Pharmacological Management of Knee Pain

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Outline of Presentation

1. **Algorithm** to work out cause of **knee pain**

2. Treatment of:
   (a) **Inflammatory arthritis**:
       (i) Crystal arthritis – Gout and Pseudogout
       (ii) Psoriatic arthritis
       (iii) Rheumatoid arthritis
   (b) **Osteoarthritis**
Referrals to a **Rheumatologist** – patient with Knee Pain

1. **General Practitioner** – OA vs Inflammatory
2. **Emergency Department** – Acute Inflammatory (Septic/Crystal/new onset Inflammatory Arthritis)
3. **Orthopaedic Surgeon** – often post arthroscopy: Gout or “Synovitis” due to unsuspected “inflammatory arthritis”
4. **Physiotherapist / Orthotist** – often unsuspected inflammatory arthritis (“not getting better”)
Algorithm to determine cause of knee pain

Knee Pain

- Mechanical: Worse with activity
- Inflammatory: Better with activity, worse in morning and with rest
- Fibromyalgia: Several tender spots, tiredness/poor sleep, "exercise intolerance"n
Knee Swelling

- Mechanical: Cool or mildly warm effusion
- Inflammatory: Warm effusion

Knee Stiffness – early morning/inactivity

- < 30 mins: Mechanical
- > 30 mins: Inflammatory
Knee Pain/Stiffness/Swelling

Mechanical = Osteoarthritis
Knee Pain/Stiffness/Swelling

**Inflammatory**

- **Exclude Septic Arthritis**

- **Crystal Arthritis**

- **Gout**

  - Middle age men
  - Never in premenopausal women
  - Older men and women with poor renal function/metabolic syndrome/diuretics
  - Normal serum UA possible
  - Joint aspirate for MSU crystals

- **Pseudogout**

  - Knee commonest site
  - Occurs in OA knee
  - Joint aspirate for CPPD crystal
  - Joint aspirate cell count can be similar to septic arthritis
  - Occurs in inpatient with intercurrent infection or post surgery

+/- Systemic Symptoms
Joint Aspirate for M&C, cell count
Knee Pain/Stiffness/Swelling

Inflammatory

Reactive Arthritis
Within 1 month of gastrointestinal or urogenital infection
Often HLA B27 +ve

Psoriatic Arthritis
Always ask for past or present hx of Psoriasis or family hx of Psoriasis
3% of population = Psoriasis
Up to 30% with Psoriasis = PsA

Rheumatoid Arthritis
10% of initial presentation with knee monoarthritis
ESR/CRP can be normal
20% negative for RhF/Anti CCP

Peripheral Spondyloarthritis (SpA)
Ask for spinal symptoms – Axial SpA
HLA B27 +ve
Pharmacological Treatment of Inflammatory Arthritis

1. Crystal Arthritis – Gout & Pseudogout

2. Psoriatic & Rheumatoid Arthritis
Stages of Gout – *NEW*: Natural Evolution of Gout showing the worsening outcome if deposits are allowed to grow with persistent hyperuricaemia. 

GOUT = Commonest inflammatory arthropathy worldwide.
When gout goes to the heart: does gout equal a cardiovascular disease risk factor?

Jasvinder A Singh

Cardiovascular disease is among the leading causes of mortality in the world and its prevalence is rising over time. Inflammatory disorders such as rheumatoid arthritis and others are commonly associated with a higher risk and an earlier onset of cardiovascular disease. This increased risk may be mediated at least partially by non-traditional cardiovascular risk factors. Inflammation and other diseases who are healthy or do not have g

Thus, the study’s findings may be gene applicable to the UK population, but may not have the same confidence in t findings as one would from a populat based cohort study.

