Musculoskeletal and Pain

Gout

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Signs/Symptoms

- Classic symptom: severe pain in the big toe
- Redness, warmth, painful, swollen joint(s)
- Often at night
- Formation of urate crystals contributed by elevated uric acid

Target Levels and Hyperuricemia

- Normal uric acid levels (2.5-6 mg/dL)
  - Generally elevated in gout
- Urate crystals can form and cause kidney stones
- Tophi
  - Nodules at a joint or joint(s) because of crystallized urate deposits
  - Usually develop over longer periods of time
  - Can impact joint function
  - Generally more painful during a gout attack
- Guidelines recommend treating to a target goal urate level of 6mg/dL or less

Classic Risk Factors

- Alcohol use
- Metabolic disease/obesity
- Seafood (foods high in purines)
- Family history
- Males more common than females

Classic Drugs That Increase Uric Acid

- Loop/thiazide diuretic use decreases uric acid excretion
- Niacin
- Cyclosporine
- Tacrolimus

Acute Treatment Options

- Initiation and Discontinuation: Sooner the better, and discontinue within a couple of days of resolution
- NSAIDs
  - GI, CHF, Kidney
  - Naproxen may be easier on the gut versus indomethacin
- Steroids
  - Hyperglycemia, GI, Insomnia, OP
- Colchicine
  - Diarrhea
  - 3A4 inhibitors may increase concentrations

Chronic Management

- Allopurinol (Zyloprim)
  - Mechanism of Action: Inhibits xanthine oxidase which reduces the formation of uric acid
  - Used for PREVENTION, reduction of uric acid, NOT for acute treatment of a gout attack
  - Side effects – rash, GI
    - Patients with HLA-B*5801 genotype may be at higher risk of skin reaction (Asian subpopulations may be at higher risk – Thai, Han Chinese, Korean)
  - Increase dose by 100 mg every 2-4 weeks to a target uric acid of <6mg/dL
  - Dose adjust with worsening kidney function
  - ACE inhibitors/thiazides/penicillin's may increase risk for allergic reaction with allopurinol
  - May be used in combination with an NSAID or colchicine to prevent a gout flare during initiation

Chronic Management

- Febuxostat (Uloric)
  - Mechanism of Action: Inhibits xanthine oxidase which reduces the formation of uric acid
  - Meant for prophylaxis
  - More expensive than allopurinol, but alternative if allopurinol ineffective/intolerable
  - Can increase azathioprine concentrations like allopurinol
  - FDA safety warning for an increased risk of cardiovascular death compared to allopurinol (because of this, this drug is often avoided or considered more of a last line option)

Chronic Management

- Colchicine (Colcrys)
  - Mechanism of Action: tubulin disruptor which leads to reduced activity of inflammatory pathways
  - Dose limiting side effect is most often diarrhea (high percentage of patients)
    - Low dose has similar efficacy to high dose in acute treatment of flares with reduced adverse effects
  - Dose adjustments in CKD
  - Can be used for both treatment and prevention
  - CYP3A4 inhibitors may increase concentrations of colchicine
    - Including grapefruit juice
  - May increase risk of myopathy/rhabdomyolysis in patients on statins

Chronic Management

- Probenecid (Benemid)
  - Removal of uric acid in the body by increasing kidney excretion
  - GI upset adverse effect
  - Probenecid can raise the serum concentrations of numerous other medications
    - Penicillin’s, quinolones, cephalosporins, NSAIDs, Nitrofurantoin, methotrexate,
  - Need adequate kidney function for the medication to work

Osteoarthritis

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Osteoarthritis Symptoms

- Pain after longer periods of use
- Stiffness after resting
- Potential change in the shape of ends of fingers (DIP)
- Not much inflammation (differentiator from RA)

Pain Impact

- Quality of life
- Sleep
- Function/ability
- Work/Volunteerism
- Appetite
- Exercise
- Mood

Treatment for OA

- Trial of hot/cold
- Massage
- NSAIDs
- Topicals
- Duloxetine
- Acetaminophen
- Opioids
- Steroid injections

