PHARMACY DEPARTMENT
HOSPITAL SEGAMAT

HS
FARMASI

Bulletin Pharmacy

GOUT 02/ 2014

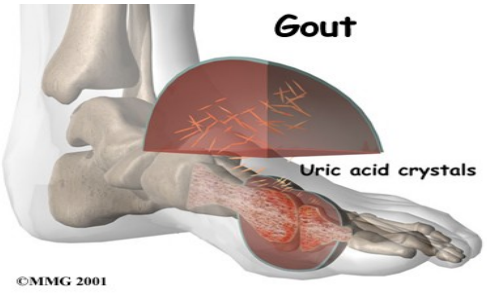
INSIDE THIS ISSUE:

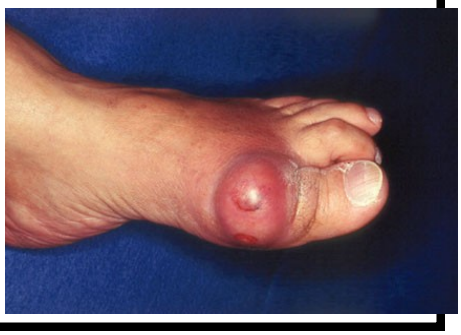
GOUT

INTRODUCTION

Gout is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected (approximately 50% of cases). However, it may also present as tophi, kidney stones, or urate nephropathy. It is caused by elevated levels of uric acid in the blood. The uric acid crystallizes, and the crystals deposit in joints, tendons, and surrounding tissues. [3]

The underlying metabolic disorder of gout is hyperuricemia (serum urate concentration > 7mg/dL (416µmol/L) in men or > 6mg/dL (357µmol/L) in women, but hyperuricemia may be an asymptomatic condition. [3]





CLINICAL PRESENTATION

Acute attack of gouty arthritis are characterized by rapid onset of excruciating pain, swelling and inflammation. The pattern of symptoms in untreated gout changes over time. The attacks can become more polyarticular. More proximal and upper-extremity joints become involved. Attacks tend to occur more frequently and last longer. Fever and leukocytosis are common. Untreated attacks may last from 3 to 14 days before spontaneous recovery. [2]

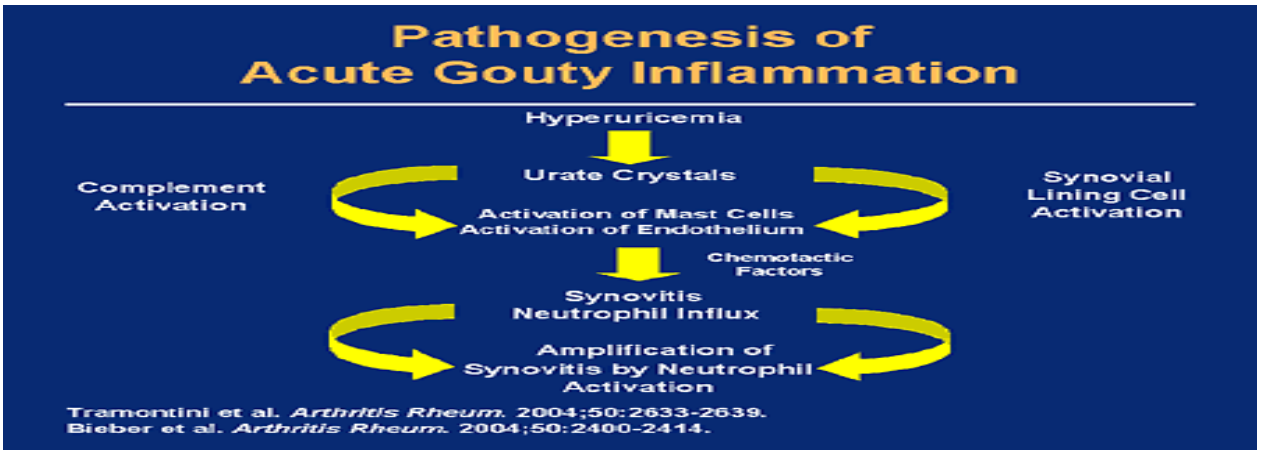
Eventually, patients may develop chronic polyarticular arthritis, sometimes nearly symmetrical, that can resemble rheumatoid arthritis. Indeed, chronic polyarticular arthritis that began as an intermittent arthritis should prompt consideration of a crystalline disorder in the differential diagnosis. Although acute attacks of gouty arthritis may occur without apparent provocation, attacks may be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by ingestion of uric acid-lowering agents, and ingestion of certain drugs known to elevate serum uric acid concentrations. [2]

