Inflammatory Arthritis

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DISCLOSURES
Speaker’s Bureau:
Takeda, Pfizer

Objectives - As a result of participating in this activity:

1. The participant will be able to discriminate degenerative from inflammatory arthritis.

2. The participant will be able to differentiate between the various causes of inflammatory arthritis.

3. The participant will be able to discuss new treatment guidelines for gout.

4. The participant will be able to discuss various treatments for rheumatoid arthritis.
The Arthritis Epidemic

100 million in US suffer joint disease
Joint complaints 10-15% of PCP office visits
“Perfect storm of arthritis”
Baby boomers in 70s
Exercise boom of 1970s
The Obesity epidemic
The Gout epidemic
Rheumatologist shortage

Arthritis Knowledge is Essential

Arthritis in US (in millions)

Degenerative (OA) vs. Inflammatory Arthritis

Degenerative (OA)
OA involves CMCs (base of thumbs)
OA involves hips

Inflammatory Arthritis (IA)
IA involves PIPs, MCPs and wrists
IA involves elbows
IA involves MTPs and IPs of Feet
Both affect DIPs, Shoulders, knees and ankles
Degenerative vs. Inflammatory Arthritis

OA bone formation (osteophytes), IA bone erosions

OA-Heberden/Bouchard bony nodules on DIPs/PIPs

IA Rheumatoid nodules rubbery diffusely

OA morning stiffness <30 min, IA >1 hr

OA Pain increased with activity, IA pain reduced

OA NO systemic inflammatory symptoms

OA Joint Effusions are NON-inflammatory-Transparent and Stringy (newspaper and string tests)

What is Inflammatory Arthritis (IA)?

IA is joint tenderness, warmth, and swelling

Infectious
Bacterial-Staph/Strep, GNB, Lyme
Fungal
Mycobacterial
Viral
Spirochete
Viral-Hep C/HIV

Crystalline
Monosodium urate (gout)
Calcium pyrophosphate dihydrate
Hydroxyapatite
Calcium oxalate

Systemic Rheumatic Disease
Rheumatoid arthritis
Spondyloarthropathies
Systemic Lupus Erythematosus
Sarcoidosis
Mixed Connective Tissue Disease

Suspicion of septic arthritis = aspiration

Red and purple top for culture, gram stain, crystal exam, diff
Joint destruction within 24 hours, blood cultures (-) 50%

Lyme Disease Signs and Symptoms

Early Signs/Symptoms (3-30 days after bite)
Fever, chills, fatigue, muscle and joint aches, swollen lymph nodes, headache

Erythema migrans (EM) rash:
70 to 80 percent of infected persons
At site of tick bite after delay of ~7 days
Warm, rarely itchy or painful
Clears as it enlarges, resulting in a target or "bull's eye" appearance

Later Signs/Symptoms (weeks-months after bite)
Severe headaches and meningitis
Multiple EM rashes throughout body
Mononuclear Arthritis, particularly the knees and other large joints NOT small joints
Bell's palsy
Intermittent pain in tendons, muscles, joints, and bones
Heart palpitations or an irregular heart beat
Dizziness or shortness of breath
Shooting pains, numbness, or tingling in the hands or feet
Problems with short-term memory

http://www.cdc.gov/lyme/
Who SHOULD be tested for Lyme Disease?
Need High Pretest Probability of Positivity
A recent history of having resided in or traveled to an area endemic for Lyme disease.
AND
A risk factor for exposure to ticks.
AND
Symptoms consistent with early disseminated disease or late Lyme disease.

Who should NOT be tested for Lyme Disease?
Everyone Else

Endemic Lyme Areas

http://www.cdc.gov/lyme/

http://www.cdc.gov/mmwr/preview/mmwrhtml/00038469.htm

First perform ELISA or IFA, if negative STOP.
If positive, confirm with Western immunoblot.

If <30 day, test both IgM and IgG.
If >30 days, just test IgG.

An IgM test alone is NOT recommended because a false-positive test result is high.

Persons with disseminated or late-stage LD have a strong IgG response to Borrelia burgdorferi antigens.

An IgM immunoblot is considered positive 2/3 bands are present: 24 kDa (OspC) *, 39 kDa (BmpA), and 41 kDa (Fla)
An IgG immunoblot is considered positive 5/10 bands are present: 18 kDa, 21 kDa (OspC) *, 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa


Southern Tick-Associated Rash Illness (STARI)
Lone star tick, Amblyomma americanum

Lone star ticks have NOT been shown to transmit Borrelia burgdorferi, the cause of Lyme disease. In fact, their saliva has been shown to kill Borrelia.

