Chapter 15
Crystal Arthritis

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Gout

Gout is the most common crystal arthropathy, with a prevalence of approximately 3.9% in the United States [1]. Overall, gout is significantly more prevalent in men than women (ratio of 4–10:1), although prevalence tends to increase in women after menopause [2]. In both sexes, gout is associated with significant morbidity and mortality [3]. The links between gout and myriad other medical conditions, including cardiovascular disease, metabolic syndrome, renal disease, cancer, and diabetes, are being actively explored.

Risk Factors

Both genetic and environmental factors contribute to the onset of gout. Genome-wide association studies (GWAS) have identified variants in genes encoding urate transporters in the kidney (notably *SLC2A9* and *ABCG2*) and the gut (*ABCG2*) that are thought to contribute to hyperuricemia and therefore increased gout risk [4].

Multiple lifestyle factors are also associated with increased predisposition to gout [5]. A variety of foods and beverages have been associated with increased risk

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for hyperuricemia and gout flares, including alcohol, purine-rich foods such as red meat and shellfish, and fructose-sweetened beverages [6]. In addition, the use of certain medications, including diuretics, low-dose aspirin, cyclosporine, tacrolimus, nicotinic acid, and teriparatide, may promote hyperuricemia and therefore increase the risk for gout [6].

Pathophysiology

The mechanisms of inflammation that lead to acute gout flares center around monosodium urate (MSU) crystal formation and phagocytosis by macrophages, leading to activation of an inflammatory cascade. The sine qua non of MSU crystal formation is hyperuricemia, which results from either excessive production or inadequate excretion of urate, or both. Excessive urate production may be either primary, resulting from genetic aberrancies in enzymes involved in the purine synthesis and/or salvage pathways (e.g., Kelley-Seegmiller syndrome), or secondary, resulting from increased cell turnover, such as in myeloproliferative disorders or tumor lysis syndrome. In the kidney, urate is filtered by the glomerulus and simultaneously resorbed and secreted in the proximal tubule. Primary urate under-excretion may result from inherited defects of renal urate secretory transporters in the setting of otherwise normal renal function (e.g., ABCG2 defects). Among patients with hyperuricemia in the absence of secondary causes, approximately 90% are primary under-excreters, and 10% are primary overproducers [7]. Alternatively, secondary defects in renal uric acid excretion may occur in the setting of chronic kidney disease (i.e., glomerular dysfunction), use of certain medications (see the risk factors section), exposure to lead (saturnine gout), or as a response of the kidney to metabolic abnormalities such as lactic or ketoacidosis [8].

Once MSU crystals have formed and been phagocytosed by local tissue macrophages, they activate intracellular assembly of the NLRP3 inflammasome, a multiprotein complex that triggers the activation of caspase-1, leading to cleavage, activation, and secretion of 1L-1β (as well as IL-18). Secreted 1L-1β binds to IL-1 receptors in an autocrine and paracrine manner, inducing the release of additional pro-inflammatory cytokines, leading to local inflammation and systemic effects such as fever. Thus IL-1β plays a central role in the genesis of gouty inflammation. Among the cytokines secondarily produced in response to 1L-1β are IL-8, IL-17, IL-6, and CXCL8, which promote upregulation of adhesion molecule families of selectins and integrins on the luminal surface of endothelial cells, facilitating neutrophil adherence and recruitment into the synovium [9]. Concurrently MSU crystals have the ability to activate complement, directly stimulating neutrophils, and providing a signal gradient to attract them to the inflammatory site [10].

In addition to triggering the inflammatory response, MSU crystals stimulate negative feedback mechanisms that eventually lead to the resolution of a gout flare. Important mechanisms in inflammation resolution include the formation and release by neutrophils of neutrophil extracellular traps (NETs), structures composed of

DNA and associated proteins. While NETs initially promote further proinflammatory cytokine release, later in the inflammatory process they reverse their role and promote proinflammatory cytokine degradation, ultimately leading to resolution of the acute gout flare [8].

Clinical Presentation

In its early stages, gout is characterized by recurrent episodes of pain and swelling in one or a few joints, occasionally associated with systemic symptoms such as fever. The episodes are self-limited, with symptoms usually peaking in intensity within the first 24 hours after symptom onset, and resolving (even without treatment) after 5–10 days. Among men, at least 50% of initial gout flares occur in the first metatarsophalangeal joints, and 85% of gout flares occur in the lower extremities, although any joint in the body can be affected. Among women, the first MTP is involved less frequently, with the knee being another common site of first gouty flares. Over time, the attacks become more frequent, and smoldering chronic inflammation may persist between attacks [11]. After years of recurrent, untreated gout flares, patients may develop chronic tophaceous gout, characterized by granuloma-like masses composed of complexes of MSU crystals and NETs surrounded by macrophages, multinucleated giant cells, and fibroblasts.

Diagnosis

Making a diagnosis of gout requires the potential integration of clinical, laboratory, and radiographic components. These components are summarized in the 2015 American College of Rheumatology (ACR) gout classification criteria (Table 15.1), which have a reported sensitivity of 92% and specificity of 89% [12]. However, diagnosing gout as a chronic disease state must be distinguished from the diagnosis of an acute gout flare. Even in a patient with an established diagnosis of gout, the occurrence of an acute mono- or polyarticular arthritis requires the consideration of a range of alternative diagnoses, including a joint infection (a rheumatologic emergency), or a flare driven by an alternative type of crystal (see calcium crystals, below). Indeed, the coexistence of a gout flare with either of these other entities is a well-recognized occurrence. Definitive diagnosis of an acute gout flare therefore usually requires the aspiration and examination of synovial fluid, with the gold standard for an acute gout flare being the identification of MSU crystals along with inflammatory cells, mainly neutrophils, in the joint aspirate of a patient with acute arthritis, including evidence that some neutrophils are actively phagocytosing MSU crystals. MSU crystals are needle-shaped and negatively birefringent under polarized microscopy, making them easily recognizable. Even when MSU crystals are present, the possibility of a co-existing alternative etiology requires careful consideration [13].

Table 15.1 2015 ACR classification criteria for gout[a, b]

		Points
Clinical		
Pattern of joint or bursa involvement during past or present symptomatic episodes	Ankle or midfoot without first MTP joint	1
	First MTP joint involved	2
Number of typical characteristics (reported or observed erythema overlying affected joint, can't bear touch or pressure, difficulty walking and inability to use joint)	One characteristic	1
	Two characteristics	2
	Three characteristics	3
Time course of episodes (time to maximal pain <24 hours, resolution of symptoms in <14 days, complete resolution between symptomatic episodes)	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus	Present	4
Laboratory		
Serum urate—ideally not on urate-lowering therapy and at least 4 weeks after the start of an acute flare	<4 mg/dL	−4
	6–8 mg/dL	2
	8–<10 mg/dL	3
	≥10 mg/dL	4
Synovial fluid analysis of symptomatic joint or bursa	MSU negative	−2
Imaging		
Double-contour sign on ultra sound or urate depositoin on dual-energy CT	Present	4
X-rays of hands and/or feet demonstrating at least 1 erosion	Present	4

Adapted from Neogi et al. [12]
[a]Entry criteria: at least one episode of swelling, pain, or tenderness in a peripheral joint or bursa
[b]Presence of MSU crystals in the synovial fluid of a symptomatic joint or bursa, or in a tophus, is sufficient for classification of gout without applying this criteria

Treatment

Treatment of an acute gout attack focuses on reducing the inflammation associated with gout flares, whereas chronic treatment of gout centers around lowering serum urate levels. The ACR offers guidelines for treatment of acute gout attacks, prophylaxis against repeat flares, and therapies for chronic treatment [14, 15] (Fig. 15.1). In the setting of an acute gout flare, patients may be treated with either monotherapy or combination therapy (depending on the severity of the attack and number of joints involved) using non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, colchicine, and/or intra-articular steroid injections. The choice of an anti-inflammatory agent is based on safety (e.g., consideration of patient comorbidities) as well as physician and patient preference. NSAIDs and oral steroids should not be used in combination. When the aforementioned agents are ineffective or contraindicated, biologic agents that block IL-1β activity, most notably anakinra, may be considered, although these are not FDA approved. If the patient is already using urate-lowering agents, these should not be discontinued during the acute flare as the resultant rise in urate may exacerbate the attack.

