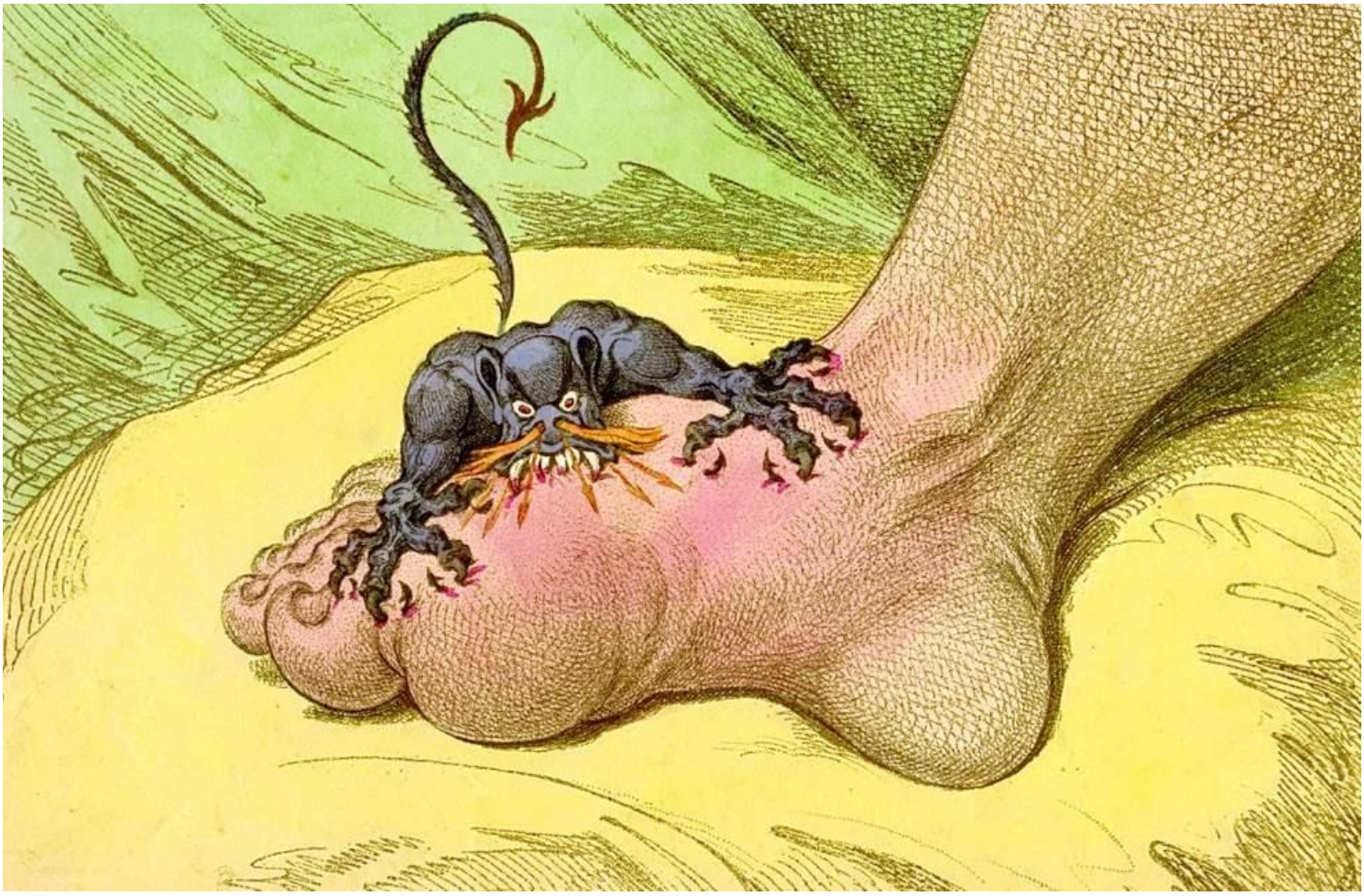
THE NORTHERN HOSPITAL

GOUT (ACUTE)