PATHOPHYSIOLOGY

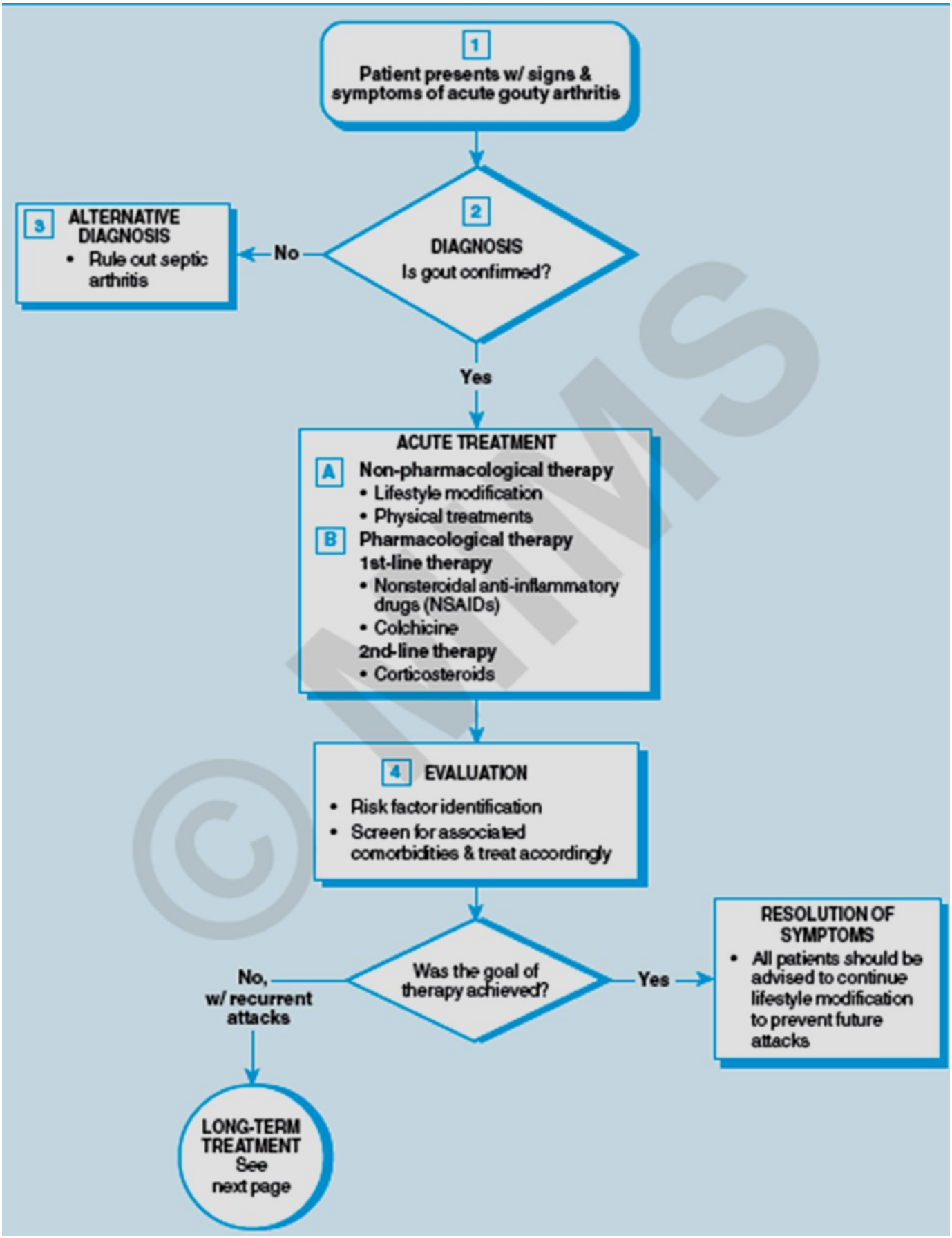
- In human, uric acid is the end product of purine degradation. It is a waste product that serves no known physiologic purpose. The size of the urate pool is increased several fold in individuals with gout. This excess accumulation may result from either overproduction or underexcretion. The purines from which uric acid is produced originate from three sources; dietary purines, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases. [2]