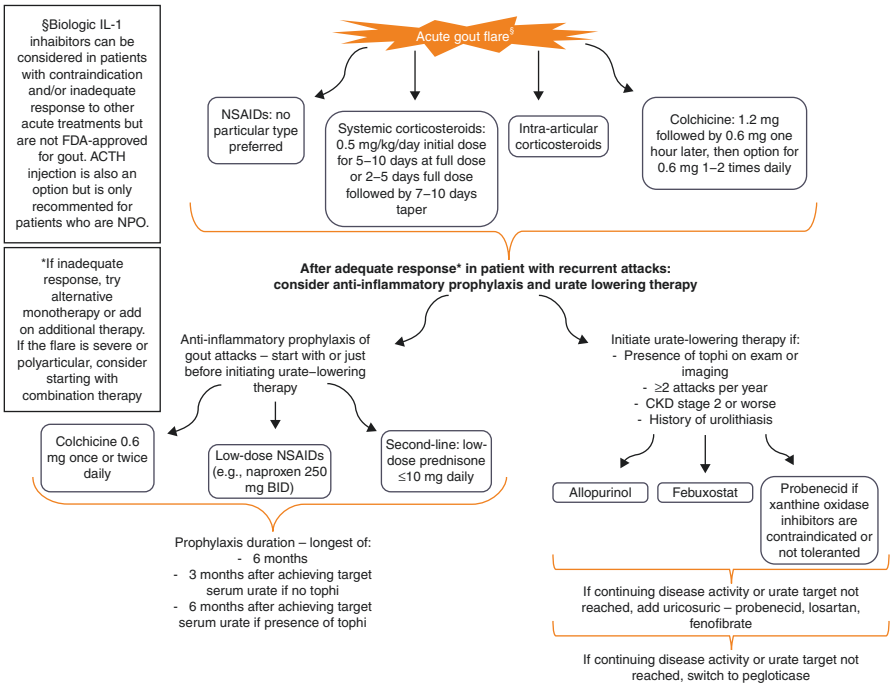

Fig. 15.1 American College of Rheumatology (ACR) guidelines for the management of gout. Summarized here are the ACR guidelines for treating gout, beginning with the management of acute flares and moving on to the indications for, and approaches to urate lowering. (For the complete guidelines, see *Khanna* et al [14, 15])

For patients with frequent attacks (>2/year), or who have had a single attack in the setting of chronic kidney disease or a history of tophi or renal stones, urate-lowering therapy (ULT) should be initiated. First-line options for ULT include the xanthine oxidase inhibitors allopurinol and febuxostat. A choice between these two agents may be made based on cost (allopurinol much cheaper), risk of potentially fatal allopurinol hypersensitivity syndrome (greatest among certain Asian populations who are HLA B58∗01-positive, requiring that these populations be checked for HLA type before starting allopurinol), and recent reports that use of allopurinol may be associated with reduced cardiovascular mortality relative to febuxostat [16]. The target serum urate level should be less than 6.0 mg/dL, or lower in the case of tophaceous gout (typically less than 5.0 mg/dL), or as needed to prevent attacks and resolve tophi. ULT should be started simultaneously with, or just after initiation of anti-inflammatory prophylactic colchicine or a low-dose NSAID (or low-dose steroids as a third-line agent), as ULT initiation has been found to paradoxically increase the risk of gout flares at the onset of therapy [17]. Prophylaxis is typically continued for at least 6–9 months. If both allopurinol and febuxostat are contraindicated or not tolerated by a particular patient, the uricosuric agent probenecid may be started instead. Probenecid or the alternative uricosuric lesinurad (not to be used as

monotherapy) may also be “added on” to xanthine oxidase inhibitor therapy if a patient has had an inadequate response to treatment. Losartan and fenofibrate also have ULT potential and may be added on to a xanthine oxidase inhibitor, particularly if they are also indicated for hypertension or cardiovascular disease. Finally, the highly potent uricase pegloticase may be considered in patients with refractory disease, or with a significant tophus burden.

Calcium Crystal Diseases

Calcium Pyrophosphate Deposition Disease

Calcium pyrophosphate crystal deposition (CPPD) is a broad term used to describe the varying presentations associated with the formation and deposition of calcium pyrophosphate dihydrate (CPP) crystals. In many cases, CPPD is asymptomatic, but in some patients CPPD can provoke an acute inflammatory arthritis. In other cases, patients can develop a more chronic arthritis reminiscent of either osteoarthritis (non-inflammatory) or rheumatoid arthritis (inflammatory). The prevalence of CPPD varies from 7% to 10% in different studies [18]. Of these, a significantly smaller percentage will have symptomatic disease.

Risk Factors

CPPD is idiopathic in most cases, with no apparent underlying condition. However, several factors have been associated with an increased risk for crystal deposition. CPPD risk tends to increase with age, being most common among individuals over 80 years old [18]. Hyperparathyroidism raises the risk of CPPD approximately threefold above that of the general population [19]. Other conditions associated with increased CPPD risk include gout (~2.5 times more likely), osteoarthritis (~2 times more likely), rheumatoid arthritis (~2 times more likely), hemochromatosis (~2 times more likely), hypomagnesemia (~1.25 times more likely), and osteoporosis (~1.25 times more likely) [19]. In contrast, certain medications, including proton pump inhibitors, thiazide diuretics, and loop diuretics, have been associated with a decreased risk of CPPD. Other conditions that have been inversely associated with CPPD include alcohol and tobacco abuse disorders, coronary artery disease, congestive heart failure, diabetes, and hypertension [19].

Pathophysiology

CPP crystals are formed within the cartilage, as a result of the interaction of inorganic pyrophosphate with calcium ions. Inorganic pyrophosphate is a breakdown product of extracellular ATP. Although most ATP is generated within chondrocytes,

it may be transported out into cartilage where ectonucleotidases enzymatically liberate pyrophosphate. Additionally, a membrane transport protein termed ANKH may directly secrete pyrophosphate from the chondrocytes into the extracellular milieu. Gain-of-function mutations of the ANKH protein have been seen in familial cases of CPPD, but ANKH up-regulation may also occur secondarily in the setting of cartilage damage [20]. Although CPPD crystals are formed from a combination of inorganic phosphate and calcium, the exact mechanism of crystal formation is not well understood.

Once CPPD crystals are liberated from the cartilage into the synovial fluid, they drive acute inflammation in a manner similar to that of MSU crystals. In vitro, CPPD and MSU crystals can be shown to have many similar effects, including activation of the NLRP3 inflammasome in macrophages [21].

Clinical Presentation

Most cases of CPPD are asymptomatic and are discovered incidentally when a radiograph of a joint shows CPPD deposition within the cartilage, the condition known as chondrocalcinosis. As noted earlier, however, CPPD may also present as an acute inflammatory arthritis, or as a chronic arthritis similar to osteoarthritis or rheumatoid arthritis.

Acute CPPD arthritis (colloquially known as pseudogout) usually presents as a rapid onset of mono- or oligoarticular pain but may rarely present with polyarticular involvement. The most common joint involved is the knee, followed by the wrist and the metacarpophalangeal joints [22]. In contrast to gout, bursal involvement is uncommon. Symptoms during an acute episode include pain, erythema, and swelling of the joint that occasionally spreads to the surrounding soft tissues [21]. Due to the inflammatory nature of the pain, patients may develop fevers, chills, and other constitutional symptoms. Occasionally, CPP crystals may deposit in the ligaments at the superior aspect of the dens in the cervical spine, which may intermittently cause acute pain (presumably relating to inflammatory flares) and may be seen on cervical computed tomography scans (crowned dens syndrome).

Symptoms of acute CPPD arthritis are similar to those of an acute gout attack. However, there are several notable features that may distinguish CPPD arthritis from a gout flare, including the fact that CPPD less commonly involves the first metatarsophalangeal joint. Acute CPPD arthritis is typically less severe than gout. On the other hand, whereas gout attacks usually resolve after a few days, acute CPPD arthritis may smolder for weeks to months if not adequately treated [21].

In contrast to acute CPPD arthritis, chronic CPPD arthritis may mimic osteoarthritis, with a mono- or polyarticular presentation. However, chronic CPPD arthritis generally affects different joints than those commonly affected in primary osteoarthritis, namely, the wrists, glenohumeral joints, metacarpophalangeal joints, the midfoot, or the hindfoot [21–23]. In these cases, the presumption is that cartilage damage from CPPD leads to osteoarthritis in atypical locations [22]. On the other hand, the presence of established osteoarthritis appears to promote the risk for

CPPD, including up-regulation of the ANKH protein in chondrocytes, suggesting that CPPD and OA can be reiterative processes. Patients with osteoarthritis as a phenotype of chronic CPPD arthritis may also develop acute flares, as well as severe articular destruction, out of proportion to that seen primary osteoarthritis. As noted above, in some cases, CPPD deposition may result in a smoldering polyarthritis similar to rheumatoid arthritis (pseudo-RA).

Diagnosis

As with gout, the gold standard for diagnosis of CPPD is identification of calcium pyrophosphate crystals within the synovial fluid of an affected joint. CPPD crystals are classically rhomboid-shaped, smaller than MSU crystals, and are weakly positively birefringent on polarized light microscopy [23]. They are often pale and may be missed without vigorous and persistent examination. As with gout, the presence of CPPD crystals does not preclude the simultaneous presence of other inflammatory arthritis, most commonly gout or joint infection [13].

Imaging of joints in CPPD often shows the presence of chondrocalcinosis. This can readily be seen on plain radiographs, computed tomography, and musculoskeletal ultrasound, where it presents as a hyperechoic dotted line *within* the cartilage, in contrast to the appearance of MSU, which is visible on ultrasound as a hyperechoic line *along the surface* of the cartilage ("double contour" sign) [21, 24].

Treatment

Acute CPPD arthritis is treated using many of the same anti-inflammatory medications as gout. In patients with mono-arthritis, intra-articular glucocorticoids are often an effective choice. In patients who have oligo- or polyarticular joint involvement, or who are not amenable to injections, treatment with oral colchicine at a daily dose of 0.6–1.2 mg, oral NSAIDs, or systemic glucocorticoids (oral, or intravenous) may be given [21]. As with gout, anti-IL-1β biologic therapy may be considered for refractory cases [25]. In contrast to gout, in which ULT can provide long-term management by preventing the formation of new crystals and promoting the dissolution of established ones, there are currently no medications available to remove or prevent the formation of CPP crystals, except perhaps in the rare cases of underlying metabolic diseases such as hyperparathyroidism. Thus, patients with frequent recurrent attacks may require chronic anti-inflammatory prophylaxis, most commonly with daily colchicine.