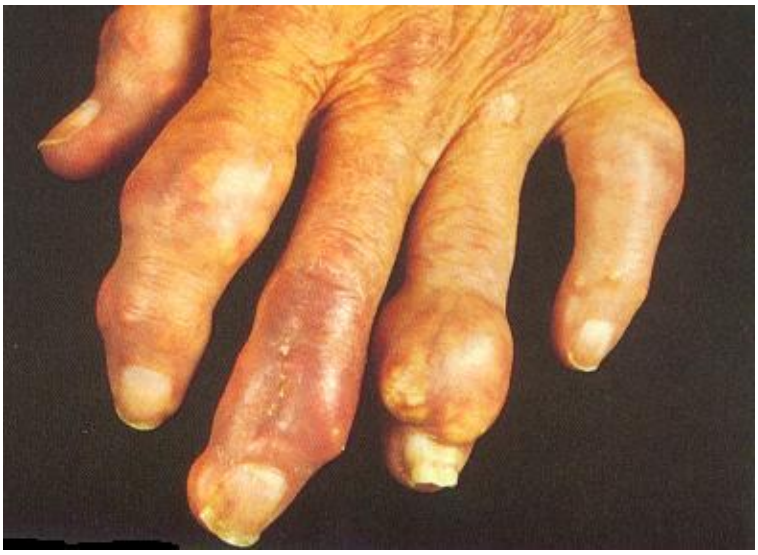


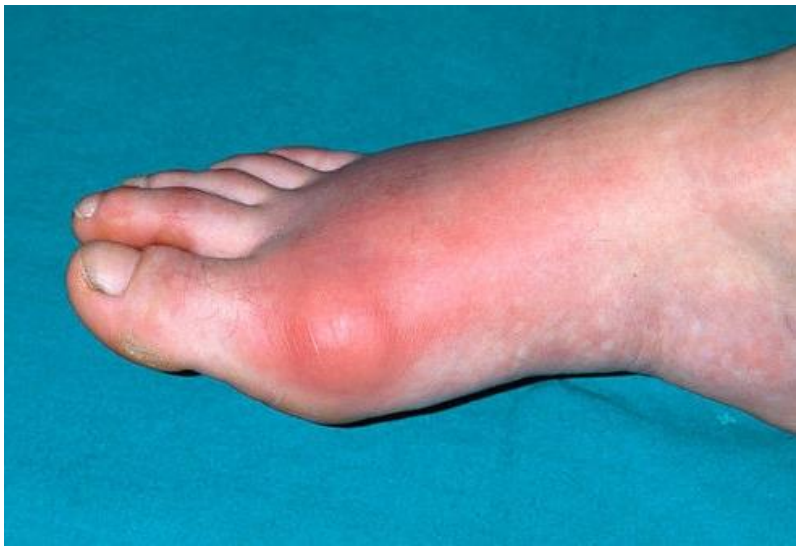
"The Gout", 14 May 1799, James Gillray (1757-1815)

The Gout generally attacks those aged Persons who have spent most part of their Lives in Ease, Voluptuousness, High-living, and too free an Use of Wine, and other Spirituous Liquors; and at length, by reason of the common Inability to Motion in Old Age, have entirely left off those Exercises which Young Persons commonly use. Moreover, such as are liable to this Disease have large Heads, and are generally of a plethoric moist and lax habit of Body, and withal of a strong vigorous Constitution proffered of the best Materials for Life. The Gout however doth not only seize the Gross and corpulent, but sometimes, tho' not so often, attacks Lean and slender Persons : neither doth it always wait till Old Age comes, but sometimes attacks such as are in the Prime of Life, when they have received the Seeds of it from Gouty Parents, or have otherwise occasioned it by an over-early use of Venery, or by leaving off such exercises as they formerly indulged to a great degree ; and who besides have had a voracious Appetite, and used Spirituous Liquors immoderately, and afterwards quitted them on a sudden for those of a Thin and Cooling kind.

A FULL AND PLAIN ACCOUNT OF THE GOUT;
By FERD. WARNER, LL. D. 1772

GOUT (ACUTE)





Left: Typical appearance of severe chronic tophaceous gout [3] *Right: Typical "classic" site of acute gout at the first metatarsopharyngeal joint. (Science Photo Library).*

Introduction

Gout is a chronic inflammatory arthritis resulting from the deposition of **urate crystals** primarily in and around joints, and to a lesser extent around tendons and other connective tissue and the kidneys.

The management of a patient presenting to the ED with **acute** gout involves:

- Exclusion of sepsis
- Confirmation of the diagnosis whenever possible
- Prompt treatment with an anti-inflammatory drugs.
- An assessment of patient mobility and coping ability, especially in the elderly or those with significant comorbidities.

