Gout in the Elderly
Dr. Kanna Alagiakrishnan

Disclosure

I have no relationship that could be perceived as placing me in a real or apparent conflict of interest in the context of this presentation.

Learning Objectives

- Discuss about late onset gout.
- Review the current understanding of the risk factors and the clinical presentation of gout in the elderly.
- Understand the treatment challenges and new therapeutic options.
Case

- 69yo female with sudden onset of acute pain in her right hand fingers and both elbows. The patient reported that she has had one previous episode of the same symptoms lasting 4-5 days and treated by ED physicians. PMHx HTN treated with thiazide diuretic, osteoarthritis and patient is trying to lose weight BP 138/86 BMI 32. PE remarkable for swollen and tender right elbow and swollen interphalangeal joints of the right hand. UA 480 micromol/L and white cell count is normal.
- What is the next step to diagnose this condition?
- What are the risk factors?
- How will you treat this patient?

Definition

- **Gout is a heterogenous 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.
- Late- onset is the appearance of gout after the age 65 years and may present with atypical findings.

Epidemiology of Gout

Prevalence

[Graph showing the prevalence of gout by age group and gender]

Incidence

Risk Factors

- Dietary factors and alcohol
- Medications
- Systemic causes
  - Increased production (10%)
  - Decreased excretion (90%)

Food Induced Gout

- Increased risk:
  - High seafood and meat consumption.
- Decreased risk:
  - High dairy product consumption.

Effect of total alcohol intake on relative risk of first attack of gout (Adapted from Choi et al)

Underwood, M. BMJ 2006;332:1315-1319

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Geriatric Grand Rounds
Glenrose Rehabilitation Hospital, Edmonton, AB, Canada

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### Effect of one additional daily portion on first attack of gout

<table>
<thead>
<tr>
<th>Portion</th>
<th>Relative risk [95% CI]</th>
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<tbody>
<tr>
<td>Alcohol:</td>
<td></td>
</tr>
<tr>
<td>Beer 335 ml</td>
<td>1.49 [1.32 to 1.70]</td>
</tr>
<tr>
<td>Spirits 44 ml</td>
<td>1.15 [1.04 to 1.28]</td>
</tr>
<tr>
<td>Wine 118 ml</td>
<td>1.04 [0.88 to 1.25]</td>
</tr>
<tr>
<td>Food:</td>
<td></td>
</tr>
<tr>
<td>Meat</td>
<td>1.21 [1.04 to 1.41]</td>
</tr>
<tr>
<td>Seafood (fish)</td>
<td>1.07 [1.01 to 1.13]</td>
</tr>
<tr>
<td>Purine rich vegetables</td>
<td>0.91 [0.79 to 1.11]</td>
</tr>
<tr>
<td>Total dairy products</td>
<td>0.82 [0.75 to 0.90]</td>
</tr>
<tr>
<td>Low fat dairy products</td>
<td>0.79 [0.71 to 0.87]</td>
</tr>
<tr>
<td>High fat dairy products</td>
<td>0.99 [0.89 to 1.10]</td>
</tr>
</tbody>
</table>

Data from health professionals follow-up study.\(^{9,10}\)

*Calculated from weekly intake.

### Medication Induced Gout
- Diuretics,
- Cyclosporine,
- low-dose salicylates, (?)
- Ethambuthol,
- Pyrazinamide,
- Nicotinic acid.

### Pathogenesis of Gout
- Uric acid is the end product of dietary and endogenous purines.
- Humans lack uricase, the enzyme that breaks down uric acid into allantoin and carbon dioxide.
- The kidney eliminates approximately two-thirds of total urate while the gastrointestinal tract eliminates the remaining third.
- Most plasma uric acid is filtered freely at the glomerular level, then reabsorbed almost completely in the proximal tubule, to undergo processes of tubular secretion and reabsorption.
- Hyperuricemia can result from two processes: decreased renal excretion (as high as 90% of patients) or hyperproduction of uric acid (10% of patients).