NSAIDs

- Mechanism of Action: Non-selective inhibition of COX-1/COX-2 which leads to a reduction of inflammation via reduced prostaglandins
- Naproxen (Naprosyn, Aleve), ibuprofen (Motrin, Advil), diclofenac (Voltaren), meloxicam (Mobic), piroxicam (Feldene), nabumetone (Relafen), indomethacin (Indocin), ketorolac (Toradol), etodolac (Lodine), sulindac (Clinoril), aspirin
- More efficacious than acetaminophen for knee and hip OA
- Lots of concerns with oral NSAIDs in our elderly population
- If necessary, use short term and/or minimize dose

NSAIDs – Risk

- CHF exacerbation risk, can contribute to resistant hypertension
- Possible negative impact on kidney function (especially in combo with ACE/ARB and/or diuretics)
- Avoid very high risk GI NSAIDs (i.e. indomethacin and ketorolac) for OA if possible
  - Ketorolac recommended for 5 days only (boxed warning for increased GI bleed risk)
  - Assess antiplatelet and anticoagulant use – generally avoid NSAIDs
- Monitoring parameters
  - Kidney function
  - CBC (anemia/bleed risk)
- Possible increased risk of cardiovascular events (boxed warning)
  - Naproxen typically considered safest with this adverse effect
- Topical NSAID – diclofenac gel (Voltaren)
  - Preferred over oral NSAIDs when possible due to improved safety profile
  - Best efficacy in knee and hand OA

COX-2 Inhibitor

- Celecoxib (Celebrex)
  - Same issues as NSAIDs
  - Exception: GI bleed is less
    - Remember that elderly patients are usually on antiplatelet/anticoagulant therapy
    - Risk similar if on baby aspirin

SNRI

- Duloxetine
  - Option for those with OA symptoms in multiple joints and those with contraindications to oral NSAIDs or non-responders
  - See depression for more information

Topical Medications

- Topical agents can be helpful especially if only a joint or two is affected by osteoarthritis
  - Topical NSAID – diclofenac gel (Voltaren)
  - Capsaicin (Salonpas)
  - Menthol type product, salicylate (i.e. Bengay)

Acetaminophen

- Mechanism of Action: weak inhibition of prostaglandin synthesis, really not totally understood; because of only weak activity on prostaglandins, acetaminophen is less beneficial in reducing inflammation
- Not first-line therapy for osteoarthritis
- Usually tolerable, even in the elderly (much more so than NSAIDs) when used at recommended dosages
- Liver toxicity only concerning at >4 grams (possibly less if patient is already at risk for liver failure, i.e. cirrhosis)
- Patient education, monitoring of combo opioid products and use of the over-the-counters incredibly important to avoid accidental overdose
- Acetylcysteine is antidote

Common Opioids

- Examples: Oxycodone (Oxycontin), hydrocodone/acetaminophen (Vicodin, Norco), morphine (MS Contin), fentanyl (Duragesic), methadone (Dolophine), hydromorphone (Dilaudid), codeine/acetaminophen (Tylenol #3)
- Mechanism of Action: Full opioid agonist activity by stimulating mu receptors in the CNS which provides analgesic effect

Important Approximate Conversions

- Morphine (oral) 30 mg
- Oxycodone 20 mg
- Tramadol 300 mg
- Fentanyl (patch) 12 mcg
- Hydrocodone 30 mg

Opioid Adverse Effects

- GI
- Constipation
- Sedation
- Cough suppression
- CNS
- Itching
- Tolerance/Dependence/Addiction risk
- Avoid with other high risk agents (i.e. benzodiazepines)

Opioid Pearls

- Oxycodone
  - In combo with APAP or alone
  - Very commonly used
  - Long acting and short acting available
- Hydrocodone
  - Combo with APAP
  - Active metabolite is hydromorphone (created via CYP2D6)

Opioid Pearls

- Morphine
  - Gold standard for conversion (multiple dosage forms, i.e. oral, rectal, injectable etc.)
  - Caution in renal impairment
  - Possible interaction with reduction in P2Y12 inhibitors effectiveness
  - Metabolite morphine-3-glucuronide associated with neurotoxicity
  - Long acting and short acting available
- Codeine
  - CYP 2D6 converts to morphine
  - Rapid metabolizer of 2D6 will lead to more opioid effects
  - Drugs that inhibit 2D6 will lead to less opioid effects
  - Less potent than morphine, oxycodone etc.

