Swollen joints, Renal stones & Life-threating Infection

- Ms. Chung, a 67 yrs lady transferred from acute surgical ward to our unit in early Jan
- She has been stayed in the intensive care unit for nearly a month because of severs sepsis developed after an urological operation
- Transferred to our rehabilitation unit for training, reconditioning and extended care

In 2003, when she was 59 yrs

- Good past health, lived with her family, housewife, walked unaided, basic and advance activity of daily living were independent
- No family history of significant illness
- No symptom cognitive impairment
- Occasional stress urinary incontinence, otherwise normal
- Fu at GOPD for hypertension, hyperlipidemia, obesity, occasional joint pain
- Given NSAID for joint pain; Adalat Retard for HT

An episode of drug reaction

- Admitted to acute medical unit in 8/2003 for itchy skin rash , fever and sore throat for 3 days
- She has taken allopurinol and NSAID for few days before admission
- Physical exam showed urticaria, soft palate ulcer
- WBC 10.5 (Neutrophil 8.7, Eosinophil 1.0)
- Urate 0.41 mmol/l, deranged RFT (Cr 202)
- Deranged LFT (AST 332, ALT 406, ALP 200), hepatitis (B, A, C) serology negative

- Treated with piriton, steroid (hydrocortisone→prednisolone), and supportive therapy
- Rash and soft palate ulcer subsided, RFT and LFT normalized gradually
- Labeled as allopurinol allergy
- Scheduled USG abd in 8/2003
  - Gallstones
  - Multiple renal stones
  - Size of kidney normal (right: 11 cm; left: 10.9 cm)
  - No hydronephrosis
- Referred to urologist for management of renal stone
  - Observatory management of renal stone at that stage

- Condition stable
- According to patient, more frequent gout attack and noted to have hard swelling over joints since 2008, after the knee arthroscopy performed in private sector for suspected OA Knee
- when acute gout attack, visited GP or informed medical officer in GOPD, treated with NSAIDs
- Dietary advices have been given and followed

First episode of urinary sepsis

- Admitted to acute medical unit in 3/2007 for fever, loin pain, vomiting and hematuria
  - RFT derangement (Cr 239), urate 0.415
  - Blood and urine culture grew E. coli
  - Developed septic shock, required ICU admission
  - bedside USG showed right hydronephrosis
  - Assessed by urologist, pyelonephritis was suspected
  - JJ stent inserted, right ureteric stone noted
  - Sepsis subsided and RFT normalized

- Right ureteric stone no longer seen in ureterorenoscopy scheduled in 7/2007
- Scheduled USG abd in 9/2007
  - large renal stone over lower pole of left kidney
  - No hydronephrosis
  - No stone over right kidney
- KUB: faint opacity over lower pole of left kidney
- Patient preferred observatory treatment at that time.
- Reported on and off gouty attack when attended GOPD fu. Documented tophi over bilateral big toe (9/2010)

Years of recurrent renal stones

- A new 1cm stone over pelvic-ureter junction (PUJ) of right kidney was seen in KUB taken 9/2010
- CT abd (3/2011)
  - Right slightly atrophic kidney (right: 7.7 cm; left : 9.2cm)
  - right PUJ stone, right lower pole renal stone, left staghorn stone
- At the same time, RFT deteriorated gradually (Cr ~300; CrCl 22 ml/min, urate 0.58)
- Developed an episode of UTI in 5/2011 and also found to have right hydronephrosis again, so inserted JJ stent into right side
- Scheduled right side percutaneous nephrostomy lithotripsy (PCNL) in late May, and it was uneventful. Stone analysis showed uric acid stone.