STARI can cause EM rash similar to Lyme with fatigue, headache, fever, and muscle pain. STARI has NOT been linked to arthritis, neurologic disease, or chronic symptoms. The cause of STARI remains unknown, it is NOT caused by a spirochete and doxycycline may or may not speed recovery.


http://www.cdc.gov/staridisease/
Tickborne Diseases Endemic to Tennessee that can Cause Arthralgia/Arthritis

Inflammatory Arthritis Evaluation

History is the basis for diagnosis
ROS: AM stiffness, distribution/symmetry of joint pain, constitutional symptoms, rash, SOB/pleurisy, GI symptoms
PMHx: blood transfusion prior to 1995 (Hep/HIV), +PPD
SocHx: IVDA, Hep risk factors, TB exp, pets, hunting, bites
FamHx: autoimmune or rheumatic disease, TB
PE: complete (pulm, cardiac, abd, neuro, lymph, skin)
MS: passive ROM pain=arthritis, move distal to proximal

Punch and Pray for Passive ROM in Hands
Crossed Finger, Kissing Hand exam
MCP and MTP squeeze tests
Knees are normally cooler than the surrounding skin
Skin: palate, ears, scalp, natal cleft, umbilicus, extensor area

IA Laboratory Evaluation

• CBC with diff and CMP with LFTs, Hep B&C/HIV
• ESR and CRP (Normal ESR ½ age if female, ¾ age -10 if male)
  – Either or both can be normal and still have IA
• Rheumatoid Factor (RF)
  – 90% with +RF do NOT have RA, early RA negative
  – Can be positive in Hep C, Sjogren’s, infection, lupus
• HLA-B27 for spondyloarthropathy
  – 92-95% do NOT have spondyloarthropathy
• serum Uric Acid (sUA) for gout
  – Can be falsely low during an attack
• Anti-nuclear antibody (ANA) with reflex titer and pattern
  – Non-specific - 95% with +ANA do NOT have lupus
  – Only test if high pretest probability
Need 3+ Lupus criteria before ANA test

**MD SOAP BRAIN**
- Malar rash
- Discoid lupus
- Serositis
- Oral ulcers
- Arthritis
- Photosensitivity

Only 5% with +ANA have lupus, rest don’t

ANA is a Confirmatory test, not a screen

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**Anti-Cyclic Citrullinated Peptide Assay (anti-CCP)**

- Proteins become citrullinated (arginine replaced with citrulline) during inflammation
- Exposure of citrullinated proteins in susceptible individuals leads to anti-CCP Ab production
- CCP2 assay 70% sens and 96% specific to dx RA
- Anti-CCP Abs play a role in RA pathogenesis
  - Higher levels increase risk of developing RA
  - Predicts future severity of joint destruction
  - Smoking and gingivitis cause citrullination
- Not 100% specific

PsA 12%, Sjogren’s 9%, SLE 5%, AS 3%, Hep C 2%

Goldman et al. Isr Med Assoc J. 2013, 15(9), 584-7

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**Xray, Xray, Xray**

Rheumatoid Arthritis Erosion Progression
- Early
- Late

Osteoarthritis

Gout

ACR Rheumatology Image Bank.
www.rheumatology.org
Rheumatoid Arthritis Prevalence Decreasing


From http://rheumatoidarthritis.net/what-is-ra/ra-statistics/

Gout Prevalence in US Over Time


The Perfect Storm of Gout

• 8.3 MILLION US Adults have gout
  – Up from ~6 million 10 years ago
  – Due to Aging, Obesity, Diabetes, Renal Disease
  – Gout outnumbers RA by over 6 times
• Post-menopausal Females get gout, but they can present differently than men
  – Often present with mild bilateral hand/wrist pain
    • Think gout and check sUA before treating for RA
  – Arthritis often less severe than in men

Gout Pathophysiology

- Hyperuricemia is necessary but not sufficient
  - Uric acid has limited solubility
  - When serum UA (sUA) > ~6mg/dL crystals form
  - Only ~20% of hyperuricemic patients develop gout
  - Immune system must react to the UA crystals
- UA crystals can deposit anywhere
  - UA solubility inversely related to temperature
  - Big toe coldest joint in body and this is why 50% of gout patients present with podagra first

Improperly Treated Gout/RA Timeline

INFLAMMATION AND JOINT DAMAGE

ASYMPTOMATIC HYPERURICEMIA

J O I N T P A I N S E V E R I T Y

T I M E
TOPHACEOUS GOUT

Untreated Gout can ruin a Life

PROPERLY TREATED Gout/RA Timeline
Gout Is Two Diseases that require Different Treatments