Opioid Pearls

- Fentanyl patch
  - Long onset/long offset – not appropriate for acute pain relief or as needed use
  - Can cover with a Tegaderm patch or another adhesive
  - Heat can increase rate of absorption – avoid
  - Should NOT be used in opioid naïve patients
- Methadone
  - Conversion from or to methadone is a huge burden
  - Highest QTc prolongation risks of any opioids
    - Careful with other QTc prolonging meds
  - Role in managing opioid use disorder
  - Very long half-life compared to other opioids

Tramadol

- Max of 300mg in the elderly (differs from usual 400 mg)
- Be careful in elderly as they may have seizure disorder or condition that may predispose them to seizures
- Serotonin activity (caution in patients who are receiving high doses or multiple other serotonergic drugs
- Sedation, constipation, dizziness, CNS effects
- Risk of dependence/addiction, controlled substance
- Active metabolite formed via CYP2D6
  - Fluoxetine, paroxetine, and bupropion are examples of medications that may inhibit CYP2D6

Steroids

- Acute inflammation
- Benefit is usually transitory
- Injection to site of pain
  - Still has systemic effects

Glucosamine/Chondroitin

- Potential option for OA
- Takes time to work
- Be sure dose is adequate – target 1,500 mg
- If beneficial continue…if not, DC

Osteoporosis

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WHO Classification

- Normal; T-score greater than or equal to -1.0
- Osteopenia; -1.0 to -2.5
- Osteoporosis; -2.5 or below

FRAX Scoring

- Only recommended in patients who are untreated
- T-score -1.0 to -2.5
- Treat if 10 year risk:
  - 3% or greater risk for hip fracture
  - OR
  - 20% or greater risk for any osteoporotic fracture

Risk Factors – FRAX Assessment

- Female
- Age
- Low BMI
- T-score
- Steroid use
- Smoking
- ETOH
- Hyperthyroidism (chronic)
- Prior Fracture
- RA

Treatment

- Bisphosphonates
- Denosumab
- Calcitonin
- SERM (Raloxifene)
- Anabolic agents - Teriparatide abaloparatide, romosozumab
- Estrogen

Bisphosphonates

- Bone resorption inhibitors; Inhibit osteoclasts, osteoclasts breakdown bone to help pull calcium into the blood stream
- Administration Procedure
  - Before other meds/food
  - Glass of water, remain upright
  - Try to avoid esophageal ulceration
- Low Calcium
- Bone/muscle/joint pain
- Osteonecrosis
  - Extremely rare, most occurrences surrounding oral surgery
- IV (zoledronic acid, ibandronate)
  - Alternative for those who have contraindications to oral (AKI risk)
- Reassess use after 5 years (IV after 3 years)

Denosumab

- Monoclonal antibody that targets RANKL and prevents activating RANK which is important in activating the action of osteoclasts; thus reducing bone resorption and increasing bone strength
- Alternative when bisphosphonates aren’t an option
- 2 times per year injection
- Significant expense compared to oral bisphosphonates
- Can be used with impaired renal function
- Association for increased vertebral fracture risk when discontinued
- SE’s – low calcium, muscle pain, injection pain, weakness

Calcitonin

- Mechanism of Action: Opposes the action of parathyroid hormone and inhibits the activity of osteoclasts which results in an increase in bone strength
- Nasal spray used most often
  - Rhinitis and nose bleed
- Potential compression fracture benefit
- Storage/Admin pearls
  - Store upright
  - Prime 5 times before use
  - Discard after 30 doses or 35 days

Raloxifene

- Mechanism of Action: Stimulates estrogen receptors selectively in bone tissue leading to an increase in bone strength (also acts as an estrogen antagonist in other pathways)
- Breast cancer indication
- DVT/Cardiovascular disease warning
- Side effects
  - Hot flashes
  - Edema

Parathyroid Hormone Analog

- Teriparatide (Forteo), abaloparatide (Tymlos)
- Mechanism of Action: Works on building bone (anabolic) by stimulating osteoblasts
- Lab monitoring parathyroid hormone (PTH) and calcium/vitamin D
- ONLY use for 2 years
  - Black box warning for osteosarcoma
- Typically only reserved for severe osteoporosis patients

Other Considerations

- Vitamin D
- Calcium
- Exercise, strength building, weight bearing
- Fall risk

Classic Medication Contribution

- Steroids
- Anticonvulsants
- Thyroid supplements
- PPI’s
- TZD’s

Rheumatoid Arthritis

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Rheumatoid Arthritis

- Autoimmune disorder
- Inflammation
- Painful
- Joint Swelling (big difference with OA)
- Typically symmetrical
- Patients with RA may have elevated C-reactive protein (CRP) as well as elevated Erythrocyte Sedimentation Rate (ESR)