Normal size in 2003

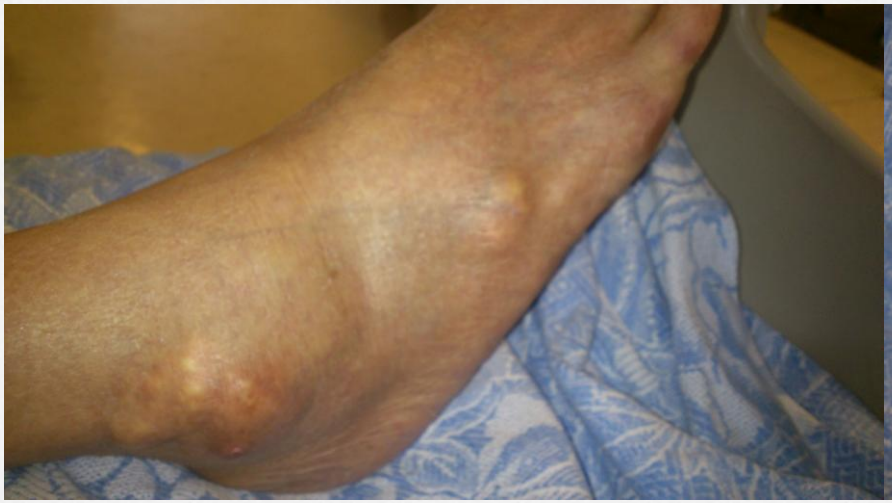
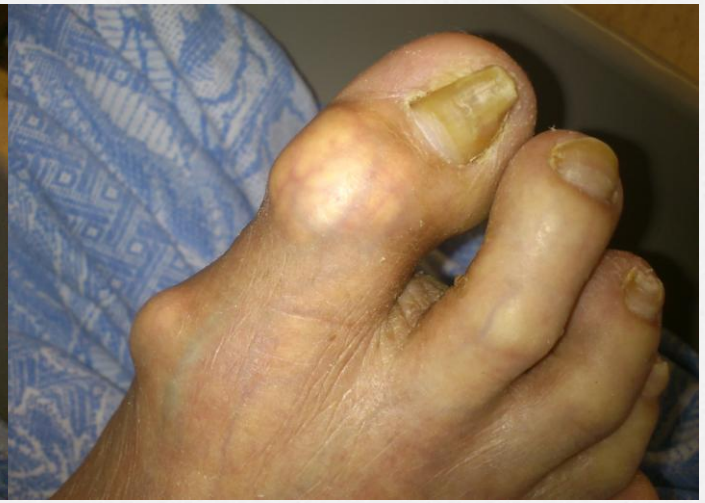
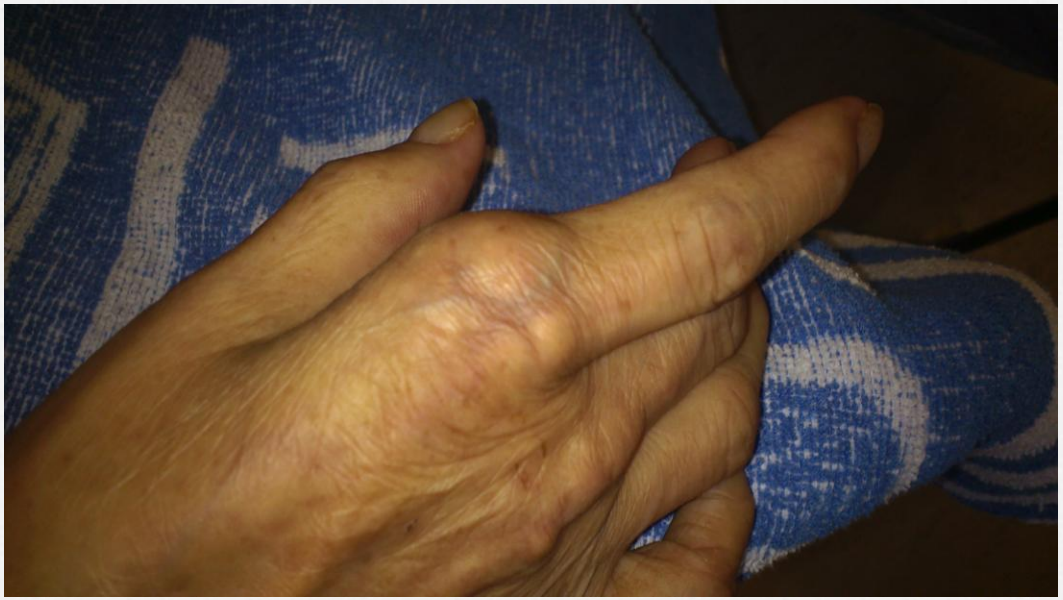
This episode

- Clinical admission to urology unit in 11/2011 for PCNL of left kidney staghorn stone.
- Developed fever, shock, deranged RFT after the operation
- Admitted to ICU, required inotropic support and intubation
- CT abd showed residual left side renal stone, left hydronephrosis and left perinephritic collection
- Inserted JJ stent over left side, performed percutaneous drainage of left perinephritic collection once

- Cr has gone up to ~ 450, then gradually down to ~ 150
- Performed tracheostomy in view of prolonged intubation
- Put on Ryle's tube feeding
- Transferred to our rehabilitation unit for further management in early Jan.

