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CONTENTS

MEDICINE

Obstetrics and gynecology

Therapy

Pediatrics

Clinical medicine

Therapy

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Current issues in the diagnosis and treatment of gout

Gout is a heterogeneous disorder that results in the deposition of uric acid salts and crystals in and around joints and soft tissues or crystallization of uric acid in the urinary tract. Gout metabolic disorder characterized by hyperurecamia (normal plasma urate 1-4mg/dl). Acute gout: sudden onset of severe inflammation in the small joint due to precipitation of urate crystals in the joint space. Chronic gout: pain and stiffness persist in the joint between attacks [12].

Epidemiology. Gout is the most common of microcrystalline arthropathy. Incidence has increased significantly over the past few decades [1].Affects about 2.1 million worldwide [12].Peak incidence occurs in the fifth decade, but can occur at any age [1].Gout is 5 times more common in males than pre-menopausal females; incidence in women increases after menopause. After age 60, the incidence in women approaches the rate in men [12].People of South Pacific origin have an increased incidence [1].

Predisposing Factors: heredity, drug usage, renal failure, hematologic disease, trauma, alcohol use, psoriasis, poisoning, obesity, hypertension, organ transplantation, surgery[2, 3].

Stages of Classic Gout

Asymptomatic hyperuricemia. Very common biochemical abnormality. Defined as 2 SD above mean value. Majority of people with hyperuricemia never develop symptoms of uric acid excess [5].

Acute Intermittent Gout (Gouty Arthritis). Episodes of acute attacks. Symptoms may be confined to a single joint or patient may have systemic symptoms [5].

Intercritical Gout. Symptom free period interval between attacks. May have hyperuricemia and monosodium urate crystals in synovial fluid [14].

Chronic Tophaceous Gout. Results from established disease and refers to stage of deposition of urate, inflammatory cells and foreign body giant cells in the tissues. Deposits may be in tendons or ligaments. Usually develops after 10 or more years of acute intermittent gout [12].

Pathogenesis. Urate crystals stimulate the release of numerous inflammatory mediators in synovial cells and phagocytes [4].The influx of neutrophils is an important event for developing acute crystal induced synovitis [4].Chronic gouty inflammation associated with cytokine driven synovial proliferation, cartilage loss and bone erosion [3].

Criteria for the classification of acute gouty arthritis[7, 12]

A. Presence of characteristic urate crystals in the joint fluid or ...

B. A torphus proven to contain gouty crystals or...

C. Presence of 6 or more of 12 clinical/ lab:

1. >1 attack;
2. maximal inflammation developed within 1 day;
3. attack of monoarticular arthritis;
4. joint redness observed;
5. 1st MTP joint painful or swollen;
6. unilateral attack involving IstMTP joint;
7. unilateral attack involving tarsal joint;
8. suspected tophus;
9. hyperuricaemia;
10. asymmetrical swelling within a joint (X-ray);
11. subcortical cysts without erosions (X-ray);
12. negative culture from joint fluid during attack.

Clinical manifestations

Systemic:fever rare but patients may have fever, chills and malaise [12].

Musculoskeletal:Acute onset of monoarticular joint pain. First MTP most common. Usually affected in 90 % of patients with gout. Other joints knees,

footandankles. Less common in upper extremities [6].

Skin:warmth, erythema and tenseness of skin overlying joint. May have pruritusand desquamation [5, 12].

Kidney:Renal colic with renal calculi formation in patients with hyperuricemia is frequent [5, 8].

Investigations[8, 12]

- Uric Acid. Limited value as majority of hyperuricemic patients will never develop gout. Levels may be normal during acute attack.

- CBC. Mild leukocytosis in acute attacks, but may be higher than 25 000/mm.

- ESR. Mild elevation.

- 24hr urine uric acid. Only useful in patients being considered for uricosuric therapy or if cause of marked hyperuricemia needs investigation.

- Trial of colchicines. Positive response may occur in other types of arthritis to include pseudogout.

Differential diagnosis: bursitis, calcium pyrophosphate dihydrate crystal deposition disease (CPPD, pseudogout), osteoarthritis, osteomyelitis, psoriatic arthritis, rheumatoid arthritis, septic arthritis, synovitis, tendinitis, traumatic arthritis [9].

Treatment and management

EULAR evidence based recommendations for gout

1. Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of serum uric acid(SUA) level below a target level [10].

2. Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:

a. specific risk factors (levels of serum urate, previous attacks, radiographic signs) [11];

b. clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous

gout) [12];

c. general risk factors (age, sex, obesity, alcohol consumption, urate raising drugs,drug interactions, and comorbidity) [11, 12].

3. Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and *reduced alcohol (especially beer)* are core aspects of management [11, 12].

4. Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the management of gout [11, 12].

5. The choice of drug (s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved [10].

6. Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an non-steroidal anti-inflammatory drugs(NSAID), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin [10].

In Ukraine, as an alternative to colchicine, homvio-revman used for long-term treatment.

7. In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares [10].

8. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment [10].

9. Intra-articular aspiration and injection of long acting steroid is an effective and safe treatment for an acute attack [12].

10. The therapeutic goal of urate lowering therapy is to promote crystal

dissolution and prevent crystal formation; this is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (≤360 μmol/1) [10].

11. In patients with normal kidney function, allopurinol is recommended for first-line urate-lowering therapy (ULT), starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemia target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated [10].

