Since when did Gout require admission to hospital?

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Gout - acute arthritis

acute synovitis, ankle & first MTP joints
Possible Differential Diagnosis

Septic arthritis: clinical picture can be indistinguishable from acute septic arthritis, including fever, leucocytosis, elevated inflammatory markers. Rare occasions acute gout and septic arthritis can coexist.

Trauma: gouty attacks of lesser severity may be mimicked by stress fracture or traumatic process in the bone or joint.

Pseudo-gout

Reactive Arthritis
An intracellular calcium pyrophosphate crystal is shown, which is pale blue when aligned with the axis of the compensator on polarized light microscopic examination. Note the rhomboid shape of the calcium-pyrophosphate crystal.
Urate precipitation leads to acute gouty arthritis

- Local factors – temperature, pH, trauma, joint hydration
- Systemic factors – hydration state, fevers, meds, alcohol, co-morbid conditions

Attack resolves spontaneously 10-15 days
ACUTE GOUT
– First attack 4\textsuperscript{th}-6\textsuperscript{th} decade for men
– Women almost always postmenopausal
– Classically monoarticular – podagra (50%), (vs pseudopodagra) > ankle > gonagra > upper extremity.
– Proximal joint, central arthropathy uncommon
Intercritical Period

- 70% prevalence of MSU crystals remain in the joint
- Lasts months to years for 75-80%, 20% never have another attack
Drug Actions In Acute Gout

- Colchicine inhibits
  - E-selectin mediated PMN adhesion
  - PMN L-selectin expression
  - IL-1 expression
  - IL-8 production
  - PMN motility
  - Chemotaxis
Indications

Urate-lowering in gout is a long-term treatment for which there is no evidence that initiation during an acute flare promotes better outcomes or long-term adherence.

- Serum urate levels are in a normal range in 25 to 40 percent of patients with acute flares, and immediate addition of urate-lowering medication precludes obtaining an accurate baseline (pre-treatment) serum urate level, unless this has been established earlier in the patient’s course.

- Introduction of urate-lowering therapy in the course of intense antiinflammatory flare treatment has the potential to cloud the interpretation of adverse events accompanying flare treatment, a problem of some significance given the rather narrow range of available urate-lowering agents of substantial efficacy.

- There is no evidence that such early treatment hastens accomplishment of goal range serum urate levels, for which periodic titration of the selected agent to effect is recommended.
Drug Actions In Acute Gout

- **NSAIDs**
  - Inhibits PGE$_2$

- **Corticosteroids**
  - Inhibit PGE$_2$ and LTB$_4$
  - Stabilize lysosomal membranes

- **ACTH**
  - Agonist of the leukocyte melatonin receptor-3
Urate-lowering therapy

- no anti-inflammatory activity
- can precipitate acute gout
- can prolong attack of gout
- Seek advice
Gout – rule

Concept
“Don’t mess with the uric acid level”

Don’t change your urate-lowering therapy during an acute gout attack
Uricostatic Drugs

- **Allopurinol** - developed 1957
  - Reduce annual gout attacks
  - Gradual resolution of tophi
  - Titrate dose up to ? mg /day
  - Increased toxicity with Chronic Renal Impairment
  - Allopurinol hypersensitivity – rare but can be fatal
  - Multiple interactions – Imuran, 6MP, warfarin, theophylline, ampicillin, diuretics

- Treatment is lifelong ..
**Mechanism** — Allopurinol inhibition of uric acid production is in large part due to inhibition of xanthine oxidase (xanthine dehydrogenase) by both the native drug and the active metabolite oxypurinol.

Allopurinol and oxypurinol are pyrazolo-pyrimidine analogs of the purine bases hypoxanthine and xanthine, respectively.

Allopurinol has multiple effects on human purine and pyrimidine metabolism:

- It is a competitive inhibitor of xanthine oxidase and, along with oxypurinol, produces pseudo-irreversible inactivation of the enzyme. As a result, urate production falls, but hypoxanthine and xanthine accumulate in body fluids, producing a state of pharmacologic xanthinuria.

- It substantially reduces total urinary purine (uric acid plus hypoxanthine plus xanthine) excretion in most patients. This effect is due to inhibition of purine synthesis by drug-derived and endogenous nucleotide products of enhanced purine base reutilization. This effect requires activity of the enzyme HPRT and potentiates the fall in serum urate levels.

- Through nucleotide derivatives of oxypurinol, it induces a state of orotic aciduria and orotidinuria, due to inhibition of the enzyme orotidylate decarboxylase in the pathway of pyrimidine nucleotide synthesis.
Febuxostat

- **Mechanism** — Febuxostat is a xanthine oxidase inhibitor. It is a thiazolecarboxylic acid derivative that, unlike allopurinol, is not a purine base analogue.

- **Efficacy** — Febuxostat produces a dose-dependent decrease in serum urate levels [86]. A daily dose of 40 mg produces a reduction that is roughly equivalent to that seen in patients who are treated with allopurinol at a dose of 300 mg per day.
Burden of gout..

