

TREATMENT OF ACUTE & CHRONIC GOUT

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INTRODUCTION

- **Gout is a familial metabolic dx**
- **It most often affects middle-aged to elderly men & postmenopausal women**
- **Gout is characterized by recurrent episodes of acute & chronic arthritis due to depositn of monosodium urate crystals in joints & cartilage**

Other assoc features:

- i. Formatn of uric acid calculi in the kidneys**
- ii. Hyperuricaemia (high serum levels of uric acid).**
 - **Uric acid is a poorly soluble substance c is the major end product of purine metabolism**

Other assoc features 2

- iii. Tophi: hard deposits of crystalline uric acid & its salts in the skin, cartilage or joint.**
- iv. Interstitial nephritis**

Events c may precipitate acute gouty arthritis

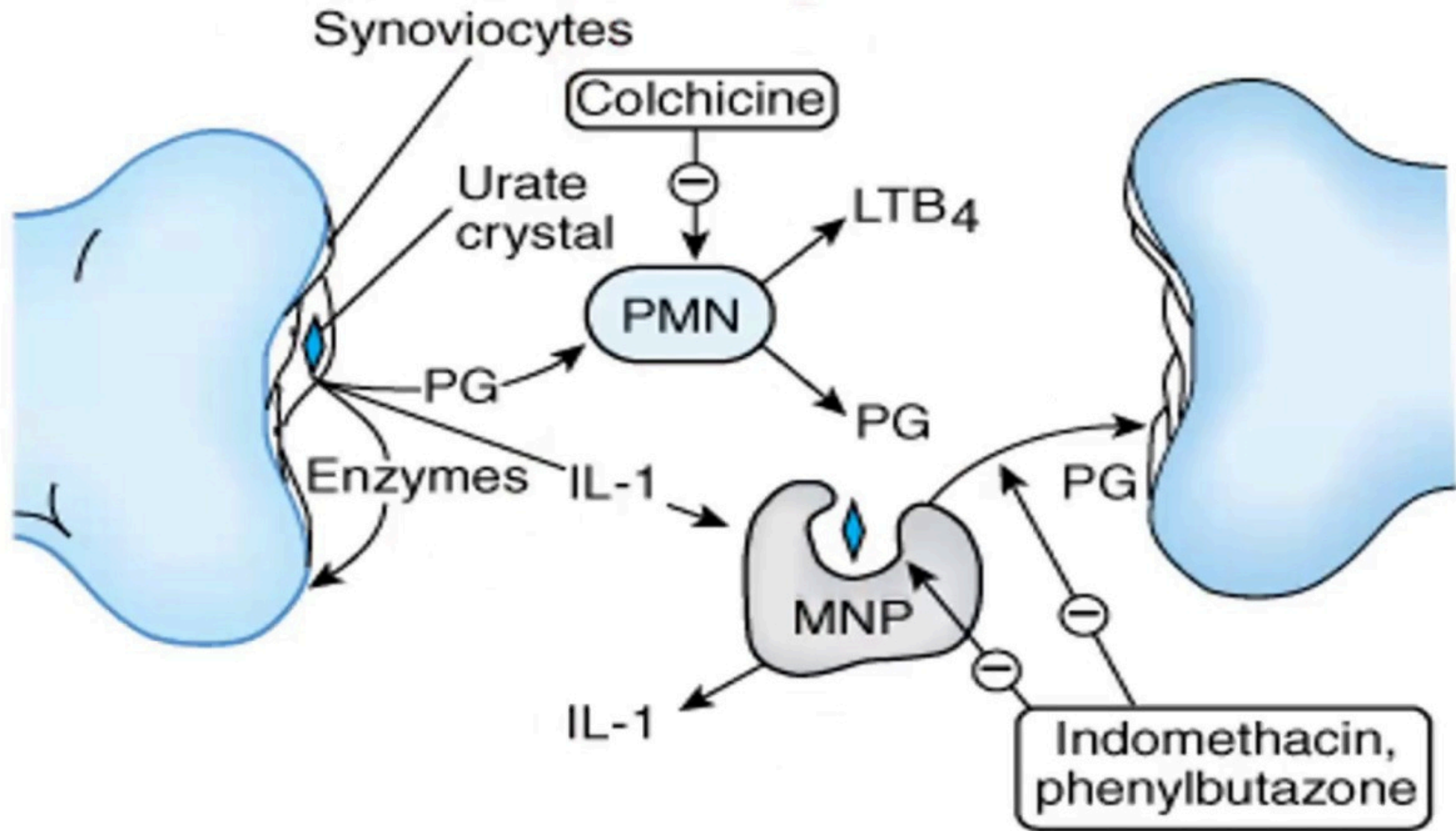
- 1. Dietary excess**
- 2. Trauma**
- 3. Surgery**
- 4. Excessive ethanol ingestion**
- 5. Hypouricemic therapy &**
- 6. Serious medical illnesses s.a myocardial infarction & stroke.**