Similarly, there are no disease-modifying medications used in the treatment of primary chronic CPPD crystal arthritis. However, several studies report that use of intra-articular steroids, or the oral medications described, may provide pain relief and prevent recurrence [22]. As with acute CPPD arthritis, screening for and correcting underlying causes such as hyperparathyroidism may provide ameliorative opportunities, although such instances are rare.

Basic Calcium Phosphate

In clinical practice, basic calcium phosphate (BCP) crystals constitute three different types of calcium phosphate crystals, including carbonated-substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate [22]. BCP crystals can cause two types of pathogenic syndromes affecting the musculoskeletal system, depending on where they deposit. If they infiltrate within the joint capsule, they may cause a severe destructive inflammatory arthritis. When found in the tissues around the joint, namely tendons, or bursae, they cause a calcific periarthritis. These presentations are not mutually exclusive, however. Rotator cuff calcification is common, with a prevalence of 2.7–7.3% in asymptomatic patients [26, 27].

Risk Factors

BCP crystal disease appears to be more common in women than men [28]. Risk factors that predispose to BCP crystal deposition include metabolic abnormalities, specifically elevated levels of circulating calcium or phosphate, calciphylaxis in end-stage renal disease, and familial hypophosphatasia (genetic deficiency in alkaline phosphatase activity leading to hyperphosphatemia) [29]. BCP crystal disease has also been described in patients with endocrinopathies including adult onset diabetes mellitus, hypothyroidism, and aberrant estrogen metabolism (menstrual disorders such as endometriosis, ovarian cysts, polycystic ovarian syndrome, or those with recurrent miscarriages) [30].

Pathophysiology

The formation of BCP crystals occurs in areas where there are elevated levels of extracellular calcium and phosphate along with conditions favorable to encourage mineralization of the crystals. When present, BCP crystals may promote production of matrix metalloproteinases and other substances associated with joint damage and erosion of connective tissue [31].

Clinical Presentation

BCP crystal deposition is often asymptomatic and discovered incidentally on x-rays. However, when BCP crystals infiltrate the soft tissues around a joint, they may cause calcific periarthritis, most commonly in the shoulder. Periarthritis is more common in women than men and usually occurs around or after age 50. The supraspinatus tendon is most frequently involved, followed by the infraspinatus tendon. The subscapularis and long biceps tendon are less frequently involved [32]. Other common locations for calcific periarthritis include the gluteus medius tendon and

the reflected head of the rectus femoris [33]. More than one tendon may be involved. Symptoms included chronic pain along with self-limited flares of acute inflammatory pain. Calcification may cause tendon tears or adhesive capsulitis [32].

BCP-associated arthritis occurs when the crystals deposit within the joint capsule or cartilage [33]. In these cases an acute self-limiting arthritis may ensue, with edema, erythema, and joint tenderness, along with decreased joint motion. BCP infiltration in the joint capsule of the shoulder may rarely be associated with Milwaukee shoulder, a rapidly destructive arthritis most prevalent in elderly women [32]. As with other acute crystal diseases, systemic signs, including fevers and chills, may be present.

Diagnosis

A definitive diagnosis of BCP disease is made by identifying the crystals. However, because of their small size and relatively amorphous structure, BCP crystals are not birefringent and are invisible under polarizing light microscopy. Based on their calcium content, the alizarin red S stain may be used to identify BCP crystals under light microscopy, where they will resemble reddish-orange clumps. Unfortunately, alizarin red S staining is neither sensitive nor specific as a test for BCP crystals, and is uncommonly performed by hospital labs. Other calcium-sensitive dyes have been used along with flow cytometry to identify the crystals but are costlier and less available. Similarly, electron microscopy may be used but is not available at most centers.

Imaging using x-rays may show erosions, severe joint degeneration, and soft tissue calcifications, the presence of which are usually presumed to represent BCP deposition. MRI and ultrasonography may show tissue destruction and ligament damage, but these are not specific for BCP disease.

Treatment

For calcific tendonitis most patients are treated conservatively with oral NSAIDs or acetaminophen, along with physical therapy to improve function. For acute BCP arthritis NSAIDS, oral steroids and/or colchicine may be tried, but data supporting these strategies is limited. In patients with more severe pain, or who fail oral therapy, intra-articular glucocorticoids may be used. If pain is resistant to injections, in cases of severe joint damage from Milwaukee shoulder surgery may be needed, up to and including joint replacement. At present, there are no available pharmacologic options to prevent or resolve BCP crystals, although managing underlying metabolic defects is always recommended.

Calcium Oxalate

Calcium oxalate crystals are a rare cause of inflammatory arthritis. The underlying cause for calcium oxalate arthritis is oxalosis, most commonly diagnosed as

hyperoxaluria [34]. Primary hyperoxalurias are a group of rare autosomal recessive diseases, with a prevalence of 0.8–2.9 in one million, that cause an abnormally increased conversion of glyoxylate to oxalate [35]. In contrast, secondary hyperoxaluria occurs due to increased intestinal absorption of dietary oxalate, most commonly as a consequence of diseases of fat malabsorption [36]. Oxalate is primarily excreted by the kidneys (raising the risk for oxalate kidney stones), but in both primary and secondary hyperoxaluria, the oxalate concentration exceeds the excretory capacity of the kidney, causing kidney failure and systemic buildup of oxalate, which may then deposit in various tissues of the body, including bones, tendons, cartilage, and joints. Oxalate arthritis is typically a symmetric, polyarticular disease with inflammatory joint effusions. The gold standard for diagnosis is microscopic identification of the crystals. Calcium oxalate crystals may be monohydrate or dihydrate. Monohydrate crystals are irregular squares or rods that look similar to CPP crystals, while the dihydrate crystals have a pathognomonic envelope-like or bipyramidal shape and are the most common ones seen. The crystals have variably positive birefringence and can also be stained with alizarin red S due to the calcium content. X-ray findings may show chondrocalcinosis, sclerosis, fractures, pseudofractures, subperiosteal resorption next to the oxalate deposits, and dense metaphyseal bands [34]. Treatment of the acute arthritis is similar to other inflammatory joint diseases with NSAIDs, colchicine, or steroids; treatment of hyperoxaluria requires dietary adjustment and management of the underlying cause, and in patients with primary hyperoxaluria, may require kidney and/or liver transplant [34].

Other Crystals

A number of other crystals can cause inflammation in joints. Perhaps most commonly seen, but uncommonly appreciated, are inflammatory reactions to *intraarticular corticosteroid crystals*. Most steroids are insoluble in lidocaine, and each forms their own unique and recognizable crystal structure. Injection of such steroids may therefore induce a transient acute inflammatory reaction, occurring within the first 24 hours and resolving with the dissolution of the crystals and the anti-inflammatory effect of the steroids themselves. Treatment is conservative, with NSAIDs and/or topical ice. *Cholesterol crystals* are characteristically reported in the joint or bursal fluid of individuals with rheumatoid arthritis, or occasionally other forms of inflammatory arthritis. Their presence is not typically associated with hyperlipidemia. Cholesterol crystals are negatively birefringent, plate-like, and notched. They are thought to have weak inflammatory potential; management addresses the primary underlying arthritis [37]. *Lipid liquid crystals* are positively birefringent lipid spherules that appear as Maltese crosses and stain positive with Sudan Black B. Their presence is associated with an acute inflammatory arthritis. Treatment with colchicine or NSAIDs has been reported to improve the arthritis [38].

Questions

1. A 59-year-old man presents for evaluation after his brother was hospitalized with an acute gout flare. The patient has not seen a doctor in 10 years but decided to come in because he is worried about his chances of developing a painful gout attack. He denies any past medical history and takes no medications other than an occasional aspirin for pain less than once a week. He actively smokes 0.5 packs of cigarettes daily and drinks 3–4 glasses of wine per week.

   Further workup demonstrates the following findings:

   - T 98.2 °F, BP 145/91 mm Hg, P 83/min and O_2 saturation 100% on room air
   - Physical exam: negative for tophi.

   Laboratory studies:

   - AST 23 U/L (Reference range 0–40 U/L)
   - ALT 21 U/L (Reference range 0–40 U/L)
   - Alkaline phosphatase 75 U/L (Reference range 40–150 U/L)
   - Total bilirubin 0.3 mg/dL (Reference range 0.2–1.2 mg/dL)
   - Albumin 4.1 g/dL (Reference range 3.5–5.2 g/dL)
   - Blood urea nitrogen 31 mg/dL (Reference range 7–20 mg/dL)
   - Creatinine 1.8 mg/dL (Reference range 0.8–1.2 mg/dL)

   Which one of the following features of this patient's case is most predictive for possible future development of gout?

   A. Aspirin use
   B. Chronic kidney disease
   C. Family history of gout in his brother
   D. Smoking history
   E. Wine intake

   Correct answer: B
   This patient's creatinine suggests that he has chronic kidney disease (CKD), probably secondary to hypertension, particularly since he has not had any medical follow-up in many years. CKD is considered an important risk factor for the development of gout, with studies demonstrating a 60% increase in gout risk for patients with chronic renal insufficiency.
   Low-dose aspirin use has been associated with decreased clearance of uric acid in the kidney. However, a study among healthy volunteers found no change in the renal clearance of urate after they were given a single dose of aspirin 100 mg. Given this patient's sporadic use of aspirin, it is unlikely that his aspirin use confers a greater risk of gout flare than his renal disease. Thus, choice A is incorrect.
   Studies of gout heritability suggest that gout arises from multiple factors, including a combination of multiple different genes, as well as environmental

contributors. A study from 2000 found a correlation of 0.19 for uric acid levels between siblings. Certain genetic polymorphisms have been found to increase risk for gout, particularly polymorphisms in the genes *SCLA2* and *ABCG2* encoding urate transporters in the kidney and gut, but the specific amount of risk conferred by these polymorphisms remains unclear. Because the impact of family history appears to be less potent than CKD, choice C is incorrect.