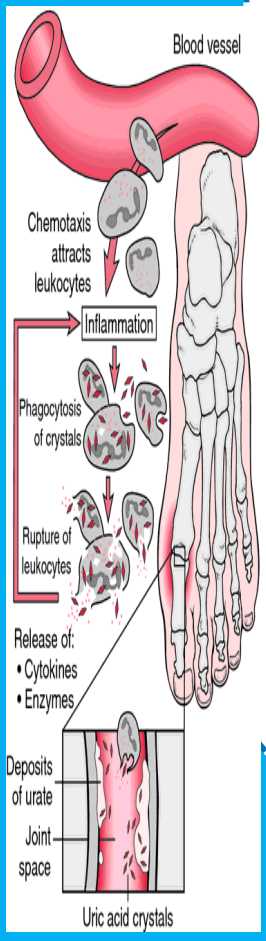
- Abnormalities in the enzyme systems that regulate purine metabolism may result in overproduction of uric acid. Increased activity of phosphoribosyl pyrophosphate (PRPP) synthethase leads to increased concentration of PRPP, a key determinant of purine synthesis and uric acid production. A deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT) may also result in overproduction of uric acid. HGPRT converts guanine to guanylic acid and hypoxanthine to inosinic acid. These two conversions PRPP as the co substrate and are important reutilization reactions involved in nucleic acid synthesis. A deficiency in the HGPRT enzyme leads increased metabolism of guanine and hypoxanthine to uric acid and more PRPP to interact with glutamine in the first step of purine pathway. Uric acid may be overproduced as a consequence of increased breakdown of tissue nucleic acid. [2]

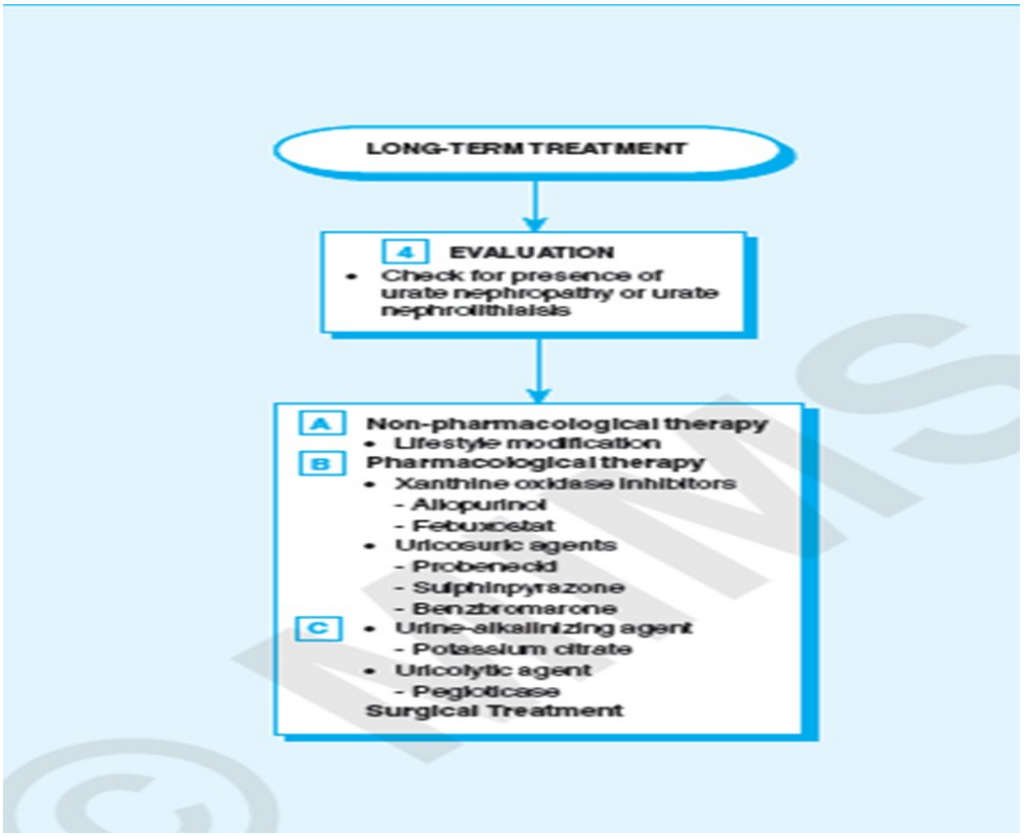
- About two thirds of the uric acid produced each day is excreted in the urine. The remainder is eliminated through the GI tract after enzymatic degradation by colonic bacteria. A decline in the urinary excretion of uric acid to a level below the rate of the production leads to hypeuricemia and an increased miscible pool of sodium urate. [2]
- Deposition of urate crystals in synovial fluid results In an inflammatory process involving chemical mediators that causes vasodilation, increased vascular permeability compliment activation, and chemotactic activity for polymorphonuclear leukocytes. [2]
- Phagocytosis of urate crystals by leukocytes results in rapid lysis of cells and a discharge of proteolytic enzymes into the cytoplasm. [2]
- The ensuing inflammatory reaction is associated with intense joint pain, erythema, warmth and swelling. [2]



