Clinical basics

Rheumatology: 4. Acute monoarthritis

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The case

Mrs. R, a 72-year-old woman with a history of osteoarthritis of the knees, consults her physician because she has a fever, malaise and a swollen, painful right knee. She is unable to bear weight on her right leg because of the pain. Two years earlier she experienced gastrointestinal bleeding while taking nonsteroidal anti-inflammatory drugs for osteoarthritis; currently, she is taking only acetaminophen as needed for pain. Mrs. R is otherwise healthy and has not travelled recently. During examination the physician finds that Mrs. R is slightly confused. Her pulse rate is 80 beats/min and regular; her blood pressure is normal, and her temperature is 37.9°C. Her right knee is warm, erythematous, swollen and tender. Flexion ranges from 10° to 80° with pain. Her leukocyte count is above normal at 14.8×10^9 cells/L (normal range: 4–11 $\times$ 10^9 cells/L). Her serum uric acid level, measured at an earlier office visit, was slightly above normal at 450 μmol/L (normal range: 90–360 μmol/L).

Acute monoarthritis is a potential medical emergency that must be investigated and treated promptly. Common diagnoses include crystal-induced arthritis and mechanical complications of osteoarthritis, fractures and ligamentous or meniscal injury; less common causes are ischemic necrosis (osteonecrosis), hemarthrosis or tumour. However, first and foremost, acute monoarthritis should be considered septic until proven otherwise.

An accurate diagnosis of acute monoarthritis depends on a good history and physical examination that are supplemented by the appropriate investigations. In particular, the physician must verify that the patient has arthritis, as manifested by joint swelling, and that the arthritis is limited to a single joint.[1,2] Determining whether the arthritis is inflammatory or mechanical in nature and whether the disease is acute or chronic will then help the physician arrive at a presumptive diagnosis.

Investigations should include joint aspiration of synovial fluid for a leukocyte count, Gram's stain, cultures and an examination for crystals; radiographs of the joint may also be required. Occasionally, a radionuclide scan, computed tomography (CT) or magnetic resonance imaging (MRI) is useful. Treatment is based on the underlying diagnosis, but antibiotics are sometimes required until septic arthritis is excluded.

If acute monoarthritis is apparent from the history and physical examination the most common differential diagnoses are infectious arthritis, crystal-induced arthritis and trauma-induced arthritis[3] (Fig. 1); these can be differentiated by history, physical examination and synovial fluid analysis[4] (Table 1).

Causes

Infectious arthritis

Acute monoarthritis should be considered infectious until proven otherwise.[5–7] Septic arthritis is usually caused by an infectious agent that is spread through the blood system. It often affects the knee and is characterized by systemic symptoms of sepsis (e.g., fever and malaise), as well as swelling, warmth and local pain in the involved joint, sometimes so severe that the patient refuses to allow even passive movement. Redness around the joint is an important clue, limiting diagnosis to either infectious or crystal-induced arthritis.