### Pathogenesis (cont)
- Most patients with idiopathic gout have a defect (possibly inherited) leading to underexcretion of uric acid, even when renal function is otherwise normal.
- Decreased urate clearance could be explained by possible reduced urate filtration, enhanced uric acid reabsorption or decreased urate secretion.
- Patients with renal impairment, regardless of cause, have diminished excretion of uric acid.
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
- Acute Intermittent Gout (Gouty Arthritis)
  - Episodes of acute attacks. Symptoms may be confined to a single joint or patient may have systemic symptoms.
- Intercritical Gout
  - Symptom free period interval between attacks. May have hyperuricemia and MSU crystals in synovial fluid
- 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.

HYPERURICEMIA

Definition

- Males > 7.0 mg/dL (420 micro mol/ L)
- Females > 6.0 mg/dL (360 micro mol/ L)

Primary Hyperuricemia

- The majority of patients who develop gout have been hyperuricemic for about two decades, however the majority of individuals with hyperuricemia never develop gout.
- An elevated body uric acid pool is therefore the necessary, however not sufficient, metabolic abnormality for development of gout.
- Essentially, hyperuricemia is the biochemical abnormality and gout its clinical expression
Primary Hyperuricemia (Cont)

- Primary hyperuricemia usually begins in men at puberty and in women after the menopause.
- The prevalence of asymptomatic hyperuricemia is estimated to be 5% to 8% for adult American males.
- For hyperuricemic individuals, the risk of developing gout has been assessed prospectively.
  - People with uric acid level lower than 7 mg/dL have had an annual incidence of gout of 0.09%;
  - in those with uric acid of over 10 mg/dL, the annual incidence increased to 7%.
- The annual incidence of urolithiasis in longitudinal studies was approximately 0.9% for patients with gout and 0.4% for previously asymptomatic hyperuricemic individuals.

Hyperuricemia

- Uric acid overproduction
  - Accounts for 10% of hyperuricemia
  - Defined as 800 mg of uric acid excreted
  - Diet: meat, fish, alcohol (particularly beer and spirits), obesity, and weight gain
  - Drugs: including diuretics, low dose salicylates, pyrazinamide, ethambutol, cytotoxics, and lead poisoning
- Acquired disorders
  - Excessive cell turnover rates such as myeloproliferative disorders, Paget’s disease, hemolytic anemias
  - Reduced renal excretion—hypertension, hypothyroidism, sickle cell anemia, hyperparathyroidism, chronic renal disease
- Genetic disorders: derangements in mechanisms that regulate purine nucleotide synthesis.
  - Deficiency HGPRT, or superactivity PRPP synthetase

Hyperuricemia (Cont)

- Uric acid underexcretion
  - Accounts for >90% of hyperuricemia
  - Diminished tubular secretory rate, increased tubular reabsorption, diminished uric acid filtration
    - Systemic disease that predispose people to renal insufficiency. Reduced renal excretion—hypertension, hypothyroidism, sickle cell anemia, hyperparathyroidism, chronic renal disease
  - Diet: low fat dairy products
  - Drugs: xanthine oxidase inhibitors (allopurinol, febuxostat), uricosuric drugs (sulfipyrazone), uricase drugs (rascburicase), coumarin anticoagulants, and oestrogens

Typical Clinical Presentation

- Common signs of gout is a nighttime attack of swelling, tenderness, redness, and sharp pain in the affected area.
- Pain can be so intense that even a blanket touching the skin over the affected joint can be unbearable.
- Patients can develop fever with the acute gout attacks.
- These painful attacks can last for hours or days, some times even weeks.
- Another attack may not happen for months or years.
- Most persons with gout will experience repeated attacks of arthritis over the years.
Typical Clinical Presentation (Cont)
- 90% of initial gout attacks are monoarticular, leaving only 10% of cases that are oligoarticular or polyarticular.
- Asymmetric arthritis.
- 50% of initial gout attacks occur in the great toe.