MANAGEMENT [6]







ACUTE TREATMENT

Non Pharmacological Therapy

Recommended dietary and lifestyle changes include weight reduction, restriction of alcohol intake, reduced intake of purine-rich food (e.g.: organ meats) and control of co-morbidities (e.g.: hyperlipidemia, hypertension). 1

Joint rest for 1-2 days should be encouraged, and local application of ice may be beneficial. [2]

Pharmacological Treatment

In an acute attack of gout, effective treatment must target both the pain and the underlying inflammation. The choice of a drug depends on an assessment of its efficacy as compared with its toxicity in the individual patient. Rest and prompt treatment with full doses of non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first-line treatments. In addition, co administered with a proton pump inhibitor should be considered in elderly patients. [1, 2]

NSAIDs

Non-streoidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy because of their excellent efficacy and minimal toxicity with short-term use. [2]

Any NSAIDs can be used but aspirin should be avoided because it causes urate retention unless given in very high doses. Most potent NSAIDs are rapidly effective in relieving pain and reducing inflammation in patients with acute gout, particularly if the drugs are taken soon after the onset of the attack and in full therapeutic doses. Examples of NSAIDs that are used are diclofenac, indomethacin and ketoprofen. Parenteral NSAIDs can also be administered. [1]

The most common adverse effects involve the GI system (gastritis, bleeding and perforation), kidneys (renal papillary necrosis and reduced creatinine clearance), cardiovascular system (increased blood pressure and sodium and fluid retention), and CNS (impaired cognitive function, headache and dizziness). [2]

Caution should be exercised in elderly patients and those with a history of peptic ulcer disease, hypertension, renal impairment and cardiac failure. Alternative drug therapy should be considered in these patients. In addition, co administered with a proton pump inhibitor should be considered in elderly patients. [1, 2]

COX-2 Inhibitors

Since a prolonged course of treatment is likely to be required, COX-2 inhibitors are an alternative in those at risk of peptic ulcer disease or intolerant of traditional NSAIDs or those presenting with an acute attack of gout of several days duration. [1]

The efficacy and safety of COX-2 inhibitors (e.g.: celecoxib and etoricoxib) have not been fully assessed in gouty arthritis and they are more costly than conventional NSAIDs. However, studies have shown that etoricoxib, a COX-2 inhibitor, has equally efficacy to indomethacin in the treatment of acute gout, with etoricoxib showing an improved safety profile. [2]

Similar cautions as for NSAIDs should be exercised in those with active peptic ulcer disease, hypertension, renal impairment and cardiac failure. [1]

Colchicine

Colchicine is an antimitotic drug that is highly effective in relieving acute gout attacks but has a low benefit-to-toxicity ratio. It is an alternative drug for those whom NSAIDs and COX-2 inhibitors are contraindicated but is poorly tolerated by elderly people. Its therapeutic index is narrow and side-effects associated with colchichine treatment such as nausea, vomiting, abdominal pain and profuse diarrhea can be so intense as to limit its usefulness. In order to reduce the risks of side effects (especially diarrhea), it should be used in dose of 0.5mg-0.6mg bd-qds. In patients with renal impairment, the dose should not be repeated more often than once every two weeks. [1, 2]

Caution should be exercised in those who have renal or hepatic dysfunction and in elderly. It should also not be used concurrently with P-glycoprotein or strong CYP450 3A4 (e.g.: clarithromycin) because reduced biliary excretion may lead to increased plasma colchicines levels and toxicity. [2]

IV colchicine has resulted in fatalities and is no longer available. [2]

Glucocorticoids

In elderly patients and those with renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease and hypersensitivity to NSAIDs or COX-2 inhibitors, glucocorticoids can be considered. They can be used either systemically or by intra-articular injection. [1]