PATHOPHYSIOLOGY

- **Urate crystals are initially phagocytosed by synoviocytes**
- **Synoviocytes then release inflammatory mediators (prostaglandins, lysozomal enzymes & interleukin 1[IL-1])**

Pathophysiologic events in a gouty joint



Pathophysiology 2

- **The inflammatory mediators attract & activate polymorphonuclear leukocytes (PMN) & mononuclear phagocytes (MNP) i.e macrophages(M ϕ).**

Pathophysiology 3

- **The PMN & MNP migrate into the joint space & amplify the ongoing inflammatory process.**
- **In the later phases of the attack, MNP ingest the urate crystals & release > inflammatory mediators (ref fig 36-5 Katz 11th/12th/13th Ed)**

Aims of Rx of Gout

A. Relieving the acute gouty attack

B. Rx of chronic gout = Urate-lowering therapy (hypouricemic therapy)

➤ **It aims to prevent:**

- i. Recurrent gouty attacks &**
- ii. Complications of gout(e.g urate crystal formation)**

A. Rx OF ACUTE GOUTY ARTHRITIS

- **The mainstay of Rx during an acute attack of gout is the admin of an anti-inflammatory drug s.a Colchicine, NSAIDS or Glucocorticoids depending on**
 - i. The age of the patient &**
 - ii. Other underlying illnesses.**

Rx of acute gout 2

- **Both Colchicine & NSAIDS may be poorly tolerated & dangerous in the elderly, particularly in the presence of renal insufficiency & GIT disorders.**

Rx of acute gout 3

- **In elderly ptnts with attacks involving 1 or 2 large joints, intra-articular glucocorticoid injections may be preferable & effective.**
- **Ice pack applications & rest of the involved joints can also be helpful.**

Rx of acute gout 4

- **IL-1 inhibitors** may be used for Rx of acute gout in patients with C/Is to, or who are refractory to, traditional therapies like NSAIDs or colchicine.

1. NSAIDS IN GOUT

- **NSAIDS are the 1st line drugs for Rx of acute gout**
- **They are most often used in ptnts without complicating co-morbid conditns**

NSAIDS 2

- **NSAIDs given in full anti-inflammatory doses are effective in ~90% of ptnts, & the resolutn of signs & symptoms usually occurs in 5–8 days.**

NSAIDS 3

- **The most effective NSAIDs are those with a short $t^{1/2}$ including:**
 - i. Indomethacin, 25–50 mg tid;**
 - ii. Ibuprofen, 800 mg tid;**
 - iii. Diclofenac, 50 mg tid.**
 - iv. Naproxen, 500 mg bid or**
 - v. Celecoxib 800 mg, then 400 mg bid**

NSAIDS 4

- **COX- 2 selective inhibitors are thought to be equally effective but with less short-term GIT toxicity**
- **All other NSAIDS except ASA, Salicylates & Tolmentin have been successfully used to Rx acute gouty episodes**

