

## Postgraduate Refreshing and Update for the Medical Practitioners

### Frequent Asked Questions

#### Short, Medium, and Long-term Outcome of Chronic Gout by Treatment of Acute/Chronic Gouty Arthritis and Hyperuricemia

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#### What is Chronic Gout?

Attack of Acute Gouty Arthritis at least 3X annually and/or an urate crystal-proven tophus classified a patient as suffering from Chronic Gout.

#### What is Acute Gouty Arthritis?

Pain, stiffness, tenderness, swelling, and warmth of a joint induced by urate crystals in the synovial fluid.

#### What are short, medium, and long-term outcome of treatment of Chronic Gout?

Short-term outcome is the final result of treatment after less than 5 years

Medium term outcome is the final result of treatment after 5-10 years

Long-term outcome is the final result of treatment after 10 years or longer

#### What is the ideal outcome in the therapy of Chronic Gout?

Long-term treatment-free normouricemia without flare of Acute Gouty Arthritis. Serum urate < 5 mg% by low purine diet only, after tapering off Allopurinol, without flares of attack of Acute Gouty Arthritis.

#### A patient is diagnosed with Gout by clinical diagnosis or by urate crystals-proven joint fluid or urate crystal-proven tophus[1]. What are the treatment options for Acute Gouty Arthritis?

The Standard Therapy for Acute Gouty Arthritis is by daily oral Indomethacine or Colchicine. Medical practitioners nowadays rarely prescribe colchicines because of gastrointestinal adverse effects and less efficacy compared with NSAIDs.

Treatment has evolved into additional intramuscular NSAID after oral one became less effective. However, frequent therapy with intramuscular and oral NSAID increases tolerance of Acute Gouty Arthritis to these drugs. Attack of Acute Gouty Arthritis will take longer and longer periods to dissolve. Ultimately, Acute Gouty Arthritis of Chronic Gout become refractory to intramuscular and oral NSAID.

#### What is meant refractory to intramuscular and oral NSAID?

The pain including other signs and symptoms from Acute Gouty Arthritis is only partially or not at all relieved by intramuscular and oral NSAID.

#### What is the most effective treatment for the patients with Acute Gouty Arthritis in Chronic Gout?

Initial Intramuscular Dexamethasone and Depo Triamcynolone and daily oral NSAID will dissolve Acute Gouty Arthritis within half to 2 days[2].

#### Why are Intramuscular Dexamethasone and Depo Triamcynolone chosen?

The patients have continuous 24 hours excruciating pain and cannot walk for several days, and demand immediate relief. Dexamethasone exert efficacy after 4 hours and lasts up to 4 days. After 4 hours patients will experience increasing relief of pain and decreasing stiffness, tenderness, redness, and warmth of arthritic joint(s). The pain of Acute Gouty Arthritis may dissolve within half to 2 days. Ice compress is most soothing to the acutely inflamed joint when required.

Depo Triamcynolone induces efficacy after 4 days and lasts up to 1-2 months. In Chronic Gout this will prevent flare, 2-4 weeks after dissolution of Acute Gouty Arthritis when the antihyperuricemic therapy is initiated. In Chronic Gouty Arthritis of Chronic Gout this will provide at least anti-inflammatory effect for up to 1-2 months.

#### **What is flare of Chronic Gout?**

Acute Gouty Arthritis re-appears with abnormal CRP, ESR, and leukocyte count of  $\geq 10,000$ [3]

#### **What is NSAID-refractory Chronic Gouty Arthritis of Chronic Gout?**

Chronic Gouty Arthritis of Chronic Gout is continuous arthritis in particular in polyarticular Chronic Tophaceous Gout. The patients have daily and nightly pain refractory to intramuscular and oral NSAID.

#### **What are the treatment options for Chronic Gouty Arthritis in Chronic Gout?**

When the Chronic Gouty Arthritis is refractory to intramuscular and oral NSAID, then low dose oral Methylprednisolone is prescribed for 6-24 months and then taper off. When the Chronic Gouty Arthritis is also refractory to low dosages of oral Methylprednisolone, intramuscular Dexamethasone is the best alternatives combined with depo Triamcynolone[2,4].

