Update on the Management of Gout

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- Background Overview
- National / International Guideline Updates
- Management Overview
- Advances
Case History

- 46 year Taxi driver, male, obese
- 2-3 years of intermittent joints flares: toes, ankles, knees, fingers, olecranon
- Developed tophi over 18 months, Xrays feet - 1st MTPJ ‘punched out’ erosions, urate 650 µmol/L
- Symptoms now every day, debilitating, unable to work
- GP tried NSAID & Colchicine - not effective, Allopurinol - flares. Referred on Pred 40mg daily (flares at doses below) taken for 4 months
Case History

- **Lifestyle review:** high sweetened drinks intake (fructose)
- **No alcohol (previously high), no red meat / shellfish, no renal disease / psoriasis, no iatrogenic causes, no FH**
- **Acute attack(s): IV Steroids?**
- **Rasburicase (uricase) - lowered sUA to unrecordable levels. Allopurinol started but then flared badly within 1 week**
- **Re-tried Rasburicase and then followed with Febuxostat - same issue, mild reaction to uricase**
- **MDT held: Anakinra daily SC - after 2 weeks then Rasburicase, followed immediately by Febuxostat120mg daily. Consider Benzbromarone.**
Background Overview

- Most common inflammatory arthritis

- UK Incidence steadily increased from 1.5% in 1997 to 2.5% in 2012

- More common in men - male:female ratio 4:1

- Most important risk factor is sustained hyperuricaemia
  - Caused by overproduction or under-excretion of urate
  - Deposition of monosodium urate crystals in joints and tissues

- Studies have repeatedly identified increased cardiovascular mortality with gout
Epidemiology - prevalence increases with age
Risk factors for gout

Non-modifiable
- Age
- Male gender
- Race
- Genetic factors
- Impaired renal function

Modifiable
- High-purine diet
- Alcohol consumption
- Obesity
- Certain medications
  - Diuretics
  - Hyperuricaemia
Modifiable risk factors for gout: purine-rich foods

Relative risk of gout in the highest quintile of purine-rich foods and dairy intake compared to the lowest quintile of intake

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Total meat (n=161)</td>
<td>1.41</td>
</tr>
<tr>
<td>Seafood (n=171)</td>
<td>1.51</td>
</tr>
<tr>
<td>Purine-rich vegetables (n=133)</td>
<td>0.96</td>
</tr>
<tr>
<td>Total dairy (n=102)</td>
<td>0.56</td>
</tr>
<tr>
<td>Low-fat dairy (n=101)</td>
<td>0.58</td>
</tr>
<tr>
<td>High-fat dairy (n=142)</td>
<td>1.00</td>
</tr>
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</table>
Modifiable risk factors for gout: alcohol intake

<table>
<thead>
<tr>
<th>Alcoholic Beverage</th>
<th>Relative Risk of Gout</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>2.51</td>
<td>45</td>
</tr>
<tr>
<td>Spirits</td>
<td>1.6</td>
<td>64</td>
</tr>
<tr>
<td>Wine</td>
<td>1.05</td>
<td>18</td>
</tr>
</tbody>
</table>
Modifiable risk factors for gout: obesity

Relative risk of gout

BMI (kg/m²)

- 21-22.9: 1
- 25-29.9: 1.95
- 30-34.9: 2.33
- ≥35: 2.97
Diagnosis

Four Stages of Gouty Arthritis

- Asymptomatic hyperuricaemia
- Acute gouty arthritis
- Intercritical gout
- Chronic tophaceous gout
Gout is recurrent and progressive

- **High uric acid**
- **Recurrent acute gouty arthritis**
- **Advanced gout**

**Intensity of pain**

- **First acute flare**
- Flares become longer and more severe
- **Start of advanced gout**

**Time**

- **No symptoms**
- **This period could be 5 years or longer**
- **Intercritical periods grow shorter**
Gold standard Gout diagnosis

- Demonstration of monosodium urate crystals by microscopic examination for negatively birefringent crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout

- Urate crystals are intra- or extracellular
  - Long needles, typically 10-20 μm

- Crystals examined under a polarizing filter will be:
  - Yellow when aligned parallel to the axis of the red compensator
  - Blue when aligned perpendicular to the direction of polarization
**Clinical examination for tophi**
- Extensor surface of forearm, olecranon, Achilles tendon, pinna

**Imaging**
- No juxta-articular osteopaenia of other inflammatory arthritides
- Punched out lateral erosions with sclerotic margins and over-hanging edges (so-called “rat-bite erosions”)

**sUA measurement**
- May decrease during an acute attack

**Full blood count**
- To exclude myeloproliferative disorders; raised WBC may suggest septic arthritis

**Renal function**
- Association of renal failure with hyperuricaemia
- Lower allopurinol dose in renal impairment

**Urinary urate excretion**
- Risk of renal stones?
- Uricosurics contraindicated in patients with high urate excretion

**Fasting lipids and glucose**
- Association of gout with metabolic syndrome

**Thyroid function**
- Association with hypothyroidism and possibly hyperthyroidism
Men with gout are at risk of other complications

- Joint Damage / Deformity
- Cardiovascular risk
- Kidney Stones
- Kidney Damage
Acute attack - likely to require treatment with a NSAID + PPI or colchicine

ULT is targeted to patients with recurrent attacks, tophi, urate arthropathy, or renal damage and to symptomatic patients with very high serum uric acid levels
  - Allopurinol is the first line option

Shared decision making about ULT

All patients taking ULT require regular monitoring of renal function and serum uric acid level to ensure that the dose is appropriate
  - For most, allopurinol 300 mg daily will be insufficient to achieve target serum uric acid reductions