Early recognition and diagnosis of the disease is necessary for commencing prompt, appropriate treatment in order to minimize complications like joint destruction, tendon rupture, and renal disease, which may arise from delayed diagnosis.

The diagnosis of gout has traditionally been based on **clinical findings, laboratory results** and **joint aspirates**, with imaging modalities as an **adjunct**.

Recently however **dual energy CT scanning with color coded images** has become available, which can diagnose gout directly by imaging, with a high degree of specificity and sensitivity.

Although the identification of **negative birefringent monosodium urate crystals** on polarized light microscopy from joint aspirates remains the "gold standard" for the diagnosis of gout, this is **not always possible**, especially when there is insufficient volume

of joint fluid to be aspirated, or in cases where the affected joint is relatively inaccessible to needle aspiration. In the acute setting of gout, joint aspirates may also be negative in up to 25% of cases.

In addition, joint aspiration remains an **invasive** procedure, and although considered relatively safe, it still carries a small risk of complications, most significantly infection of the joint.

Dual energy CT scanning offers an *important new* **additional method of diagnosis** especially in *confounding* situations including:

1. Atypical presentations:

   For example:

   - Soft tissue (as opposed to joint) involvement.
   - Multiple joint involvement (i.e polyarthropathy)
   - Unusual site of involvement

2. Joint fluid cannot be obtained.

3. Acute gout with discordant (e.g. normal) urate levels

4. Hyperuricemia or a past history of gout coincident with another inflammatory disease mimicking gout, (e.g. infection).

5. In patients with chronic gout, where a "flare up" is occurring, i.e distinguishing an acute attack from chronic "burnt out" disease.

Dual energy CT scanning can also provide sensitive and specific **volumetric quantification** of tophi, thus providing an *objective* measure of **disease progression** and/or **response to treatment**.

History

Gout is a ancient human scourge. Its classical symptom of "podagra" or severe pain affecting the first metatarsophalangeal joint was described in ancient Egyptian sources as early as third millennium B.C.

It was not, however, until the latter half of the Twentieth century that it was appreciated that gout was due to **urate crystal deposition**.

This fact was established by the introduction of **polarized light** microscopy into medical science, that demonstrated urate crystals in synovial fluid the cause of gout. Prior to this the relationship between hyperuricemia and gout was uncertain.

Epidemiology

The incidence of gout increases with age and usually appears in men by the fourth or fifth decades of life and in women by the sixth or seventh decades.

In women gout rarely occurs before menopause.

Gout is rare in children unless the child has a genetic defect in urate metabolism.

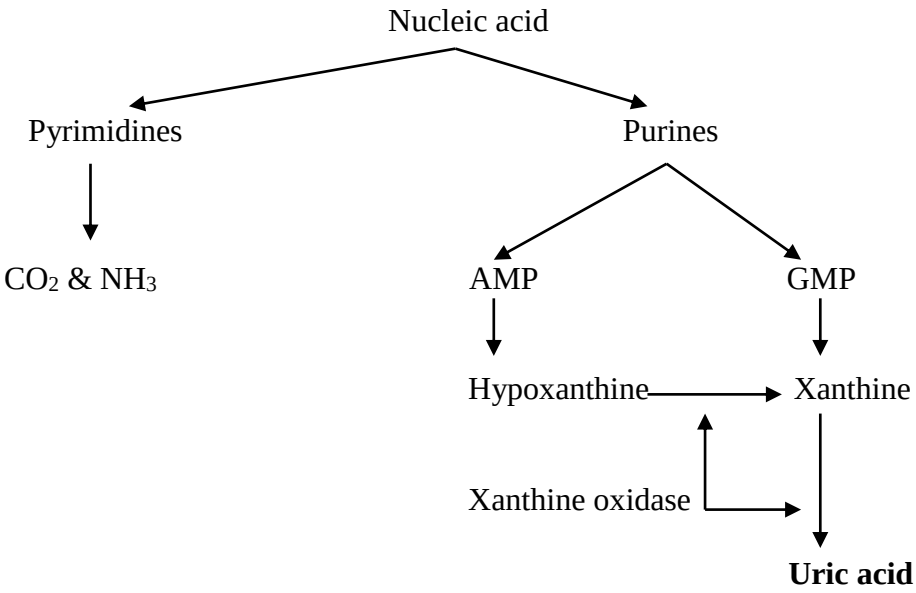
The prevalence of gout is increasing worldwide, particularly in affluent countries such as Australia and New Zealand. In these countries, increasing prevalence relates to the ageing population, higher consumption of alcohol and fructose-sweetened drinks, other changes in dietary habits, and increasing rates of obesity.