12. When gout associates with diuretic therapy, stop the diuretic if possible: for hypertension and hyperlipidaemia consider use of losartan and fenofibrate, respectively [12].

Classification of drugs for the treatment of Acute Gout (Figure 1)

- NSAIDs. Dose of NSAIDs for acute attack of gout: NSAIDs in high doses taken with food are: Naproxen – 750 mg immediately, then 500 mg every 8-12 hours. Diclofenac: 75-100 mg immediately, then 50 mg every 6-8 hours. Indomethacin: 75 mg immediately, then 50 mg every 6-8 hours. After 24-48 hours, reduced doses are given for a further week. Contraindications: active peptic ulcer disease/impaired renal function/allergy to NSAIDs [11].

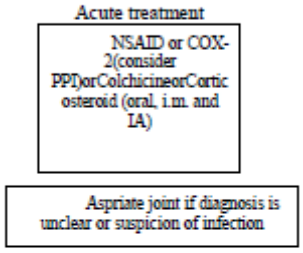
- Colchicine.Colchicine is alkaloid from Colchicum autumnale. Suppresses gouty inflammation neither analgesic nor anti-inflammatory. No effect on blood uric acid level [13].

Treatment of Acute attack: effective within first 24h of attack. A small dose (0.5-1.5 mg) taken at first symptom of attack abort it. Dose: lmg PO followed by 0.25 mg 1-3 hourly till the acute attack is over or total dose of 6 mg is given or diarrhea starts. Maintenance dose 0.5-1 mg/day for 4-8 weeks. Prophylaxis of gout: 0.5-1 mg/day (prevents further attack). Doses should be decreased in renal and hepatic dysfunction [12].

- Corticosteroid. Corticosteroid gives dramatic symptomatic relief. Used if

NSAIDs are contraindicated, if Gout is monoarticular: intra-articular administration (e.g., triamcinolone, 10-40 mgdepending of size of joint). For Polyarticular gout: IV or Orally Methylprednisolone 40 mg/day IV tapered over 7 days. Prednisolone 40-60 mg/day orally tapered over 7 days [12].

Figure 1. **Algorithm for the medical treatment of acute gout. PPI: proton pump inhibitor [12].**



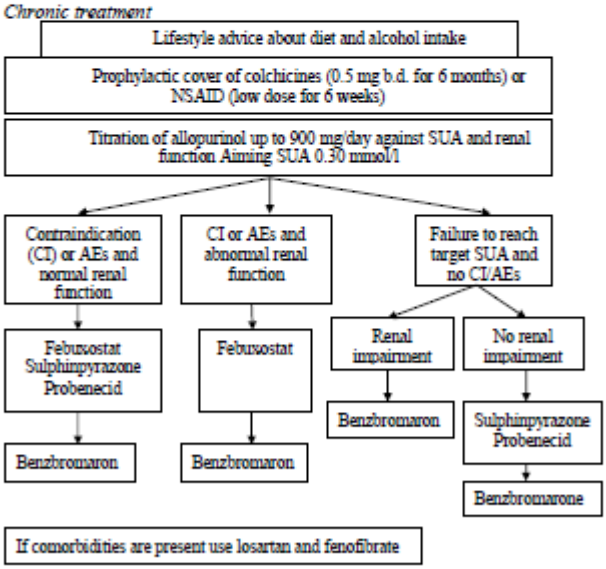
Drugs for Chronic gout(Figure 2)

- Probenecid. Probenecid Uses: Chronic gout and hyperuricaemia: (2nd line/ adjuvant drug) 0.5 g/dayinitially, with gradual increase to 1-2 g daily. It gradually lowers blood urate level. Ineffective in the presence of renal insufficiency (serum creatinine >2 mg/dl). Adverse effects: rashes, allergic dermatitis, upper GIT irritation, and drowsiness. Inhibits excretion of penicillin, dapsone indomethacin, and acetazolamide [11].
- Sulfinpyrazone. Sulfinpyrazone Uses: In chronic gout: start with 100-200 mg BD, gradually increatseaccording to response (max. dose 800 mg/d). Uricosuric action is additive with probenecid but antagonized by Salicylates. It inhibits platelet aggregation. Adverse effects: gastric irritation/rashes/ hypersensitivity reaction [12].
- Uric acid synthesis inhibitor Allopurinol. Competitive inhibitor of uric acid synthesis by inhibiting xanthine oxidase. Xanthine oxidase is involved in the metabolism of hypoxanthine and xanthine to uric acid. Promptly lowers plasma urate and urinary uric acid concentration and facilitates tophus mobilization. Allopurinol is very effective in uric acid

overproducers. Dose: initially 100 mg/d of allopurinol is given for 1 week, the dose is increased to 200-300 mg/d, if serum uric acid is still high. ADRs: precipitation of acute gouty arthritis in the initial month of therapy/GI upset/skin rash/alopecia. Probenecid increases the excretion of allopurinol. If patient taking both Probenecid and Allopurinol, than increase dose of allopurinol and decrease dose of Probenecid [13].

At this time, the question remains to optimize treatment methods and prevention of not onlygout exacerbations but also asymptomatic hyperuricemia, which increases the risk of cardiovascular diseases. Perhaps the solution to this problem will, in the future, identification of genes that affect the propensity to develop gout in patients with asymptomatic hyperuricemia, search for new drugs, which become the target genetic loci.

Figure 2. **Algorithm for the medical treatment of chronic gout [12].**



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