CRYSTAL INDUCED ARTHRITIS: AN OVERVIEW

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Introduction:

There are a variety of crystals that may be associated with joint and soft-tissue problems, due to their deposition in and around joints (Table 1). This review will focus primarily on the potential problems associated with monosodium urate monohydrate (MSU) crystal deposition and the calcium crystal associated problems.

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A. Calcium Crystal Induced Inflammation:

Calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphate hydroxy-apatite (BCP), are the common calcium containing crystals that can result in a variety of joint symptoms due to their deposition in and around joints. CPPD crystals may be deposited in fibrous and articular cartilage, where they are associated with degenerative changes. The crystals may provoke an acute attack of synovitis- referred to as pseudo-gout. The deposits are often visible as a fine layer of calcification overlying the menisci and articular cartilage of the knee- termed chondrocalcinosis; and BCP crystals can also cause acute inflammatory attacks of arthritis, usually around the shoulder, referred to as calcific periarthritis.

1. Calcium pyrophosphate dihydrate (CPPD) crystal associated arthropathies: CPPD crystal deposition disease is usually idiopathic and presents as sporadic episodes in the majority of patients. There are rare familial forms of the disease and an association with some metabolic disorders- such as hyperparathyroidism, haemochromatosis, hypophosphatasia, Wilson’s disease, ochronosis, hypo-calcuic hypercalcaemia (and perhaps other hypercalcaemic states), diabetes mellitus and hypomagnesaemia- has been documented. Treatment of osteoarthritis (OA) of the knee with intra-articular injections of hyaluronic acid preparations (such as Hylan GF-20) has also been associated with triggering of an acute attack of pseudo-gout.

Familial CPPD deposition disease generally may present in one of two ways: A rather benign, early onset (< 50 yrs), usually acute presentation, having a polyarticular distribution involving the knee, wrist, shoulder, elbow, hip or ankle and recurrent episodes of crystal-positive acute pseudo-gout and chondrocalcinosis. The second a more chronic arthropathy, with a late onset (> 50 yrs), destructive oligo/mono-arthropathy, affecting the knees, wrists, shoulders or hips.

Thus CPPD crystal associated disease is clinically heterogeneous and may cause both an acute or chronic arthritis. Some of the recognised clinical patterns of CPPD deposition disease are: Pseudogout is the most common form (also called CPPD disease type A) and presents as acute episodes of synovitis at a single joint, most often at the knee. More common in men, the ‘attack’ typically lasts from a few days to 3-4 weeks and is characterised by acute pain, swelling and warmth at the affected joint, often indistinguishable from gout. X-ray of the knee may reveal typical calcification of the meniscus- chondrocalcinosis (figure 1) and the joint synovial fluid examination will reveal the typical positively birefringent CPPD crystals, on polarising light microscopy. Attacks may be precipitated by any intercurrent illness, recent surgery or trauma and rapid diuresis.
Pseudorheumatoid arthritis is seen in less than 5% of all CPPD patients. It is also called CPPD disease type B. This is associated with a sub-acute inflammatory polyarthritis, which may persist for a few months and therefore may ‘mimic’ RA.

Asymptomatic is probably the most common form of CPPD disease, also referred to as type E. It is clinically silent and asymptomatic. It is usually diagnosed by the presence of chondrocalcinosis, detected by radiology, usually done for other reasons.

Pseudoarthropathic also referred to as type F CPPD disease, is rare. It has been described in tertiary syphilis and severe neurotrophic arthritis. However, a similar clinical picture of severe joint destruction can also be seen in the absence of any associated neurological abnormalities. Joint aspiration reveals a non-inflammatory synovial fluid with a large number of CPPD crystals.

CPPD deposits can in addition, occasionally cause problems at other sites: a) they may cause median nerve compression at the wrist; b) may cause spinal canal stenosis due to involvement of the ligamentum flavum; c) and may even cause a cervical spine myelopathy.