#### **What are the treatment procedures of oral corticosteroid in Chronic Gouty Arthritis of Chronic Gout?**

Daily morning dose of 4 mg Methylprednisolone after breakfast for 6 months to 2 years. When C-Reactive Protein (CRP) is  $< 3$  mg or negative, Erythrocyte Sedimentation Rate (ESR) is  $< 10$  mm per 1 hour (women  $< 20$  mm), and leukocyte count  $< 10,000$ , then tapering off Methylprednisolone must be commenced after 6-24 months.

#### **What to do with persistent Chronic Gouty Arthritis in Chronic Gout?**

A joint-size dependent dose of the cocktail comprising Lignocain 20%, Dexamethasone 20%, and depo Triamcynolone 60% is intraarticularly injected. Efficacy of Lignocain is direct and last 4 hours, Dexamethasone commence after 4 hours and last 4 days, and depo Triamcynolone starts after 4 days and last at least a fortnight or longer.

#### **How many intraarticular injections can be given in a patient and after how long can it be repeated again?**

The myth of limiting maximum intraarticular injection to 3 joints and only repeated 3 times annually has been overturned. Mind you that the Pyramid principle of therapy of Rheumatoid Arthritis has been reversed and then the pyramid system is discarded. The reasons given that too frequent intraarticular injections into too many joints are detrimental have been proven incorrect by comparative trials.

In a comparative study it was evident that intraarticular injection protect the joints and has an improved outcome compared with not injected joints. Intraarticular injection of Chronic Gouty Arthritis of Chronic Gout can be safely repeated every 2 weeks when the efficacy of the depo Triamcynolone commences to wears off.

#### **Should a joint with Acute Gouty Arthritis intraarticularly injected with the cocktail?**

Acute Gouty Arthritis is suppressed within 12-24 hours by intramuscular Dexamethasone. The excruciating pain elicited by sticking a needle into an acute inflamed joint is not worthwhile for the patient. Chronic Gouty Arthritis of Chronic Gout does not respond well to intramuscular injection of Dexamethasone and Depo Triamcynolone. Therefore, it is appropriate to inject intraarticularly multiple joints with Chronic Gouty arthritis with minuscule amount of the cocktail

#### **How is oral Methylprednisolone tapered off?**

The ESR, CRP, leukocyte count should be monitored at presentation, after 4 days, and thereafter every 3 months[3]. When the CRP is  $< 3$  mg%, ESR  $< 10$  mm, and the leukocyte count  $< 10,000$ , the dose of Methylprednisolone is reduced to 2 mg every morning. If the CRP, ESR, and leukocyte count are still normal without flare after another 3 months, the Methylprednisolone is given 1 mg every morning. After another 3 months with normal CRP, ESR, and leukocyte count, then Methylprednisolone of 1 mg is given

on alternate day. If the CRP, ESR, and leukocyte count are still normal after another 3 months, the final dose of Methylprednisolone is 1 mg every 3 days for 3 months when it is finally terminated. The slow tapering off Methylprednisolone is to avoid flare.

#### **What causes an attack of Acute Gouty Arthritis?**

The first attack of Acute Gouty Arthritis is induced by hyperuricemia. Subsequent attacks are precipitated by a sudden rise or drop in the serum urate level. In > 50% of attacks, the serum urate level is > 7 mg%. In < 50% the patients are normouricemic when an attack of Acute Gouty Arthritis occurs.[5]

#### **Why does a serum urate level of 5-7 mg% precipitate an attack of Acute Gouty Arthritis, yet these are normal or even subnormal uric acid levels?**

For the healthy population without gout the normal serum urate level is < 7 mg%. For the patients with gout the normal levels of serum uric acid levels are 4.5[6] to 5.0[2] mg%. An attack of Acute Gouty Arthritis very rarely occurs when the serum urate level is < 5.0 or < 4.5 mg%.

At a serum urate level of > 5 mg%, an attack of Acute Gouty Arthritis may be precipitated by a sudden rise of the serum urate by overeating or consumption of purine rich food and/or alcoholic beverages. A sudden drop of the serum urate level by fasting will also precipitate an attack of Acute Gouty Arthritis. However, over day fasting with 2 full meals a day (early morning and evening) will not induce an attack of Acute Gouty Arthritis, unless very rich purine food and/or beverages are taken.