Atypical Presentation
- Any joint can be affected.
- Symmetric or asymmetric arthritis.
- Tophi common in presentation. Earlier development of tophi.
- Equal incidence in both sexes.
- Polyarticular insidious onset in presentation.

Atypical Presentation (Cont)
- Polyarticular onset with hand involvement
- Older patients, particularly women, tend to have small joints of fingers involved early on.
- In a series of patients with late-onset gout, 25% of women (zero for men) have had initial symptoms in the fingers. In these patients, gouty attacks were less painful and more frequently noted on inter-phalangeal joints affected by osteoarthritis, particularly on Heberden's nodes.

Atypical Presentation (Cont)
- Association with use of diuretics: Diuretic use has been reported in over 75% of patients with late-onset gout, almost 100% in women.
- Specifically, older patients starting thiazide diuretic therapy were 2 times more likely to be on treatment for gout in 2 years compared with non-thiazide controls.
- Gout and osteoarthritis can co-exist.
- Gout and septic arthritis can co-exist.
American College of Rheumatology  Criteria for the Clinical Diagnosis of Gout

Six or more of these criteria are needed to make a diagnosis:

- More than one attack of acute arthritis
- Maximum inflammation developed within one day
- Attack of monoarthritis
- Redness over joints
- Painful or swollen first metatarsophalangeal joint
- Unilateral attack on first metatarsophalangeal joint
- Unilateral attack on first tarsal joint
- Tophus (proved or suspected)
- Hyperuricaemia
- Asymmetric swelling within a joint on radiograph
- Subcortical cysts without erosions on radiograph
- Joint fluid culture negative for organisms during attack

Tophi

- Patients who develop tophaceous deposits are more likely to be:
  - alcohol abusers
  - on diuretics
  - noncompliant
  - to have longer (for at least 10 years) and untreated disease
  - frequent attacks
  - higher uric acid level

Case

Chronic Topaceous Gout

- Chronic tophaceous gout is characterized by the development of solid urate deposits (tophi) in connective tissues, which lead to destructive arthropathy.
- 75% of untreated patients developed tophaceous gout within two decades of the initial attack. With treatment, this proportion decreased significantly to less than 5%.
- Tophi involve predominantly the upper extremity on the fingers, volar surfaces of the hands, sites of Bouchard and Heberden nodes, over the olecranon bursa or ear helix.
- The tophi are associated with a chronic destructive deforming arthritis, may ulcerate or get infected.
Refractory Gout

- These are patients who have repeated attacks of gout and who have no response or suboptimal response to standard allopurinol dose.

Diagnostic studies

- **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. To exclude myeloproliferative disorders. Raised white cell count may indicate an associated septic arthritis.

- **Renal function**
  - Hyperuricemia can occur with reduced renal function. Reduce dose of allopurinol.

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

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

Diagnosis

- Definitive diagnosis only possible by aspirating and inspecting synovial fluid or tophaceous material and demonstrating MSU crystals.

- Polarized microscopy, the crystals appear as bright birefringent crystals that are yellow (negatively birefringent).

Synovial Fluid Findings
Synovial fluid findings

Management of Gout
- Prevent and treat gouty arthritis.
- Urate lowering and tophus reduction (Chronic or Prophylaxis).
- Treat co-morbidities. Gout is part of a clinical spectrum of conditions (obesity, diabetes mellitus, hyperlipidemia, coronary artery disease) and need for better patient education on management of these associated conditions is emphasized.