**PATHOGENESIS:**

CPPD deposition disease is essentially a primary disorder of the articular cartilage with alterations in the chondrocytes being implicated in CPPD crystal formation. Excess formation of inorganic pyrophosphate (PPi) by the chondrocytes, correlates with CPPD deposition. Other changes associated with CPPD disease include; cartilage matrix abnormalities, presence of articular cartilage vesicles that act as sites of CPPD crystal formation, abnormalities of growth factors and cytokines such as transforming growth factor β (TGF-β) that stimulate chondrocyte PPi generation. Once formed, calcium crystals induce a variety of cellular signalling molecules. Calcium crystals induce interleukin 8 (IL-8) expression in monocytes. IL-8 is a key mediator of inflammatory synovitis and possibly also of chronic cartilage degeneration associated with CPPD deposition disease.

**DIAGNOSIS AND TREATMENT:**

An awareness of the clinical pattern of presentation is essential for the diagnosis of CPPD disease. However, confirmation of the diagnosis is by the demonstration of typical crystals of CPPD in synovial fluid of an affected joint, by polarising light microscopy. Features that help to distinguish CPPD disease from OA are the presence of chondrocalcinosis on radiology and the involvement of joints not usually involved in OA. Radiological screening for CPPD disease is done by AP views of the knees, pelvis (for pubis and hips) and both hands including wrists. Once CPPD disease is diagnosed, the patient should be screened for the presence of any associated metabolic disorders (vide supra). Treatment of CPPD disease remains empirical and symptomatic. Non-steroidal anti-inflammatory drugs (NSAIDs) are the main-
stay of initial therapy. In pseudo-gout, aspiration of the joint followed by an intra-articular steroid injection, would be the treatment of choice. Intra-muscular injection of a long acting steroid preparation such as triamcinalone or methyl-prednisolone may also be helpful to abate an acute attack. Intravenous colchicine is effective in acute pseudo-gout, however its toxicity precludes routine use. Low dose oral colchicine (0.5 mg twice or thrice a day) in addition to NSAIDs, may however have an additive effect without significant toxicity.

II. Basic calcium phosphate hydroxy-apatite (BCP) crystal associated arthropathies:

The BCP crystals include hydroxy-apatite, octacalcium phosphate and tricalcium phosphate. BCP crystals may be associated with a number of clinical situations such as:

- **Periarthritis / tendonitis:** BCP crystals often cause a periarthritis, usually around the shoulder joint, or a calcific tendonitis or bursitis. Patients present with acute pain and warmth in the affected area and the diagnosis is suggested by the presence of extra-articular calcium deposits on radiology. Patients usually respond to NSAIDs, low-dose colchicine and/or intra-lesional injection of steroids. Recently, EDTA treatment has been reported to be effective in the removal of calcific deposits.

- **Milwaukee shoulder syndrome (MSS):** This condition is more common in women. MSS usually affects a single joint- most often the shoulder, or the knee. There is a gradual onset synovitis and there may be a history of preceding trauma or overuse of the joint. There are marked degenerative changes on radiology, with the presence of loose bodies and calcification. At the shoulder, large and extensive rotator-cuff tears maybe present. Diagnosis may not be easy, as recognition of BCP crystals is difficult and the diagnosis may eventually depend upon excluding other causes such as gout or septic arthritis. CPPD disease may cause diagnostic confusion, particularly as CPPD crystals maybe seen in about 30% of patients with MSS. There is no specific treatment and various measures include- NSAIDs, repeated joint aspiration, intra-articular steroid injections and eventually (if joint destruction is marked) arthroplasty.

- **Osteoarthritis:** BCP crystal deposition may present as osteoarthritis (OA). The quantity of BCP deposition correlates with the extent of degenerative change. The exact role of BCP crystals in this situation however, remains unclear.

- **Erosive arthritis:** An erosive arthritis associated with BCP crystals has been described. Patients may show a peripheral or axial arthritis. Radiology reveals bony erosions with calcification. Intramuscular steroid and low dose colchicine orally, may be helpful.

III. Calcium oxalate associated arthritis:

Calcium oxalate crystals produce an unusual form of arthritis and the clinical situations that may be associated with calcium oxalate arthritis are end stage renal disease on dialysis; short bowl syndrome; diets rich in rhubarb, spinach or ascorbic acid; thiamine or pyridoxine deficiency; primary oxalosis (a rare inborn error of metabolism).