Certain ethnic groups have a higher prevalence of gout; in particular, the prevalence of gout is higher in indigenous populations, including in Australia and New Zealand.

Physiology

Purine Metabolism

Uric acid is a breakdown product of nucleic acid metabolism. It is formed in the liver from both dietary and endogenous purine precursors.



Urate is eliminated by the kidneys (two thirds) and the gut (one third).

Renal excretion can be inhibited by a range of drugs which compete for active transport of uric acid into the tubules. These especially include, diuretics

Other drugs enhance urate excretion by blocking reabsorption in the renal tubule.

Any drug or condition which causes a rapid rise or lowering of serum urate levels can precipitate an attack of acute gout.

Pathophysiology

Virtually all cases of clinical gout are associated with elevated uric acid levels.

Only a *small number* of patients with hyperuricemia however will get clinical gout.

This is because sodium urate crystals only sometimes form in patients with hyperuricaemia and clinical gout then only develops if there is an inflammatory reaction to these crystals.

The Inflammatory Response to Urate Crystals

In body fluids, sodium urate reaches saturation at a uric acid concentration of about **0.42 mmol/L.**

The formation of urate crystals only occurs in about 20% of people with uric acid concentrations above the saturation level, however the likelihood increases as the concentration increases.

Crystals form initially within joints (synovium) and subsequently in other connective tissue sites such as bones, skin and tendons.

An chronic aggregation of crystals is called a tophus.

Although hyperuricaemia is required for crystal formation, it is not the full explanation.

Urate crystals form in only certain locations, and not at all in most people with hyperuricaemia. Various biological substances, such as IgG, influence the nucleation and growth of urate crystals. The balance between inhibitors and promoters of crystal formation probably plays a major role in determining if and where urate crystals form.

Urate crystal formation occurs slowly (weeks to months) and does not produce symptoms.

The inflammatory system largely (but not completely) ignores the crystals most of the time, but eventually an inflammatory response does occur and results in an attack of clinical gout. Many components of the inflammatory system are involved in acute gouty inflammation and neutrophils play a key role.

Causes

Acute gouty arthritis results from overproduction or reduced secretion of uric acid.

Traditionally gout has been divided into primary types or secondary types.

1. Primary Gout:

   There is often a familial history

   - There may be an idiopathic under excretion of uric acid, (90% of cases)
   - There may be an idiopathic overproduction (10% of cases).

2. Secondary Gout (less commonly):

   Causes here include:

   Overproduction of uric acid:

- **Increased cellular turnover**, especially seen with myeloproliferative disorders, or malignancy and following cytotoxic therapy.

- Foods rich in **purines**:

  Uric acid is formed in the liver from dietary and endogenous purines.

  Consumption of purine-rich foods can increase serum uric acid concentration and the risk of gout in susceptible individuals, in particular:

  - ♥ Meats
  - ♥ Seafoods
  - ♥ Alcohol (particularly beer and spirits)
  - ♥ Fructose-sweetened drinks

- A small number of cases are due to specific enzyme defects (such as **Lesch-Nyhan** syndrome)

Under excretion of uric acid:

- Drugs such as thiazide diuretics (other diuretics to a lesser extent), aspirin and others
- Chronic renal failure

Complications

1. Gouty arthritis:
   - Pain and edema of the acute inflammatory crystalline arthritis can be extremely debilitating.
   - Chronic tophaceous gout is destructive and may, unless it is treated, eventually leave the patient completely disabled. Such progression is usually completely preventable with correct treatment.
2. Renal disease in chronic gout:
   - Chronic urate nephropathy
   - Urate renal stones, (nephrolithiasis)
3. Chronic gout:
   - If gout remains untreated with urate-lowering therapy, recurrent attacks may fail to resolve completely, slowly leading to a chronic crippling, destructive arthritis.

Even in the absence of recognized recurrent attacks, urate crystals can deposit in the joints, soft tissues and kidneys, and can lead to joint damage and chronic kidney disease.