After the first attack of Acute Gouty Arthritis, most hyperuricemia has been treated by uricosuric (Benzbromarone or Probenecic) or uricostatic (allopurinol), albeit irregularly in most of the cases by ignorance of the patients. The serum urate level tends to hover around 5-7 mg% (normouricemic). It is at these levels that the patients and attending physician drops their guard and considered the hyperuricemia controlled. There is no comprehension why at the normal serum uric acid level an attack of Acute Gouty Arthritis occurs. Nevertheless, almost 50% of attack of Acute Gouty Arthritis occurs in normouricemic patients based on 2 scientific research[2,5].

#### **What are other associated risks of hyperuricemia besides attack of Acute Gouty Arthritis or Chronic Gouty Arthritis?**

Hyperuricemia has a strong relative risk of death in coronary heart disease, hypertension, stroke, and renal impairment. Long-term hyperuricemia is a considerable risk factor for reduced life expectancy.[7] After hyperuricemia was controlled to < 5 mg% over a period of ten years, impaired renal functions were significantly improved with serum creatinine reduced to < 2 mg% and creatinine clearance improved to > 60 CC.[2,8]. Serum creatinine and Creatinine Clearance are not fixed figures and can be improved unless irreversible kidneys damage has occurred (WHO Class VI renal biopsies).

#### **Can symptomatic treatment of Acute or Chronic Gouty Arthritis be initiated together with anti-hyperuricemic therapy?**

No, because a sudden drop of serum urate level may induce flare of Acute Gouty Arthritis during symptomatic treatment. The urate-lowering drugs should be administered 2-4 weeks after suppression of the Acute or Chronic Gouty Arthritis. Initiation of anti-hyperuricemic therapy may induce flare when serum urate level is suddenly lowered during symptomatic treatment of Acute or Chronic Gouty Arthritis.

#### **How do we prevent an attack of Acute Gouty Arthritis when anti-hyperuricemic therapy is initiated?**

Half of the standard dose of a NSAID should be concomitantly prescribed with the Allopurinol for 6-24 months in Chronic Gout, when anti-hyperuricemic therapy is initiated. This will prevent flare of Acute Gouty Arthritis when the serum urate is suddenly lowered by allopurinol.[2]

#### **How long must Allopurinol be taken in patient with Gout?**

In patients with Gout with attack of Acute Gouty Arthritis only once annually, Allopurinol must be taken for at least 2 years. It is hoped that after 2 years allopurinol therapy with a prudent low purine diet, Acute Gouty Arthritis will not flare as the stock of urate in the body is depleted. Short or medium or long term treatment-free gout or intercritical gout is then achieved.[2]

**How long must Allopurinol be taken in patients with Chronic Gout?**

Allopurinol must be taken long-term to prevent tophus or urolithiasis or urate nephropathy, and associated complications.

**How long must Allopurinol be taken in patients with Chronic Tophaceous Gout?**

Allopurinol must be taken lifetime to prevent renal complications. A tophus means continuous precipitation of urate in the kidneys, which ultimately, may lead to development of urolithiasis and chronic urate nephropathy.

**How long must Allopurinol be taken in patients with Chronic Gout with urolithiasis?**

Allopurinol must be taken lifetime to prevent increasing size and number of uroliths [2], and renal failure, although urate is not the sole risk factor in the development of urolithiasis.

**Keeping the serum urate down to < 5 mg% is hardly possible. How do we abort an impending attack of Acute Gouty Arthritis with a serum urate level of 5-7 mg% in Chronic Gout?**

You must carry with you a few tablets of Methylprednisolone anywhere you go. Patients with Chronic Gout can feel an impending attack of Acute Gouty Arthritis coming. Taken on time, the Methylprednisolone will abort the impending attack of Acute Gouty Arthritis. Methylprednisolone comes in 4 mg and 16 mg tablets. When the 4 mg tablet fails to abort the impending attack of Acute Gouty Arthritis then 8 mg or 16 mg Methylprednisolone must be taken next time and in time to abort an impending attack.[2]

**How effective is a strict low purine diet to lower serum urate level in hyperuricemia of patients with Chronic Gout without uricosuric and/or uricostatic?**

Notwithstanding of all the discomfort of stringent abstinence from delicious food and alcoholic beverages, the maximum lowering of hyperuricemia is only 1-2mg% with a strict low purine diet. With a serum urate level of > 8mg% it is not feasible to achieve serum urate level of < 5 mg% by diet alone. Nevertheless, level of serum urate level of < 3 mg% has been obtained with allopurinol or Benzbromarone combined with a stringent low purine diet.