Acute Treatment of Gout
- NSAIDS
- COLCHICINE
- STEROIDS
  - Interleukin (IL)-1 antagonism by Anakinra, Rilonacept (IV off-label use)

NSAIDS
- Most commonly used.
- No NSAID found to work better than others
- Regimens:
  - Indocin 50mg po bid-tid for 2-3 days and then taper
  - Ibuprofen 400mg po q6th hrly
  - Continue meds until pain and inflammation have resolved for 48hr.
  - Side effect: GI (upper and lower) and renal complications
Colchicine

- Inhibits microtubule aggregation which disrupts chemotaxis and phagocytosis
- Inhibits crystal-induced production of chemotactic factors
- Administered orally 0.6 mg three times daily (0.6 mg twice daily for crcl<60 ml and 0.6 mg once for<30 ml).
- IV Colchicine not recommended and withdrawn by FDA in 2008.
- Contraindicated in dialysis patients.
- Drug interactions: cyclosporine, statins, macrolides (colchicine myopathy, death).
- Colchicine should be continued for 3 months of normalisation of uric acid (below 6mg/dl) with hypouricosuric treatments.

Steroids

- **Corticosteroids**
  - Patients who cannot tolerate NSAIDs, or failed NSAID/colchicine therapy
  - Daily doses of prednisone 40-60mg a day for 3-5 days then taper 1-2 weeks
  - Improvement seen in 12-24hr

- **ACTH**
  - Peripheral anti-inflammatory effects and induction of adrenal glucocorticoid release
  - 40-80IU IM followed by second dose if necessary

- **Intra-articular injection with steroids**
  - Beneficial in patient with one or two large joints affected
  - Good option for elderly patient with renal or PUD or other illness
  - Triamcinolone 10-40mg or Dexamethasone 2-10mg alone or in combination with Lidocaine

Treatment of Asymptomatic Hyperuricemia

- Unless uric acid level is over 13 mg/dL (810 micro moles/L) for males and 10 mg/dL (600 micro moles) for females.
- Setting of tumor lysis syndrome.
Hypouricemic drugs

- **Under-excretors** - Uricosuric agents
- Probenecid
- Sulfinpyrazone
- Losartan
- Fenofibrate

- **Overproducers** - Xanthine oxidase inhibitor.
- Allopurinol
- Febuxostat

Prophylaxis

- **Urate Lowering drugs**
  - Used for documented urate overproduction
  - Goal is for serum urate concentration to 6mg/dL or less
  - Start of therapy can precipitate acute attack; therefore, may need to use colchicine as long as six months
  - Xanthine oxidase inhibitors
    - Allopurinol: blocks conversion of xanthine to uric acid. works for underexcretors and overproducers.
    - Start typically 300mg/day and titrate weekly 100mg/day until optimal urate levels achieved.
    - Start lower doses with renally impaired patients
  - Uricosuric drugs
    - Probenecid or Sulfinpyrazone: increase renal clearance of uric acid by inhibiting tubular absorption
    - Side effects may prohibit use-GI and kidney stones
    - Need measurement of 24hr urine in anyone for whom Probenecid therapy is initiated

Medications on the Pipeline

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drug</th>
<th>Progress to clinical use</th>
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</thead>
<tbody>
<tr>
<td>Xanthine oxidase inhibitors</td>
<td>Febuxostat</td>
<td>Phase II trials complete</td>
</tr>
<tr>
<td>Xanthine oxidase inhibitors</td>
<td>SBIC 604</td>
<td>Phase I trials ongoing</td>
</tr>
<tr>
<td>Uricosuric</td>
<td>SBIC 594</td>
<td>Phase I trials complete</td>
</tr>
<tr>
<td>Uricosuric</td>
<td>SBIC 590</td>
<td>Phase I trials complete</td>
</tr>
</tbody>
</table>

**Note:** European Union; FDA, Food and Drug Administration; PEG, polyethylene glycol.

Probenecid

- **Probenecid-** 250 mg po b.i.d (with a maximum daily dose of 2 gm)
- Renal function (ineffective if creatinine>2 mg/dl).
- Drug interactions with aspirin.
- Target serum urate not always achieved.
- Risk of nephrolithiasis.
Allopurinol

- Effective in urate excretors and overproducers.
- Do not initiate until 4-6 weeks after an acute attack.
- Concurrent prophylaxis with colchicine 0.6 mg once or twice daily for six months.
- Urate lowering therapy to address hyperuricemia is generally a lifelong commitment as intermittent therapy can lead to recurrent gout flares.
- Renal function may require dose adjustment.
- Target serum urate not always easily achieved; high doses may be necessary.