Clinical Features

There are five recognized “stages: of gout:

1. Asymptomatic hyperuricaemia
2. Acute gouty arthritis
3. Inter-critical gout (i.e between acute attacks)
4. Chronic tophaceous gout
5. Gouty nephropathy

The clinical features of **acute gout** include:

1. **Acute** onset of **severe** pain and tenderness in the affected joint or tissue.
2. Joint involvement:

   With first attacks there is usually only **one joint involved**, however, polyarticular acute flares are also possible, where multiple joints in the same limb may be involved, as when inflammation begins in the great toe and then progresses to involve the midfoot and ankle.

   In decreasing order of frequency, involvement is lower limb > upper limb and distal > proximal, as follows:

   - First metatarsopharyngeal joint
   - Other metatarsopharyngeal joints
   - Ankle
   - Knee
   - Fingers / wrist
   - Elbow

   The shoulder and spine are rarely affected by gout.

3. Tendon involvement:

   In particular:

   - Achilles

- Popliteal/ quadriceps
- Peroneal
- Cruciates
- Triceps

4. Cartilage:
    - Meniscus
5. Bursae:
    - Prepatella

If the acute attack is not treated, symptoms usually subside over a few days to 1 to 2 weeks. [2]

Most patients who are not started on urate lowering therapy once the initial episode has subsided will have a second acute attack of gout within 2 years. [2]

Ischaemic heart disease, hypertension and chronic kidney disease are independent risk factors for recurrent attacks.

Initially, recurrent attacks may be separated by long intervals of relatively normal joint function, but eventually, without prophylaxis recurrent attacks occur more frequently, are of longer duration, and involve more joints.

Differential diagnoses

Important differential diagnoses include:

1. **Infection**:
    - This is the most important differential diagnosis.

      Fever, chills, and malaise do not reliably distinguish cellulitis or septic arthritis from crystal-induced arthritis because all 3 illnesses can produce hese signs and symptoms.

      As a general rule acute however acute gout has a more abrupt onset of symptoms than a septic joint and there is less fever and "constitutional" symptoms with acute gout as compared to a septic joint.

      When a patient presents with an identical recurrent attack of crystal-induced arthritis, the diagnosis is rarely in question, however the possibility of septic arthritis nonetheless must always be borne in mind.
2. Pseudogout:

- Although gout and pseudogout cannot reliably be distinguished on clinical grounds, a tendency exists for gout symptoms to develop rapidly over a few hours, whereas the onset of symptoms in pseudogout is usually more insidious and may occur over several days.

3. Rheumatoid arthritis

4. Osteoarthritis

Investigations

Blood tests:

1. FBE:

   - There may be a mild leukocytosis.

2. U&Es and glucose

   - To establish renal function.

3. Inflammatory markers (ESR/ CRP) may be elevated.

4 Uric acid levels:

   - The tendency of laboratories to report a range of "normal" values (which differ considerably between laboratories) contributes to confusion. It makes little sense to consider what is "normal", what matters is whether the concentration level places the person *at risk* of crystal formation.

     The "normal" uric acid concentration is **< 0.42 mmol/L.**

     The incidence of gout increases greatly with serum uric acid concentrations **> 0.54 mmol/L**

     Note however that plasma urate levels do not always correlate well with clinical gout

     While the presence of hyperuricaemia is important in the diagnosis of gout, patients with acute gout may have a normal serum uric acid concentration.

     Furthermore, the presence of hyperuricaemia does not necessarily indicate that gout is the explanation for a patient's symptoms. Patients can also have *asymptomatic hyperuricaemia*, which is simply a risk factor for developing gout.

Plain Radiology:

1. Plain radiographs:

   - Patients with new onset of **acute** gout usually have **no** radiographic findings, apart from some associated soft tissue swelling.

- In **chronic** gout the following may be seen:
  - ♥ Joint destruction, including secondary osteoarthritic changes.
  - ♥ Gouty erosions:

    These tend to be deep, with the center of the circular erosions lying within the bone (as compared with the erosions of rheumatoid arthritis which are more m superficial and the center of the lesions tend to lie outside the bone).

2. Tophi:
   - Tophi may be seen if calcified.
3. Renal involvement:
   - Pure uric acid renal stones are radiolucent on plain x-ray, (but are readily detected by CT scan).

CT Scan / Dual Energy Colour Coded CT Scanning:

Conventional, *single*-energy CT can demonstrate erosions and hyperdense tophi with high sensitivity, however, these findings remain of insufficient specificity to make a *definitive* diagnosis of gout.

Dual energy CT scanning with **colour coded images** on the other hand can make a *specific* diagnosis of gout.