**You go to a party and are required to honor the host and enjoy the sumptuous meal offered, what can be done for the patient with Chronic Gout to prevent an attack of Acute Gouty Arthritis?**

Just take 1 extra tablet of 300 mg Allopurinol before the meal, besides the daily maintenance dose of 100-200 mg. The sudden rise of serum urate level by the purine rich meal will be prevented. Of course it depends on how big and how purine rich the meal is and how frequent your low purine diet is violated.

**Are there medicines that may induce an attack of Acute Gouty Arthritis?**

Patients with Chronic Gout and impaired renal function are likely to have flares of Acute Gouty Arthritis when diuretics and low dose aspirin are taken after some time for cardiovascular disease.[9] However, without renal impairment it is unlikely that diuretic and low dose aspirin will induce flares of Acute Gouty Arthritis.[2]

**Is it possible for patients with Chronic Gout without complication to have long-term treatment-free (without Allopurinol) period?**

A 10-years observational study has shown that more than one-thirds (36.8%) of patients with Chronic Gout without complication have an 8 years treatment-free period or intercritical gout after Allopurinol was tapered off.[2] Chronic Gout with complications such as tophi, hypertension, urolithiasis, and renal failure, requires lifetime therapy with Allopurinol. Sooner or later flares of Acute Gouty Arthritis occur when Allopurinol is tapered off in Chronic Gout with complications.

**Are herbal medicines effective for treatment of Acute Gouty Arthritis and as anti-hyperuricemic in hyperuricemia?**

A 5-years comparative study with the most popular herb formula “danggui-nian-tong-tang” (mixture of 30 herbs) in China and Taiwan compared with Indomethocin and Allopurinol show inefficacy in the treatment of Acute Gouty Arthritis and as anti-hyperuricemic in hyperuricemia.[10] Any herb capsule or sachet that

is effective in Acute Gouty Arthritis and lowers serum urate level should be suspected of containing illicit corticosteroid and/or NSAID, and uricosuric and/or uricostatic compounds. Disguising these drugs with herbs is common in developing countries where strict law enforcement of prescription drugs are lacking.

#### **Do we need to treat hyperuricemia without Gout, Chronic Gout, and urolithiasis?**

A level of serum urate of  $> 9$  mg% is a risk factor for development of urolithiasis, albeit the risk is small. In a tropical country, where sweating may be profuse and chronic dehydration may be common, high prevalence rate of urolithiasis was found in a tropical country.[11] These factors may facilitate formation of urolithiasis. Serum urate of  $> 9$  mg% is only one of the many risk factors for development of urolithiasis. From the point of view that hyperuricemia has a strong relative risk of death in coronary heart disease, hypertension, stroke, and renal failure[2], it may be prudent to lower serum urate level to  $< 7$  mg% in these patients without Gout by diet with or without uricostatic or uricosuric.

#### **What is the difference of the treatment of Acute and Chronic Gouty Arthritis compared with therapy of hyperuricemia?**

Suppression of Acute and Chronic Gouty Arthritis is only symptomatic treatment and does not influence the course of Gout. Chronic Gout initially without and ultimately with complications may develop when hyperuricemia is not suppressed to  $< 5$  mg% over a period of  $> 10$  years.[2]

In lowering and maintaining serum urate level to  $< 5$  mg%, attack of Acute Gouty Arthritis is prevented. Chronic Gouty Arthritis of Chronic Gout is also ultimately prevented after keeping serum urate level to  $< 5$  mg% for short or medium or long term. Without suppression of hyperuricemia and maintaining serum urate level to  $< 5$  mg%, acute or chronic arthritis sooner or later flares. Chronic Gouty Arthritis of Chronic Gout may even torture the patient on a daily and nightly basis with excruciating pains. Therapy of hyperuricemia is thus disease modifying and Chronic Gout is prevented. Long term treatment of hyperuricemia of Chronic Gout, the risk of associated complications such as hypertension, urolithiasis, renal failure, stroke, and myocardial infarct is reduced[2].