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Review

Synthèse

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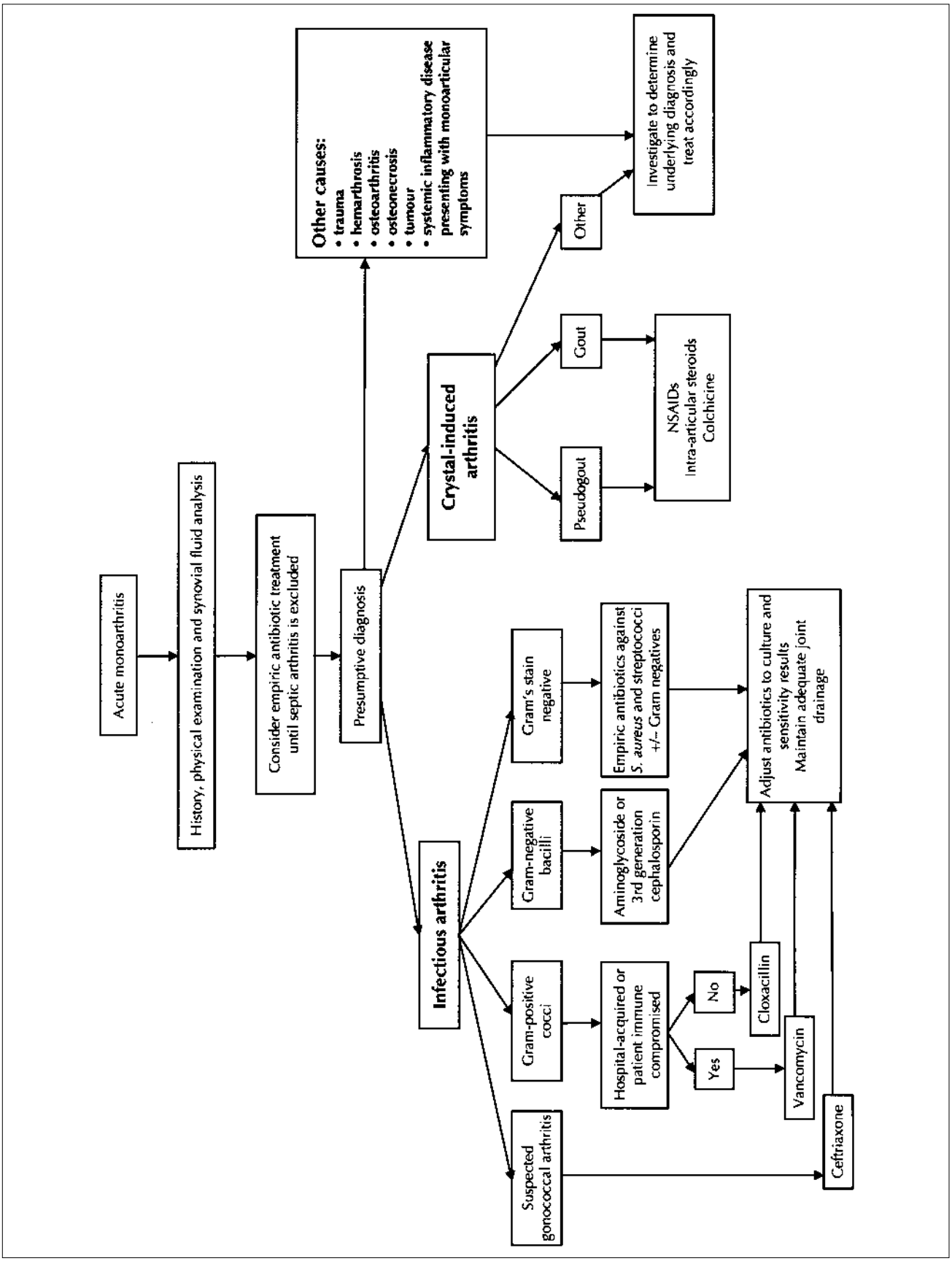

Fig. 1: The diagnosis and management of acute monoarthritis.[7,21,30]

The inflammatory response may be blunted in immunocompromised patients (such as those taking immunosuppressants); patients with rheumatoid arthritis, diabetes mellitus or HIV; intravenous drug users and those with prosthetic joints. However, suspicion of infectious arthritis in these patients should be maintained, despite limited physical signs, until infection has been excluded.

Staphylococcus aureus causes most nongonococcal cases of septic arthritis in adults.[5–8] However, gonococcal infections are the most common cause of septic arthritis in sexually active young adults.[9,10] These cases are often characterized by migratory arthritis and associated with tenosynovitis and maculopapulovesicular skin lesions before manifesting as a monoarthritis.

Although arthritides caused by mycobacteria and fungi are usually chronic in nature, they can also resemble acute monoarthritis. If the patient's history suggests prior tuberculosis, recent exposure to tuberculosis or an immunodepressed state, mycobacterial or fungal arthritis should be considered.

Viruses such as hepatitis B, HIV and human parvovirus and the spirochete *Borrelia burgdorferi*, which causes Lyme disease, rarely cause acute monoarthritis; they more commonly manifest as acute or chronic oligoarthritis.

Crystal-induced arthritis

Crystal-induced arthritis is another main cause of acute monoarthritis. Gout, which is caused by monosodium urate crystals in the synovial fluid, can give rise to acute arthritis in any joint, but predominantly affects the first metatarsophalangeal joints, midfoot, ankles or knees. Pseudogout, caused by calcium pyrophosphate dihydrate crystal deposition, affects mainly the knees and wrists, but can occur in the first metatarsophalangeal and other joints as well.