Allopurinol- Dosage Adjustments

- >90 ml Crcl = 300 mg
- 60-89ml = 200mg
- 30-59ml = 100 mg
- 10-29ml = 50-100 mg

(From J. Med 1988)

Allopurinol (cont)

- Therapy compliance is generally poor in elderly patients.
- 20% of patients who takes allopurinol reports side effects (most frequent is a rash).
- Rare but potentially fatal hypersensitivity syndrome
- Hypersensitivity syndrome includes:
  - Fever
  - Bone marrow suppression
  - Hepato-renal failure
  - Hypersensitivity vasculitis
  - 20% mortality risk

Allopurinol (cont)

- Allopurinol, the first-line drug for serum urate-lowering therapy in gout, is approved by the US Food and Drug Administration for a dose up to 800 mg/d and is available as a low-cost generic drug.
- However, the vast majority of allopurinol prescriptions are for doses ≤ 300 mg/d, which often fails to adequately treat hyperuricemia in gout.
- This situation has been promoted by longstanding, non-evidence-based guidelines for allopurinol use calibrated to renal function (and oxypurinol levels) and designed, without proof of efficacy, to avoid allopurinol hypersensitivity syndrome.
- Severe allopurinol hypersensitivity reactions are not necessarily dose-dependent and do not always correlate with serum Allopurinol levels.
- Limiting allopurinol dosing to < or = 300 mg/d suboptimally controls hyperuricemia and fails to adequately prevent hypersensitivity reactions.
- However, the long-term safety of elevating allopurinol dosages in chronic kidney disease requires further study.
- The emergence of novel urate-lowering therapeutic options, such as febuxostat and uricase, makes timely this review of current allopurinol dosing guidelines, safety, and efficacy in gout hyperuricemia therapy, including patients with chronic kidney disease.
## Newer therapies

**Uricase**
- Enzyme that oxidizes uric acid to a more soluble form
- Natural Uricase from Aspergillus flavus and Candida utilis under investigation
- Phase 3 trials completed

**Febuxostat**
- New class of Xanthine Oxidase inhibitor
- More selective than allopurinol
- Little dependence on renal excretion

**Losartan**
- ARB given as 50mg/dL can be uricosuric. When given with HCTZ, it can blunt the effect of the diuretic and potentiate its antihypertensive action

**Fenofibrate**
- Studies note when used in combo with Allopurinol produced additional lowering of the urate

## Prevention

- Maintaining adequate fluid intake
- Weight reduction
- Dietary changes
- Reduction in alcohol consumption
- Medications to reduce hyperuricemia

## Barriers

- Barriers against an optimal control of gout in elderly include
  - lack of patient education
  - presence of comorbid conditions, particularly renal impairment
  - use of multiple drugs such as diuretics
  - cognitive decline

## Case

- Next step is aspiration of the elbow joint and examine for uric acid crystals.
- Risk factors are postmenopausal women, obesity, diuretic therapy.
- Start colchicine at 0.6mg bid and start anti-hyperuricemia therapy in 4 weeks.
- Stop diuretics and consider Losartan.
Conclusions

- Most patients develop disabling arthropathy in late-onset gout.
- Atypical presentation is common in the elderly.
- Colchicine and NSAIDs should be used with care in older adults given their toxicity profiles.
- Gout management in older adults remains unsatisfactory.
- Epidemiologic analysis, animal models of hyperuricemia and human interventional studies have reintroduced urate as an etiologic agent in cardiovascular disease.