Primary oxalosis is quite rare, though about 90% of patients on chronic haemodialysis may show evidence of deposition of calcium oxalate in kidney and bone tissue. The clinical picture is that of an acute mono- or oligo arthritis mainly affecting the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands. Bursal involvement and teno-synovitis may be associated and the arthritis may become chronic. The diagnosis can be confirmed by identifying the typical calcium oxalate crystals (bipyramidal, positively birefringent, calcium oxalate dihydrate crystals) in synovial fluid. There is no specific treatment. Symptomatic measures such as NSAIDs, intra-articular injections, colchicine and increased frequency of dialysis, may be tried, but the response is poor.

B. Monosodium urate Monohydrate Crystal Induced Inflammation- GOUT:

Gout is the term given to a group of metabolic conditions, in which the signs and symptoms result from the deposition of crystals of monosodium urate monohydrate (MSU) in various connective tissues and joints. The deposition of these crystals, results from raised levels of uric acid in blood (hyperuricaemia) and various body fluids. Hyperuricaemia is however, not an essential requirement for the diagnosis of gout and its presence in a patient with arthritis does not necessarily establish the diagnosis. However, the risk of gout increases with the degree and duration of hyperuricaemia. Established classification criteria for the diagnosis of gout include:

- The presence of typical urate (MSU) crystals in synovial fluid.
- The development of a tophus (figure 2).
- The presence of a characteristic clinical picture, which typically, is an acute onset of severe, mono-articular arthritis in a peripheral joint in the leg (most often the 1st metatarso-phalangeal- MTP- joint).

The clinical manifestations of gout relate to the acute or chronic situations and the renal syndromes associated with uric acid and include:

- **Acute gout,** an acute inflammatory arthritis (synovitis); which may be associated with teno-synovitis; bursitis; and/or cellulitis. There are recurrent attacks of acute synovitis and the intervening period between attacks, is referred to as the inter-critical period.
Chronic tophaceous gout; a chronic, erosive, deforming arthritis, associated with peri-articular and sub-cutaneous urate deposits (called tophi).

Renal disease and gout: Three main renal syndromes may be associated with gout:

1. Urate nephropathy: This is due to the formation of urate (MSU) crystals in the renal interstitium associated with renal insufficiency. The exact relationship between the renal dysfunction and the deposition of urate crystals is, however, not clear. Renal dysfunction may be contributed by associated uncontrolled hypertension or other medical conditions.

2. Uric acid nephropathy: This is an acute obstructive uropathy, due to the rapid formation of uric acid crystals in the collecting tubules, in an acutely ill and dehydrated patient (usually a patient with a lymphoproliferative disorder treated with cytotoxic drugs- 'tumour lysis syndrome').

3. Uric acid nephrolithiasis: This is due to the formation of uric acid calculi in the renal tract. The risk factors include: elevated urinary uric acid levels, low urine pH and hyperuricaemia.

The biochemical hallmark of gout is hyperuricaemia (even though it is not absolutely essential in establishing the diagnosis). Individuals may exhibit long periods of asymptomatic hyperuricaemia, before developing clinical symptoms. Hyperuricaemia in turn, maybe caused by: a) Dietary excess of purines; b) an overproduction (metabolic or genetic) of urate; or c) an under-excretion of urate from the kidneys. Gout therefore, may be classed as primary or secondary, depending upon the cause of hyperuricaemia:

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<tr>
<td>A. The presence of characteristic urate crystals in synovial fluid or</td>
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<td>B. A tophus proved to contain urate crystals by chemical means or polarising light microscopy or</td>
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<td>C. The presence of 6 of the following 12 parameters:</td>
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<td>1. More than one attack of acute arthritis</td>
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<td>2. Maximal inflammation developed within one day</td>
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<td>3. Attack of monoarticular arthritis</td>
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<td>4. Observed joint redness</td>
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<td>5. First metatarsophalangeal (MTP) joint painful or swollen</td>
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<td>6. Unilateral attack involving 1st MTP joint</td>
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<td>7. Universal attack involving tarsal joint</td>
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<td>8. Suspected tophus</td>
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<td>9. Hyperuricaemia</td>
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<td>11. Subcortical cysts without erosions on radiology</td>
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<td>12. Negative culture of joint fluid for microorganisms during an attack of joint inflammation</td>
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Primary denotes the absence of any underlying disease causing hyperuricaemia. In most (75%-90%) individuals an under-excretion of urate at the renal tubular level is the mechanism involved. There is a reduced urinary uric acid excretion/clearance. A minority of patients (<2%) with primary gout will have an excessive purine biosynthesis due to an inborn enzymatic defect. This rather rare clinical situation should be suspected if gout presents at an unusually early age and is associated with a strong family history of gout.

Secondary maybe due to a) an overproduction of urate due to increased metabolic activity as seen in the various myelo-proliferative disorders, haemolytic anaemia and psoriasis; or b) due to an under-secretion of uric acid due to renal disease or drugs (such as diuretics, pyrazinamide, cyclosporine etc).

CLINICAL FEATURES/DIAGNOSIS OF GOUT:

Acute gout is eight times more common in men than women and the first attack commonly occurs between the third to sixth decades. It is extremely uncommon in women before the menopause. The commonest joint to be affected is the first metatarsophalangeal (1st MTP) joint, also referred to as podagra. A typical attack is sudden in onset and awakens the patient from sleep. The joint becomes red, hot, and swollen,
with shiny overlying skin, which may desquamate later. The joint is exquisitely painful and tender and the patient is usually unable to bear weight on it. The attack is not uncommonly mis-diagnosed as local infection. During an acute attack, there may be constitutional symptoms such as anorexia, nausea and fever. Leucocytosis and an elevated ESR may also be present. An elevated serum uric acid is usually (but not invariably) present.

With the above clinical features, the diagnosis of acute gouty arthritis, is fairly certain. However, in about 10% of patients, the initial presentation may be polyarticular with sparing of the 1st MTP joint, especially in elderly females on thiazide diuretics. Asymptomatic hyperuricaemia, is relatively common and a raised serum uric acid alone, does not necessarily prove the diagnosis of Gouty arthritis. Conversely, serum uric acid will be elevated at some point in the clinical spectrum of gout and must be documented in the patient, to make the diagnosis. Occasionally acute attacks may occur with normal serum uric acid levels.

To establish the diagnosis of gout beyond doubt, synovial fluid should be aspirated from an affected joint whenever possible and examined under polarising light microscopy to look for typical MSU crystals. These crystals will appear as needle shaped, negatively birefringent crystals.

Following the initial acute attack, some patients may remain free of symptoms for long periods- the ‘intercritical’ period. Others experience repetitive attacks with shortening of the intercritical period and may even get polyarticular symptoms leading to diagnostic confusion. Recurrent acute attacks may result in chronic tophaceous gout, with tophi being found typically in the periarticular tissues, cartilaginous helix of the ear, bursae and tendon sheaths. The tophi appear as peri-articular swellings, filled with a soft, ‘cheesy’ or ‘chalky’ material. This tophaceous material will reveal numerous typical MSU crystals, when examined under polarising light microscopy.

Gout and hyperuricaemia are often associated with obesity, type IV hyperlipidaemia, impaired glucose tolerance and ischaemic heart disease. It is important to identify these associations, in the overall management of the patient.

RADIOLOGICAL CHANGES:
X-rays are usually normal early in the disease. After a few repetitive acute attacks, the typical change is a punched out erosion, with sharp margins and overhanging edges (figure 3). Other non-specific changes are a reduction in joint space and presence of sub-articular cysts. The erosions may however, be indistinguishable from those seen in other inflammatory joint diseases. Para-articular tophi may be detected as soft tissue swelling with partial calcification.

DIFFERENTIAL DIAGNOSIS:

Acute gouty arthritis must be distinguished from other causes of acute mono-arthritis, such as infective (septic) arthritis; traumatic synovitis; palindromic rheumatism or palindromic onset rheumatoid arthritis; the sero-negative spondarthritides, such as psoriatic arthritis or spondarthritis with peripheral joint synovitis, or sarcoid arthritis. Chronic tophaceous gout maybe confused with nodular rheumatoid arthritis; osteoarthritis with Heberden’s / Bouchard’s nodes; xanthochromatosis with joint involvement; and reticulohistiocytosis.