When first arrived rehab unit……

- On Ryle's Tube, Foley catheter and tracheostomy
- generalized weakness, limb power ~ 2-3/5, impaired trunk control, bed-ridden
- Body weight 63.7 kg, BMI 28.7
- tophi was noted over bilateral big toe, bilateral malleoli, metacarpophalangeal joints of finger
- inflamed ankle and big toe metatarsophalangeal joints
- communicable, attentive, mentally sound , MMSE 21/28

- On and off gouty attack, treated with low dose colchicine, simple analgesic and ice therapy, occasionally with oral prednisolone
- put on prolonged low dose colchicine (0.5mg daily) to prevent acute flare, but stopped in view of persistent muscle weakness despite normal creatinine kinase
- urate level 0.631 – 0.7 mmol/l, Thyroid function normal
- Reviewed the status of allopurinol allergy and considered the option of long term urate lowering therapy
- Checked HLA-B*58:01 : detected

- has been transferred back to acute urology unit twice for management of left perinephritic collection and removal of JJ stent
- RFT further improved, CrCl 25 ml/min
- resumed oral feeding, removed Ryle's tube, tracheostomy tube and Foley catheter
- rehabilitation exercise
- walks with frame with supervision, basic ADL are mostly independent except bathing
- body weight 54 kg, BMI 25
- Discharged home in early May, lives with family and helper

Current problems

- longstanding hyperuricaemia, and on and off gouty attack
- deformity of joint due to tophi deposition
- recurrent formation of renal stones
- renal impairment related to obstructive uropathy, recurrent urinary tract infection, hyperuraemia, use of NSAIDs
- deconditioning after severe sepsis and prolonged bed rest

Gout & Hyperuricaemia

- Gout is a disorder of purine metabolism and results from urate crystal deposition in and around the joints caused by longstanding hyperuricaemia.
- Monosodium urate (MSU) crystals are formed when super-saturation concentrations are reached ~0.41 mmol/L at 37 °C.
- A common disease world-wide

Diagnosis

- Clinical diagnosis
  - The history of episodic self-limited pain, swelling and erythema over joints (sensitive but non-specific)
  - gouty tophi
  - ± hyperuricaemia
- Definite diagnosis
  - identification of monosodium urate (MSU) crystals in synovial fluid
  - needle-shaped, strong negative birefringence crystal under polarized light microscopy

Causes of hyperuricaemia

- high purine ingestion and subsequently increase de-novo synthesis in liver and small intestine cells
- increase production secondary to HGPRT deficiency and phosphoribosylpyrophosphate (PRPP) synthetase (PRPPS) superactivity (secondary gout)
- Diseases (myeloproliferative and lymphoproliferative disorders, psoriasis, and haemolytic anaemia) are associated with enhanced turnover of nucleic acid, which in turn lead to overproduction
- Alcohol and fructose consumption causes acceleration of ATP degradation to AMP, a precursor of uric acid
- Under-excretion related to renal insufficiency
- Drugs

Drugs

Raise serum urate conc.	Lower serum urate conc.
Diuretics (frusemide, thiazide)	Ascorbic acid
Tacrolimus	ACEI (captopril, enalapril, ramipril)
cyclosporine	calcitonin
ethambutal	citrate
pyrazinamide	Estrogen
Cytotoxic chemotherapy	fenofibrate
ethanol	losartan
Salicylates (low dose)	Salicylate (high dose)
levodopa	Indomethacin
Ribavirin & interferon	atorvastatin
Teriparatide	

Genetics play a role?

- associations between polymorphisms in the GLUT9 (SLC2A9) gene, urate concentrations, and gout
- a polymorphism in the URAT1 (SLC22CA12) gene was confirmed as a genetic risk factor for hyperuricaemia in Chinese men.

Hyperuricaemia & Renal impairment

- Renal stone
  - serum urate concentration, extent of renal uric acid excretion and low urine pH
  - radiolucent
- Raised uric acid concentrations can independently increase the risk of chronic renal dysfunction.
- In animal models, uric acid induces afferent arteriolopathy through proliferation of vascular smooth muscle cells, inflammation, and activation of the renin-angiotensin system, which leads to ischaemia in postglomerular circulation.

Hyperuricaemia & CVDs

- Hyperuricaemia and metabolic syndrome
- Hyperuricaemia has been reported in nearly 90% of children with newly diagnosed untreated hypertension, and uric acid concentrations were directly related to systolic and diastolic blood pressure in these patients.
- Hyperuricaemia is associated with increased risk of myocardial infarction, peripheral arterial disease, and death related to cardiovascular diseases.