Tobacco use has not been associated with a higher risk for developing gout. Indeed, some studies suggest a possible lower risk of gout in patients who smoke, for unclear reasons. ACR nevertheless strongly recommends smoking cessation for all patients. Choice D is therefore incorrect.

While this patient does report regular alcohol use, a 2004 study utilizing the NHANES database did not find an increased risk for hyperuricemia among wine drinkers in the general population, as opposed to beer and liquor, both of which were associated with significantly increased serum uric acid levels. Other studies did find an association between wine drinking and increase risk for gout, but not at the level of wine consumption indicated here. Therefore Choice E is incorrect.

2. A 64-year-old Korean man presents for follow-up after experiencing an acute gout flare in his right 1st MTP joint during a recent hospitalization. Gout was confirmed by aspiration and microscopic examination for crystals, and he was treated with prednisone 30 mg with good response. He denies any history of prior gout flares. Today, he says he is feeling well, with minimal toe pain. Medical history is significant for chronic renal insufficiency, hypertension, coronary artery disease complicated by a myocardial infarction 1 year ago, and diabetes. Laboratory studies reveal the following:

   - Na 134 mmol/L (Reference range 134–146 mmol/L)
   - K 4.3 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 109 mmol/L (Reference range 98–108 mmol/L)
   - CO2 25 mmol/L (Reference range 22–29 mg/dL)
   - BUN 40 mg/dL (Reference range 7–20 mg/dL)
   - Cr 2.1 mg/dL (Reference range 0.8–1.2 mg/dL)
   - eGFR 38 ml/min/1.73m^2 (Reference range > 60 mL/min/1.73m^2)

   What would be the most appropriate next step in management?

   A. Initiate allopurinol
   B. Initiate febuxostat
   C. Initiate probenecid
   D. No management needed at this time
   E. Send HLA-B∗5801 testing

   Correct answer: E

   This patient has confirmed gout and stage 3 CKD. ACR guidelines recommend initiating urate-lowering therapy in patients with two or more attacks of gout in the prior year or after a single attack in patients with stage 3 or greater CKD,

tophi, or a history of renal stones. In this setting, allopurinol would be a reasonable first-line agent. However, ACR guidelines recommend HLA-B∗5801 testing before starting allopurinol in Korean patients with stage 3 or worse chronic kidney disease, as well as Han Chinese and Thai patients irrespective of renal function. These patients have a high prevalence of HLA-B∗5801 positivity, which conveys a high risk of potentially life-threatening allopurinol hypersensitivity. As this patient is Korean with stage 3B CKD, it is mandatory to assess HLA-B∗5801 status before deciding whether to institute allopurinol treatment.

While allopurinol would be a good and cost-effective first-line agent for this patient, it should not be started until HLA-B∗5801 has been assessed to be negative. Therefore choice A is incorrect.

Febuxostat is an alternative first-line option for urate-lowering therapy but is much more expensive than allopurinol. Additionally, some but not all studies suggest that patients taking allopurinol, particularly those with significant cardiovascular risk, may have lower risks of cardiovascular death than those taking febuxostat, an observation that is a current subject of active investigation. Until further evidence provides clarity, preferring allopurinol in high-risk cardiovascular patients is an appropriately prudent as well as cost-effective strategy, except in circumstances where allopurinol is not an option or has already been determined to be ineffective. Therefore choice B is incorrect.

Probenecid is considered an alternative first-line urate-lowering therapy for patients for whom a xanthine oxidase inhibitor is not an option. However, this patient's ability to use a xanthine oxidase inhibitor has not yet been ruled out. Moreover, probenecid's efficacy is markedly diminished in patients with creatinine clearances <50 mL/min, and it is not recommended in such cases. Therefore choice C is incorrect.

While urate-lowering therapy is not recommended in otherwise healthy adults after a first attack or in the setting of very rare gout attacks, it is recommended after even one attack in patients with stage 3 or greater CKD. Therefore this patient should be treated, and choice D is incorrect.

3. A 45-year-old man with tophaceous gout presents for his scheduled pegloticase infusion. He was initiated on pegloticase infusions 1.5 months ago, and his uric acid decreased from 9 mg/dL to 1.5 mg/dL 2 weeks after the first infusion. At his last infusion 2 weeks ago, his serum urate level was found to be 4.4 mg/dL. Today, he has bloodwork performed prior to pegloticase administration, and he is found to have the following:

   - Serum urate 6.1 mg/dL (Reference range 2.5–6.0 mg/dL)
   - Na 136 mmol/L (Reference range 134–146 mmol/L)
   - K 3.7 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 102 mmol/L (Reference range 98–109 mmol/L)
   - CO2 29 mmol/L (Reference range 22–29 mmol/L)
   - BUN 28 mg/dL (Reference range 7–20 mg/dL)
   - Cr 1.3 mg/dL (Reference range 0.8–1.2 mg/dL)

- WBC 5.3 × 10^3 /uL (Reference range 4.0–10.0 × 10^3/uL)
- Hgb 13.6 g/dL (Reference range 12–16 g/dL)
- Hct 40.1% (Reference 34–45%)
- Plt 356 × 10^3/uL (Reference range 150–400 × 10^3/uL)

Which of the following would be the best next step in management?

A. Hold pegloticase dose and check serum urate level again in 2 weeks.
B. Initiate allopurinol 100 mg daily.
C. Initiate lesinurad 200 mg daily.
D. Proceed with the administration of pegloticase.
E. Send glucose-6-phosphate-dehydrogenase enzyme test.

Correct answer: D

Pegloticase is a pegylated intravenous uricase that is recommended for patients with gout that has been refractory to more conventional urate-lowering therapy. It is highly effective in significantly lowering serum levels but is associated with a high rate of infusion reactions as well as tachyphylaxis, both thought mainly due to the development of anti-pegloticase antibodies. In order to reduce the risk of infusion reactions, the prescribing information for pegloticase recommends that patients have their serum urate levels evaluated prior to every infusion and that pegloticase be discontinued if a patient is observed to have two or more consecutive serum urate levels of >6 mg/dL (implying the development of antibodies). While this patient should be monitored carefully given his rising serum urate level at today's appointment, he has not yet had two consecutive levels >6 mg/dL. He can receive his pegloticase infusion today, but his serum urate level must be evaluated again prior to his next infusion in 2 weeks.

Because pegloticase should not be held at this time, choice A is incorrect.

Initiating allopurinol to reduce this patient's urate level might be effective but would interfere with the ability to evaluate the patient for the development of immunologic response to pegloticase (i.e., as rising serum urate level). In fact, co-treatment with pegloticase and another urate-lowering drug is contraindicated. Therefore, choice B is incorrect.

Lesinurad is a uricosuric agent which has been approved by the FDA for administration only in conjunction with a xanthine oxidase inhibitor, so this patient should not receive this medication. Moreover, there is no role for additional urate-lowering therapy in this patient at this time, as mentioned above. Therefore choice C is incorrect.

Individuals starting pegloticase should first be checked for glucose-6-phosphatase-dehydrogenase (G6PD) deficiency, since pegloticase generates a large oxidant load that can cause hemolysis in the setting of G6PD deficiency. However, this patient has not had any adverse hematologic effects since being initiated on pegloticase 1.5 months ago; even absent a prior test it is extremely unlikely that he is G6PD deficient and choice E is incorrect.

4. A 61-year-old man presents to your office for follow-up after a visit to the emergency department 5 days ago for an acute episode of pain and swelling in his right first MTP joint. He has a history of crystal-proven gout that was diagnosed 10 years ago, and since then he had had one episode of gout in his right first MTP joint, one episode in his left ankle, and a third episode in his left knee. His last gout flare was approximately 18 months ago. He is currently not taking any medications. On evaluation today, his exam is notable for minimal erythema and tenderness to palpation in his right first MTP joint, and no tophi. He denies pain with walking. His bloodwork is notable for the following:

   - Na 134 mmol/L (Reference range 134–146 mmol/L)
   - K 4.3 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 109 mmol/L (Reference range 98–109 mmol/L)
   - CO2 25 mmol/L (Reference range 22–29 mmol/L)
   - BUN 40 mg/dL (Reference range 7–20 mg/dL)
   - Cr 1.1 mg/dL (Reference range 0.8–1.2 mg/dL)
   - AST 35 U/L (Reference range 0–40 U/L)
   - ALT 33 U/L (Reference range 0–40 U/L)
   - Alkaline phosphatase 54 U/L (Reference range 40–150 U/L)
   - Total bilirubin 0.3 mg/dL (Reference range 0.2–1.2 mg/dL)
   - Serum Urate 7.2 mg/dL (Reference range 2.5–6.0 mg/dL)

   Which of the following would be the best next step in management?

   A. Give colchicine 1.2 mg once, followed by 0.6 mg 1 hour later, then every 12 hours.
   B. Inject the patient's right first MTP joint with corticosteroid.
   C. Prescribe colchicine 0.6 mg pills to take at home as needed.
   D. Start allopurinol 100 mg daily.
   E. Start prednisone 10 mg daily.