#### **How to terminate an allergic reaction that may develop into Steven-Johnson syndrome?**

By daily intravenous drips in the dilution of 0.1-0.5 CC Epinephrine in 100-200 CC 0.9% NaCl[12] combined with Methylprednisolone of 25-125 mg.[2]

#### **How to terminate annoying allergic skin reaction to Allopurinol when it has to be taken in the short, medium, and long term?**

Desensitize the patient to Allopurinol. Dissolve 100 mg of Allopurinol in 100 CC of drinking water. Drink 1 CC of the dilution on the first day and double on every subsequent day. The dosages will be 1, 2, 4, 8, 18, 32, 64, and 100 CC of the dilution. When the patient can tolerate the dose of 100 CC dilution of 100 mg Allopurinol without itching or urticaria, then switch to oral tablet of 100 mg daily[13].

#### **Why are premenopausal women not affected with Gout?**

The Estrogen hormone is protective against Gout. Renal excretion of urates is increased by estrogen and hyperuricemia is less frequent in premenopausal compared with postmenopausal women. Primary Gout does not occur in premenopausal women.

#### **Why are some premenopausal women seen with Gout?**

These premenopausal women have secondary Gout due to renal failure.

#### **Why are postmenopausal women equally affected by Gout as in men?**

Postmenopausal women lost their Estrogen protection against Gout.

#### **What are the long-term outcomes of maintaining a serum urate level of $< 5$ mg% in Chronic Gout with tophi, urolithiasis, and renal impairment?**

Tophi : the number of small tophi are dissolved, the size of large tophi are reduced, and formation of new tophi are terminated.  
 Urolithiasis : notwithstanding that serum urate level of  $< 5$  mg% is maintained over 10 years, the number and size of urolithiasis increased. Hyperuricemia is not the only risk factor for

development of urolithiasis

Serum Creatinine : even serum creatinine level of  $> 5\text{mg}\%$  may be reduced to  $< 2\text{mg}\%$  with significant reduction of serum urea to normal.[8]

Creatinine Clearance of  $< 30\text{CC/minute}$  may increase to  $> 60\text{CC/minute}$

Renal function is reversible unless irreversible damage has occurred to the kidney

Tissues with renal biopsy of WHO Class VI.[2].

**Is self-medication without medical supervision (by a medical practitioner) by the patients with Gout safe in the short term ( $< 5$  years)?**

Self-medication of attack of Acute Gouty Arthritis is not safe even in the short term, without control of hyperuricemia. The disease develops into Chronic Gout after 10 years.[2]

**Why is self-medication so popular?**

The natural course of Gout lends itself to self-medication by the patient for the following reasons:

1. In Gout after the initial (first attack) of Acute Gouty Arthritis, flare may be still infrequent. The second attack of Acute Gouty Arthritis may recur once after several years (once after 2-3 years) before it become once annually.
2. Acute Gouty Arthritis may last from a few days to a fortnight without treatment
3. There is abundance of all sorts of cheap NSAIDs or prednisone available over the counter
4. Taking a few tablets of over the counter NSAIDs and/or Prednisone dissolves the Acute Gouty Arthritis within a few days without any sequelae.
5. Herbal medicines may contain NSAID and/or Prednisone disguised by herbs in a capsule or sachet. These are effective against the initial attacks of Acute Gouty Arthritis.
6. Ultimately, the frequency of attack of Acute Gouty Arthritis increases to twice and thrice annually within 10 years and the status of Chronic Gout is established.
7. The principle therapy for Gout is keeping serum urate level to  $< 5\text{mg}\%$ . Without therapy of the hyperuricemia, Gout is inclined to develop into Chronic Gout and subsequent complications.

**What is the long term outcome if self-medication is continued in Chronic Gout without medical supervision?**

Over 10 years with suppression of Acute Gouty Arthritis of Gout by self-medication without control of hyperuricemia, Chronic Gout developed. In the subsequent decade complications slowly developed such as tophus, urolithiasis, renal insufficiency, hypertension, and joint destruction. During the second decade of Chronic Gout, the complications slowly get worse from tophus to tophi, single to multiple urolithiasis, renal insufficiency to renal failure, hypertension to stroke and myocardial infarct, and joint destruction to joint deformities. After 30 years of Gout, it is common for End Stage Renal Disease, stroke, cardiovascular accident to occur and may induce early unnecessary mortality. If only from the very beginning hyperuricemia is treated adequately for long term, Chronic Gout and its complication would not have developed.

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