Gout in Elderly

- More common in elderly, with an incidence of 8% in those aged 70 to 79 years compared with only 1.7% in those aged <50 years.
- Incidence of gout in women increases dramatically after menopause, from <1% in those aged <50 years to >5% in women age ≥70 years
- Renal insufficiency and under-excretion of urate
- Atypical presentation
- Co-morbidities limit the choice of drugs for acute attack and urate lowering

Traditional presentation	Presentation in the elderly
monoarticular	May be polyarticular
Sudden onset	May be gradual onset
Incidence in women < 1%	Incidence in women similar to that in men
Variable etiology	Decline in RFT and polypharmacy are the major etiology
Monosodium urate crystal formation; primarily affects great toe	Possible calcium pyrophosphate dihydrate crystal formation (pseudogout); primarily affects knee, wrist, shoulder, and ankle

Pharmacological management

- Acute attacks
- Urate lowering

Acute attacks

- NSAIDs
- Colchicine
- Steroid
- Interleukin-1β inhibitor

NSAIDs

- British Society for Rheumatology (2007)
  - Fast-acting NSAIDs at maximum dose for short-term use are the oral drugs of choice for symptom relief in acute gouty arthritis provided that there are no contraindications to their use.
  - All NSAIDs are equally effective when given in optimum doses
  - Treatment should be continued until the attack is terminated (1–2 weeks).
  - In patients with an increased risk of peptic ulcers, bleeds or perforations, co-prescription of gastro-protective agents should follow standard guidelines for the use of NSAIDs and COX2

- European League Against Rheumatism [EULAR] evidence based recommendations for gout (2006)
  - NSAIDs are first line agents for systemic treatment of acute gout. In the absence of contraindications an NSAID is a convenient and well accepted option
  - different NSAIDs give similar benefits in acute gout, with no evidence for individual superiority in terms of clinical efficacy
  - though NSAIDs are commonly used, it is largely based on personal experience and tradition as NSAIDs and colchicine have not been directly compared.

- Use of NSAIDs is largely limited by……
  - age
  - comorbidities (peptic ulcer, renal insufficiency, CHF)
  - con-current drugs (warfarin, antiplatelet agent)

Colchicine

- British Society for Rheumatology (2007)
  - Colchicine is effective at reducing the severity of an acute attack but is slower to work than NSAIDs.
  - Colchicine has a high risk of toxicity, in particular diarrhea.
  - Colchicine can be effective in reducing the severity of an acute attack of gout with diminished risk of adverse effects in doses of 0.5 mg bd-qid.
  - More frequent (2 hourly) dosing should be avoided.

- EULAR evidence based recommendations for gout (2006)
  - Oral colchicine, same as NSAIDs, is first line agents for acute gout
  - High doses of colchicine lead to side effects, and low doses (for example 0.5 mg tds) may be sufficient for some patients with acute gout.

Side effect & Toxicity

- diarrhea, abdominal cramps, nausea, vomiting
- rarely bone marrow suppression, myopathy, neuropathy
- more common in long term use, patients with renal/hepatic dysfunction
- Colchicine should not be used if the CrCL is less than 10 mL/min
- dose should be decreased by at least half if the CrCl is less than 50 mL/min
- dose adjustment in elderly, not ≥ 1mg /day

Corticosteroid

- British Society for Rheumatology (2006)
  - Corticosteroids are an effective treatment in the management of acute gout in patients who cannot tolerate NSAIDs or are refractory to other treatments. They can be given orally, im, iv or intra-articularly.
  - In those with a monoarthritis, an intra-articular corticosteroid injection is highly effective in terminating an attack.

- EULAR evidence based recommendations for gout (2006)
  - intra-articular injection of a long acting steroid is an effective and safe treatment for an acute attack.
  - This may be especially useful for patients with a severe mono-articular attack and in those in whom an NSAID and colchicine are contraindicated.

- Cochrane review of systemic steroid for acute gout (2008)
  - 3 small scale studies compared 1. intramuscular triamcinolone acetonide injection with oral indomethacin; 2. intramuscular triamcinolone acetonide injections with intramuscular injections of adrenocorticotropic hormone (ACTH); 3. oral prednisolone to intramuscular diclophenac combined with oral indomethacin
  - Systemic steroid is as effective as the compared treatment modalities used In those studies
  - important safety problems attributable to the short duration use of corticosteroids were not reported