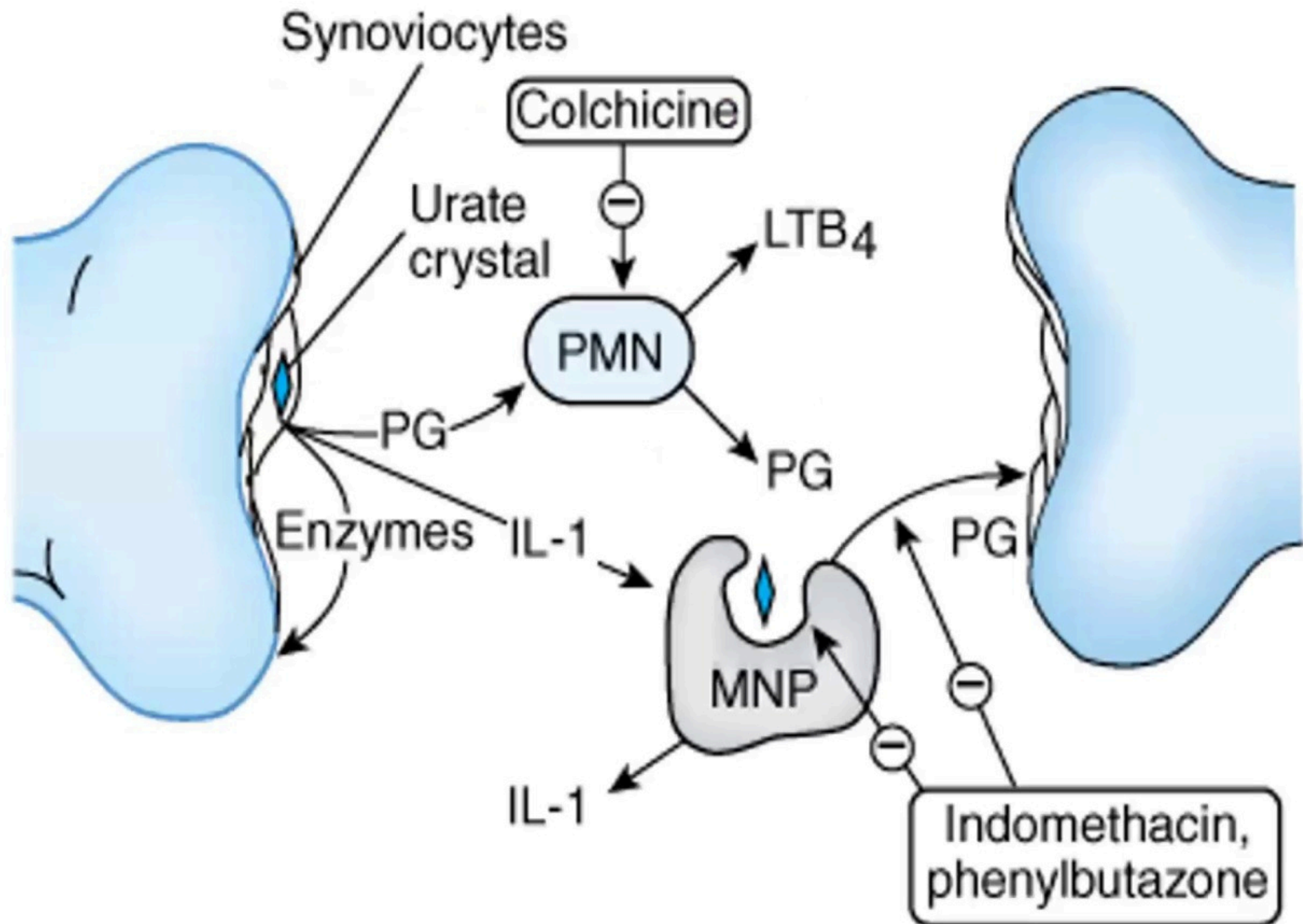
NSAIDS 5

- **Oxaprozin** lowers serum uric acid & should not be given to ptnts with uric acid stones becos it ↑ses uric acid excretn in the urine

MoA NSAIDS in gout

- **They inhibit prostaglandin synthase (COX)**
- **They also inhibit urate crystal phagocytosis**

Pathophysiologic events in a gouty joint



2. COLCHICINE

- **When given orally it is effective Rx, when used early in the attack.**
- **One to two 0.6-mg tablets can be given every 6–8 h over several days with subsequent tapering.**
- **Colchicine must be stopped promptly at the 1st sign of loose stools, & symptomatic Rx must be given for the diarrhea.**