An important clue in the diagnosis of crystal-induced arthritis is a history of acute attacks of monoarthritis that resolved spontaneously. Crystal-induced arthritis is characterized by redness around the joint, and it can present with fever, mimicking infectious arthritis. With gout the pain is often so severe that patients complain of an inability to tolerate the weight of a light bed sheet on the involved joint.

Tophi — deposits of urate crystals — in soft tissues is highly suggestive of chronic gout. Tophi appear as soft, subcutaneous nodules usually on fingers and toes, around the elbows and, classically, on the helix of the ear. They can be differentiated from rheumatoid nodules by their asymmetric distribution, yellow–white appearance and occasional overlying skin erythema.

Noninflammatory monoarthritis

Trauma causing fractures (or microfractures), as well as ligamentous or meniscal injuries, can lead to acute monoarthritis. It is often associated with mild-to-moderate joint swelling, and the pain is characteristically exacerbated on movement and relieved at rest. Although a history of trauma is usually evident, this may not be the case for patients with osteoporosis. The pain of traumatic arthritis is felt within seconds to minutes of the trauma, in contrast to

Table 1: Differential diagnosis of acute monoarthritis[3,4]

Possible diagnosis	Cause	History and physical examination	Synovial fluid analysis	Common pitfalls
Infectious arthritis	Bacteria Mycobacteria Fungi Spirochetes causing Lyme disease Viruses (e.g., HIV, hepatitis B)	Severe joint pain and tenderness Heat, marked swelling Redness Patient unable to move joint; often refuses passive movement Patient unable to bear weight	Opaque Leukocyte count elevated (often > 100×10^9/L) PMNs > 85% Culture positive	Inflammatory response may be blunted in immunocompromised patient Culture may be negative if patient previously treated with antibiotics
Crystal-induced arthritis	Monosodium urate crystals (gout) Calcium pyrophosphate dihydrate crystals (pseudogout) Apatite crystals Calcium oxalate crystals	Severe joint pain and tenderness Heat, marked swelling Redness Patient unable to move joint and often refuses passive movement Patient often unable to tolerate any pressure on joint	Translucent Leukocyte count $1–75 \times 10^9$/L Often > 50% PMNs Culture negative Crystals positive	Patient may have concomitant infectious arthritis with positive culture
Trauma-induced arthritis	Fracture Internal derangement Hemarthrosis	Joint tenderness on movement Warmth, mild-to-moderate swelling No redness Pain worse with activity History of trauma; onset of pain within minutes of trauma	Fluid transparent or blood stained Leukocyte count < 1×10^9/L	History of trauma may not be elicited with osteoporosis

HIV = human immunodeficiency virus, PMN = polymorphonuclear leukocyte.

the pain of infectious and crystal-induced arthritis which often develops over hours. Acute hemarthrosis (bleeding into a joint) should be suspected in patients with bleeding disorders and in those taking anticoagulants.

Other noninflammatory causes of monoarthritis include osteoarthritis and osteonecrosis. Osteoarthritis occurs mostly in elderly patients, is usually chronic and is characterized by pain with activity. Joint swelling is minimal but can be present when an acute exacerbation of pain occurs. Osteonecrosis, also called avascular or ischemic necrosis, results from bone death secondary to an impaired blood supply.[11–13] The femoral head is commonly involved, leading to hip-joint arthritis, but any other joint can be affected. Symptoms include pain, especially when bearing weight, limping and the eventual restricted movement of the involved joint. Osteonecrosis should be considered in young people with risk factors such as corticosteroid use, hemoglobinopathies or sickle cell disease, as well as in alcoholic and elderly diabetic patients.

Key points

- Acute monoarthritis should be considered infectious until proven otherwise.
- A red joint can indicate infectious arthritis or crystal-induced arthritis.
- A history of acute attacks of monoarthritis that resolve spontaneously is indicative of crystal-induced arthritis.
- Patients with crystal-induced arthritis can also present with fever, mimicking infectious arthritis.

Tumour-associated monoarthritis is rare in adults but should be suspected in patients with chronic, progressive monoarthritis with no clear underlying diagnosis.