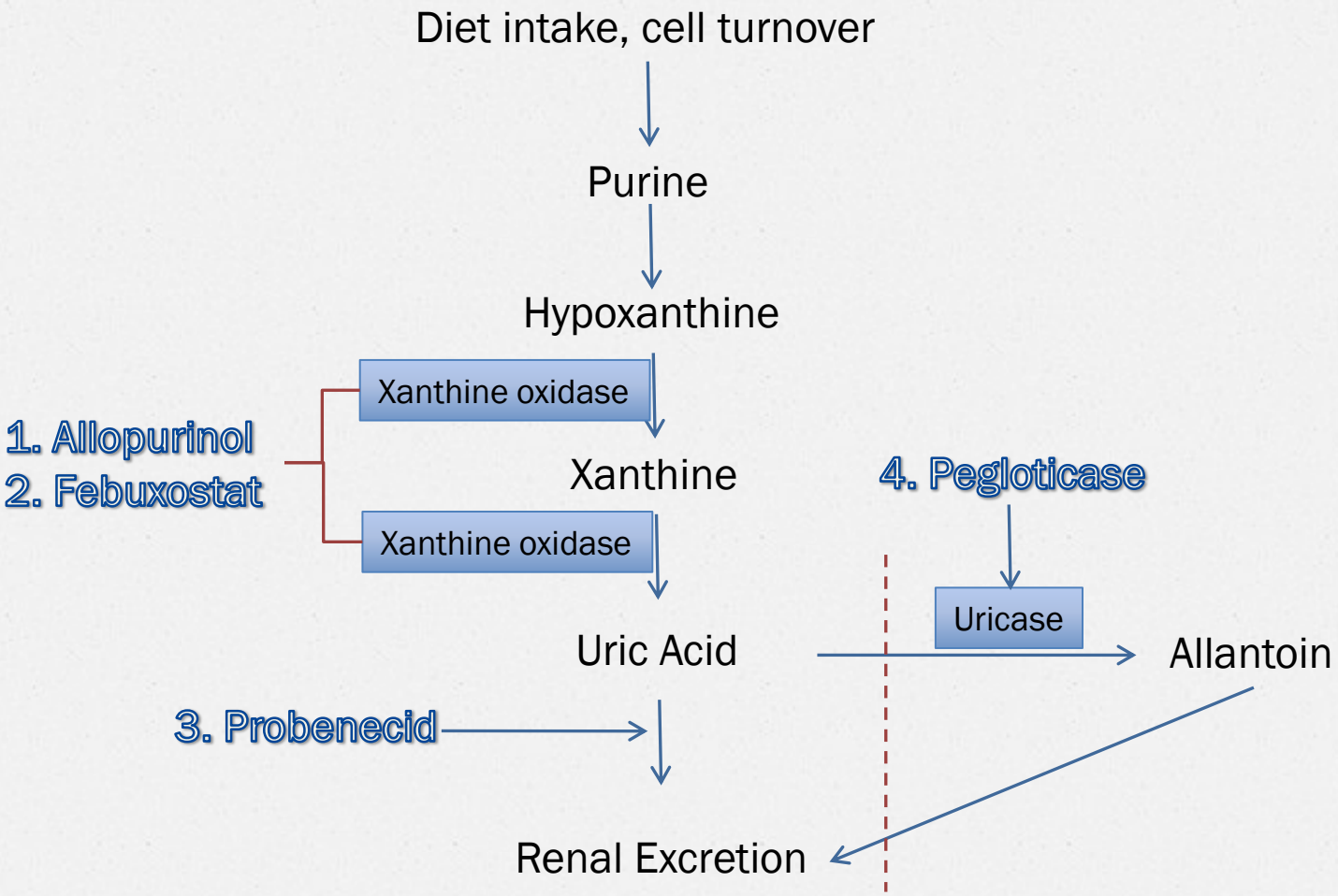
- Prednisone can be given orally at a dose of approximately 35 mg to 40 mg for 1-3 days and then tapered over 1 to 2 weeks. Tapering more rapidly can result in a rebound flare
- exclude septic arthritis, which can coexist with acute gouty attack, before intra-articular injection

Interleukin-1β Inhibitors

- interleukin 1β and its pathway is crucially associated with the inflammatory response induced by monosodium urate, suggesting that interleukin 1β is a pivotal mediator of inflammation in acute gout
- Canakinumab is a fully human monoclonal antibody of interleukin-1β receptors. It is first used in patients with Cryopyrin-Associated Periodic Syndromes (CAPS), and induces rapid and sustained complete remissions.
- Monthly, 150mg, subcutaneous injection
- Study showed significant effect in pain relief in acute gouty attack and reducing risk of flare.
- S/E: infection, injection site reaction
- expensive