RA Versus OA

- RA
  - Onset middle age/anytime in life
  - Quick onset – Weeks to months
  - Inflammation/Swelling
  - Both sides of the body affected
  - Stiffness can last much longer throughout the day
  - Whole body symptoms possible (fatigue, feeling sick)

Goals of RA Therapy

- Minimize flares
  - Troublesome to patients
  - Reduce adverse effects from NSAIDs and steroids
- Early initiation of DMARD therapy
  - Reduces joint damage
- Minimize side effects
  - Infection risks

Flare Management - NSAIDs

- GI bleed risk (especially patients with history of GI bleed/issues, and those on anticoagulants or antiplatelet medications)
  - Celecoxib may reduce this risk but increase CV risk
- Impact platelet function
  - May increase risk of bleeding with surgical procedures
- CHF exacerbation risk
- Can contribute to resistant hypertension
- Possible negative impact on kidney function (especially in combo with ACE/ARB and/or diuretics)

Flare Management - Steroids

- Alternative to NSAIDs
- Minimize length of therapy if at all possible
  - Immune suppression risk
  - Exacerbates diabetes – causes hyperglycemia
  - Can cause GI upset, increase ulcer risk (generally try to avoid both steroids and NSAIDs together due to high GI risk)
  - Insomnia, anxiety
  - HPA suppression risk
  - Osteoporosis risk if used longer term
  - Heart failure risk
  - Increased hypertension
  - Possible increased risk of elevated intraocular pressure (monitor in patients on longer term use) – glaucoma
  - Increases the risk of cataracts

DMARDs

- DMARDs delay the progression and worsening of the disease
  - Examples: Methotrexate (Rheumatrex, Trexall), hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), leflunomide (Arava), azathioprine (Imuran)
  - Monitor CBC, LFT
  - Watch immunosuppression risk (WBC)
  - DMARDs do not work quickly, takes weeks to months
  - 3-6 month trial is typically done before declaring failure and switching agents unless side effects are incurred
  - Often started with NSAIDs or steroids in a new diagnosis, acute flare type situation; NSAID or steroid covers the acute pain and inflammation

DMARDs

- Methotrexate
  - Mechanism of Action: inhibits dihydrofolate reductase which ultimately blocks purine production and inhibits DNA synthesis (primary mechanism in oncology) – Not well understood in RA but immunosuppression may be helpful in suppressing inflammation/pain
  - Once weekly up to 20-30 mg
  - LFT’s, CBC, immune system suppression
  - Folic acid

DMARDs

- Sulfasalazine
  - Mechanism of Action: Not well understood, thought to affect tumor necrosis factor and possibly leukotrienes
  - GI upset, rash, CBC, LFT's
  - Can impair folic acid absorption
  - BID dosing
- Hydroxychloroquine
  - Mechanism of Action: Not well understood in management of RA
  - CBC, LFT's, eye exams
- Leflunomide
  - Mechanism of Action: inhibits dihydroorotate dehydrogenase which has an important role in synthesis or uridine monophosphate; uridine monophosphate is necessary for DNA/RNA production – leads to an immunosuppressive type effect
  - LFT's, CBC, diarrhea, skin reactions, hair loss

DMARDs - Biologics

- Mechanism of Action: Binds and prevents the action of tumor necrosis factor (TNF), TNF plays an important role in the inflammatory process
- Usually not used first line due to cost considerations
  - Oral DMARD first, then dual oral DMARDs, possibly even triple therapy with MTX, sulfasalazine, and hydroxychloroquine
- Etanercept (once weekly), adalimumab (every 2 weeks), infliximab (infusion), etc.
- Injection site reaction
- Infection risk

Biologics

- Infection warnings
- Malignancy warnings
- Screen for latent TB or hepatitis B/C as they may be activated by a suppressed immune system
  - If patients have a latent TB infection, they should be treated prior to initiation of the biologic agent
  - If taking a biologic when they are diagnosed with a new infection, they should stop therapy and receive treatment for the infection
- Cost/insurance often regulates selection
- Can be used with oral DMARDs, typically methotrexate