TREATMENT:
It is important to emphasise that amongst all forms of inflammatory joint disease, the drug treatment of gout, often produces the most satisfactory results. The treatment of
gout can be considered under the following situations:
A. Treatment of acute attack;
B. Prevention of subsequent attacks and treatment of hyperuricaemia;
C. Management of gout in special situations.

A. TREATMENT OF ACUTE ATTACK:
NSAIDs, colchicine and steroids (intra-articular or systemic) form the main-stay of treatment of an acute attack of gout10-12.

NSAIDs: The first line of therapy is to rest the affected joint and to use full doses of a non-steroidal anti-inflammatory drug (NSAID). The NSAIDs that are of particular benefit in this situation, are indomethacin 50mg 8 hrly (or maximum 50mg 6 hrly); naproxen 500mg 12 hrly; ketoprofen or flurbiprofen 100mg 8 hrly; or diclofenac 50mg 8 hrly. However, any NSAID can be used in optimum doses, provided the patient’s renal function is normal. The use of the newer class of cox-II inhibitors of NSAIDs may be a therapeutic option for patients where GI side effects preclude the use of the previous non-selective NSAIDs. However, currently there does not seem to be any specific information on this13.

Colchicine: Colchicine can be a useful adjunct to NSAIDs if the acute attack does not settle rapidly. In a dose of 0.5 mg twice or three times a day, one can avoid the GI side effects seen with higher doses of colchicine and still obtain added therapeutic benefit. The ‘traditional’ way of using oral colchicine was to give an initial dose of 0.6-1.2 mg, followed by 0.6mg every 2 hours until relief of symptoms occur or diarrhoea develops13. Colchicine is certainly effective in relieving most acute attacks of gout however, invariably, GI side effects (nausea, cramps, vomiting or diarrhoea) will intervene, if it is used in this manner. Intravenous colchicine has been reported to be very effective in treating acute gout and some rheumatologists advocate this as the treatment of choice. However, others caution against the use of intravenous colchicine, due to the potential for serious side effects, which include bone marrow suppression, renal failure, alopecia, disseminated intravascular coagulation, hepatic necrosis, diarrhoea, seizures and death11. Therefore, the current recommendation would be to use colchicine in a dose of 0.5mg twice or three times a day, in addition to an NSAID for the acute attack of gout. Following an acute attack, a patient is at increased risk of further acute attacks and therefore, colchicine in a dose of 0.5mg twice a day can be continued for a few weeks, to prevent this13.

Steroids: Most acute attacks respond satisfactorily to either full doses of an NSAID, or to the combination of an NSAID and low dose colchicine, as described above. Occasionally, the clinical response may not be as rapid as desired, or it may prove necessary to aspirate the affected joint for diagnostic synovial fluid analysis. In either situation, injecting the affected joint with steroid (methyl-prednisolone or triamcinolone) may prove to be extremely useful in rapidly resolving the synovitis. Intra-articular steroid can also be very useful in situations where NSAID use is contra-indicated, either due to GI intolerance or renal involvement. Intra-articular steroids are beneficial when one or at most two joints are inflamed. In situations where more than 2 joints are involved and renal/GI side-effects preclude the use of NSAIDs and colchicine, systemic steroids have been shown to be beneficial14. Intra-muscular long acting steroid (either methyl-prednisolone or triamcinolone) 40mg or 80mg can be very effective in this situation, in relieving the acute attack. A note of Caution: an intra-articular injection should be given, only if one can be clinically sure, that one is not dealing with a septic arthritis. If in any doubt, the synovial fluid should be sent for microbial cultures (in addition to being subjected to polarising microscopy) and if still indicated, the joint can be injected once the culture and Gram’s stain examination rule out infection. It is also extremely important to remember that allopurinol or uricosuric drugs should not be commenced during an acute attack of gout. These drugs should be initiated only after satisfactory resolution of the acute attack10 and on adequate colchicine/NSAID prophylactic cover (vide infra).

