, ethambutol, pyrazinamide, nicotinic acid, intravenous heparin, tacrolimus, and other cytotoxic drugs.[11,43,44] Diuretics are associated with 75% of cases in the elderly. This proportion approaches 95-100% in geriatric women. There also is increasing evidence of an association between gout and coronary artery disease, especially in women.[24,43]

Clinical Presentation. Gout presents as an acute onset of pain with inflammation, including erythema, redness, and joint warmth. An attack often follows the intake of purine-rich foods, minor trauma, alcohol

Table 5: Criteria for a Presumptive Diagnosis of Acute Gouty Arthritis Proposed by the American College of Rheumatology[44]

The presence of characteristic urate crystals in the joint fluid, or a tophus provide to contain crystals by chemical means or polarized light micrsocopy
OR
The presence of 6 of the following 12 clinical, laboratory, and radiographic phenomena:

- **More than one attack of acute arthritis**
- **Maximal inflammation developed within 1 day**
- **Attack of monoarticular arthritis**
- **Joint redness observed**
- **First metatarsophalangeal joint painful and swollen**
- **Unilateral attack involving first metatarsophalangeal joint**
- **Unilateral attack involving tarsal joint**
- **Suspected tophus**
- **Hyperuricemia**
- **Asymmetric swelling within a joint (radiograph)**
- **Subcortical cysts without erosions (radiograph)**
- **Negative culture of joint fluid for microorganisms during attack of joint inflammation**

intake, surgery, or infection.[43] A single joint is involved in about 85-90% of first attacks[44]; more than half of first attacks occur in the first metatarsophalangeal joint.[11,42,43] Other commonly affected joints include the wrist, elbows, knees, and ankles. The patient may have systemic symptoms including fever, chills, and fatigue. Gout in elderly patients may be more indolent or chronic and more commonly polyarticular.[11]

In select cases, the clinical diagnosis of acute primary gout arthritis can be made without synovial fluid analysis. The criteria developed by the American College of Rheumatology are outlined in Table 5. If the patient does not meet these criteria, consider an alternative diagnosis such as infection.

Pain occurs abruptly, reaching its maximum in one day. Pain that continues to worsen after one day should increase suspicion for another process such as septic arthritis. If there is pain out of proportion to typical flares or pain in a previously unaffected joint, consider septic arthritis.[25]

Diagnostic Testing. Radiographic findings suggestive of gout include asymmetric joint swelling and subcortical cysts without erosions. (*See Figure 2.*) Laboratory tests are not useful in diagnosing gout; in some cases, the uric acid level is normal. Definitive diagnosis of gout requires synovial fluid analysis,[11,13] with monosodium urate monohydrate crystals in the synovial fluid and negative cultures.

Treatment. Treatment focuses on treating acute pain and decreasing recurrent attacks.[11] Early treatment is important to achieve rapid and complete relief of symptoms.[44] NSAIDs are considered first-line treatment. They typically reduce major symptoms within 24 hours of initiation.[40] More than 90% of patients with acute attacks achieve complete resolution of symptoms within 5-8 days of starting NSAIDs. The maximum dose commonly is started at the time of onset, continued for a full 24 hours, then tapered over the next 2-3 days.[42] Potential side effects of NSAIDs include peptic ulcer disease, gastritis, renal insufficiency, and fluid retention. When given to high-risk patients, short-term NSAID use is recommended.[11] Gastrointestinal bleeding risk also can be reduced with co-administration of a proton-pump inhibitor.[42] COX-2 inhibitors also have been effective in reducing the rate of GI bleeds, but the benefit must be weighed against the risk of cardiovascular events.[32]

