Updates in Rheumatology

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Question #1

56 year old samoan man with known gout was initiated on allopurinol but after 2 wks developed a swollen knee. Which choice is not correct?

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  4. Point scoring classification
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A 48 yo woman with longstanding RA is being pre-op’d for TKA. She has been on long term methotrexate and is tolerating it well at 20 mg once weekly with overall good control. She is on no prednisone and no TNF inhibitor. Which does evidence suggest is appropriate:

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A 28 yo hispanic woman G2P1 was diagnosed with lupus at age 18 and now presents to the OB office for her 32 wk appt and has several physical and lab results to review with you since her perinatologist is on vacation. Which of the following is the best clinical feature that can help differentiate lupus manifestations vs pregnancy complications?

1. Worsening arthralgias
2. Worsening anemia
3. New thrombocytopenia
4. Leukopenia
5. Facial erythema
#5 “RHEUMATIC TMZ”
Overview/Learning Objectives

• Review and update crystal induced arthritis
• RA – new classification criteria (for earlier diagnosis) and treatments
• Peri-operative management of methotrexate and other anti-rheumatics
• Common obstetric complications in rheumatic disease
Challenges in Medicine

- “Affordable” Care Act
- Metabolic syndrome
  - Gastric bypass
- Aging Population
- Chronic diseases
- Strain on Primary Care
Gout Principles

• Most common inflammatory arthritis, men >40 yrs
  – ↑prevalence (4%)
  – aging, ↓GFR
  – ↑obesity
  – meds

• Initially: Acute arthritis
  – Inflammatory response → MSU crystals
  – MSU crystals from aspirated joint fluid is diagnostic

• Uric acid:
  – end product of purine metabolism
  – serum uric acid > physiologic limit of solubility (6.8mg/dl)
    → Tissue crystallization
  – often deceptively low/normal during attacks
Famous Men Who Have Had Gout

Sir Isaac Newton in Kneller's portrait of 1689.

Henry VIII
King of England and Ireland by Hans Holbein the Younger

Portrait of Benjamin Franklin

Thomas Jefferson

Wikipedia Encyclopedia Available at http://Hen.wikipedia.org/wiki/Gout
Differential Diagnosis of Gout

- Septic joint (risk factors)
- Reactive arthritis (antecedent infection – GU/GI)
- Spondyloarthritis – young men, psoriasis
- Trauma, hemarthrosis
- Pseudogout (coming up)
Evaluation

• Clinical
  – Family history
  – Prior events
  – Medications (diuretics)
  – Diet, alcohol
  – Metabolic Syndrome

• Labs
  – CBC, ESR/CRP
  – BUN/CRE, uric acid
  – Mg, PO4, PTH

• Examination
  – Evaluate all joints
  – Tophi
  – Bursae, Tendons
Advanced Chronic Tophaceous Gout
Pathogenesis of Gout

Precipitating Factors

• Trauma/Surgery
• Low dose aspirin
• Diuretics, other meds
• Diet
• Alcohol
• Systemic illness
Causes of Hyperuricemia

• **>90% Under-excretors:**
  - reduced tubular excretion of uric acid
  - genetics: proximal tubular defects
  - medications: impaired urate clearance
  - renal insufficiency
  - Pb poisoning

• **<10% Over-producers:**
  - purine biosynthesis
  - psoriasis
  - myeloproliferative syndromes, tumor lysis
  - Lesch Nyhan (hypoxanthine-guanine phosphoribosyl transferase)
Medications Affecting Urate Excretion

• thiazides and loop diuretics
• low dose aspirin
• calcineurin inhibitors (cyclosporine)
• TB meds:
  – pyrazinamide
  – ethambutal
• niacin
Dietary Risk Factors

• “Low purine diet” - modest -1 mg - reduction in uric acid

• Risk from alcohol intake: Beer > liquor > wine

• High meat/seafood consumption  \(\uparrow\) risk of gout

• High dairy consumption \(\downarrow\) risk of gout

• High purine-rich vegetables  no association
Gout: One Chronic Disease - 4 Stages

- Asymptomatic hyperuricemia
- Acute attacks: urate crystallization → joint inflammation
- Inter-critical Phase: Interval between acute attacks
  - Tissue damage occurs during this period!
- Chronic tophaceous gout
  - ↓ inter-critical periods

Erosions and hypertrophic adjacent bone
New imaging modality: DUAL ENERGY CT

Pseudogout (CPPD)

- Inflammatory or non-inflammatory response to the intra-articular deposition of calcium pyrophosphate dihydrate (CPPD) crystals

- Age is major risk factor:
  - ~3% in >60 yo
  - ~50% in >90 yo

- Often presents similar to gout, thus “Pseudogout”

- Can also cause a chronic synovitis (“pseudo-RA” or “pseudo-OA”)