   Correct answer: C
   This patient with gout and occasional attacks has just recovered from his most recent attack and is feeling no pain. Although he still has some evidence of mild inflammation, since gout attacks are self-limited it is not necessary to treat him at this time. However, early treatment of the next attack (should it occur) is more effective than delayed treatment, particularly in the case of colchicine. Sending him home with a self-treatment option therefore represents good gout management. Other options for as-needed home use would include prednisone and NSAIDs, neither of which is offered as an option here.
   If anti-inflammatory treatment for his acute attack *were* needed, colchicine might be considered. The current ACR recommendations for acute gout treatment with colchicine are for patients to receive colchicine 1.2 mg as soon as possible at symptom onset, followed by an additional 0.6 mg 1 hour later, then to potentially continue colchicine 0.6 mg once or twice daily 12 hours later. However, colchicine is only recommended as an acute gout treatment if it can be started within 36 hours of treatment initiation, as the efficacy of colchicine

beyond this treatment window is unclear. Since this patient's gout symptoms first began 5 days ago, colchicine would be an incorrect choice even if acute treatment were needed. For multiple reasons, therefore, choice A is incorrect.
Since treatment of the asymptomatic residual inflammation of his current attack is not necessary, choices B (MTP injection) and E (prednisone) are both incorrect.
Allopurinol is a good choice for urate lowering in gout patients who require such treatment, and current ACR guidelines permit the initiation of urate-lowering therapy during a flare if the flare is being adequately treated with anti-inflammatories (a recommendation that remains somewhat controversial). The starting dose of allopurinol for patients with normal kidney function or CKD up to and including stage 3 is 100 mg. However, ACR guidelines do not recommend initiating urate-lowering treatment in patients who have had a single attack of gout, or fewer than two attacks in the past year in the absence of CKD, kidney stones, or tophi. This patient does not meet ACR criteria for initiation of urate-lowering therapy, and allopurinol should not be initiated. Therefore, choice D is incorrect.

5. A 58-year-old Han Chinese male with gout comes to your office seeking treatment advice. The patient was diagnosed with gout several years ago but has never been treated. He reports experiencing several attacks each year, each of which renders him incapacitated. Most of his attacks have been in his first MTP joint, but one was in his knee, at which time a joint aspiration confirmed the presence of negatively birefringent crystals. He has been tried on febuxostat in the past but experienced nausea and is unwilling to try the medicine again. Past medical history includes type 2 diabetes mellitus and mild chronic kidney disease. Current medications include rosiglitazone and low-dose aspirin daily. He denies any history of nephrolithiasis. Physical examination demonstrates no acute or chronic arthritis at the present time, and no tophi. Laboratory studies include

   - Serum urate 8.4 mg/dL (Reference range 2.5–6.0 mg/dL)
   - Serum creatinine 1.3 mg/dL (Reference range 0.8–1.2 mg/dL)
   - eGFR 66 ml/min/1.73m^2 (Reference range > 60 ml/min/1.73m^2)
   - HgB A1C 6.8%.
   - An HLA-B∗5801 test is positive.

   Which of the following is the next best treatment intervention for this patient?

   A. Discontinue aspirin.
   B. Initiate allopurinol, 50 mg daily, and titrate to target.
   C. Initiate lesinurad, 200 mg daily.
   D. Initiate losartan, 50 mg daily.
   E. Initiate probenecid, 500 mg daily, and titrate to target.

   Correct answer E
   American College of Rheumatology guidelines recommend a xanthine oxidase inhibitor, either allopurinol or febuxostat, as first-line therapy for urate lowering. When neither agent is an option, probenecid is recommended as the next

choice. Probenecid inhibits the renal tubule pump URAT1 to promote renal urate excretion. Probenecid should be started at 500 mg daily and then increased to achieve target urate or maximal permissible dose. Probenecid is not recommended for gout patients with a history of tophi or kidney stones and is not considered to be efficacious in the setting of eGFR less than 50 ml/min/1.73 m^2, but such features do not apply to this patient.

Low-dose aspirin has effects on the kidney that can reduce uric acid excretion and raise serum urate (in contrast, high-dose aspirin is urate lowering). ACR guidelines recommend considering whether non-essential medications that may raise urate can be discontinued or substituted with another agent (e.g., treating hypertension with losartan instead of hydrochlorthiazide). However, this 59-year-old male with cardiovascular risk (diabetes and CKD) meets US Preventive Services Task Force criteria for daily aspirin use. Since urate lowering can be accomplished even in the setting of aspirin use, aspirin should not be discontinued. Therefore choice A is incorrect.

While allopurinol is a first-line therapy for urate lowering in gout, the presence of HLA-B∗5801 renders patients at markedly increased (hundreds-fold) risk of allopurinol hypersensitivity syndrome, a potentially fatal illness. Because the gene is common in certain specific populations, HLA-B∗5801 testing is currently recommended prior to allopurinol use in Han Chinese (constituting more than 90% of all Chinese individuals) and Thai populations, and in Koreans with stage 3 CKD or worse. This patient was therefore appropriately tested for HLA-B∗5801 and, in the presence of this gene, should not receive allopurinol. Therefore choice B is incorrect.

Like probenecid, lesinurad inhibits URAT1 to promote renal urate excretion. Lesinurad is more potent than probenecid and can lower urate in patients with eGFR as low as 30 ml/min. However, lesinurad may promote transient or—much less commonly—permanent renal dysfunction when used as monotherapy and is therefore approved only as combination therapy with a xanthine oxidase inhibitor and only in patients with eGFR greater than 50 ml/min. While this patient's eGFR is not low enough to be a contraindication to use, he cannot take a xanthine oxidase inhibitor, and the use of lesinurad as monotherapy is not an acceptable option. Therefore choice C is incorrect.

Losartan is an angiotensin receptor blocker that has an incidental ability to inhibit URAT1 and can therefore lower serum urate. However, it is not as potent as probenecid or lesinurad. It is recommended as an off-label add-on to a xanthine oxidase inhibitor in individuals who have not achieved target serum urate when taking a xanthine oxidase inhibitor alone, particularly when such patients also need an anti-hypertensive agent. Losartan is therefore not a good option for this patient who does not have hypertension and needs a single agent, not an add-on agent. Therefore choice D is incorrect.

6. A 72-year-old male calls your office for advice about an acutely swollen and painful knee joint.

   The patient, who has a history of right knee osteoarthritis, was seen in your office for a routine visit the afternoon before. At that time, he was requesting a

corticosteroid knee injection preceding a vacation. You aspirated 20 cc of fluid from the knee. The synovial fluid aspirate was noteworthy for a white blood cell count of 1200/mm^3 (Reference range 0–200/mm^3), mainly neutrophils. No crystals were seen, and a gram stain was negative at the time. You injected 40 mg of triamcinolone hexacetonide, along with 3 cc of 1% lidocaine, which afforded the patient some immediate relief.

At approximately 3 AM, the patient was awakened by pain in the knee. He tossed and turned until morning, when he examined the knee and found that it was red and swollen. He took his temperature, which was 100.0 °F. Past medical history is noteworthy for diet-controlled type 2 diabetes mellitus. Laboratory studies from the day before demonstrated a normal complete blood count and serum chemistries.

Which of the following is the most appropriate action at this time?

A. Initiate ibuprofen, 800 mg three times daily.
B. Initiate vancomycin and ceftriaxone empirically.
C. No action.
D. Obtain serum urate level and erythrocyte sedimentation rate.
E. Re-aspirate the joint for white count, gram stain, and culture.

Correct answer: A

This patient has received an injection of triamcinolone hexacetonide for osteoarthritis. When viewed under a polarizing microscope, triamcinolone hexacetonide in synovial fluid appears as a rod-shaped negatively birefringent crystal and, like naturally occurring pathogenic crystals, has the ability to induce an acute inflammatory response. While different glucocorticoids form differently shaped crystals, all have the potential to elicit an inflammatory response. Such responses are reported to occur in about 2–25% of patients who receive steroid injections, may occasionally be severe (including low-grade fever, as in this patient), and may mimic other forms of inflammatory monoarthritis. Management is symptomatic; attacks resolve spontaneously when the crystals dissolve and the steroid medication exerts its anti-inflammatory effects. Common approaches to treatment include NSAIDs, colchicine, and topical ice. In this case, instructing the patient to take high-dose ibuprofen is an appropriate option.

Joint infection occurring after injection is a rare (between 1:750 and 1:10,000, based on several reports) but dreaded consequence of joint injection, possibly occurring even in the setting of meticulous sterile technique. However, the time to onset of symptomatic infection is delayed by several days, presumably owing to the time required for the infecting organism to achieve a clinically impactful population. Accordingly, infection in this patient whose flare began within hours is unlikely, and treatment with antibiotics in the absence of evidence of infection would be unnecessary at best. Therefore, B is an incorrect option.

If no action is taken in this patient, his inflammatory episode is likely to resolve within 24–48 hours. However, this patient is in distress, and not treating would only be a reasonable option if harm would be expected from treatment. Accordingly, C is an incorrect option.

Obtaining a serum urate and erythrocyte sedimentation rate will do the patient no harm but will also be of little or no clinical benefit. The erythrocyte sedimentation rate can be predicted to be elevated and will not help distinguish between etiologies of the joint swelling. Similarly, whether the serum urate is high or low will not provide any information on the etiology of the current attack. Therefore, choice D is incorrect.

Re-aspirating the joint for gram stain and culture would be an appropriate strategy if there were concern for infection, but as discussed above, the timing of onset of the attack (mere hours after the joint injection) makes an infection very unlikely, even in the setting of well-controlled diabetes. Moreover, the procedure will result in unnecessary discomfort and itself will convey the low but real risk for infection accompanying every joint procedure. If the patient's joint inflammation had occurred 48–96 hours after the joint injection, concern for infection would have been significant, and re-aspiration would have been imperative. In the current setting, choice E is incorrect.