Despite limited evidence, patients should be encouraged to manage their weight & increase exercise
EULAR recommendations 2016

- General principles:
  - (a) Provide education
  - (b) Implement lifestyle interventions
  - (c) Screen for co-morbidities (esp CVD)

- 11 Recommendations:
  1. Treat acute flare asap
  2. 1st line acute flare Rx Colchicine, others: NSAIDs, Steroids (PO/IA)
  3. If frequent / recurrent flares: consider IL1 inhibitor
  4. Prophylaxis against flares for 6 months (Colchicine / NSAIDs)
  5. ULT should be considered in all patients with definite Dx esp those with recurrent flares, tophi, urate arthropathy and/or renal stones, CVD risk
  6. With ULT, aim to reduce sUA to <360 μmol/L (<300μmol/L in higher risk cases)
  7. ULT should be started at lower dose and titrated
  8. In normal renal function, 1st line is Allopurinol 100mg / day, increase by 100mg every 2 -4 weeks until sUA target reached. Febuxostat and other medications
  9. In renal disease, consider lower Allopurinol dose, switch to other agents
  10. In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, Pegloticase is indicated
  11. If diuretic used, consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate
2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT

Determine the SUA target

> 6mg/dl or <6mg/dl

If appropriate:
- Stop diuretics
- Use heparin
- Use benzbromarone or allopurinol

Education about the disease
- Individualised lifestyle advice
- Screening for comorbidities

Start prophylactic treatment

Initiate ULT

History of allergy to allopurinol

Start Allopurinol 100mg/d
- Adjust the dosage to the renal function
- Slow titration up to the maximum allowed dosage

Switch to Febuxostat or switch to a uricosuric

Achieve target

Yes

Consider a combined therapy
(SOD and a uricosuric)

No

Start Pegloticase

SUA target not achieved

Yes

Continue

No

Achieve target

Yes

Continue

No

Achieve target

Yes

Continue
Lifestyle modifications

- **Diet**
  - Reduce purine intake (reduce red meat, avoid liver, kidneys, shellfish and pulses)
  - Reduce fructose-containing drinks
  - Include skimmed milk, low fat yoghurt, vegetable protein and cherries
  - Vitamin C is uricosuric

- **Decrease alcohol consumption (especially beer)**

- **Weight loss**
  - 1 kg/month (avoid crash diets)
  - Avoid high protein diets

- **Patients with urolithiasis should be encouraged to drink >2 litres of water/day**

- **Moderate exercise**
Goals of treatment

- **Acute attacks:**
  - Relieve pain rapidly and reduce inflammation
    - Non-pharmacological (coldpacks)
    - NSAIDs or Coxibs (Etoricoxib)
    - Colchicine
    - Corticocosteroids
  - There is no need to discontinue allopurinol during an acute attack
  - Never commence allopurinol during an acute attack

- **Long-term treatment (gout is curable by dissolving all crystals and preventing further crystal formation):**
  - Prevent further acute attacks
  - Prevent joint damage
  - Eliminate tophi
**Diagram of Gout Treatment Pathways**

- **Purine Nucleotide Metabolism**
  - Xanthine Oxidase Inhibitors: allopurinol, oxyphenuric, febuxostat
  - Xanthine
  - Uric Acid
  - Allantoin
  - Uricases: rasburicase, pegloticase

- **Uricosurics:** probenecid, benzbromarone, RDEA594
  - Renal excretion
  - Gastrointestinal tract excretion
  - Uricosuria

- **Inflammation Inhibitors:** Non-steroidal anti-inflammatory drugs, colchicine, steroids, interleukin-1 inhibitors

- **Inflammasome Activation with Acute Gout Attack**

**Inhibitory effect**

**Stimulatory effect**
Effective gout management

**Acute treatment** (NSAIDs, colchicine, or steroids)

- 1-2 gout attacks

**Initiate long-term urate-lowering therapy (ULT)** plus prophylaxis (low-dose colchicine or NSAIDs)

- (2 weeks)

**Remove prophylactic therapy and maintain patient on ULT**

- (6 months)

**Asymptomatic hyperuricaemia**

- Check initial sUA level

- Check sUA level at 3-monthly intervals in first year, annually thereafter

  **If not below 360µmol/l, Increase ULT**
## Allopurinol and renal failure

<table>
<thead>
<tr>
<th>Estimated GFR ml/min/1.73 m²</th>
<th>Allopurinol starting dose</th>
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</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>5–15</td>
<td>50 mg twice weekly</td>
</tr>
<tr>
<td>16–30</td>
<td>50 mg every 2 days</td>
</tr>
<tr>
<td>31–45</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>46–60</td>
<td>50 mg and 100 mg on alternate days</td>
</tr>
<tr>
<td>61–90</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>91–130</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>&gt;130</td>
<td>200 mg/day</td>
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Advances in Gout

- **New drug targets**
  - IL1 inhibitors - Canakinumab, Anakinra

- **New approaches to serum urate lowering**
  - Uricases - Pegloticase, Raburicase
  - Lesinurad - selective, highly potent uric acid reabsorption inhibitor - CLEAR 1, CLEAR 2, CRYSTAL, LIGHT studies showed that Lesinurad + either Allopurinol or Febuxostat was more effective by as much as 2.5-fold
  - Arhalofenate - pipeline drug with a dual mechanism of action (ULT and anti-inflammatory effects)

- **New Guidance** - ACR, BSR, EULAR

- **New genetics for screening**
  - HLA-B*58:01 - predicts risk of reaction to Allopurinol (recommended in ACR guidelines for at risk populations)
Imaging Advances

- Ultrasound
- Duel-Energy CT (DECT)
Thank You

Now let’s go enjoy a drink!