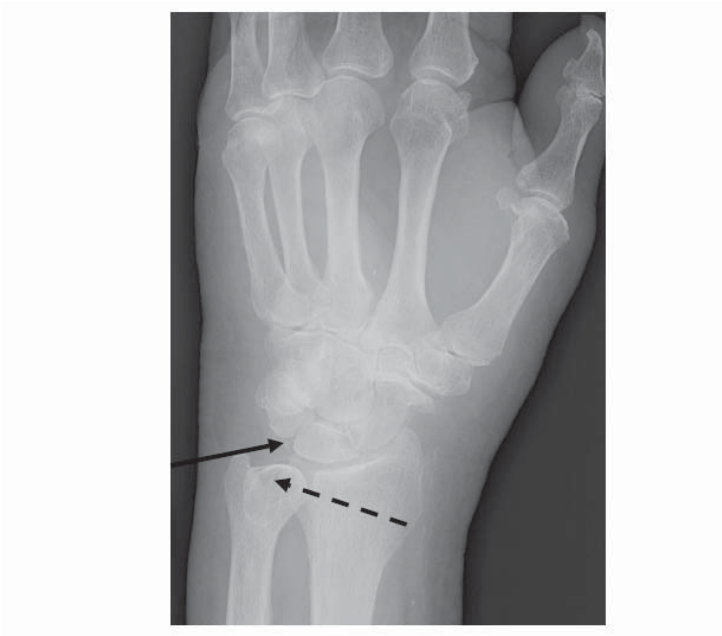
Intra-articular steroid injection is an effective treatment for patients with one or two actively inflamed joints. Pain typically resolves 24-48 hours post-injection.[42,45] It is recommended in patients with contraindications to NSAID use. The risk of systemic side effects is low, but ensure that the joint is not infected prior to injection.[11] The dose for triamcinolone is 10 mg in knees and 8 mg in smaller joints.[42]

Systemic steroids are an alternative treatment and are recommended in those with contraindications to NSAIDs and in the elderly. Oral prednisolone, 35 mg daily for 5 days, is equivalent in effectiveness to naproxen.[12] Alternatively, oral prednisone at 30-60 mg daily followed by a steady taper over 10-14 days is recommended. The taper should be extended to 3 weeks in patients with involvement of five or more joints.[40,42] Use of a taper may reduce the chance of a rebound gout flare.[42] Side effects of systemic steroid use include renal failure, fluid retention, ulcers, hypertension, and hyperglycemia. These are all rare and short-lived following the discontinuation of steroids.[11]

Synthetic adrenocorticotropin hormone (ACTH) can be used in the treatment of acute gout. ACTH stimulates cortisol and acts to inhibit inflammation.[42] Its effectiveness is comparable to corticosteroid therapy.[11,41] ACTH treatment can be given as a taper as follows: Day 1: 80 IU q 8 hrs, Day 2: 40 IU q 12 hrs, Day 3-14: 40 IU daily.[42]

Colchicine can be effective in up to 75% of young healthy patients who present shortly after onset of an acute gout flare.[11] The exact mechanism of action is not clear, but it is believed that colchicine

Figure 3: Pseudogout



Radiographic image of a left hand demonstrating chondrocalcinosis (solid arrow). Dash arrow indicates a large subchondral cyst at the distal ulna. Courtesy of Bassett Healthcare.

down-regulates cytokine function and suppresses crystal-protein complex induced inflammation.[42] The recommended regimen for colchicine is 1 mg orally, followed by 0.5 mg every 2 hours until symptoms are relieved or toxicity develops.[42] Relief typically occurs within 24 hours when given orally and within 8 hours when given IV.[42] Even though intravenous colchicine is useful in rapidly aborting attacks, its use is not recommended. Extravasation of colchicine can cause tissue necrosis and thrombophlebitis. Colchicine has a narrow therapeutic window. Almost all users exhibit side effects, with the most common being nausea, vomiting, diarrhea, and/or abdominal pain.[42,46] Colchicine is metabolized by the kidney and liver, so its use in patients with hepatic or renal insufficiency is problematic.[11,42] It has been lethal at cumulative doses as low as 6-7 mg.[42] Lethal side effects are more common when it is used intravenously or when it is administered to patients with renal or hepatic dysfunction. Side effects include alopecia, bone marrow suppression, neuromyopathy, renal failure, disseminated intravascular coagulation, seizures, arrhythmias, and hepatic necrosis.[42,44] Given the high rate of experienced side effects compared to therapeutic benefit and its potential lethality, colchicine is recommended as second-line therapy when both NSAIDs and steroids are contraindicated.[46]