7. You are called to consult on a 16-year-old male with a painful swollen elbow that he is unable to move. The patient has a history of kidney stones at age 13. His father died of complications of end-stage renal disease when he was 6 years old. You aspirate the joint and observe birefringent, bipyramidal crystals. The synovial fluid white blood cell count is 35,000/mm^3 (Reference range 0–200/mm^3), predominantly neutrophils, and gram stain is negative; culture is pending. Laboratory studies are noteworthy for an ESR of 43 mm/hour (Reference range < 20 mm/hour), a serum creatinine of 5.8 mg/dL (Reference range 0.8–1.2 mg/dL), and a normocytic, normochromic anemia.

   In addition to treating the patient with oral prednisone, which of the following is the most appropriate action at this time?

   A. Initiate dialysis.
   B. Initiate empiric antibiotics.
   C. Institute low-purine diet.
   D. Refer for hepatorenal transplantation.
   E. Refer for renal transplantation.

   Correct answer: A

   Early onset of renal stones and end-stage renal disease, along with the presence of bipyramidal crystals (classic for calcium oxalate) in the joint, are evidence of oxalosis, a late complication of hyperoxaluria that occurs when the kidneys can no longer excrete adequate amounts of oxalate to keep serum and tissue levels down. Primary forms of this condition are autosomal dominant, consistent with the report that this patient's father died of complications from end-stage renal disease at an early age. The presence of oxalosis indicates that this patient is at risk for potentially fatal systemic involvement of oxalate deposition, which requires early action. In addition to reducing the other harms of end-stage kidney disease, the use of dialysis can help clear the total body oxalate load and reduce risk, although dialysis is not as effective as renal oxalate

excretion, and kidney transplantation will likely be required in the future. In addition to dialysis, a low-oxalate diet is essential.

This patient's joint effusion demonstrates the presence of oxalate crystals and inflammation in the appropriate clinical setting, with a negative gram stain and a WBC count that is not intrinsically suspicious for infection (i.e., less than 50,000 WBCs/mm^3). Infection is therefore unlikely and empiric antibiotics are not warranted. Therefore, choice B is incorrect

A low purine diet would be useful for a patient with hyperuricemia and gout, since purines are metabolized to urate. In this case the problem is clearly oxalate, not urate, and a low purine diet would not be of value. Therefore, choice C is incorrect

In cases of primary genetic hyperoxaluria, as this one appears to be, management often requires renal transplantation, since dialysis may be inadequate to lower serum and tissue oxalate levels. In such cases, renal transplantation not only restores renal function but also promotes the removal of oxalate to control systemic disease. For Type I primary hyperoxaluria, in which excessive oxalate production is limited to the liver, combined hepatorenal transplantation is recommended, not only to restore renal function but also to normalize oxalate production. For Type II primary hyperoxaluria only renal transplantation is recommended, because oxalate production occurs in multiple tissues and is not significantly reduced by replacing the liver. In this patient, transplantation would be premature, since the efficacy of dialysis and diet are not yet established, and genetic testing will be required to determine which type of transplantation is warranted, if needed. Therefore, choices D and E are both incorrect.

Patients with secondary hyperoxaluria less commonly experience oxalosis and more commonly present with oxalate kidney stones and less severe renal impairment than is seen in primary hyperoxaluria. Secondary hyperoxaluria may be a result of diet alone, or more likely, of diet plus excess oxalate absorption from the gut that occurs in states of fat malabsorption such as Crohn's disease, gastric bypass, or short small bowel syndrome. In those cases, a low oxalate diet, plus changes to reduce fat malabsorption, may be sufficient management.

8. A 47-year-old female comes to your office complaining of left olecranon bursitis of recent onset. She reports a 10-year history of rheumatoid arthritis, currently managed with methotrexate 20 mg weekly, along with daily folic acid. On examination you confirm that her left olecranon bursa is enlarged and fluctuant, and mildly warm and erythematous. The elbow joint has full range of motion. Further examination demonstrates moderate bogginess of the MCP and PIP joints of the hands, bilaterally. Laboratory values are significant for an ESR of 42 mm/hour (Reference range < 20 mm/hour) and a positive rheumatoid factor. Complete blood count and basic metabolic panel are within normal limits. Aspiration of the bursa yields 10 cc of slightly cloudy yellow fluid. The bursal fluid WBC count is 22,000/mm^3 (Reference range 0–200/mm^3) (predominantly

neutrophils), and gram stain is negative. Under polarizing microscopy, you observe multiple birefringent, notched, plate-like crystals.

Which of the following is the most appropriate intervention at this time?

A. Aspirate elbow joint.
B. Initiate adalimumab.
C. Initiate lovastatin.
D. Initiate oral antibiotics.
E. Perform bursectomy.

Correct answer: B

This patient has cholesterol crystal-associated bursitis, a not uncommon finding in patients with rheumatoid arthritis. Cholesterol crystals may also be found in joints, and similar findings may less commonly occur in psoriatic arthritis, lupus, and Lyme arthritis. The reason for cholesterol crystal formation in systemic inflammatory arthritis is not fully known but appears to relate to a local phenomenon within the inflamed joint, as the phenomenon is not associated with hyperlipidemia. While cholesterol crystals are thought to be mildly inflammatory, in this case the presence of bursitis is indicative of inadequately treated rheumatoid arthritis, a presumption supported by the active symmetrical small joint synovitis of the patients hands. Management is therefore focused mainly on better treatment of the patient's rheumatoid arthritis; since she is already on maximal-dose methotrexate, adding adalimumab is a reasonable next intervention.

Aspirating the elbow joint would not be a useful strategy in this case (choice A). The elbow joint is asymptomatic and has full range of motion, suggesting it is uninvolved in the current problem, and is unlikely to be involved in the current clinical situation. Indeed, the elbow joint is not in communication with the olecranon bursa, and conditions affecting one rarely directly affect the other. Initiating lovastatin (choice C) would also not be a useful strategy; most cases of cholesterol crystal arthritis are unrelated to systemic hyperlipidemia and do not require therapeutic lipid lowering. Oral antibiotics (choice D) may be an acceptable treatment for an infected bursa (in contrast to infected joints which need intravenous antibiotics) but are not warranted here; the inflammation is local, the white count is only moderately elevated, the gram stain is negative, and the patient's rheumatoid arthritis/cholesterol crystal deposition are sufficient to account for the bursitis (though of course, sending and following up on fluid for culture constitutes proper medical practice). Bursectomy (choice E) is occasionally required for chronic refractory uncomfortable or painful olecranon bursitis, but that is not the clinical scenario here, and the current bursitis is likely to respond to rheumatoid arthritis treatment.

9. A 71-year-old female presents to your clinic complaining of pain in her right shoulder for the past 2 months. The shoulder hurts with movement, and pain also renders her unable to sleep on her right side. Acetaminophen 1000 mg afforded her no improvement. Her medical history includes adult-onset diabetes mellitus, hypertension, hypothyroidism, hyperlipidemia, coronary artery disease, and end-stage renal disease on dialysis for the past 4 years. Her current

medications include insulin, amlodipine, atorvastatin, and levothyroxine. On physical examination, she is afebrile with blood pressure of 148/86, and pulse of 92. Her heart and lung examinations are unremarkable. She has a normal arteriovenous fistula in her left forearm. Musculoskeletal examination is significant only for anterior fullness and diffuse tenderness in her right shoulder. The right shoulder is severely limited on active range of motion in all directions, and she is unable to lift her right arm above her head. Passive range of motion is slightly decreased in all directions, and she experiences significant pain upon abduction and elevation of the arm above her head. She denies any preceding trauma. Her left shoulder exam is normal. Laboratory studies include:

- White blood cell count: 4.6×10^3/uL (Reference range $4.0–10.0 \times 10^3$/uL)
- Hemoglobin: 8.2 g/dL (Reference range 12–16 g/dL)
- Platelet count: 218×10^3/uL (Reference range $150–400 \times 10^3$/uL)
- Potassium: 4.4 mmol/L (Reference range 3.5–5 mmol/L)
- Creatinine: 4.5 mg/dL (Reference range 0.8–1.2 mg/dL)
- Calcium 10.9 mg/dL (Reference range 8.4–10.2 mg/dL)
- Urate 4.2 mg/dL (Reference range 2.5–6.0 mg/dL)

Thyroid-stimulating hormone is within normal limits. Rheumatoid factor and CCP are negative.

An X-ray of her shoulder shows sclerosis and joint space narrowing of the glenohumeral and acromioclavicular joints, with calcification in the soft tissue around the humeral head and in the area of the rotator cuff tendons.

A joint fluid aspiration reveals a white cell count of 16,500 cells/mm^3, predominantly neutrophils. Gram stain shows no organisms, and cultures are negative. No crystals are seen under polarized light microscopy.

What is the most likely diagnosis?

A. Basic calcium phosphate arthritis
B. Calcium pyrophosphate deposition disease
C. Erosive osteoarthritis
D. Gout
E. Rheumatoid arthritis

Correct answer: A

This patient presents with an acute inflammatory monoarthritis affecting her shoulder, with calcific periarthritis, consistent with basic calcium phosphate arthritis, which most commonly affects the shoulder in women over the age of 50. Individuals with underlying metabolic abnormalities including hypercalcemia, end-stage renal disease, and endocrinopathies such as diabetes mellitus or hypothyroidism are particularly affected. Basic calcium phosphate crystals cannot be seen under polarized light microscopy but can be seen using electron microscopy and/or calcium staining with alizarin red S, neither of which is routinely done. When found in an acute setting with severe shoulder inflammation, tendinitis, and destructive arthritis, this condition is known as Milwaukee shoulder.