IS GOUT A RISK FACTOR FOR INCIDENT HEART DISEASE?
Pathways for higher risk of CV disease in GOUT
Pharmacological Treatment of Acute GOUT

Newer guidelines = Can use *either* NSAID, Colchicine or Steroids

Choice dependent on other co-morbidities
(eg: Steroids in Diabetic - relatively c/I or NSAIDs in CKD)

**Duration of Rx**: 7 – 10 days; recurrence if stopped too soon

**MUST address risk factors** but 90% due to under-excretion of UA rather than overproduction
Pharmacological Treatment of Acute GOUT

1. **Non steroidal Anti-Inflammatory Drugs** (NSAIDs):

   - Is drug of choice if no contra-indication (peptic ulcer disease, renal impairment, cardiac failure, poorly controlled hypertension)
   - ALL NSAIDs equally effective, traditionally Indomethacin (Indocid) 50mg tds used. Can use Voltaren or Naprosyn
   - **NSAIDs = COX 2 inhibitors** (Celecoxib / Meloxicam) in efficacy
   - COX 2 inhibitors = 50 % less GI toxicity cf non selective NSAIDs but same cardiac (may be more) and renal toxicity
2. **Colchicine** (Colgout or Lengout) :

Inhibits neutrophil microtubule – paralyses neutrophil function = anti-inflammatory effect

Very effective if given at onset of gout

**Dose** : Low dose (0.5mg bd) = High dose (0.5mg every 2 hrs till diarrhoea!!) : Efficacy

**Side effects** : DIARRHOEA, Nausea
Pharmacological Treatment of Acute GOUT

3. Steroids:

(a) Oral: Prednisolone 30mg daily and wean off over 7 – 10 days

(b) Intra-articular: Depomedrol or Celestone chronodose with LA

Need to exclude septic arthritis
If unable to tolerate or c/I to oral Rx or refractory gout

(c) IM Steroids – Depomedrol – similar to I/A steroid
Indications for Uric Acid Lowering Therapy

1. > 2 gout attacks / year

2. Tophi – uric acid deposition in soft tissue

3. Radiographic changes of gout – erosions = disability

4. Urate nephropathy

5. Poly-articular gout
Uric Acid Lowering Therapy

1. **Xanthine Oxidase Inhibitors**
   (inhibits hypoxanthine/xanthine to Uric Acid)

   (a) **Allopurinol (1st line)** – start 50 - 100mg daily (max 900mg/day)

   (b) **Febuxostat** – start 40mg daily
   
   “Start low, go slow” and start after acute episode resolves and need concomitant (flare prophylaxis) 3-6/12 of either NSAID, Colchicine or Prednisolone to prevent precipitating episode of gout.

**Treat–To-Target**:

- **Gout**: SUA < 0.36 mmol/l
- **Tophaceous Gout**: SUA < 0.30 mmol/l
- **SUA Too Low**: Neurodegenerative disorders
Uric Acid Lowering Therapy

2. Uricosuric Drugs – inhibit renal uric acid reabsorption (URAT 1 transporter inhibitors)

(a) Probenacid
(b) Sulfinpyrazone
(c) Lesinurad

Use following inadequate response to XOIs, alone or less commonly in combination.
Treatment of Pseudogout

1. NSAIDs

2. Colchicicine

3. Steroids – oral or intra-articular (rapidly effective)
Psoriatic & Rheumatoid Arthritis

Monoarthritis (Knee):

1. NSAIDs
2. Joint aspiration & *steroid/LA injection*
3. **Synovectomy** (destruction or surgical removal of membrane that lines the joint and produces synovial fluid) – *Surgical* (open/arthroscopic) *Radiation/Medical* (Yttrium 90) – radioactive isotope/half life 2.5 days/beta radiation
4. **Disease modifying anti-rheumatic drugs**:
   csDMARDs, bDMARDs (biologics = genetically engineered drugs that block cytokines, proteins needed to cause an immune response)
Disease Modifying Anti-Rheumatic Drugs (DMARD)

1. Early initiation /early arthritis clinics/”window of opportunity”
2. Reduces joint damage/erosions/disability
3. Reduces CV risk (commonest cause of death in RA / PsA is Acute Myocardial Infarction)
4. Monotherapy/Combination DMARDs – may need steroids as “bridging therapy”
Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (DMARD)