Intra-articular injection of glucocorticoids into the affected joint can be administered but it needs to be given by a doctor who is trained to perform such a procedure. Intramuscular injection of glucocorticoids such as triamcinolone (40-80mg/day) or methylprednisolone (80mg/day) can be given stat. [1]

Alternatively, a short course of oral glucocorticoids can be considered. Oral prednisolone up to 0.5mg/kg/day or its equivalent can be given and tapered off over 4-10 days.[1]

As the duration of treatment is usually short, side effects due to steroids are rare. There is no role for long-term glucocorticoids in the treatment of gout. Patients should not be given repeated courses of glucocorticoids; if this is required, they should be referred for specialist. opinion. [1]

Chronic Gouty Arthritis Treatment

Recurrent attacks of gouty arthritis, erosive arthritis and tophaceous deposits require therapy to lower serum urate levels. The aim of hypouricaemic therapy is to reduce the serum urate level <0.36mmol/L (6.0 mg/dL). Hypouricaemic therapy should only be started after an acute attack is well-controlled (about two weeks after the attack). This is because hypouricaemic therapy started during an attack may prolong the attack or lead to rebound flares. For the same reason, hypouricaemic drugs should not be stopped or adjusted during acute attack.[1]

Xanthise Oxidase Inhibitor

Allopurinol is a xanthine oxidase inhibitor and is most commonly available and widely prescribes agents for long term prevention of recurrent gout attacks. It reduces uric acid by impairing the conversion of hypoxanthine to xanthine and xanthine to uric acid. It is primarily excreted by kidneys and therefore the dose of allopurinol must be adjusted for patients with renal impairment. In patients with normal renal function, start at 100-150mg once daily, increasing by 100-150mg steps every 4 weeks to a dose of 300mg once daily. Serum uric acid level can be checked about 1 week after starting therapy or modifying dose.

Adverse effects include rash, bone marrow suppression, aplastic anemia, agranulocytosis, granulomatous hepatitis and jaundice. Life threatening hypersensitivity syndrome which consist of fever, rashes, hepatitis, eosinophillia and renal impairment has been well documented. [1]

Uricosuric Drugs

Probenecid is a uricosuric agent. It can be used as an alternative to allopurinol in patients with normal renal function. It is contraindicated in patients with uric acid overproduction and over excretion (24 hours urinary urate excretion of more than 800mg per day) or in those with urate nephropathy or nephrolithiasis because of the risk of crystal precipitation and stone formation. Renal function and 24 hours urinary urate excretion must be assessed before commencement of probenecid. Initial doses of 0.5-1g are given and may be increased to 1.5-2 g in divided doses. [1]

The side effects of probenecid are gastrointestinal disturbance and a hypersensitive rash; serious side effects are rare. [1]

Urine Alkalinizing Agent

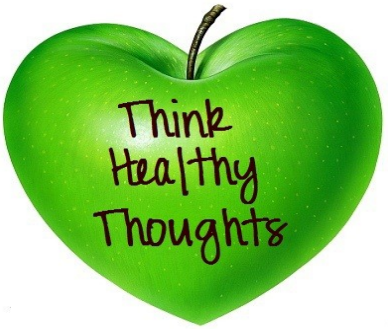
Pure urate stones are easily chemolysed using potassium citrate or sodium bicarbonate, either by means of oral ingestion or direct irrigation. Long-term chemoprophylaxis using potassium citrate has been shown to be highly effective. [1]

DIAGNOSIS

- A definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of monosodium urate monohydrate in synovial fluid leukocytes .[4, 5]
- When joint aspiration is not a viable option, a presumptive diagnosis of acute gouty arthritis is based on the presence of the characteristics signs and symptoms, as well as the response to treatment. [4, 5]

COMPLICATIONS

- Severe degenerative arthritis
- Secondary infection
- Urate or uric acid nephropathy
- Renal stones
- Nerve or spinal cord impingement. [3]



READ MORE ON:

1. Clinical Practice Guidelines on Management of Gout, October 2008.
2. Dipiro Pharmacotherapy Handbook, 8th Edition, 2012.
3. Gout and Pseudogout, Medscape Online.
4. Choi HK, Curhan G. Gout: epidemiology and lifestyle choices. *Curr Opin Rheumatol*. May 2005;17 (3):341-5.
5. So A. Gout in the spotlight. *Arthritis Res Ther*. 2008;10(3):112.
6. www.mimsgateway.com.my