The fundamental principle behind the use of **Dual energy CT scanning** is to differentiate materials based on their *relative* absorption of X-rays at different photon energy levels (typically at 80 and 140 kVp).

The differential attenuation of the material examined is directly related to its atomic weight and electron density.

Dual energy CT scanners, are able to perform simultaneous acquisitions at two energy levels (80 and 140 kVp) by using two separate sets of X-ray tubes and detectors positioned 90 degrees apart. By this technique, high-resolution images with excellent material separation are possible without an increase in radiation dose compared to conventional single-energy scans.

The sensitivity and specificity in one study has been quoted at 0.9 and 0.83 respectively.

Acute gout (< 6 weeks) may be less reliably detected where very small deposits of urate crystals may be missed in early gout.

Because dual-energy CT may *directly* depict urate crystal deposition, it can be specifically used to evaluate for gout **regardless of patients' serum urate levels**. Thus, dual-energy CT findings may easily confirm a diagnosis of gout in patients with normal serum urate levels or exclude it in patients with hyperuricemia.

After an acute attack, classic osseous findings take several years to manifest, so if these findings are seen with **no** urate crystal deposition, they may be due to **remote, currently inactive** gout, and alternative causes for acute-onset arthropathy may need to be considered.

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MRI:

Like conventional single energy CT, MRI can readily detect indirect evidence of gout.

MRI can depict cortical erosions, marrow oedema and gouty tophi.

However, as with conventional single energy CT, these imaging features are not specific for gout, and so the diagnosis can only be inferred by correlating these findings with disease distribution and other clinical features.

Joint Aspiration:

Joint aspiration for synovial fluid analysis remains for urate crystals the "gold standard" for the diagnosis of gout.

It is also essential for the ruling out of **septic arthritis**.

A prior history of gout or pseudogout does not rule out the possibility of acute septic arthritis. Septic arthritis must be diagnosed and treated promptly. Irreversible damage can occur within 4 - 6 hours, and the joint can be destroyed within 24 - 48 hours.

Joint fluid analysis includes

1. M&C:

    - Gram stain, culture and sensitivities.

2. Crystals analysis:

    - Crystals of **monosodium urate** appear as needle-shaped intracellular and extracellular crystals that exhibit **negative birefringence** when viewed by **polarized light**.

3. WBC count:

    - Elevated in acute gout and sepsis.

Management

The main dilemma in the ED is distinguishing acute gout from a septic arthritis.

This may require needle joint aspiration (often under ultrasound guidance, depending on the joint involved), in order to rule out a septic joint.

The management of acute gout relies on an understanding of what is safe and appropriate when the diagnosis is likely (but may not have been proven).

Acute therapy needs to be modified in light of other health problems, particularly contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) and /or to colchicine.

Prevention:

1. Diet:

    - Dietician referral should be considered for patients with acute gout, they can provide dietary advice on the avoidance of aggravating foods and low purine diets.

      A purine-free diet reduces urate excretion by 40%, so diet is a significant source of the urate precursors.

2. Allopurinol:

    Gout can be effectively managed and its **complications prevented** with adherence to **lifelong** urate-lowering therapy using a treat-to-target approach

    - Gout prophylaxis is achieved with allopurinol (**100-300 mg per day**)

    Note however:

- During the treatment of acute gout any sudden **change** (especially fall) in the concentration of serum uric acid will exacerbate the attack.

  Patients taking regular hypouricaemic therapy should therefore **not** stop their treatment.

  Likewise, hypouricaemic therapy should not commence until after the attack has settled.

  If patients are already taking urate-lowering therapy, advise them not to stop or change therapy during an acute attack because sudden changes in serum uric acid concentration can prolong or worsen the attack.

See Rheumatology therapeutic guidelines for full prescribing details

3. Second-line urate lowering therapies:

Allopurinol is the recommended first line treatment to lower serum uric acid concentration in patients with gout however, if allopurinol is contraindicated or not tolerated at any dose, the following second-line urate-lowering therapies are recommended:

- Febuxostat (a xanthine oxidase inhibitor)
- Probenecid

Treatment:

For treatment of acute gout:

1. NSAIDS:

- Initially, gout may subside spontaneously in less than a week, but the patient will usually seek help before this.

  Nonsteroidal anti-inflammatory drugs (NSAIDs) in full doses reduce inflammation and pain relatively quickly and should be first line therapy if there are no contraindications.