1. Methotrexate (Dominant DMARD) – dihydrofolate reductase inhibitor – oral / subcutaneous / once weekly

2. Leflunomide (Arava)

3. Sulfasalazine (Salazopyrin)

4. Hydroxychloroquine (Plaquenil) – not for PsA as may aggravate skin Psoriasis.
Biologic Disease Modifying Anti-Rheumatic Drugs (DMARD)

1. Revolutionised Rx of Rheumatoid arthritis & Psoriatic Arthritis.

2. Cost = $20,000/year/patient – continuing Rx

3. Criteria to qualify on PBS:
   (a) Fail TWO csDMARDs for 3 months for PsA and 6 months for RA
   (b) Have 4 large or 20 large and small “active” (swollen and tender) joints
Biologic Disease Modifying Anti-Rheumatic Drugs

(i) Interfere with cytokine function
   - TNF alpha blockers
   - IL 6 inhibitors

(ii) Inhibit the ‘second signal’ required for T cell activation

(iii) Deplete B cells

TNF alpha Blockers (Available for RA, PsA, AS)
1) Etanercept (Enbrel) – weekly s/c inj
2) Adalimumab (Humira) – fortnightly s/c inj
3) Infliximab (Remicade) – monthly IV infusion
4) Certolizumab (Cimzia) - fortnightly/monthly s/c injection
5) Golimumab (Simponi) - monthly s/c injection
Disease Modifying Anti-Rheumatic Biologic Drugs

**IL6 Receptor Inhibitor**
- Tocilizumab (Actemra) – for RA, monthly IV infusion

**Costimulation blockage**
- Abatacept - for RA
- weekly s/c injection or monthly IV infusion

**B Cell Depletion**
- Rituximab (Mabthera) – 6 monthly IV infusion

**Janus Kinase (JAK) Inhibitor** - Tofacitinib (Xeljanz) - Tablet – bd (csDMARD)

- Apremilast (Otezla) – small molecule inhibitor of phosphodiesterase 4 (PsA)

**IL 12 and IL 23 selective inhibitor** – Ustekinumab (Stelara) - PsA
Side effects of biological agents

1) Infections
2) Reactivation of TB (especially with TNF blockers) – screen pre starting
3) Drug-induced lupus
4) Cancer – do not use TNF alpha blockers for 5-10 years post cancer cure;
5) ? increased risk of skin malignancy
6) Live vaccines contra indicated
Non-Surgical Management of Knee Osteoarthritis


OARSI 2014 most recent

ALL guidelines agree on:

1. **Land based exercise**
2. **Weight management**: 5% weight loss within 20 week period to be effective at treating OA
3. **Strength training**
4. **Water based exercise**
5. **Self management & Education**
Yet another death knell for paracetamol in OA

David J. Hunter and Manuela L. Ferreira

Although paracetamol is widely used and recommended for the management of pain in osteoarthritis, accumulating data indicate that it lacks efficacy and is associated with severe adverse effects. A new meta-analysis adds further weight to calls for clinical practice and treatment guidelines to be updated to reflect the evidence.

Non-Surgical Management of Knee Osteoarthritis

Major highlights re Pharmacological Rx:

1. **Topical NSAIDs for ALL** patients with knee OA and safer and better tolerated compared with oral NSAIDs

2. **Oral NSAIDs** effective but consider comorbidities / short term

3. **Paracetamol** – lack of efficacy and safety concerns (GI, Renal, Liver) especially with other comorbidities

4. **Oral & Transdermal Opioids** – concern re adverse events, addiction and opioid induced hyperalgesia– if used need exit strategy

5. **I/A steroid injection** – aspirate (removes cytokines) and inject – good short term benefit (significant synovitis in OA)

6. **Duloxetine** – evaluated for 1st time appropriate for patients without comorbidities – not mainstream yet

7. **Glucosamine, Chondroitin, Curcumin** = not appropriate for disease modification and “uncertain” for symptoms relief. Used by many – “worth a try!”