Local application of cold packs reduces pain and swelling.[45] Instruct the patient to rest the afflicted joint for 1-2 days and arrange follow-up with the patient's treating physician.[42]

The presence of crystals does not rule out septic arthritis. Antibiotics can be started until culture results return.[1] Failure to respond to therapy after 1 week should prompt re-evaluation of the diagnosis and management plan.[13]

Pseudogout

Epidemiology. Pseudogout is another crystalloid arthritis that presents as acute monoarticular or polyarticular arthritis. The term "pseudogout" refers to the acute, gout-like attacks that occur in some individuals.[47] It is more common in females and typically occurs in the elderly.[11] The average age at presentation is 65 years.[11]

Pathophysiology. Pseudogout results from the deposition of CPPD into articular cartilage. As in gout, these crystals lead to the influx of inflammatory proteins and cells that lead to inflammation. Unlike gout, CPPD crystals can invade joint space without any history of serum abnormality. The majority of cases are idiopathic, but 5% of cases are associated with hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatemia, or hemachromatosis.[11]

Clinical Presentation. Pseudogout typically involves large joints, with the knee being the most common, followed by the wrist and ankle. It rarely affects the first metatarsophalangeal joint.[48] Similar to gout, acute pseudogout flares can be associated with fever and chills. Attacks can be precipitated by minor trauma or intercurrent conditions such as surgery, pregnancy, pneumonia, myocardial infarction, and cerebrovascular accidents.[48]

Diagnostic Tests. X-rays often show intra-articular calcifications called chondrocalcinosis, which appear as punctate or linear calcifications in fibrocartilage and hyaline cartilage.[11] Radiographs may show calcification of the knee menisci, triangular ligament of the wrist, and in the cartilage.[11] (*See Figure 3.*) Laboratory blood work generally is not useful.

Arthrocentesis confirms the diagnosis of pseudogout. The typical jWBC level ranges from 10,000-20,000 cells/mm^3.[11] Any abnormally elevated level should increase suspicion for another process, specifically septic arthritis. Crystal analysis demonstrates CPPD crystals, which are pleomorphic and weakly positive under microscopy light.

Treatment. Treatment is similar to that for gout. Joint aspiration often relieves the pain. NSAIDs and steroids are the mainstays of

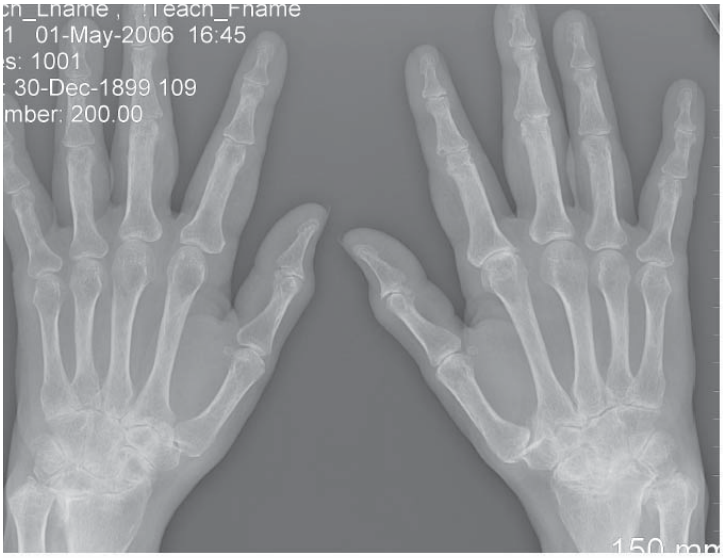
Table 6: Diagnostic Criteria for Rheumatoid Arthritis[25]

Must meet at least 4 of the 7 criteria for the diagnosis for rheumatoid arthritis:

- Morning stiffness at least 1 hr before maximal improvement
- Soft-tissue swelling of three or more joints
- Swelling of proximal interphalangeal joints, MCP, or wrist joint
- Symmetric swelling
- Rheumatoid nodules (subcutaneous nodules, over bony prominences, or extensor surfaces, or in periarticular surfaces)
- Presence of rheumatoid factor
- Radiographic erosions or periarticular osteopenia in hands or wrist joints

Criteria 1-4 must be present over 6 weeks.