B. PREVENTION/LONG-TERM TREATMENT:
Prevention of recurrent attacks of acute gout and controlling hyperuricaemia, are the long-term treatment goals in management of patients with gout. Not all patients who have had an attack of acute gout will require long-term treatment. Patients who continue to experience attacks of acute gout and have persistent hyperuricaemia despite efforts to correct other factors causing hyperuricaemia, require treatment to lower uric acid levels12.

We can consider this aspect of treatment as follows:
1. Non-pharmacological treatment involves avoiding/reducing factors that contribute to the development of gout in patients with asymptomatic hyperuricaemia. The measures found to be useful are11; to avoid diuretic therapy; weight gain; alcohol consumption; Aspirin therapy: In high doses, aspirin is uricosuric. However, when commenced in low dose (75-100 mg daily), aspirin initially causes a reduced excretion of uric acid from the kidney and may increase hyperuricaemia. Diet: Providing that the above precautions are followed, stringent dietary restrictions are not required10. However,
patients should be advised to avoid excessive (‘binge’) eating or drinking (to avoid an acute increase in serum uric acid) and overweight patients should be encouraged to undertake some regular exercise, with a view to gradual weight reduction. This is contrary to the previously held belief that a patient with gout had to be provided with a list of food articles to avoid totally, some that could be taken in moderation and some that were allowed freely. The current concept is based on the relationship between obesity, diet and insulin resistance, to gout\textsuperscript{15}. Insulin stimulates the renal tubular sodium-hydrogen exchanger and results in an increase in the tubular reabsorption of urate\textsuperscript{11}. Therefore, a diet that is low in carbohydrate content, with a proportionate increase in proteins and unsaturated fats, will help to reduce serum uric acid levels by enhancing insulin sensitivity (and thereby reducing serum insulin levels proportionately).

2. Long-term management & treatment of hyperuricaemia:

**Prevention of gouty attacks:** Colchicine is effective in preventing recurrent attacks of acute gout, in patients who have sustained a previous acute attack and also in patients who commence a uric acid lowering agent\textsuperscript{10,11,16}. Colchicine 0.5 mg twice a day, is recommended for a patient at the time of commencing a urate-lowering drug. Once serum uric acid levels are controlled and the patient has been free from acute attacks for about 2-3 months, the colchicine can be withdrawn.

Urate-lowering therapy: There is no uniform agreement on when to commence a patient on a urate-lowering drug. Some maintain that this therapy should be initiated only after a patient experiences 3-4 attacks in a year\textsuperscript{11}. Therefore, a diet that is low in carbohydrate content, with a proportionate increase in proteins and unsaturated fats, will help to reduce serum uric acid levels by enhancing insulin sensitivity (and thereby reducing serum insulin levels proportionately).

**2. Xanthine oxidase inhibitors:**

This class of drug remains the drug of choice for lowering serum uric acid and consequently the long-term treatment of gout, due to its convenience of administration and freedom from side-effects\textsuperscript{10}. Allopurinol is the only available drug in this class and can be used in both overproducers as well as underexcretors of uric acid\textsuperscript{12}. A dose of 300 mg daily is usually adequate to lower serum uric acid to normal values in about 85\% patients. A single daily dose is adequate, as its main active metabolite oxypurinol, has a long half-life. The usual practice is to start with 100mg allopurinol daily (to avoid the risk of precipitating an acute attack of gout) and to build up the dose slowly by increments of 100 mg, to the least dose (usually 200 mg-300 mg) required to adequately lower the serum uric acid. The risk of precipitating an acute attack can be reduced further, by using colchicine in a dose of 1 mg daily, starting about 2 weeks before initiating treatment with allopurinol and continuing for about 2-3 months. Once the urate-lowering therapy has been successfully introduced, the therapy should be continued life-long. Allopurinol is particularly indicated in patients with established gout and particularly if they have additional urolithiasis. The aim of therapy would be to lower the serum uric acid to 6 mg/dl to prevent recurrent attacks of acute gout and preferably to 5 mg/dl, to further reduce topohaeous deposits\textsuperscript{2}. In addition, allopurinol is indicated in patients with renal disease (vide infra) and in patients with secondary gout and myeloproliferative disorders with increased cell turnover\textsuperscript{2}.