ADVERSE DRUG REACTION REPORT

DATE	MEDICATIONS	ADR	TREATMENT	REPORTER
8/4/14	T. Diclofenac 50mg T. Colchicine 0.5mg	Facial swelling, face fullness, shortness of breath	IVHydrocortisone 200mg	Dr. Abdul Faiz
5/5/14	T. Bactrim 480mg	Toxic epidermal necrolysis	Aq cream, emulsified oint, cetrimide 2% lotion	Dr Muhammad Faiz
17/6/14	IV Metochlopramide 10mg	Oculogyric crisis	IV Kemadrin 10mg stat	Mr. Hoo Kien Heng
6/7/14	IV Sulperazone 2g BD	Skin Rashes	IV Piriton 10mg stat & IVHydrocortisone 10mg stat	Dr. Nurul Farahani
9/7/14	T. Griseofulvin 125mg	Stevens-Johnson Syndrome	cetrimide 2% shampoo, Tramadol 50mg BD & Aqueous Cream	Miss Tan Wan Xian
17/7/14	C. Phenytoin 300mg ON	Oral ulceric bleeding from hips & generalised rash	change to sodium valproate	Dr. Wendy Ter Zu Wei

NEWSLETTER OF THE DRUG CONTROL AUTHORITY,

TRADITIONAL PRODUCTS / HEALTH SUPPLEMENTS

a) Unregistered Traditional Products Containing Scheduled Poison

The NPCB has obtained information from the Health Sciences Authority (HSA) Singapore regarding three traditional products that contain scheduled poisons.

Products & Scheduled Poison Detected

1. Li Long Mei Guo Mo Bang (Sildenafil)
2. Africa Black Ant (Sildenafil)
3. Ginseng Tu Chong Wan Lin Heong (Dexamethasone)

All three products are not registered with the DCA. The product registration number MAL19991268TC and company details printed on the label for Ginseng Tu Chong Wan Lin Heong are found to be faked.

The use of scheduled poison in traditional products is strictly prohibited. Sildenafil is used to treat erectile dysfunction and should only be used when prescribed by a doctor. Its usage without proper medical advice can cause serious adverse reactions such as decreased or loss of vision and hearing, low blood pressure and other cardiovascular events such as stroke and heart attack. Dexamethasone is a potent corticosteroid and should only be used under medical supervision. Long term and unsupervised use of corticosteroids can cause serious adverse effects such as Cushing Syndrome, increased blood glucose level, high blood pressure, bone disorders such as osteoporosis and an increased risk of infections.

PELAPORAN KESAN ADVERS ALLOPURINOL

2. Seperti Y. Bhg. Datuk/Dato'/Datin/Dr./Tuan/Puan sedia maklum, ubat allopurinol telah dikaitkan dengan risiko kesan advers kulit yang serius seperti *Stevens-Johnson syndrome (SJS)* dan *toxic epidermal necrolysis (TEN)*. Justeru itu, Panel Kajisemula Senarai Ubat-ubatan KKM dalam mesyuarat Bil. 2/2011 telah memperketatkan kategori preskriber daripada 'kategori B' kepada 'A/KK' dan menghadkan indikasi ubat allopurinol.

5. Dalam usaha memperkukuhkan langkah pengurangan risiko serta memastikan ubat allopurinol digunakan secara rasional, Jawatankuasa Penasihat Kesan Advers Ubat Kebangsaan (MADRAC) dalam mesyuarat ke-137 pada 20 Februari 2014 telah memutuskan bahawa setiap laporan ADR yang melibatkan allopurinol perlu mengandungi **maklumat tambahan** seperti berikut:

(i) kategori preskriber yang memulakan ubat allopurinol bagi pesakit terlibat (cth.: pegawai perubatan, pakar perubatan, pakar kesihatan keluarga)
(ii) indikasi spesifik allopurinol
(iii) *Nama *primary prescriber*
(iv) *Nama dan alamat klinik/ hospital *primary prescriber*
(v) *No. telefon *primary prescriber*

**(iii)-(v): untuk kes pengunaan allopurinol di luar indikasi yang diluluskan sahaja*

MAKLUMAT TAMBAHAN YANG PENTING UNTUK LAPORAN ADR ALLOPURINOL

REPORT ON SUSPECTED ADVERSE DRUG REACTIONS
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING
www.bpfk.gov.my

(Please report all suspected drug reactions including those for vaccines and traditional medicines. Do not hesitate to report if some details are not known. Identities of Reporter, Patient and Institution will remain **Confidential**.)