Figure 4: Erosive Arthritic Changes



Radiographic study of bilateral hands of a 63-year-old female demonstrates advanced periarticular osteoporosis, erosive arthritic changes of the proximal interpharyngeal joints of the left middle, right ring, and right middle fingers. There is also significant destruction of the radiocarpal joint, particularly on the right. Courtesy of Bassett Healthcare.

pharmacologic treatment. Colchicine can be useful but is rarely necessary; its effectiveness is less predictable in pseudogout than in gout.[47]

Case 2 Revisited. Synovial fluid analysis shows no evidence of infection, and suspicion for septic arthritis is extremely low. The patient has contraindications to NSAID use given his underlying chronic kidney disease, so he is treated with 8 mg of intra-articular triamcinolone and discharged.

Case 3. A 52-year-old female with chronic knee, wrist, and hand stiffness and pain presents with increased left knee pain for the past 3 days. The pain and swelling have been gradual in onset. Her pain is worse in the morning and improves throughout the day. She previously tested positive for rheumatoid factor. She denies any fever or trauma.

On examination, the patient is afebrile and nontoxic. The left knee is warm and tender with a palpable effusion. The wrists exhibit mild swelling bilaterally, and the hands are swollen and red at metacarpophalangeal joints. The CBC is normal; ESR and CRP are slightly elevated. X-rays of the left knee reveal joint effusion, periarticular osteopenia, and erosions. An arthrocentesis reveals cloudy fluid with jWBC 5,000 cells/mm^3. The Gram stain is negative, and the cultures are pending. There are no crystals on microscopy.

Rheumatoid Arthritis (RA)

Epidemiology. RA is the most common inflammatory arthritis,[26] affecting approximately 1% of the general population.[11,26] There is a four-fold increase in the incidence in those older than age 50, and it is 2-3 times more common in women.[12] RA is associated with high levels of morbidity and shortened life span.[26,49] Those afflicted are at greater risk for cardiovascular diseases, infection, cancer and lymphoproliferative malignancies, and renal disease.[49] There has been a strong association between septic arthritis and RA. Septic arthritis can precede rheumatoid arthritis; however, it is unclear whether there is a causal relationship.[26]

Pathophysiology. RA is primarily an inflammation of the synovium. A proliferation of synovial cells leads to increased growth of the surrounding vasculature, causing increased tissue volume and edema. The inflammatory process produces cytokines and proteases that ultimately destroy the joint.

Clinical Presentation. RA is a systemic disease. Patients often present with fever, weight loss, or fatigue.[50] They may have complaints of joint pain or swelling in multiple joints, which have been present for weeks or months. Swelling and pain are almost always symmetric. If they are not, consider alternative diagnoses such as gout or septic arthritis.[11]

Diagnostic Tests. The diagnosis of RA is based on clinical findings, radiologic findings, and laboratory tests. Patients must meet four of the

six criteria outlined by the American College of Rheumatology in Table 6. Laboratory tests are not useful for diagnosing RA in the emergency department. Rheumatoid factor is not specific and may be positive in septic arthritis, lupus, Sjögren's syndrome, and even in normal patients.[25,51] Radiographs typically show periarticular osteopenia in the hands or wrists. Over time, periarticular bony erosions and symmetrical joint space narrowing develop.[50] Arthrocentesis is performed when patients present with pain out of proportion to their typical exacerbations.[25] Synovial fluid aspirated from rheumatic joints typically is translucent and the jWBC is between 2,000 and 10,000 cells/mm^3 with > 50% PMNs.[20] The fluid should not contain crystals and bacteria.[20]