**Metabolic Disease**
- Hyperuricemia forms UA crystals
- Treat with Urate Lowering Therapies (ULTs)
- ULTs can dissolve crystals over time but can increase FLARES in the near-term

**Inflammatory Disease**
- Innate Immune System reacts against UA crystals = FLARES
- Treat with Anti-Inflammatory Medications
- Anti-Inflammatory Medications do NOT lower UA levels and do NOT modify disease long-term

You Must Ask About Gout Attacks
- Many patients do not know what gout is
  - Run in families—may not know it’s a disease
- Ask patient if they’ve ever had episode where joint got hot, red and painful that lasted a week
- Ask if they’ve ever received treatment or had a joint aspiration
- Ask how many episodes they’ve had and if anything seemed to precipitate the attacks
  - Seafood Buffet, NASCAR/Football/Hunting (beer)

2015 ACR Gout Classification Criteria
- At least 1 episode of swelling, pain, tenderness in a peripheral joint or bursa—required
- Presence of MSU crystals in symptomatic joint, bursa or tophus—sufficient for diagnosis
- If no joint aspiration/crystals, 8 or more points:
  - Pattern of joint/bursa involvement: ankle/midfoot 1 pt, 1st MTP 2 pts
  - Characteristics of symptoms: erythema, can’t touch, can’t use: 1, 2, or 3 points
  - Time course: ≥2, time to maximal pain <24 hrs, resolution ≤14 days, complete resolution between attacks: 1 pt single episode, 2 pts recurrent episodes
  - Clinical episode of tophus: 4 points
  - Laboratory (not on ULT and > 4 weeks from start of episode):
    - sUA <4 mg/dL: -4 points
    - sUA 4-6 mg/dL: -2 pts
    - sUA 6-8 mg/dL: -1 pt
    - ≥8 mg/dL: 3 pts
    - MSU negative: -2 points
  - Imaging: 4 points if imaging evidence of urate deposit in symptomatic [ever] joint or bursa
  - Imaging: 4 points if evidence of gout-related joint damage

2012 ACR GOUT TREATMENT GUIDELINES

- **Acute Gout Flare Treatment**
  - Treat flares ASAP-nitroglycerine analogy
  - Treat with NSAIDs, steroids or colchicine
- **Gout Flare Prophylaxis** for at least 6 months upon starting urate lowering therapy
- **Chronic Gout Management**
  - Allopurinol or febuxostat 1st line, probenecid 2nd line
  - Pegloticase for tophaceous or treatment resistant
  - Target sUA <6 at minimum, <5 often required
  - sUA monitored every 2-5 weeks during ULT titration
  - sUA every 6 months once target sUA achieved


ACUTE GOUT FLARE TREATMENT

- Colchicine (COLCRYS)
  - 2, 0.6 mg tablets ASAP then 1, 0.6mg tablet 1 hour later; WAIT 12 HOURS then once or twice daily
  - Reduce dose if severe renal or hepatic impairment
  - Reduce or avoid if CYP3A4 or Pgp transport inhibitor
- NSAIDs – Any NSAID will work
- Steroids – Either intra-articular, IM or PO
- IL-1 receptor antagonists - anakinra (Kineret)
- Since all work by different mechanisms, can combine meds for severe flares
  - Pegloticase (Krystexxa) flares very difficult to treat


PROPHYLAXIS

- Colchicine (COLCRYS)-only FDA approved drug
  - 0.6 mg tablet once or twice a day
  - Reduce dose if severe renal or hepatic impairment
- NSAIDs – Any NSAID will work
- Steroids – try to use <5mg per day, up to 10mg
- IL-1 receptor antagonists – anakinra (Kineret)
- Long-acting IL-1 inhibitor - rilonacept (Arcalyst)¹
  - 320mg SQ loading dose followed by 160mg weekly
  - 0.15 flares vs 0.79 flares placebo (p=0.001)
  - 14.6% had flare vs 45.2% placebo (p=0.004)
  - Infection rate lower for rilonacept (24 vs 14%)

CHRONIC GOUT MANAGEMENT

- As long as there are UA crystals there will be inflammation
  - Joint damage can continue between flares
  - Must continue prophylaxis until all crystals gone
- Must keep sUA levels low dissolve all crystals
  - <6mg/dL at a minimum, <5mg/dL for many
  - The lower the sUA the faster crystals will dissolve
  - “Trust but verify” monitor sUA levels to ensure patients are compliant with therapy
  - It takes ~2 years of low sUA to stop flares
  - If tophi present, 2 years after tophi resolve


Why do patients flare when starting ULT?