- Most commonly: knee, wrist, shoulder, 2nd and 3rd MCP
CPPD vs MSU Crystals

- CPPD crystals are weakly positively birefringent, rhomboid, rods, squares, or irregular under compensated polarized light
Pseudogout
EULAR CPPD Treatment (June 2010)

• Acutely:
  – Ice, arthrocentesis and steroid injection
  – NSAIDs
  – Low dose colchicine up to QID acutely ($$$)
  – Systemic steroids (intramuscular, PO)

• Long term:
  – Low dose colchicine qd to bid
  – Methotrexate
  – Hydroxychloroquine

• Correct underlying risk factors:
  – CKD and hyper PTH and phosphate disorders
Gout Treatment Principles

• Terminate the acute attack as rapidly as possible
  – NSAIDs
  – corticosteroids
  – colchicine

• Protect against further attacks
  – prophylaxis against future attacks

• Treat hyperuricemia and prevent disease progression
  – Long-term correction of the metabolic problem
  – Lower serum uric acid
  – Resorption of tophi over time
Medications: anti-inflammatory

• Colchicine
  – Best used early in attack (low dose for prophylaxis)
  – Optimal regimen not clear until 2009
    • 1.2 mg then 0.6 an hour later then qd-tid
  – Contraindicated in CKD patients, grapefruit juice
  – AE’s include GI, marrow, neuromuscular toxicities

• NSAIDs
  – high dose early

• Corticosteroids
Medications: anti-hyperuricemics

- **Urostatic**: Xanthine oxidase inhibitors
  - Allopurinol (hypoxanthine $\leftrightarrow$ xanthine)
  - **Febuxostat/Uloric (2009)**

- **Uricosuric Agents** (contra-indicated in over-excretors):
  - Probenecid
  - Sulfinpyrazone
  - Losartan
  - Fenofibrate

- **Enzymatic**:
  - **Pegloticase/Krystexxa (2011)**
Treatment Pearls

- Treat associated co-morbidities and address risk reduction behavior
- Initiate urate lowering therapy (ULT) in patients with two or more attacks a year
- Do not start ULT during an acute attack
- Do not discontinue ULT if patient on ULT has an acute attack
- Allopurinol is drug of choice for initial ULT
- Uricosurics useful in allopurinol allergic patients with normal renal function, under-excretion, and no history of nephrolithiasis
- Uricosurics – not indicated in overproducers
- Use concomitant prophylaxis when initiating ULT to prevent treatment induced attacks
- Measure serum uric acid levels every 3-6 months. Adjust medications until a target uric acid of < 6mg/dl is obtained

Now onto RA....
Dr Philip Hench, 1950, Nobel Prize in medicine → synthetic cortisone
General Points

• Systemic autoimmune disease ➔ chronic inflammation (swelling, stiffness) of multiple joints
• Affects ~1-2% of the population
• Genetic links similar to SLE
• Loss of joint function, destruction of bone/cartilage
• Shorter life expectancy ➔ systemic inflammation
Clinical Features
“New World” Epidemiology

• Environmental triggers (since Columbus?)
  – Industrialization
    • Crystalline silica dust
    • Automotive exhaust
    • Travel and connectivity (EBV, other agents?)
  – Refinement of lifestyle
    • Tobacco processing, use (↑ 2.4X risk) and distribution
    • Sugar refinement, ubiquity → gingival disease

Costenbader KH, Cigarette smoking and autoimmune disease: what can we learn from epidemiology? Lupus. 2006

Hart JE, 2009 Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect.

“Associations of P. gingivalis titers with RF, antiCP suggests that infection with this organism plays a role in disease risk and progression in RA.” Mukuls TR, Payne, J.B., Reinhardt, R. A. et al Int. Immunopharmacol. 9:38-42 2009.

ACR 1987 Classification Criteria for Rheumatoid Arthritis

Patients Must Have Four of Seven Criteria:

- Morning Stiffness Lasting at Least 1 Hour*
- Swelling in 3 or More Joints*
- Swelling in Hand Joints*
- Symmetric Joint Swelling*
- Erosions or Decalcification on X-ray of Hand
- Rheumatoid Nodules
- Abnormal Serum Rheumatoid Factor

* Must Be Present at Least 6 Weeks.
Real Case…

• 29 yo caucasian female smoker
  – 9 yr history of L wrist, R MTP swelling/pain
  – No stiffness or nodules
  – No FH of RA
  – Previous dx: “overuse”, “tendonitis”, ‘wrist DJD’

• Does she fulfill 1987 RA classification criteria?
• 3/7 classification criteria
Ref Rng

CRP  <10.0  6/22/2011

ESR 0 - 20 MM/HR  20.0 (H)

CCP IGG  <5.0  23 (H)