Urate lowering agents

- The aim of urate lowering therapy is to maintain urate concentration below the saturation point for monosodium urate. [0.41 mmol/l at 37 °C]
- The time needed for disappearance of crystals in synovial fluid increases with duration and severity of gout, and hence preventive therapy should be prolonged for patients with severe tophaceous gout.
- Therapy should be continued indefinitely, because gout usually recurs a few years after treatment stops.
- Start 1-2 weeks after acute flare subsided
- Prophylaxis for acute flare (low dose colchicine for 6M, NSAIDs/steroid for 6 weeks)


Diet intake, cell turnover
Purine
Hypoxanthine
Xanthine oxidase
1. Allopurinol
2. Febuxostat
Xanthine
Xanthine oxidase
4. Pegloticase
Uricase
Uric Acid
Allantoin
3. Probenecid
Renal Excretion

When to start?

- British Society for Rheumatology (2007)
  - The plasma urate should be lowered to, and maintained < 0.3 mmol/l (using a uricase assay) by treatment.
  - In uncomplicated gout, specific long-term treatment to reduce plasma urate concentrations should normally only be given if a second attack or further attacks of gout occur within 1 yr.
  - Specific treatment should be considered, and then begun as soon as the acute attack of gout has settled in the following groups: 1. Patients with visible gouty tophi; 2. Patients with renal insufficiency (CrCl <80 ml/min); 3. Patients with uric acid stones and gout; 4. Patients who need to continue to take diuretics

- EULAR (2006)
  - Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radio-graphic changes of gout.
  - 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 ($\leq$ 0.36 mmol/l)

1. Allopurinol

- inhibit the action of xanthine oxidase, and thus production of uric acid
- start with low dose (50-100mg), gradually titrate up the dose according to serum urate level over 2-4 weeks
- mainly renal excreted, reduced dose in patient with renal insufficiency, but what is the right dose?
- Risk of adverse reaction vs. adequate control of serum urate level

- British society of Rheumatology (2006)
  - first line urate lowering agents
  - suggest maximum dose upto 900mg
  - dose modification according to creatinine clearance

Creatinine Clearance	Usual dose of allopurinol
>80 ml/min	200-300 daily
60-80 ml/min	100-200 daily
30-60 ml/min	50- 100 daily
15-30 ml/min	50-100 alternate day
On dialysis	50-100 weekly

Side effects

- Approximately 3-10% of patients taking allopurinol develop headache, GI discomfort (nausea, dyspepsia, diarrhea) and/or pruritic maculopapular rash
- Interaction with large number of drug, especially important in azathioprine, warfarin, theophylline, frusemide and amoxicillin
- thiazide diuretic decreases renal clearence of the allopurinol active metabolite (oxypurinol) and raises the risk of adverse reactions

Allopurinol Hypersensitivity Syndrome (AHS)

- < 2 % of patient treated with allopurinol developed severe cutaneous reaction
- Features include fever, toxic epidermal necrolysis, bone marrow suppression, eosinophilia, leukocytosis, renal failure, hepatic failure, and vasculitis.
- higher frequency in patients with chronic renal insufficiency
- A hypothesis of drug accumulation has been suggested. However, adjusting the dosage of allopurinol did not significantly reduce hypersensitivity reactions

HLA-B*58:01 & Allopurinol

- Human leucocyte antigen (HLA) genes have been implicated in drug- induced hypersensitivity with allopurinol
- The carrier rate of HLA-B*58:01 allele is approximately 15–20% (allelic frequencies 8–11%) in Han Chinese. The carrier rate of the HLA-B*58:01 allele was reported as 14% in Han Chinese in Hong Kong.
- In both Taiwan and Hong Kong study, HLA-B* 58:01 was found in all patients with allopurinol induced severe cutaneous adverse reaction, compared with only 13-15% in allopurinol tolerant patients.

- A test with high positive predictive value to severe cutaneous reaction, but not simple cutaneous reaction
- Test for HLA* 58:01 is not readily available, no rapid test method yet
- It is only available in 2 university hospital laboratories at this stage
- Pretreatment screening?
- Test for patients developed mild cutaneous reaction shortly after taking allopurinol, before considering drug desensitization/re-challenage?