Choice B, calcium pyrophosphate deposition disease is incorrect. Although CPP crystals can cause an acute inflammatory arthritis affecting the shoulder with an inflammatory synovial fluid count, isolated shoulder involvement is not the most common presentation, tendons are less commonly affected than in basic calcium phosphate disease, and polarizing microscopy (especially in such a severe case) should have revealed positively birefringent rhomboid shaped crystals.

Choice C, erosive osteoarthritis, is incorrect. Erosive osteoarthritis is a condition that typically affects the distal interphalangeal and proximal interphalangeal joints of patients with hand osteoarthritis, causing inflammation and central joint erosions. Although basic calcium phosphate deposition may contribute to erosive osteoarthritis, the presentation in the shoulder is not consistent with such a diagnosis.

Choice D, gout, is incorrect. This patient, who is post-menopausal and has end-stage renal disease, may indeed be hyperuricemic and therefore susceptible to gout. However, a first attack in the shoulder would be uncommon, as would the duration of this condition in a first gouty attack. Most importantly, the absence of negatively birefringent needle-shaped crystals in the synovial fluid makes gout unlikely in this case.

Choice E, rheumatoid arthritis, is incorrect. Although rheumatoid arthritis can present later in life, and is more common among females, the lack of symmetrical small joint involvement of the hands, the monoarticular nature of the complaint, and the absence of RF and anti-CCP antibodies make rheumatoid arthritis unlikely.

10. A 52-year-old woman presents to your clinic with 5 days of severe neck pain. She denies any preceding trauma. She states that the pain is greatest in the back of her neck and that she has had trouble turning to look either left or right. The pain has continued to worsen over the past few days and did not improve with acetaminophen. Her past history is significant only for hypertension. On physical examination, she is afebrile with normal vital signs. She has decreased passive and active range of motion to a maximum of 30° in any direction, with increasing pain at the ends of the range. Her neurologic examination is normal. Laboratory studies, including complete blood count, basic metabolic profile, and creatinine, are all within normal limits. Her ESR is 51 mm/hour (normal range < 20 mm/hour), and her CRP is 1.60 mg/dL (normal: <0.8 mg/dL). An X-ray of her cervical spine shows a calcification slightly posterolateral to and abutting the odontoid process. An MRI showed a low signal intensity encircling the odontoid process.

    Which of the following is the best next treatment for this patient?

    A. Cervical epidural injection of corticosteroid
    B. Infliximab
    C. Isoniazid, rifampin, pyrazinamide, and ethambutol for 6 months
    D. Meloxicam
    E. Soft cervical collar with extra-strength acetaminophen

Correct answer: D

This patient most likely has crowned dens syndrome, a condition of calcification and crystal deposition around the odontoid process which can induce inflammation that most commonly causes neck pain, but may also cause headaches, fevers, and meningismus. Crowned dens syndrome is most commonly a consequence of calcium pyrophosphate deposition but may also be seen with basic calcium phosphate deposition. Diagnosis can be made by visualization of a crown-like calcified mass around the odontoid on x-ray. CT scans of the cervical spine may be more sensitive and specific and frequently show calcification of the transverse ligament. Biopsy of the mass is usually not needed but is diagnostic, typically revealing the crystals that cause the disease. First-line medications for crowned dens syndrome without acute neurologic complications are similar to any acute crystal disease—NSAIDs or colchicine—and most patients experience complete symptom resolution. Refractory cases may need oral prednisone, and if there is spinal cord compression, surgical debridement may be necessary.

This patient does not have evidence of spinal stenosis or foraminal narrowing to suggest degenerative joint disease requiring epidural injections. Therefore, choice A is incorrect.

Although spondyloarthropathy or rheumatoid arthritis may result in pannus that could be mistaken for the lesion of crowned dens syndrome, this patient has no peripheral joint involvement and has an acute inflammatory cause of her neck pain, consistent with crowned dens syndrome. Therefore, choice B is incorrect.

Although tuberculous spondylitis (Pott disease) may affect the cervical spine, it usually affects patients at high risk for tuberculosis and presents with a more subacute course with worsening pain which may eventually lead to destruction of the intervertebral joints and discs, leading to vertebral collapse and spinal compression. Therefore, choice C is incorrect.

This patient has an inflammatory condition and needs to be treated with anti-inflammatory therapy. While a soft cervical collar and acetaminophen would do no harm, they would be unlikely to adequately relieve her symptoms. Therefore, choice C is incorrect.

11. A 53-year-old man is referred to the rheumatologist for evaluation of chronic joint pains. He reports pain and swelling in his fingers, knees, and shoulders. His pain is chronic and does not wax and wane. He was recently seen by a community provider, who aspirated his knee and performed x-rays of his hands and knees, and he brings the reports with him today. He has been treating his pain with acetaminophen with modest relief but wants to know if there is anything better that he can do. His medical history is significant for diet-controlled diabetes mellitus. On physical examination, he is afebrile and hemodynamically stable. His musculoskeletal exam is significant for bony hypertrophy of the bilateral second and third metacarpophalangeal joints, along with mild warmth and minimal tenderness to palpation. He has bony hypertrophy of his knees with mild tenderness along the joint line and coarse crepitus. He complains of

pain with active and passive internal rotation of both shoulders, but has no edema or erythema of these joints, and has no pain over the acromioclavicular joint or evidence of impingement. A complete metabolic panel obtained the week before shows a creatinine of 1.1 mg/dL (Reference range 0.8–1.2 mg/dL), an AST of 72 U/L (Reference range 0–40 U/L), and an ALT of 68 U/L (Reference range 0–40 U/L).

Synovial fluid analysis from the knee aspiration the week before is as follows:

- 12,000 WBC/uL (Reference range 0–200/uL)
- 2000 RBC/uL (Reference range 0–50/uL)
- No organisms on gram stain with negative cultures
- Positively birefringent rhomboid crystals found in fluid

Hand X-rays: joint space narrowing along with hook-shaped osteophytes present in bilateral second MCP's, along with chondrocalcinosis of the triangular fibrocartilage above the ulnar styloid of the left hand. There is a subchondral cyst in the left third metacarpal head.

Knee X-rays: chondrocalcinosis with mild tricompartmental joint space narrowing and sclerosis

What is the most important next step in the assessment and management of this patient?

A. Continue acetaminophen and begin hand and knee exercises for osteoarthritis.
B. Order serum ferritin and transferrin saturation.
C. Order a serum urate level and start urate-lowering therapy together with colchicine.
D. Perform intra-articular corticosteroid injections of his tender joints.
E. Start celecoxib.

Correct answer: B

This patient is presenting with likely hereditary hemochromatosis based on the chronic arthritis, transaminitis, and diabetes. About one-third of patients with hereditary hemochromatosis arthropathy also have chondrocalcinosis, with CPPD crystals found in their synovial fluid. Classic joints affected in hemochromatosis (as well as CPPD arthritis) include the second and third metacarpophalangeal joints. Other joints frequently affected include the knees, shoulders, hips, and feet. Specific X-ray findings in hereditary hemochromatosis arthropathy include joint space narrowing and hook or beak-shaped osteophytes in the second or third metacarpophalangeal joints (along with CPPD deposition in some cases), as well as the presence of subchondral cysts and sclerosis indistinguishable from osteoarthritis. While not diagnostic, the presence of elevated transaminases and diabetes are also consistent with hemochromatosis involvement of the liver.

Even though the patient has joint space narrowing, osteophytes, and sclerosis on his X-rays, he clearly also has an inflammatory arthritis with CPPD crystals.

Additionally, osteoarthritis most frequently affects the distal interphalangeal or proximal interphalangeal joints and rarely affects the metacarpophalangeal joints. Thus, the patient has three joint diseases—osteoarthritis, CPPD arthritis, and hemochromatosis. Although the use of acetaminophen and occupational therapy may afford him transient relief, missing a diagnosis of hemochromatosis will put the patient at risk for additional long-term problems. Therefore, choice A would not be the most important action to take at this time.

The rhomboid-shaped, positively birefringent crystals seen in the synovial fluid are calcium pyrophosphate crystals. In contrast, urate crystals are negatively birefringent, needle-shaped crystals. Given lack of metatarsophalangeal or ankle/midfoot involvement, lack of episodic symptoms, and calcium pyrophosphate crystals, this patients presentation is not consistent with a gout attack and does not require gout assessment or treatment as an immediate activity. Therefore, choice C is incorrect.

This patient has chronic arthritis affecting multiple joints, with other findings compatible with hereditary hemochromatosis. Since corticosteroid injections are more appropriate and effective for mono- or oligo arthritis, their use here would be a secondary option at best. Therefore, choice D is incorrect.

Celecoxib treatment may provide him relief and is not contraindicated, but it is not the most important step at this time. Therefore, choice E is incorrect.