Colchicine 2

- **IV colchicine is occasionally used, e.g., as pre- or post-operative prophylaxis in 1- 2mg doses when ptnts cannot take medicatns orally.**
- **The IV colchicine should be given slowly thru an established venous line over 10 min in a soluset.**

Colchicine 3

- **The total dose should never exceed 4 mg.**
 - **Life-threatening colchicine toxicity & sudden death have been reported with the admin of >4 mg/d IV.**

Other modalities of Rx in acute gout

3. Glucocorticoids

- **Oral glucocorticoids s.a prednisone, 30–50 mg/d as the initial dose & gradually tapered with the resolutn of the attack can be effective in polyarticular gout.**

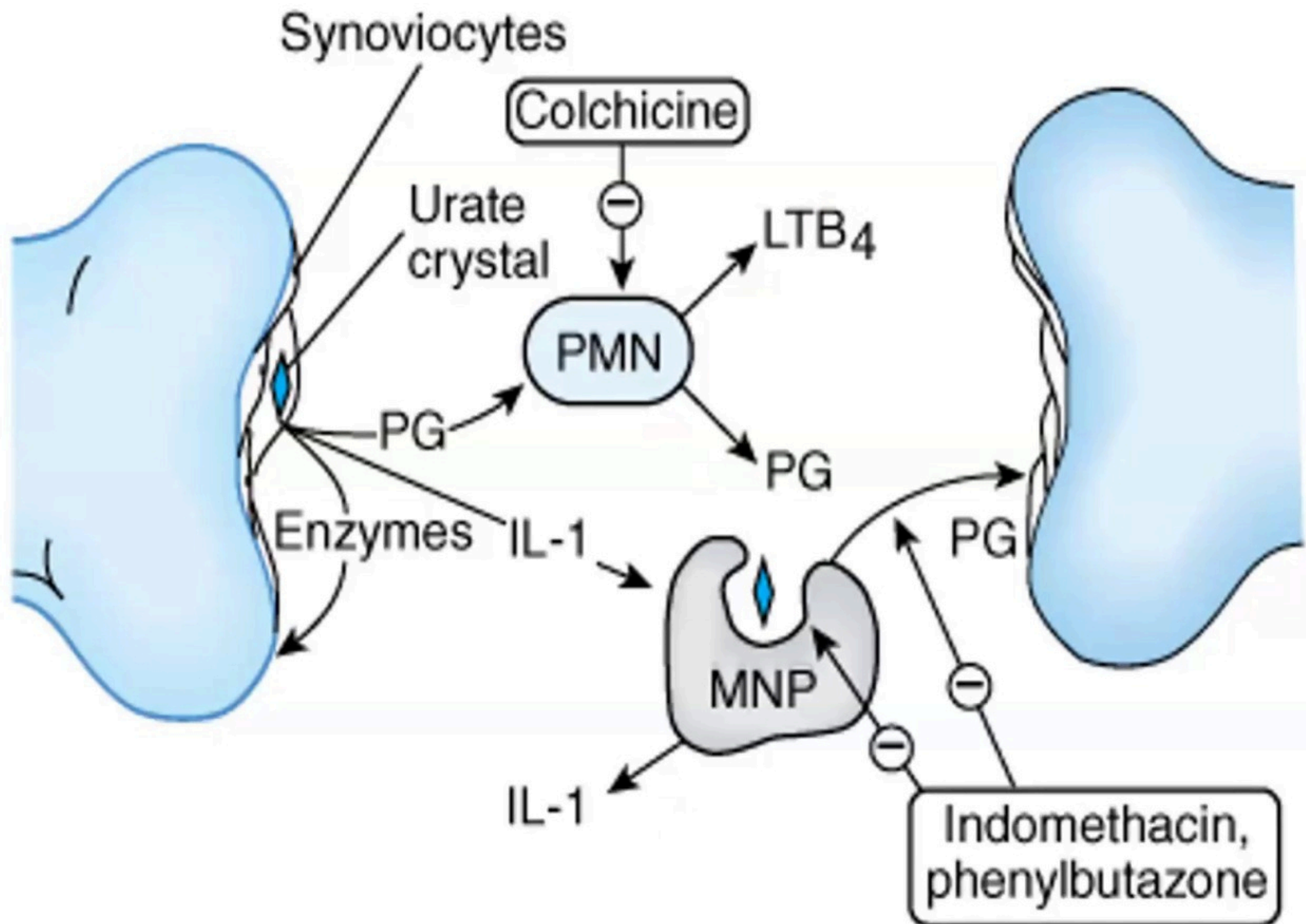
Glucocorticoids 2

- **For single or few involved joints intraarticular triamcinolone acetonide, 20–40 mg, or methylprednisolone, 25–50 mg, have been effective and well tolerated.**