Treatment. The goal of treating an RA flare is to reduce pain, prevent progression of disease, and maintain joint function. Non-selective NSAIDs and COX-2 inhibitors are useful for their anti-inflammatory and analgesic effects.[52] The use of COX-2 inhibitors can reduce GI bleeding but must be balanced against the increasing risk of cardiovascular events.[32]

Joint aspiration is an effective way to immediately reduce pain and improve joint function. Intra-articular corticosteroid injection can improve symptoms within 24 hours and may provide benefit for more than 2 months.[4] Cortisol should not be injected into any joint when there is a suspicion of septic arthritis. If adequate pain relief is accomplished, the patient can be discharged and referred to his or her rheumatologist. Chronic treatment with methotrexate, sulfasalazine, hydroxychloroquine, and/or anticytokine medications such as infliximab, etanercept, and anakira can be effective but require close evaluation.[11]

Case 3 Revisited. The patient has immediate improvement of pain after joint aspiration. The patient's pain is controlled with NSAIDs, and she is discharged to follow up with her rheumatologist.

Summary

Acute joint pain has many causes. Septic arthritis should be considered in all patients with acute joint pain. Arthrocentesis should be performed whenever septic arthritis is a concern. Early diagnosis and management is important in all forms of acute arthritis to slow the progression of disease and preserve joint function.

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Physician CME Questions

32. A patient presents with a typical gout attack. He has a history of renal failure and gastrointestinal bleeding. Which is the most appropriate treatment?
    A. allopurinol
    B. IV toradol
    C. IV morphine
    D. intra-articular triamcinolone

33. Septic arthritis is most commonly caused by which of the following?
    A. *E. coli*
    B. TB
    C. anaerobic bacteria
    D. *S. aureus*

34. A patient with history of intravenous drug abuse presents with pain and redness over his sternoclavicular joint. What is the most appropriate treatment?
    A. IV antibiotics
    B. cold compresses
    C. NSAIDs
    D. oral prednisone

35. A 50-year-old patient with a history of right knee replacement presents with erythema and pain in the right knee. What is the most appropriate next step in treatment?
    A. Discharge the patient on antibiotics with outpatient orthopedic follow-up.
    B. Perform arthrocentesis of the joint.
    C. Emergently consult orthopedics.
    D. Give IV colchicine.

36. A 19-year-old healthy, sexually active female presents with left knee pain. What is the most likely diagnosis?
    A. gout
    B. rheumatoid arthritis
    C. pseudogout
    D. gonococcal arthritis

37. Which of the following is a risk factor for septic arthritis?
    A. hypertension
    B. rheumatoid arthritis
    C. hyperlipidemia
    D. coronary artery disease

38. Which of the following is most suggestive of pseudogout (CPPD deposition)?
    A. negative birefringent needle-shaped crystals
    B. pleiomorphic and weakly positive birefringent crystals
    C. hypercalcemia
    D. hyperphosphatemia

39. Which of the following is most useful in reducing acute gout-related pain?
    A. warm compresses
    B. cold compresses
    C. increasing physical activity
    D. splinting the affected joint

40. Which of the following populations has the highest incidence of rheumatoid arthritis?
    A. prepubescent men
    B. prepubescent women
    C. post-menopausal women
    D. geriatric men

41. Which of the following is the best test to confirm the diagnosis of septic arthritis?
    A. ESR
    B. CRP
    C. radiograph
    D. joint aspiration with Gram stain and culture

CME Answer Key

32. D; 33. D; 34. A; 35. C; 36. D; 37. B; 38. B; 39. B; 40. C; 41. D

In Future Issues

Dementia Screening and Treatment

Primary Care Reports

CME Objectives

Upon completion of this activity, participants should be able to:

- summarize recent, significant studies related to the practice of primary care medicine;
- evaluated the credibility of published data and recommendations related to primary care medicine;
- discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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4. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.	○	○	○	○	○	○
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Zinc and vitamin C for pressure ulcers?