- There were 32,741 admissions due to gout in England between 1999 to 2009.
- Gout admissions rose at 7.2% per year in England over this period.
- Gout is associated with reduced health-related quality of life, increased use of health care resources, impairs function and work productivity, significant effect on the working age population with 80% aged 25–64.
- Gout is an independent risk factor for cardiovascular and all-cause mortality and associated with increased co-morbidity. Hypertension, diabetes mellitus, cardiovascular disease, renal disease and dyslipidaemia are all highly prevalent in gout patients.
- Prevalence of gout in males ≥75 years was 2.6% in 2007.
Hospital admissions

- Significant number of patients are admitted multiple times for gout management.

- Are these patients suffering from treatment refractory gout, inadequate treatment or due to poor adherence to treatment - combination of these factors?

- Low adherence to treatment has been documented extensively in gout.

- Poor adherence to guidelines and inadequate allopurinol dosing in gout patients repeatedly admitted to hospital.

- Obesity is often clinically apparent and clinicians may not document it to avoid embarrassment due to social and pejorative implications.

- Difficult to directly implicate obesity in the aetiology of gout, therefore they may not be included as complicating morbidities for admissions.
Who to admit ..

- Escalating episodes of acute gout
- Related co-morbidities
- Initiation of strategic potent interventional therapy for acute gout
- Wholistic objective work up - 24 hours urine collection, imaging, joint aspiration and intra articular injections
- Physiotherapy, reassurance, confidence
- Setting out plans of management
- But not to commence uric acid lowering therapy ..
Implications of hyperuricaemia may be broadly regarded as those related to:

Uric acid crystals deposition

Crystal deposition – unrelated associations of hyperuricaemia: hypertension, chronic kidney disease, cardiovascular disease, insulin resistance syndrome
Statistical Definition of Hyperuricaemia

Non-normal distribution of serum urate concentrations in most populations -

A definition of hyperuricaemia can be based upon the solubility limit of urate and body fluids i.e. the concentration at which a state of super saturation for urate is reached in the serum

Physicochemical definition: urate concentrations exceeding 416 µmol per litre
Definition of Hyperuricaemia appropriate to the non-crystal deposition associations

Problematic for two reasons:

1. The high prevalence of urate values exceeding saturation but within 2 standard deviations of the population mean (e.g. an estimated 5 to 8% in adult white males)

2. Associations of serum urate levels with cardiovascular and other disorders are manifested at concentrations that are clearly sub-saturating
Persistent Hyperuricaemia

2 categories:

Primary hyperuricaemia – usually lasts indefinitely, refers to urate super saturation arising in the absence of coexisting diseases or drugs that alter uric acid production or excretion

Secondary hyperuricaemia – refers to excessive urate production or to diminished renal clearance that is the result of another disease, drug, dietary product, or toxin
Potential Consequences of Hyperuricaemia

Gout

Urolithiasis

Urate nephropathy

Hyperuricaemia – associated complex conditions: Hyperuricaemia has not been established as a casual factor

With the exception of acute uric acid nephropathy, the initial clinical manifestations of urate or uric acid crystals deposition are not life-threatening and readily treatable

2013: systematic review – emphasised the lack of adequate evidence to support the use of urate lowering therapy for the treatment of hypertension in patients with hyperuricaemia
Treat or not to treat?

Decision should be based upon an estimate of the risk in each individual for the development of:

gouty arthritis, tophi, uric acid or calcium stones, chronic renal insufficiency, or acute uric acid nephropathy.

Estimated risk should be weighed against the potential benefits and risks of lifelong drug treatment (risk of therapy are rare but potentially severe, even life-threatening toxic reactions to agents such as allopurinol have been documented).
Discovery of Asymptomatic Hyperuricaemia – what to do?

Prompt and appropriately limited and focused clinical and biochemical evaluation aimed at:

Patients at particularly high risk for gouty arthritis, tophi, kidney stones who warrant anti-hyperuricaemia treatment

Individuals whose hyperuricaemia is a sign of an underlying disorder or environmental exposure requiring specific treatment

Hyperuricaemia – inducing drugs or toxins that can be removed or substituted, with relief or diminution of the hyperuricaemia state (lymphoproliferative and myeloproliferative disorders, psoriasis, vitamin B12 deficiency, pre-eclampsia)
Hyperuricaemia is not a disease

Uric acid is okay!

Monosodium urate or uric acid crystals deposition is not: this is the essential pathophysiological link between hyperuricaemia and clinical manifestations (doubt, kidney stones and tophi)

Hyperuricaemia can be viewed as a necessary (although not usually sufficient) predisposing factor for the narrow range of clinical manifestations of gout
Persistent hyperuricaemia: serum uric acid greater than 773 µmol per litre in men and greater than 595 µmol per litre in women (these values may carry some nephrotoxic risk, perhaps related to the likelihood of some component of uric acid overproduction)

Does not apply to heart failure patients who may develop marked hyperuricaemia due to renal hypoperfusion and reduced urate excretion – low risk for chronic urate nephropathy

Excretion of urinary uric acid in excess of 6.5 mmol daily is associated with a 50% risk of uric acid stones. Manage with dietary reduction first and allopurinol if excretion does not go to below 5.9 mmol per day

Patients about to receive radiotherapy or chemotherapy that is likely to result in extensive tumour cytolysis