4. INTERLEUKIN-1 (IL-1) INHIBITORS

- **Drugs targeting IL-1, s.a **Anakinra, canakinumab, & rilonacept**, are used in the Rx of gout.**
- **Data is currently limited**

Pathophysiologic events in a gouty joint



IL-1 inhibitors 2

- **However, these agents may provide a promising Rx option for acute gout in patients with C/Is to, or who are refractory to, traditional therapies like NSAIDs or colchicine.**

IL-1 inhibitors 3

- **Canakinumab** is a fully human anti-IL-1 β monoclonal antibody
- It can provide rapid & sustained pain relief at a dose of 150 mg Sc.

IL-1 inhibitors 4

- **IL-1 inhibitors are also being evaluated for prevention of gout flares while initiating urate-lowering therapy**

B. HYPOURICEMIC THERAPY

- **Ultimate control of gout requires correctn of the basic underlying defect, i.e hyperuricemia.**

Hypouricemic therapy 2

- **Hypouricemic regimens attempt to normalize serum uric acid to $<300\text{--}360\text{ mmol/L}$ ($5.0\text{--}6.0\text{ mg/dL}$) to prevent recurrent gouty attacks & eliminate tophaceous deposits (ref 2nd aim of Rx in gout)**
- **These medications are generally required for life.**

Hypouricemic therapy 3

- **Hypouricemic therapy should be considered when hyperuricemia cannot be corrected by simple means s.a :-**

I. Control of body weight

II. Low purine diets

III. Increased liquid ingestion

IV. Limitation of ethanol intake

V. Avoidance of diuretic use

Hypouricemic therapy 4

- **The decision to initiate hypouricemic therapy is usually made taking into consideration:**
 - i. The number of acute attacks (urate lowering may be cost effective after two attacks)**
 - ii. Serum uric acid levels [progresn is more rapid in ptnts with serum uric acid >535 mmol/L (>9.0 mg/dL) ...cont**

Indications for hypouricemic therapy cont

iii. Patient's willingness to commit to lifelong therapy, or

iv. Presence of uric acid stones.

- **Urate-lowering therapy should be initiated in any ptnt who already has tophi or chronic gouty arthritis.**

Two categories of Hypouricemic drugs can be used

1. Uricosuric drugs

- **These ↑se the excretion of uric acid & there4 reduce the concentrations in plasma**

Hypouricemic drugs 2

2. Xanthine oxidase inhibitors (XOI), c ↓ce the synthesis of uric acid by inhibiting xanthine oxidase(XO), the enzyme involved in the terminal steps of the biosynthesis of uric acid:

Allopurinol & Febuxostat

1. URICOSURIC AGENTS

- **Probenecid & Sulfapyrazone** are uricosuric drugs used to decrease the body pool of urate in
 - i. **Ptnts with tophaceous gout or**
 - ii. **Those with increasingly frequent gouty attacks**

Uricosuric agents 2

NB

- **Uricosuric agents should not be used in ptnts who excrete large amounts of uric acid becos they can precipitate the formatn of uric acid calculi**

Uricosuric agents 3

- **Uricosuric agents, can be used in ptnts with good renal fn who underexcrete uric acid, with <600 mg in a 24-h urine sample.**
- **Urine volume must be maintained by ingestn of $\geq 1.5\text{L}$ of H_2O /day.**

Uricosuric agents 4

- **Probenecid** can be started at a dosage of 250 mg B.D & ↑sed gradually as required up to 3 g in order to maintain a serum uric acid level <300 mmol/L (5 mg/dL)

Uricosuric agents 5

- **Probenecid is generally not effective in ptnts with serum creatinine levels of >177 mol/L (2.0 mg/dL).**
 - **These ptnts may require **allopurinol or benzbromarone**, a uricosuric drug that is **> effective in ptnts with renal failure.****