Source: Jamshed N, Schneider JI. Is the use of supplemental vitamin C and zinc for the prevention and treatment of pressure ulcers evidence-based? *Annals of Long-Term Care: Clinical Care and Aging* 2010;18:28-32.

ELDERLY PATIENTS, PARTICULARLY THOSE residing in nursing homes, are at risk for pressure ulcers (PrU) with recent reviews indicating a nursing home prevalence approximating 10%. Prevention and treatment of PrU commonly includes zinc and vitamin C (Z&C), based upon observations (animal studies) that both are necessary for optimum wound healing. Additional support for this concept comes from recognition of the sometimes marginal nutritional status of senior citizens. Some studies have shown malnutrition to result in an increase risk for PrU by as much as two-fold, but other studies disagree.

For vitamin C, a study performed in the 1970s reported increased wound healing, but the study only contained 20 patients, and subsequent trials have not been able to consistently show similar improvements.

For zinc, one study of senior citizens (n = 672) showed a small but statistically significant difference favoring supplementation, but study design and confounding issues preclude a final word on the subject. Overall, studies have been infrequent, small, and unable to provide a definitive conclusion.

Although generally considered safe, zinc and vitamin C do have associated adverse effect profiles, including increased risk of oxalic acid stones (vitamin C) and copper deficiency (high-dose zinc).

Based upon their literature review, the authors conclude that supplementation of Z&C above recommended dietary intake is not supported, and could have important adverse effects.

Dutasteride reduces prostate cancer risk

Source: Andriole GL, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-1202.

THE PROSTATE CANCER PREVENTION TRIAL did not ignite advocacy among clinicians for chemoprevention of prostate cancer (PCA). Although this large trial showed an overall reduction in total cancers (about 23%), high-grade tumors were actually statistically significantly increased. Several reasonable explanations for this phenomenon were offered; however, the disquieting consideration that 5-alpha-reductase inhibitors might be efficacious for reduction of low-grade tumors — but not effective for the more important high Gleason score tumors — remained.

Dutasteride and finasteride are very similar in their effects on the prostate, although there are both pharmacokinetic and pharmacodynamic differences. For instance, dutasteride has a much longer half-life (5 weeks), and dutasteride blocks both arms of the 5-alpha-reductase pathway (types 1 and 2), whereas finasteride only blocks type 2. Because both agents are highly efficacious in reducing intraprostatic levels of dihydrotestosterone, the putative culprit in generating BPH and possibly related to development of PCA, many experts consider them clinically comparable.

The REDUCE Trial (Reduction by Dutasteride of Prostate Cancer Events) enrolled men age 50-75 with a PSA of 2.5-10 ng/mL with negative prostate biopsy at baseline. Subjects were randomized to dutasteride 0.5 mg/day or placebo and followed for 4 years, receiving biopsies at year 2 and year 4.

At the completion of the trial, dutasteride was associated with an overall PCA relative risk reduction of 23%; encouragingly, this trial did not show a statistically significantly increased risk of high Gleason score tumors. Because dutasteride also provides favorable symptom benefits for BPH, clinicians may want to re-examine the balance of risks and benefits of 5-alpha-reductase inhibitors.

New short-course topical treatment for actinic keratoses

Source: Swanson N, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010;62: 582-590.

ACTINIC KERATOSES (AKS) RECENTLY HAVE been recognized as both a cosmetic and a dermatopathologic problem, since they are precursors to squamous cell carcinoma. Indeed, current literature suggests that AKs be considered squamous cell carcinoma in situ. AKs treatment includes cryotherapy, excision, chemical destruction (e.g., 5-fluorouracil, diclofenac), immune activation (imiquimod [IMQ]), and others. Because topical treatment courses

are sometimes protracted, and induce unpleasant cutaneous inflammatory changes, clinicians desire simpler, gentler methods.

Swanson et al randomized patients with AKs on the face and scalp to IMQ or placebo (n = 479). IMQ was applied as pulse therapy: qd for 2 weeks, then no treatment for 2 weeks, then repeat (total = 14 days of treatment). Outcomes were measured at 8 weeks.