RF  <11  181.8 (H)

RF  <5
### 2010 ACR/EULAR RA classification criteria

- **JOINT DISTRIBUTION**
  - 1 large joint: 0
  - 2–10 large joints: 1
  - 1–3 small joints (large joints excluded): 2
  - 4–10 small joints (large joints excluded): 3
  - >10 joints (at least 1 small joint): 5

- **SEROLOGY**
  - Negative RF and negative ACPA: 0
  - Low positive RF or ACPA (≤3x ULN): 2
  - High positive RF or ACPA (>3x ULN): 3

- **SYMPTOM DURATION**
  - <6 weeks: 0
  - ≥6 weeks: 1

- **ACUTE PHASE REACTANTS**
  - Normal CRP and ESR: 0
  - Abnormal CRP or ESR: 1

RA can be classifiable or diagnosed with a score ≥6.
Treatment
Chronic Inflammation: Imbalance Between Mediators


Window for Treating RA

- Radiographic progression occurs early and continues over the lifetime of a patient.
- 70% of patients have radiographic damage within the first 3 years.


- Chronic irreversible changes
- Functional decline
- Higher mortality
RA Treatment: Optimizing Outcomes

- Early diagnosis and risk stratification
- DMARDs early (within 3 mo of symptoms)
- “TREAT TO TARGET”
- Steroids
  - bridge to effective DMARD therapy
  - prednisone >10 mg/d rarely needed for joints
  - minimize long term side effects (osteoporosis, DM)
- Co-morbidities
  - atherosclerosis
  - osteoporosis
Evolving RA Treatment Paradigm

Current Approach

Initial treatment: traditional DMARDs

Add traditional DMARD (Combination Therapy)

Evolving Paradigm

- Early aggressive treatment
- Biologics
  - Combination therapy
Traditional DMARD’s

- methotrexate/Rheumatrex
- leflunomide/Arava
- sulfasalazine/Azulfidine
- azathioprine/Imuran
- hydroxychloroquine/Plaquenil
- mycophenolate mofetil/Cellcept
- gold
- minocycline
- doxycycline
- penicillamine
- cyclophosphamide
- cyclosporine
Biologic DMARD’s

• TNFα antagonists:
  – Adalimumab (Humira)
  – Etanercept (Enbrel)
  – Infliximab (Remicade)
  – Golimumab (Simponi)
  – Certolizumab (Cimzia)

• Interleukin-1 antagonist
  – Anakinra (Kineret)

• Suppress T-Cell activation
  • Abatacept (Orencia)

• Anti B-Cell monoclonal Ab
  • Rituximab (Rituxan)

• Anti-interleukin-6
  • Tocilizumab (Actemra)
Safety and Biologic DMARD’s

- Serious Infections
- Opportunistic infections (TB, cocci, histo, blasto)
- Malignancy/lymphoma
- Demyelinating syndrome
- Hematologic abnormalities

- Congestive heart failure
- Hepatic
- Auto-antibodies and drug induced lupus
- Neutralizing antibodies
Biosimilars

• Insulin, erythropoietin
• Etanercept in Colombia (Etanar), China
• Rituximab in India (Reditux)
• Concerns:
  – Large molecules, immunogenicity

Kay, Medscape Rheumatology
06/24/2011
Surgery and Rheumatic disease

- **Safety of DMARDs for RA**
  - Methotrexate → continue in the peri-operative period
  - Stop all biologics prior to surgery and resume after wounds healed over

- **Surgery and crystal induced arthritis**
  - Continues prophylaxis as allowable
  - Peri-operative IV hydration (sensible loss)

References:


Rheumatic disease and the Obstetrician

• No increase in infertility
• Outcome is best for mother and child with preconception quiescence for >6 months
• High rates of flares otherwise
  – Preeclampsia
  – Fetal Loss
  – Preterm Delivery
  – Low Birth Weight Infant
  – Deep Vein Thrombosis/Pulmonary Embolism
• Neonatal lupus and complete heart block
  – Fetal cardiac monitoring for mothers with SSA/SSB antibodies
• Safety of plaquenil, but not methotrexate
Neonatal lupus
Pregnancy vs Pregnancy complications

**Pregnancy**
- Proteinuria
- Facial blush, melasma
- Arthralgia
- Thrombocytopenia
- Pre-eclampsia

**Lupus**
- Proteinuria with casts
- Malar rash
- Arthritis
- Leukopenia
- Hypocomplementemia, antibodies to dsDNA
In Summary….

• Recognize important old and new concepts of gout
• Earlier diagnosis and treatment of RA improves outcomes
• Newer classification and diagnostic tools are here for inflammatory arthritis
• Medications may not be as risky in per-op settings
• Recognize rheumatic disease and pregnancy
THANK YOU FOR YOUR ATTENTION!
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