Uricosuric agents 6

- **Losartan, fenofibrate, & amlodipine** also have mild uricosuric effects

2. XANTHINE OXIDASE INHIBITORS

- i. Allopurinol**
- ii. Febuxostat**
- iii. PEGylated uricase**

i. ALLOPURINOL

- **It is the most commonly used hypouricemic agent**
- **It is the best drug to lower serum urate in**
 - a. Overproducers**
 - b. Urate stone formers &**
 - c. Ptnts with renal dx.**

Allopurinol 2

- **It can be given in a single morning dose, 100–300 mg initially & ↑sing up to 800 mg if necessary**
- **In ptnts with chronic renal dx, the initial allopurinol dosage should be lower & adjusted depending on the serum creatinine conc;**

Allopurinol 3

- **Ptnts with frequent acute attacks may also require lower initial doses to prevent exacerbatns.**

Allopurinol 4

- **Toxicity of allopurinol has been recognized increasingly in**
 - a. Ptnts with renal failure who use thiazide diuretics &**
 - b. Ptnts allergic to penicillin & ampicillin.**

AEs of Allopurinol

- **The most serious A/Es include**
 - a. Skin rash with progress to life-threatening toxic epidermal necrolysis**
 - b. Systemic vasculitis**
 - c. Bone marrow suppression,**
 - d. Granulomatous hepatitis &**
 - e. Renal failure**

AEs of Allopurinol 2

- **Ptnts with mild cutaneous rxns to allopurinol can either**
 - a. Reconsider the use of a uricosuric agent**
 - b. Attempt desensitization to allopurinol**
 - c. Take febuxostat or**
 - d. They can also pay ↑sed attentn to diet**

ii. FEBUXOSTAT

- **A nonpurine inhibitor of xanthine oxidase**

PK

- **>80% is absorbed following oral admin**
- **Peak conc occurs in < 1 hr**
- **Extensively metabolised in the liver to inactive metabolites**

Febuxostat 2

- **All of the drug & its metabolites appear in the urine**
 - **However, < 5% appears as unchanged drug**
- **No dosage adjustment is necessary in ptnts with mild to mod renal impairment**

PD

- **Febuxostat is a potent & selective inhibitor of xanthine oxidase.**
 - **It decreases the formation of xanthine & uric acid**
- **At a dose of 80 – 120mg O.D it is > effective than allopurinol at a dose of 300mg daily in lowering serum urate levels**

AEs of febuxostat

- **As with allopurinol, prophylactic Rx with Colchicine or NSAIDS should start at the beginning of Rx to avoid gout flares.**
- **The most frequent Rx related AEs are liver function abnormalities, diarrhea, headache & nausea**

AEs of febuxostat 2

- **Febuxostat appears to be well tolerated in ptnts with a H/O allopurinol intolerance**

iii. PEGLOTICASE

- **It is the newest urate-lowering therapy to be approved for the Rx of refractory chronic gout**
- **It is a recombinant form of the enzyme urate oxidase or uricase (It is a pegylated uricase)**

MoA of Pegloticase

- **It Converts uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys.**

Clinical use of Pegloticase

- **It is indicated for patients with gout who fail Rx with std therapies s.a XOIs.**
- **It is administered IV usually at 8 mg every 2 weeks**
- **It can dramatically lower serum uric acid in up to 50% of such patients.**

Additional info on Hypouricemic drugs

- **Urate-lowering drugs are generally not initiated during acute attacks but after the patient is stable & low-dose colchicine has been initiated to decrease the risk of flares that often occur with urate lowering.**

Additional info on Hypouricemic drugs 2

- **Colchicine prophylaxis in doses of 0.6 mg O.D or B.D is usually continued, together with the hypouricemic therapy, until the ptnt is normouricemic & without gouty attacks for 6 months or as long as tophi are present.**

Additional info on Hypouricemic drugs 3

- **Colchicine should not be used in dialysis patients**
- **It is given in lower doses in patients with**
 - a. Renal dx or**
 - b. Those using P glycoprotein or CYP3A4 inhibitors s.a clarithromycin that can increase toxicity of colchicine.**