  All NSAIDs including COX-2 inhibitors are effective in acute gout.

  NSAIDs including COX-2 inhibitors can also be used to prevent recurrence.

  Treatment is continued at least until the attack has settled and often for one further week.

Two options include: [4]

- *Ibuprofen 400 mg orally 6 hourly prn*

Or

- *Indomethacin 50 mg orally 8 hourly as tolerated*

2. Colchicine:

Although this drug has been used to treat acute gout since the Sixth century and is of proven efficacy, it should only be prescribed as primary treatment with caution because of its toxicity.

It is also highly lethal when taken in overdose, and so a patient's psychiatric history (e.g. recurrent overdoses) should always be considered.

It may used when NSAIDs are contraindicated or ineffective.

Give:

- Colchicine 1 mg orally initially, then 500 micrograms 1 hour later, as a single one-day course (total dose is 1.5 mg).

The low-dose regimen of colchicine recommended above is as effective as higher-dose regimens and is significantly safer.

Other low-dose regimens of colchicine may also be effective but their benefit has not been proven (e.g. 500 micrograms orally, 8 - 12 hourly until symptoms abate (maximum of **6 mg** over 4 days); reduce dosage in renal impairment).

Other low-dose regimens may be considered if the patient's symptoms have not abated after the single one-day course; however, the **total dose** of colchicine given in an acute attack should not exceed **6 mg** over **4 days**.

3. Steroids:

Oral corticosteroids are very effective for acute attacks.

They are usually reserved for patients in whom NSAIDs and colchicine are contraindicated or ineffective.

Corticosteroids such as prednisolone may be preferred for patients with renal impairment or complex medical problems.

Give:

- *Prednisolone 50 mg orally daily (for 5 days then review)*

Intra-articular injection of steroid:

Intra-articular corticosteroid for a knee joint is effective and convenient when only one joint is involved and when that joint is easy to inject. In this situation it is usually possible to aspirate joint fluid to confirm the diagnosis and exclude sepsis.

It is not safe to inject a joint in which sepsis is a possibility if it has not been possible to obtain synovial fluid. Injecting corticosteroid is likely to temporarily suppress the joint inflammation and result in a delay in recognition of the joint infection.

See Rheumatology therapeutic guidelines for full prescribing details

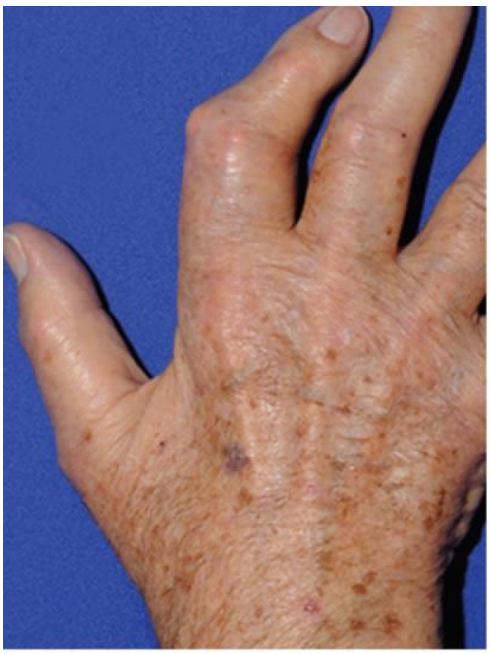
4. Physiotherapy:

- In the elderly and those with significant comorbidities, mobility issues can become very important and an assessment by the Emergency Department physiotherapist may be required to fully assess whether a patient is safe for discharge.

5. Social:

- Acute attacks of gout can be very debilitating, especially in the elderly and their ability to cope at home must be carefully assessed.

Appendix 1



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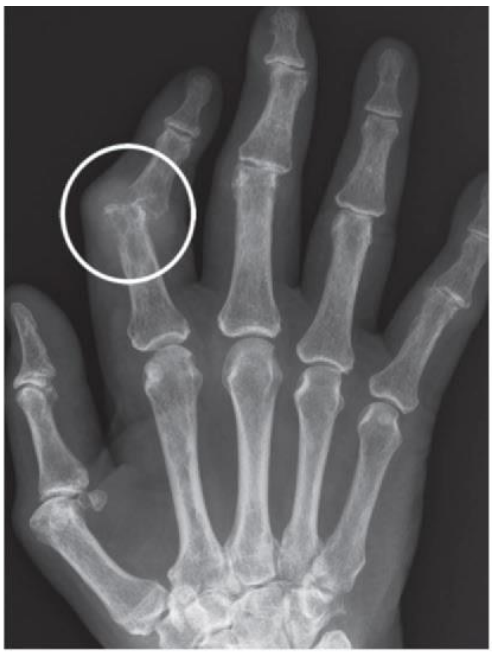