A popliteal or Baker's cyst — a swelling behind the knee caused by escape of synovial fluid — can occur with septic arthritis, chronic inflammatory arthritis, osteoarthritis or arthritis associated with internal derangement. The prevalence of popliteal cysts ranges from 4.7% among orthopedic patient populations[14] to 47.5% among patients with rheumatoid arthritis.[15] The prevalence of cysts among patients with septic arthritis is unknown. Because of the correlation between popliteal cysts and knee-joint effusions,[16] it is thought that cysts may develop as a result of a persistent knee effusion. A 1-way valve prevents popliteal cyst fluid from returning to the knee joint, and the increasing pressure may cause the cyst to rupture. When this occurs the associated pain and swelling in the calf mimics deep venous thrombosis, which is often wrongly diagnosed and treated. A crescentic hematoma below the medial or lateral malleoli of the ankle supports a diagnosis of a ruptured popliteal cyst; however, the best clue is sudden onset of calf pain.

Diagnosis

Joint aspiration and analysis of synovial fluid

Arthrocentesis is mandatory if infectious arthritis is even considered[17] and is also usually required for the diagnosis of crystal-induced arthritis and hemarthrosis. Joint aspiration and the synovial fluid leukocyte count may also be helpful in differentiating inflammatory from noninflammatory arthritis. Therapeutic indications for joint aspiration include draining of a tense effusion to relieve pain and improve function, as well as draining of pus or blood to avoid permanent joint damage.[17] Synovial fluid analysis should include a cell count and differential leukocyte count, Gram's staining, culture and an examination for crystals. If Gram's staining is not immediately available a request for the procedure should be made, at least for patients with high leukocyte counts.

The leukocyte count in the synovial fluid is helpful in distinguishing inflammatory from noninflammatory conditions but is not helpful to differentiate between the various causes of inflammatory monoarthritis.[4] Inflammatory arthritis is characterized by a synovial fluid leukocyte count > 1×10^9 cells/L; the leukocyte count will be lower in a noninflammatory arthritis. Although septic arthritis should be suspected if the leukocyte count is > 100×10^9 cells/L, it may be lower. A polymorphonuclear (PMN) cell count > 85% suggests infectious or crystal-induced arthritis. A predominant mononuclear infiltrate occurs with chronic infections and chronic inflammation.

Synovial fluid should be examined for crystals using a polarized light microscope. Monosodium urate crystals are needle-shaped and strongly negatively birefringent under polarized light; calcium pyrophosphate dihydrate crystals are rhomboid or rod shaped, only weakly birefringent and, therefore, more difficult to see. An examination of synovial fluid for crystals (especially calcium pyrophosphate dihydrate crystals) should be done promptly because crystals can dissolve when synovial fluid is stored. In addition, if the analysis is not performed by an experienced examiner, it may be falsely reported as negative. Other pathogenic crystals such as calcium apatite crystals can be identified with certainty only under an electron microscope; under a light microscope they appear as debris. A positive alizarin red stain will confirm that this debris contains calcium crystals, although the stain is not specific for calcium apatite crystals. Acute monoarthritis is likely crystal-induced if microscopy reveals crystals not only in the synovial fluid but also intracellularly. However, the presence of intracellular crystals does not exclude infection. If infection is suspected synovial fluid cultures are still necessary.

Gram's staining and culture may be falsely negative if the patient has been taking antibiotics. However, joint aspiration may still reveal the causative organism and should be performed.

If nongonococcal infection is suspected, blood and urine samples should be obtained for culture. For gonococcal in-

fection, in addition to blood and urine cultures, cervical, urethral, rectal and pharyngeal cultures are necessary.

Blood in synovial fluid may result from a traumatic tap or a true hemarthrosis. With true hemarthrosis the synovial fluid is uniformly red and the supernatant is yellow–brown (xanthochromic), whereas with a traumatic tap the synovial fluid is less uniformly red and often contains streaks of clotted blood.

Synovial biopsy

A synovial biopsy may be indicated if the diagnosis is unclear after initial investigations. Synovial biopsy is usually diagnostic in monoarthritis infections caused by *Mycobacteria*, *Neisseria* and *Chlamydia* spp. and infiltrative diseases such as sarcoidosis, amyloidosis and malignancies. Therefore, synovial biopsy specimens should be sent not only for pathologic evaluation but for mycobacterial, neisserial and chlamydial culture as well.[4]

Key points

- Arthrocentesis is mandatory if infectious arthritis is suspected.
- Synovial fluid analysis should include a cell count and differential leukocyte count, Gram's staining, culture and an examination for crystals.
- Synovial fluid should be examined for crystals promptly.
- If infectious arthritis is suspected a plain radiograph of the joint should be obtained to diagnose concomitant osteomyelitis and to monitor ongoing treatment.