C. MANAGEMENT OF GOUT IN SPECIAL SITUATIONS:

There are 3 clinical situations that pose special problems in the management of gout: 1) Management of an acute attack in a patient intolerant to NSAIDs; 2) Management of acute and chronic gout in patients with renal disease; and 3) Long-term management of gout in a patient who is hypersensitive to allopurinol.
1. **NSAID intolerance:** As has been mentioned earlier, patients in whom traditional NSAIDs cannot be used due to their GI effects can be managed by:

- Using the newer cox-II inhibitor NSAIDs;
- Using steroids- either intra-articular or intramuscular- to treat the acute attack, together with a very low dose of colchicine if needed;
- Using allopurinol as long-term therapy (possibly even after a single attack of acute gout) with the aim of trying to abolish acute attacks as far as possible, thereby obviating the need for NSAIDs.

2. **Renal disease:** The management of gout in patients with renal disease can be considered in the following situations:

   **In patients with renal impairment,** NSAIDs are contra-indicated or should be used with extreme caution. Therefore, managing an acute attack of gout in a patient with renal failure, essentially involves the use of steroids- either intra-articular or intra-muscular and if needed, even a short course of oral prednisolone- commencing with 30 mg to 40 mg prednisolone daily, and tapering the dose over 2-3 weeks. The dose of allopurinol needs to be reduced appropriately in renal failure, reducing to about 200 mg daily with a GFR below 60 mls/mt and to 100 mg daily at a GFR below 30 mls/mt respectively.

   **In patients following renal transplant,** some important issues in the management of gout need to be considered. Renal transplant recipients are usually on cyclosporine, which itself impairs the renal handling of uric acid. In addition, concomitant renal impairment and the use of diuretics, may cause further hyperuricaemia. The use of colchicine can cause a myoneuropathy and this is particularly so in transplant recipients. The diagnosis is suggested by proximal weakness and absence of deep tendon reflexes and can be confirmed by muscle biopsy. A modified regime of colchicine is proposed for renal transplant patients- a maximum dose of 1.2 mg daily for the first 2 days, reducing to 0.6mg after this and stopping after 7-9 days. Steroids are the anti-inflammatory agents of choice in transplant recipients, as NSAIDs would further compromise renal function. The incidence of tophaceous gout is perhaps more in renal transplant patients (probably aggravated due to the use of cyclosporine) and therefore uric acid lowering therapy with allopurinol, should be used in all transplant recipients with gout, who are also on cyclosporine. If a patient is on azathiaprine, then the maximum daily dose of allopurinol in this situation should not exceed 50 mg daily (due to the potentiation of azathiaprine actions by allopurinol). Alternatively, azathiaprine can be substituted by mycophenolate mofetil (MF), as this agent blocks de novo purine synthesis by its effect of inhibition of the enzyme inosine monophosphate dehydrogenase. Patients on MF should be given allopurinol in a dose of 100 mg daily. In transplant recipients, where the GFR is greater than 50 mls/mt, a uricosuric agent such as probenacoid in a dose of 250 mg twice daily could be considered as further uric acid lowering therapy, together with maintaining adequate hydration and alkalisation of the urine. A new uricosuric agent- benz bromarone available in some European countries (not yet available in India), has been found to be useful in renal transplant patients.

3. **Allopurinol Sensitivity:** Approximately 2% of patients treated with allopurinol develop a rash. Usually this is mild and resolves on stopping the drug. Allopurinol can often be cautiously re-introduced at a lower dose, without a recurrence of the rash. However, about 0.1% patients may develop the more serious problem of exfoliative dermatitis and require systemic steroids. De-sensitisation by the oral or intravenous route may be attempted and is occasionally successful. One must however be extremely cautious as a severe reaction could be provoked. In a very small minority of patients, where allopurinol cannot be used, a uricosuric agent can be substituted for long-term treatment of gout.

**References:**

Crystal induced arthritis: an overview