REPORT No. .....(for official use only)

PATIENT INFORMATION

Pt/N or Initials	Age	Sex	Wt (kg)	Ethnic Group	Institution
Nombor KP					

ADVERSE REACTION DESCRIPTION

Pelapor perlu memastikan pesakit dan rekod perubatannya boleh dikesan (cth: simpan rekod nama pesakit dan no. telefon)

Time to onset of reaction : Date of reaction : Date end of reaction :

Reaction subsided after stopping drug / reducing dose : Yes No Unknown

Reaction reappeared after reintroducing drug : Yes No Not applicable

Extent of Reaction : Mild Moderate Severe

Treatment of adverse reaction :

Outcome Recovered Not yet recovered Unknown Fatal - Date of death :

Drug Reactions Relationship : Certain Probable Possible Unlikely Unclassifiable

Suspected Drug :

Product/Generic Name	Dosage Given	MAL and Batch No.	Therapy Dates Start	Therapy Dates Stop	Indication
Allopurinol					Indikasi spesifik

Concomitant Drug:

Product/Generic Name	Dosage Given	MAL and Batch No.	Therapy Dates Start	Therapy Dates Stop	Indication

**Please attach further papers if necessary

Relevant Investigations / Laboratory Data	Relevant Medical History
Fungsi buah pinggang (jika ada)	Sertakan maklumat *primary prescriber*: (i) Kategori (MO, doktor pakar) (ii) Nama, no. tel, dan alamat

Reporter

Name : Address :

Designation : Tel No :

Email Address : Date of Report : Signature :

QUICK REFERENCE GUIDE: PRESCRIBING AND DISPENSING ALLOPURINOL

a) Prescribing

Conditions in the Ministry of Health Malaysia Drug Formulary 3/2013:	
Prescriber category	A/KK (Consultants/ Specialists/ Family Medicine Specialists)
Approved indications	i) Frequent and disabling attacks of gouty arthritis (3 or more attacks/year) ii) Clinical or radiographic signs of erosive gouty arthritis iii) The presence of tophaceous deposits iv) Urate nephropathy v) Urate nephrolithiasis vi) Impending cytotoxic chemotherapy or radiotherapy for lymphoma or leukaemia

b) Counselling Points

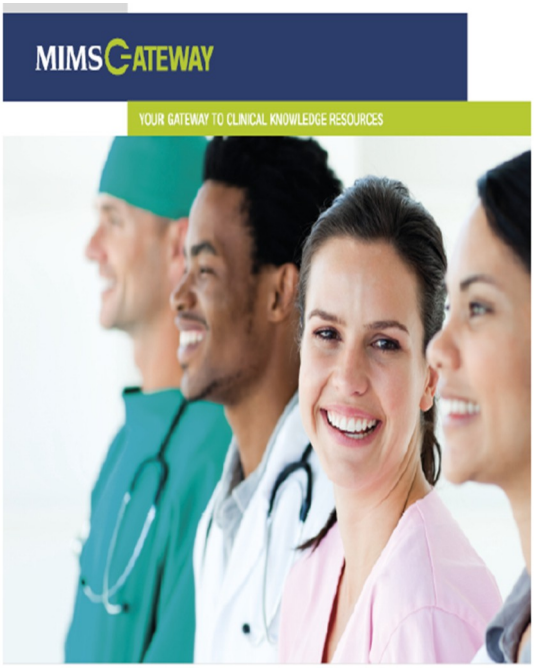
Patients should be informed of the following whenever allopurinol is given:

- Specific indication of allopurinol
- Continue taking allopurinol even if it does not seem to be working, as it may take several months to start having an effect
- Stop taking medication and notify pharmacist/ doctor immediately if develop **fever, sore throat**, fatigue, eye irritation, cough, rash, itching, swelling or joint pain.
- Check with pharmacist/ doctor before taking allopurinol with any other medication (including non-prescription, traditional products, or health supplements).
- May be taken after meals to avoid stomach upset.
- Diet: - avoid purine-rich food (e.g. liver, kidney, sardine, anchovies, crab, prawns, meat)
  - avoid excessive intake of alcohol (men: 3-4 units/day, women: 2-3 units/day)
  - avoid large doses of vitamin C (>1000mg/day)
- May cause drowsiness, therefore use caution while driving or handling machine

INTRODUCING.....