Radiologic investigations

Although plain radiographs are not always necessary in the investigation of acute monoarthritis they can be helpful to establish the diagnosis of monoarthritis and provide a baseline for follow-up (Table 2).[1,18–20] If infectious arthritis is suspected a plain radiograph of the joint should be obtained to diagnose a concomitant osteomyelitis and to provide a baseline from which to monitor treatment.[21] A patient with septic arthritis who does not respond to antibiotic treatment (i.e., with less joint pain and swelling and greater range of motion) in 5–7 days or who has persistent positive synovial fluid cultures should undergo radiographic evaluation for osteomyelitis with repeat plain radiographs; if plain radiography is inconclusive radionuclide scan, CT or MRI may be required.[5,18–20,22]

Chondrocalcinosis on plain radiographs supports the diagnosis of calcium pyrophosphate deposition disease. However, septic arthritis must still be ruled out. If acute gout is confirmed by synovial fluid analysis radiographic evaluation is not necessary, but if a patient has chronic tophaceous gout the plain radiograph may show typical joint erosions with sclerotic margins and overhanging edges.

Other indications for plain radiographs are suspected fractures and bony lesions, such as primary or metastatic malignancy, and any other cause of acute monoarthritis that eludes diagnosis.[1] If plain radiographs are inconclusive CT is used to evaluate bony lesions,[19,22] and MRI is the method of choice for diagnosing early osteonecrosis and soft-tissue injury.[11–13,20,22] Popliteal cysts are best identified and differentiated from deep venous thrombosis with duplex ultrasonography.[15,23]

Management

Infectious arthritis

Confirmed bacterial arthritis should be treated with prompt antibiotic therapy and repeat joint drainage to minimize joint destruction. The choice of antibiotic is based on risk factors, such as the patient's age and immunocompetence, whether the infection was hospital acquired, as well

Table 2: Indications for radiographic evaluations[1,18–20]

Diagnosis	Plain radiograph	Radionuclide scans	CT or MRI
Infectious arthritis	Required	Useful if osteomyelitis is suspected	Useful if osteomyelitis is suspected
Pseudogout	Not required but helpful	Not indicated	Not indicated
Gout	Not required but helpful in chronic tophaceous gout	Not indicated	Not indicated
Fractures	Required	Usually not necessary	CT useful to define extent of fracture
Osteonecrosis	Only helpful in advanced disease	May be helpful	MRI is method of choice
Osteoarthritis	Helpful	Not indicated	Not indicated
Ligamentous or meniscal injuries	Not helpful but necessary to rule out other trauma	Not indicated	MRI is method of choice

Note: CT = computed tomography, MRI = magnetic resonance imaging.

Table 3: Indications for allopurinol therapy in patients with hyperuricemia and gout[31]

- Uric acid nephropathy
- Nephrolithiasis
- Tophaceous gout
- Severe gout with renal insufficiency
- Frequent recurrent attacks of gout causing disability
- Hypoxanthine-guanine-phosphoribosyltransferase deficiency
- Pyrophosphate-ribose-phosphate synthetase overactivity

as the results of Gram's staining, if available (Fig. 1).[7] If nongonococcal arthritis is suspected antibiotics against *S. aureus* and streptococci should be used; in the immunocompromised patient Gram-negative and anaerobic bacteria should also be targeted.[3,7,8] All antibiotics should be given intravenously. Although the duration of treatment depends on the patient's response, generally, intravenous antibiotics should be continued for at least 2 weeks and followed by 2–4 weeks of oral antibiotics.[21]

Suspected gonococcal arthritis is treated with ceftriaxone (1 g/day, intramuscularly or intravenously). If the organism is reported to be sensitive to penicillin, either ampicillin (1 g every 6 h, intravenously) or penicillin G (10 million U daily in divided doses, intravenously) should be given. Parenteral therapy should be maintained until there is clinical improvement of skin and joints (usually 2–4 days) and followed by oral antibiotics to complete a 7-day treatment.[9]