IMQ produced a 72%-82% reduction in AKs lesions; higher doses produced complete clearing in 59% (vs 6% with placebo). A companion article in the same journal showed similar clearance rates for a longer regimen (3-week treatment courses). This simpler regimen was well tolerated, and provides a quick and effective route for topical treatment of AKs.

After bariatric surgery: The role of exercise

Source: Evans RK. Maintaining weight loss momentum after bariatric surgery. *Am J Lifestyle Med* 2010;4:124-127.

Bariatric surgery is increasingly recognized as a rational therapeutic option for morbid obesity and obese patients with comorbidities such as diabetes. On average, bariatric surgery produces a 35% reduction in body weight, but patients regain varying amounts of weight over time. Studies of the role of diet after bariatric surgery have helped to direct long-term postoperative dietary management, but less information is available to guide exercise advice.

In the period after postoperative weight-loss stabilization, the weekly amount of exercise does correlate with sustained weight loss. Unfortunately, 37%-51% of postoperative subjects have been found to be noncompliant with exercise recommendations. Curiously, adherence to exercise in some trial data was greater before surgery than afterward, as if subjects felt they no longer needed exercise to the same degree now that surgery had been performed.

Bariatric surgery does not completely and permanently resolve weight-management issues in obese subjects. The high frequency with which post-surgical patients are noncompliant with exercise recommendations, with anticipated weight gain consequences, should spur clinicians to bolster patient education.

What aspect of HTN produces toxicity?

Source: Rothwell PM, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895-905.

A well-established body of epidemiologic literature supports a continuous graded risk between systolic blood pressure (SBP) and CV risk. This relationship has held constant whether one considers office BP, home BP, or ambulatory blood pressure monitoring (ABPM). Because BP is variable over time, it is unclear whether the toxicity of BP to the vasculature is more strongly associated with mean BP, maximum BP, pulse pressure (SBP − DBP), or BP variability. Circadian rhythm of BP has also been recognized to be particularly associated with adverse outcomes: ABPM subjects whose BP does not decline overnight (called non-dippers) have greatly increased CV risk, well beyond what would be expected simply by having a greater total number of hours of exposure to elevated BP.

Rothwell et al used a data set comprised of persons who had sustained a TIA in large clinical trials (n = 2006), including the UK TIA Trial and ASCOT. Visit-to-visit BP variability and maximum SBP were better predictors of adverse outcome than mean SBP. Similarly, persons with episodic HTN (normal BP on some occasions, elevated on others) were also at increased stroke risk, surpassing risk for stable BP.

It remains to be elucidated why these subgroups of individuals with BP variability have a greater risk burden. Although the associations between maximum SBP, BP variability, and episodic BP elevations were consistent, this does not establish causation. Perhaps the strongest cautionary message from this trial is that clinicians should not fall prey to false reassurance when they see a mixed BP response pattern including some BP measurements at goal and others elevated; such episodic elevations are consequential.

Depression and sleep disturbance

Source: Van Mill JG, et al. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. *J Clin Psychiatry* 2010;71:239-246.

Both anxiety and depression disorders have a strong association with sleep disturbance. The association between sleep and depression is bidirectional: Depression is often manifest by or leads to sleep disturbance, and persistent insomnia increases risk of depression.

Van Mill et al sought to elucidate further the relationship between sleep disorders and depression by analyzing subjects in the Netherlands Study of Depression and Anxiety cohort (n = 2619).

In this population of subjects (approximately three-fourths suffered from depression and/or anxiety), almost half scored at least 9 on the Insomnia Rating Scale (IRS; the same metric that was employed in the Women's Health Initiative), fulfilling criteria for clinically significant insomnia. Insomnia scores were related to both anxiety and depression, but worse for depression, and highest for comorbid depression and anxiety. Interestingly, even persons with depression or anxiety in remission had elevated scores on the IRS. The authors suggest that, based upon their data, inquiry into sleep status is valuable not only during both depression and anxiety, but even during periods of remission.

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Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.