2. Febuxostat

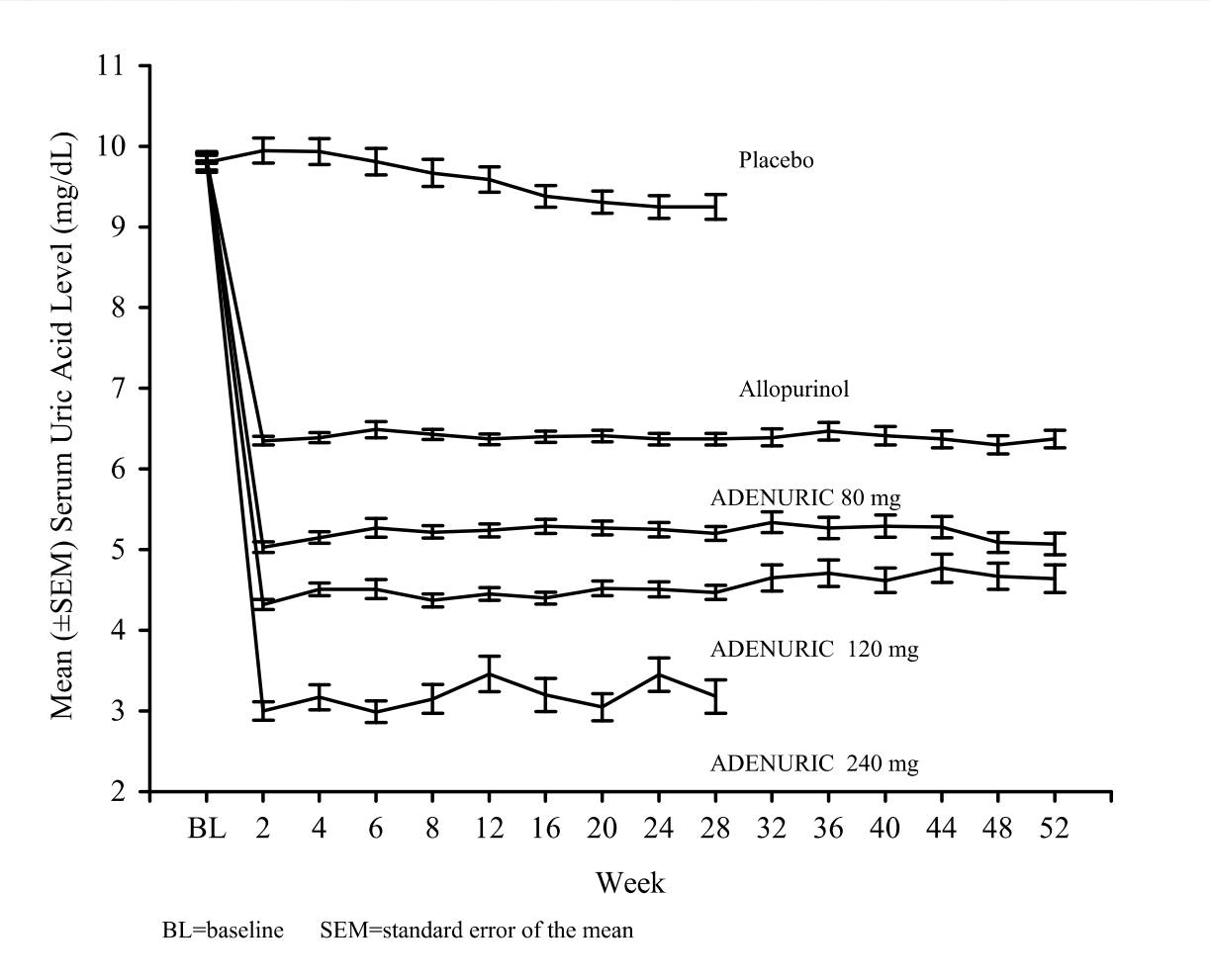
- Febuxostat is a nonpurine selective inhibitor of xanthine oxidase (XO)
- Approved by FDA in Feb, 2009
- Registered in Hong Kong in 2012 (Adenuric 80mg, 120mg)
- Self financed, non-formulary item in Hospital Authority

Febuxostat vs. Allopurinol

- more potent inhibitor towards both oxidized and reduced form of xanthine oxidase
- more selective (non-purine)
- the selectivity of febuxostat may lessen the risk of some adverse reaction as the adverse consequences of allopurinol may be related to the purine analogue action of allopurinol and its active metabolites
- less drug interaction, important interaction with azathioprine and thephyolline only
- Febuxostat primarily metabolized by the liver and not relied on renal excretion, no dose adjustment required in patients with mild to moderate severe renal impairment

- 3 phase III pivotal studies were conducted with >4000 patients with hyperuricaemia and gout. Nearly 3000 patients were treated with Febuxostat. [APEX, FACT, CONFIRMS study]
- In the first 2 studies (APEX, FACT), significantly higher percent of patients achieved serum urate level < 0.367 mmol/l in the group treated with febuxostat (80mg, 120mg daily) compared with allopurinol therapy (300mg, 100mg daily)
- However, there was higher incidence of cardiovascular events in the febuxostat though the total number was small