Infectious joint effusions require drainage to minimize joint destruction. Joint effusions tend to reaccumulate rapidly, particularly in nongonococcal arthritis and, therefore, must be aspirated at least daily.[3] Joints that are easily accessible can be drained by needle aspiration, and the synovial fluid aspirate should be sent for serial leukocyte counts and cultures.[5] The leukocyte count is an indicator of the patient's progress and should gradually decrease with antibiotic treatment. Similarly, culture results should be negative after a few days of antibiotic treatment, and cultures can then be discontinued unless clinically indicated. Arthroscopic or open drainage is indicated for patients with underlying joint pathology, for joints that are difficult to aspirate and for patients who have a poor response to antibiotics.[5]

The treatment of a popliteal cyst requires the treatment of the underlying knee effusion. In septic knee arthritis repeated knee aspiration prevents an increase in joint pressure and a further accumulation of fluid in the cyst. Intraarticular injection of corticosteroids will reduce inflammation and, therefore, joint effusion, but this should only be done after septic arthritis has been eradicated or excluded.

Key points

- Bacterial arthritis should be treated promptly with antibiotics (after all cultures have been obtained), and the joint should be drained to minimize joint destruction.
- Arthroscopic or open drainage is indicated in patients with underlying joint pathology, in those whose joints are difficult to aspirate and in patients who have a poor response to antibiotics.
- Treatment of a popliteal cyst involves treating the underlying knee pathology.
- Acute crystal-induced arthritis is treated with NSAIDs, corticosteroids or, rarely, colchicine.
- When allopurinol is initiated, it is essential to prescribe low-dose NSAIDs or colchicine concurrently to prevent acute attacks of gout.

Crystal-induced arthritis

Acute crystal-induced arthritis can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids or, rarely, colchicine.[24] The sooner the drug therapy is initiated, the quicker the patient will respond. NSAIDs are used as first-line agents because they are usually well tolerated and easy to administer; they are given at high doses and tapered over 5–10 days. NSAIDs should be avoided or used cautiously in patients with renal dysfunction and those at high risk for gastrointestinal bleeding (e.g., elderly patients, patients with peptic ulcer disease and those taking anticoagulants or corticosteroids).[25–27] They should also be used cautiously in patients with congestive heart failure, because of the risk of exacerbating fluid overload, and in those with any cardiovascular disease that may impair ability to cope with acute blood loss.[27]

If NSAIDs are contraindicated corticosteroids are a safe alternative. The most convenient route of administration is intraarticular, but a short course of oral prednisone can be given at a dosage of 30–50 mg daily, tapered rapidly over 5–10 days.[28] Rarely, parenteral corticosteroids are necessary. Single-dose intramuscular adrenocorticotropic hormone is also effective,[29] although corticosteroids are generally preferred. Oral colchicine is used infrequently now because of its toxicity, especially in the elderly. Management of acute crystal-induced arthritis in elderly or debilitated patients sometimes requires a brief hospital stay for systemic symptoms suggesting sepsis.[30]

The long-term management of gout involves treating hyperuricemia through risk modification and, once the acute episode of gout has been well controlled, drug therapy. Allopurinol is the drug of choice — 300 mg daily with dose reduction for renal insufficiency. Indications for allopurinol are shown in Table 3;[31] when it is initiated it is essential to prescribe low-dose NSAIDs or colchicine concurrently to prevent acute attacks of gout. Colchicine prophylaxis consists of 0.6 mg once or twice daily and should be continued until the patient has been attack free for 6 months or until the tophi have lysed. For patients with allopurinol allergy, uricosuric agents such as probenecid or

sulfinpyrazone could be considered if the urinary uric acid excretion is less than 800 mg/day. Alternatively, the patient could undergo allopurinol desensitization.[32]

Treating our patient

Mrs. R's arthritis was presumed to be septic, and she was admitted to hospital for treatment. Fluid from the right knee was aspirated, blood and urine samples were obtained for culture and the patient was started on intravenous cloxacillin and gentamicin. Synovial fluid analysis revealed 45×10^9 leukocytes/L with 93% PMNs; Gram's staining was negative, but intracellular calcium pyrophosphate dihydrate crystals were identified. On the second day all cultures were still negative and a radiograph of the knee showed calcification of the menisci and hyaline cartilage. The diagnosis was changed to acute pseudogout. Antibiotics were stopped and corticosteroids were injected into the affected knee. Mrs. R's symptoms improved quickly, and she was discharged with a referral for outpatient physiotherapy.

Competing interests: None declared.

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