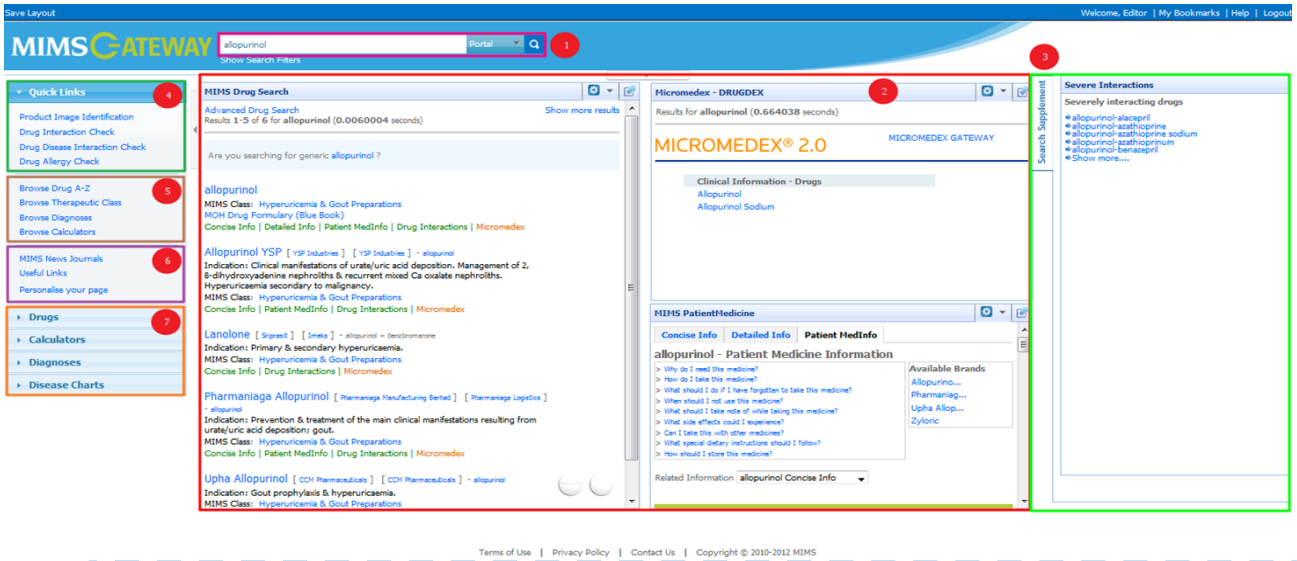
MIMS GATEWAY & MICROMEDEX

•Intelligent workflow-oriented resource designed specifically for healthcare professionals in their clinical practice needs
•High quality MIMS Drug Information integrated with clinical decision support tools and renowned international medical resources, delivering a convenient, comprehensive and seamlessly integrated suite of information through a single point of access



SYSTEM REQUIREMENTS

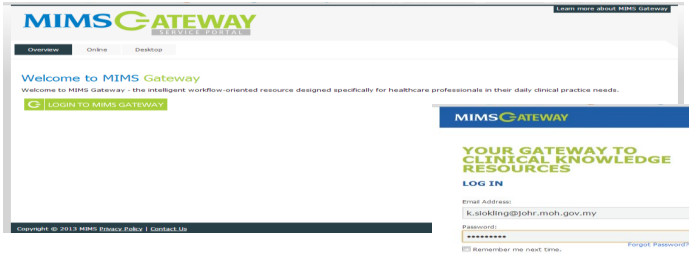
- INTERNET EXPLORER 8 AND ABOVE
- FIREFOX 13 AND ABOVE
- CHROME 19 AND ABOVE

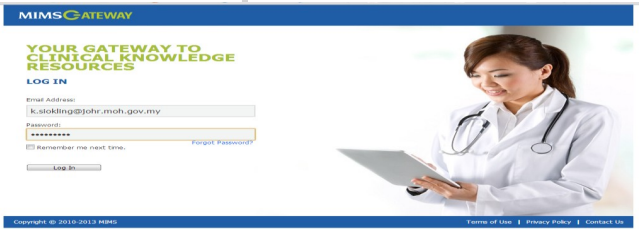


Facility email address: farmasihsegamat@moh.gov.my
Password: password1

How to Log In

- www.mimsgateway.com.my





SELAMAT HARI RAYA

Aidilfitri

1435 HIJRIAH

Maaf Zahir & Batin

From
PHARMACY DEPARTMENT
HOSPITAL SEGAMAT