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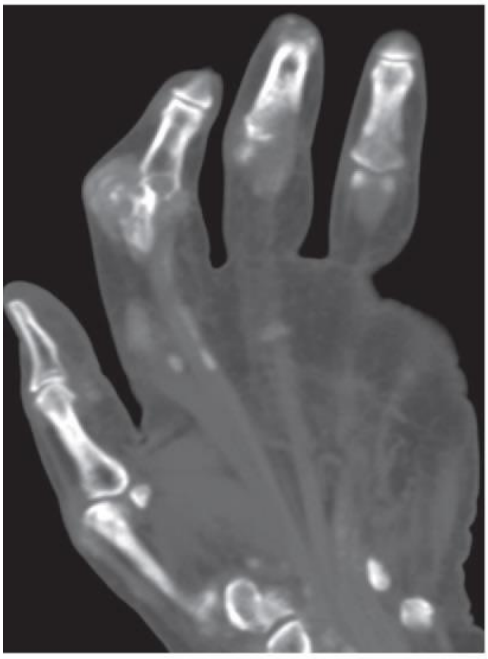

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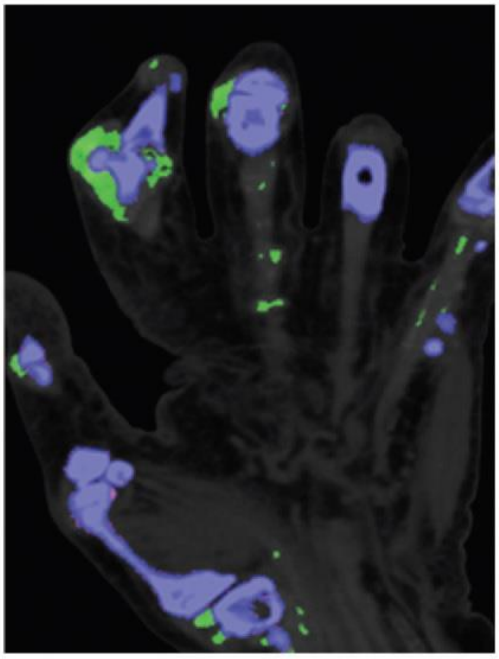

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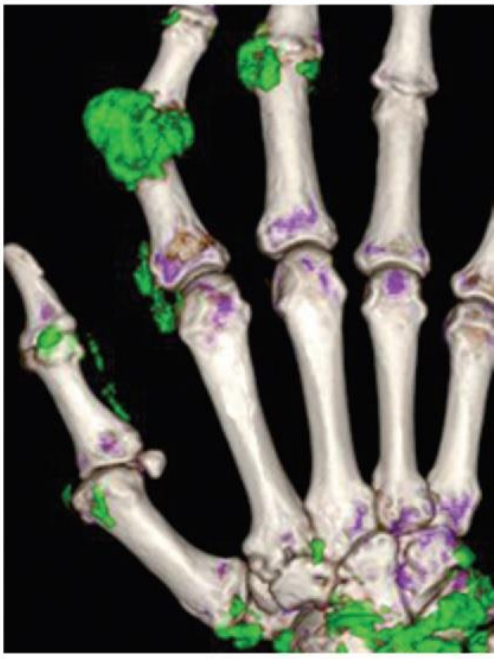

e.

A: Known tophaceous gout showing soft tissue swelling and deformity of the proximal interphalangeal joint.

B: Plain radiograph showing mineralized tophus and classic periarticular “rat bite” erosions (circle) at the proximal interphalangeal joint of the index finger.

C: Conventional CT scan image

D: Dual energy color-coded CT images obtained with post processing techniques. The CT shows uric acid deposits (green) within the tophus and at additional clinically

occult sites. These uric acid deposits are distinct from calcium-containing osseous structures (blue).

E: 3D CT image obtained with further post processing showing the anatomic relationship between the uric acid–containing tophi (green) and osseous structures (white and purple areas). [5]

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Dr J. Hayes
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