Figure 1 Mean Serum Uric Acid Levels in Combined Pivotal Phase 3 Studies



Adenuric, Annex I, Summary of Product Characteristics, European Medicines Agency

- CONFIRMS study
  - Subjects (n = 2,269) were randomized to febuxostat 40 mg or 80 mg, or allopurinol 300 mg (200 mg in moderate renal impairment). Endpoints included the proportion of all subjects with serum urate level <6.0 mg/dL (0.357 mmol/L)
  - 35% of subjects with baseline renal impairment (mild: CrCl 60-89 ml/min; moderate: 30-59 ml/min)
  - 374 patients aged ≥ 65 years enrolled in study, febuxostat (40 mg, 80mg) is effective and tolerable in elderly
  - Febuxostat 80mg (72%) was superior to both febuxostat 40mg and allopurinol (P<0.001)
  - Febuxostat 40 mg was statistically non-inferior to allopurinol (50% vs 42%)
  - Rates of AEs did not differ across treatment groups, including reported cardiovascular events and CV related death

- In 2 phase III, open labelled, long term extension studies (3 yrs and 5 yrs), the serum urate level of patients treated with febuxostat were maintained < 0.357 mmol/l overtime without dose adjustment.
- Three years data showed a significant decrease in the incidence of gout flares in febuxostat group (i.e. more than 96 % of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.
- 46% and 38%, of patients on final stable treatment of febuxostat 80 or 120 mg daily, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

Side effects

- common
  - GI disturbance
  - skin rash
  - mild liver function derangement
- Though no evidence of increase CV event risk related to febuxostat, treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended in product information.
- Rare cases of serious hypersensitivity reaction were coming from post-marketing experience, but no evidence of cross reactivity with allopurinol

3. Uricosuric agents

- Probenecid
- second-line therapy for patients with under-excretion of uric acid
- Combination with allopurinol is more effective at reducing serum urate level than either drug alone.
- in order to prevent renal stone formation, oral daily fluid intake should ≥ 2L, urine pH > 6
- Contraindicated in patient with renal impairment and established renal stone

4. Pegloticase

- Human beings and higher primates do not have the enzyme uricase that degrades uric acid to the highly soluble allantoin. Therefore, renal excretion of uric acid is less efficient
- Pegloticase is a modified porcine recombinant uricase that converts uric acid to a more soluble compound, allantoin. Subsequently, enhance renal excretion of uric acid and lower serum urate level
- Approved by FDA in Sept 2010 (8mg, every 2 weeks, IV) to treat gout in adults who do not respond to or who cannot tolerate conventional therapy.

- 2 randomized, double-blind, placebo-controlled, parallel group studies, 225 subjects randomized in 2:2:1 ratio stratified by presence/absence of tophi to:
  - Pegloticase 8 mg IV every 2 weeks
  - Pegloticase 8 mg IV every 4 weeks
  - Placebo IV infusions
- Significantly greater proportion of patients treated with pegloticase every 2 weeks achieved serum urate level < 0.36 mmol/l as compared to placebo
- Also significant reduction in tophi, no. of inflamed joints, frequency of acute flare in 4^{th} -6^{th} months, and significant improvement in pain control and function

- However, infusion reactions are common and mandatory prophylactic pre-infusion regimen is given to all patients in the treatment group
- Significant higher rate of allergic reactions and cardiovascular events in the treatment group
- Highly immunogenic, seroconversion noted over 80% of patient in the treatment group, effect of antibody on efficacy?

Back to our patient……

- Continue rehabilitation to improve physical ability and function in day hospital
- Education
  - Diet and alcohol restriction
  - Sufficient fluid intake
  - Weight control
  - Action to take in acute attack
  - Prevent further insult to the kidney (drug, prompt treatment for urinary tract infection)
  - allergic status

- Acute gout attack
  - low dose of colchicine for short, limited duration
  - oral steroid
  - simple analgesic, non-pharmacological measures
- reduce serum urate level, resolution of tophi, prevent recurrent renal stone formation
  - HLA B*5801 +ve, high risk for allopurinol induced severe hypersensitivity cutaneous reaction, not a candidate for desensitization /re-challenge
  - ? Candidate for febuxostat
    - family is willing to support financially
    - but is it safe in our patient (CrCl 25 ml/min) ?!

Nevertheless……

- Hyperuricaemia and gout are members of the metabolic syndrome family
- Control co-morbidities and risk factors (blood pressure control, diabetes screening, weight control, regular exercise)