12. A 56-year-old man is referred to your office for management of recurrent episodes of pain and swelling that have variously affected the knees, wrists, and shoulders. He reports that each episode usually affects two or three of the aforementioned joints at a time. His most recent episode, which occurred about 3 weeks ago, affected his left knee and right wrist. Overall, the episodes occur roughly every few months and usually last up to 4 weeks before resolving. He started taking diclofenac during the last episode and believes that it greatly shortened the episode and improved his pain, and he continues to take it twice a day. On your examination today, he has no tender or swollen joints, although you notice Heberden's nodes on the second and fourth distal interphalangeal joint of his left hand. He also has bilateral knee crepitus. Labs reveal an ESR of 7 mm/hour (Reference range 0–22 mm/hour), a CRP of 0.2 mg/dL (Reference range 0–0.8 mg/dL), a creatinine of 0.9 mg/dL (Reference range 0.8–1.2 mg/dL), calcium of 11.3 mg/dL (Reference range 8.4–10.2 mg/dL), a normal thyroid stimulating hormone, a negative rheumatoid factor, and a serum urate of 4.5 mg/dL (Reference range 2.5–6.0 mg/dL). An ultrasound of his right knee shows linear and punctate hyperechoic densities within the hyaline cartilage.

    If you were to aspirate the fluid during his next attack, which would be the most likely finding?

    A. WBC 15,000 with neutrophil predominance and positively birefringent rhomboid-shaped crystals.
    B. WBC 41,000 with neutrophil predominance and negatively birefringent needle-shaped crystals

C. WBC 80,000 with neutrophil predominance and gram-positive cocci and no crystals
D. WBC 300 with lymphocytic predominance and variable positive birefringent envelope-shaped crystals
E. WBC 10,000 multinucleated giant cells, macrophages with phagocytized hemosiderin, and foam cells

Correct answer: A

This patient with an episodic inflammatory arthritis affecting the knees, wrists, and shoulders, with hypercalcemia on laboratory studies and a musculoskeletal ultrasound showing linear and punctate hyperechoic lesions in the hyaline cartilage that is pathognomonic for calcium pyrophosphate deposition. Given the setting of CPPD, and the recurrent nature and joints involved, acute CPPD arthritis is the most likely explanation for his flares. A moderately elevated WBC count and positively birefringent rhomboid crystals would be characteristic of this type of acute arthritis.

Although this patient has an episodic inflammatory arthritis that could be compatible with gout, the fact that he has a serum urate level within normal limits during an asymptomatic period, along with the lack of first MTP involvement in a male, would be uncharacteristic of gout. While the ultrasound findings do not rule out gout, neither to they provide any evidence for gout (i.e., tophi or "double contour" sign, or a hyperechoic continuous band over the superficial margin of the superior border of the articular cartilage). Therefore, choice B is incorrect.

A WBC count greater than 50,000/mm^3 would be most concerning for a septic joint and can occasionally be seen in gout; it is rarely seen in CPPD arthritis. Although infectious arthritis is always on the differential for inflammatory arthritis, this patient's recurrent arthritis with multiple joints involved, lack of systemic complaints, and lack of illness would be extremely atypical for joint infection. Therefore, choice C is incorrect.

The patient's episodes are clearly inflammatory, which would be inconsistent with a WBC that is in the normal range (as 300 is). Inflammatory effusions are defined as having at least 2000 WBC/mm^3. The patient in this case has an inflammatory arthritis and should have a synovial fluid white cell count between 2000 and 50,000 during an acute episode if inflammatory arthritis. Furthermore, positively birefringent envelope-shaped crystals would be pathognomonic for calcium oxalate crystals, not CPPD crystals. Therefore, choice D is incorrect.

Pigmented villonodular synovitis (PVN) is a condition of synovial thickening and overgrowth of unknown cause that most commonly affects the knees. Although it is benign (i.e., non-malignant) it can be invasive of bone and cause significant joint destruction. PVN can cause an inflammatory arthritis, with swelling that can be either episodic or continuous in nature. A joint aspiration would reveal bloody synovial fluid with multinucleated giant cells, macrophages that have phagocytized hemosiderin and foam cells. An ultrasound of this would reveal hypoechoic synovial proliferation and hypervascularity on

color Doppler. MRI can be used to demonstrate or rule out the presence of massive synovitis. While PVN could not be ruled out in this case without additional evaluation, its rarity, together with the established presence of CPPD to support an acute CPP arthritis, makes finding a synovial fluid consistent with PVN very unlikely. Therefore, choice E is incorrect.

References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011;63(10):3136–41.
2. Hak AE, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. Ann Rheum Dis. 2010;69(7):1305–9.
3. Kuo CF, See LC, Luo SF, Ko YS, Lin YS, Hwang JS, et al. Gout: an independent risk factor for all-cause and cardiovascular mortality. Rheumatology (Oxford). 2010;49(1):141–6.
4. Dehghan A, Kottgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet (London, England). 2008;372(9654):1953–61.
5. Moi JH, Sriranganathan MK, Falzon L, Edwards CJ, van der Heijde DM, Buchbinder R. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. J Rheumatol Suppl. 2014;92:26–32.
6. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11(11):649–62.
7. Emmerson BT. Identification of the causes of persistent hyperuricaemia. Lancet. 1991;337(8755):1461–3.
8. Desai J, Steiger S, Anders HJ. Molecular pathophysiology of gout. Trends Mol Med. 2017;23(8):756–68.
9. So AK, Martinon F. Inflammation in gout: mechanisms and therapeutic targets. Nat Rev Rheumatol. 2017;13(11):639–47.
10. Tramontini N, Huber C, Liu-Bryan R, Terkeltaub RA, Kilgore KS. Central role of complement membrane attack complex in monosodium urate crystal-induced neutrophilic rabbit knee synovitis. Arthritis Rheum. 2004;50(8):2633–9.
11. Terkeltaub R. What makes gouty inflammation so variable? BMC Med. 2017;15(1):158.
12. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74(10):1789–98.
13. Shah K, Spear J, Nathanson LA, McCauley J, Edlow JA. Does the presence of crystal arthritis rule out septic arthritis? J Emerg Med. 2007;32(1):23–6.
14. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431–46.
15. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1447–61.
16. Choi H, Neogi T, Dalbeth N, Terkeltaubb R. New perspectives in rheumatology: Implications of the Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities Trial and the associated Food and Drug Administration public safety alert. Arthritis Rheumatol. 2018;70(11):1702–1709.

17. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology (Oxford). 2014;53(11):1920–6.
18. Neame RL, Carr AJ, Muir K, Doherty M. UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte. Ann Rheum Dis. 2003;62(6):513–8.
19. Kleiber Balderrama C, Rosenthal AK, Lans D, Singh JA, Bartels CM. Calcium pyrophosphate deposition disease and associated medical comorbidities: a National Cross-Sectional Study of US Veterans. Arthritis Care Res. 2017;69(9):1400–6.
20. Williams CJ, Zhang Y, Timms A, Bonavita G, Caeiro F, Broxholme J, et al. Autosomal dominant familial calcium pyrophosphate dihydrate deposition disease is caused by mutation in the transmembrane protein ANKH. Am J Hum Genet. 2002;71(4):985–91.
21. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. N Engl J Med. 2016;374(26):2575–84.
22. Ea HK, Liote F. Calcium pyrophosphate dihydrate and basic calcium phosphate crystal-induced arthropathies: update on pathogenesis, clinical features, and therapy. Curr Rheumatol Rep. 2004;6(3):221–7.
23. Zhang W, Doherty M, Bardin T, Barskova V, Guerne PA, Jansen TL, et al. European league against rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70(4):563–70.
24. Grassi W, Okano T, Filippucci E. Use of ultrasound for diagnosis and monitoring of outcomes in crystal arthropathies. Curr Opin Rheumatol. 2015;27(2):147–55.
25. Andrés M, Sivera F, Pascual E. Therapy for CPPD: options and evidence. Curr Rheumatol Rep. 2018;20(6):31.
26. Bosworth B. Calcium deposits in the shoulder and subacromial bursitis: a survey of 12,122 shoulders. J Am Med Assoc. 1941;116(22):2477–82.
27. Clavert P, Sirveaux F. Shoulder calcifying tendinitis. Revue de chirurgie orthopedique et reparatrice de l'appareil moteur 2008;94(8 Suppl):336–55.
28. Stack J, McCarthy G. Basic calcium phosphate crystals and osteoarthritis pathogenesis: novel pathways and potential targets. Curr Opin Rheumatol. 2016;28(2):122–6.
29. Whyte MP. Hypophosphatasia: enzyme replacement therapy brings new opportunities and new challenges. J Bone Miner Res. 2017;32(4):667–75.
30. Harvie P, Pollard TC, Carr AJ. Calcific tendinitis: natural history and association with endocrine disorders. J Shoulder Elb Surg. 2007;16(2):169–73.
31. O'Shea FD, McCarthy GM. Basic calcium phosphate deposition in the joint: a potential therapeutic target in osteoarthritis. Curr Opin Rheumatol. 2004;16(3):273–8.
32. Ea HK, Liote F. Diagnosis and clinical manifestations of calcium pyrophosphate and basic calcium phosphate crystal deposition diseases. Rheum Dis Clin N Am. 2014;40(2):207–29.
33. Rosenthal AK. Basic calcium phosphate crystal-associated musculoskeletal syndromes: an update. Curr Opin Rheumatol. 2018;30(2):168–72.
34. Lorenz EC, Michet CJ, Milliner DS, Lieske JC. Update on oxalate crystal disease. Curr Rheumatol Rep. 2013;15(7):340.
35. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int. 2009;75(12):1264–71.
36. Asplin JR. The management of patients with enteric hyperoxaluria. Urolithiasis. 2016;44(1):33–43.
37. Wise CM, White RE, Agudelo CA. Synovial fluid lipid abnormalities in various disease states: review and classification. Semin Arthritis Rheum. 1987;16(3):222–30.
38. Reginato AJ, Schumacher HR, Allan DA, Rabinowitz JL. Acute monoarthritis associated with lipid liquid crystals. Ann Rheum Dis. 1985;44(8):537–43.