Serum Proteins normally cover UA crystals and “hide” them from the immune system

- Serum Proteins cover UA crystals
- Resting Innate Immune Cells
- UA Crystals

When UA crystals dissolve they break apart and become exposed to immune system

- Serum Proteins
- Activated Innate Immune Cells
- Inflammatory Cytokines
- UA Crystals

Inflammatory Cytokines
ACR Guidelines for Urate Lowering Therapy (ULT) in Gout

Allopurinol (Zyloprim)

- FDA Approved August 19, 1966
- 100 and 300mg tablets
  - Up to 800mg/day, >300mg bid dosing
- Allopurinol Hypersensitivity syndrome
  - Any rash STOP
- 2012 ACR Guidelines
  - HLA-B*5801 screen Asians
  - Start 50-100mg/day
  - Increase 2-4 wk intervals
  - Monitor LFTs Quarterly

NO AZATHIOPRINE (IMURAN), NO MERCAPTOPURINE

Febuxostat (Uloric)

- FDA Approved February 13, 2009
- 40 and 80mg tablets
- FDA approved 40 or 80mg once daily
  - Recommend take with food (nausea)
  - ACR guidelines - up to 120mg/day
  - Dividing dose bid can improve response
- No adjustment for renal impairment
  - Use caution in patients CrCl<30mL/min
  - Monitor LFTs Quarterly
  - Contraindicated with azathioprine (Imuran) and mercaptopurine (6-MP)

NO AZATHIOPRINE (IMURAN), NO MERCAPTOPURINE

www.ihatemygout.com

NO AZATHIOPRINE (IMURAN), NO MERCAPTOPURINE
Why use Febuxostat instead of Allopurinol?

- Rash, allergy or intolerance to allopurinol
- Persistent flares on allopurinol
- Inability to get sUA to goal on allopurinol

Table 4: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL in Patients with Mild or Moderate Renal Impairment at Final Visit

<table>
<thead>
<tr>
<th></th>
<th>ULORIC 40 mg daily (n=187)</th>
<th>ULORIC 80 mg daily (n=85)</th>
<th>allopurinol* 300 mg daily (n=131)</th>
<th>Difference in Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52%</td>
<td>72%</td>
<td>42%</td>
<td>7%</td>
<td>20% (1%, 14%)</td>
</tr>
</tbody>
</table>

*Allopurinol patients (n=145) with estimated CL_e ≥ 30 mL/min and CL_c ≤ 59 mL/min were washed at 200 mg daily.

Pegloticase (Krystexxa)

- Pegylated uricase enzyme
  - Patients that fail allopurinol and febuxostat
  - Drops sUA to ~0 mg/dL within 24 hrs
- Infused once every 2 weeks
  - Check sUA prior to infusion, don’t infuse if >6 mg/dL
  - Anaphylaxis, CHF exacerbation
  - Pretreat with steroid, tylenol, and antihistamine
- FLARE PROPHYLAXIS essential
- No renal restrictions
- Cost prohibitive
- Test for G6PD prior to dosing-hemolytic anemia

Resolution of Tophi after 12 weeks of pegloticase treatment

Rheumatoid Arthritis: Treatment Options

• NSAIDs/Celecoxib
  - Immediate symptomatic relief, improved function
  - No change in disease progression
  - If patient fails one try others, variable response

• Low-dose prednisone (≤10 mg qam)
  - Used as bridge therapy since works immediately
  - Dose <5mg per day is safe long-term

• Intra-articular steroids
  - Useful for flares, usually given with 50% lidocaine

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Disease Modifying Anti-Rheumatic Drugs (DMARDs)

• Slow joint destruction, don’t stop it
  - Minocycline-100mg bid
  - Hydroxychloroquine (Plaquenil)-200mg bid
  - Sulfasalazine-500mg, up to 2, 3 times per day
  - Methotrexate—both oral and SQ forms
    - Oral 2.5mg tablets up to 8 (20mg) one day of the week
    - SQ 2.5/mL up to 1cc (25mg) one day of the week
  - Leflunomide (Arava) 10 or 20mg daily

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Early Treatment Improves RA Treatment Response

Felson et al., ARTHRITIS & RHEUMATISM
Vol 43, No. 1, January 2000, pp 22-29

Early “window” for treatment, if miss patient less likely to respond
Combination DMARD Therapy

- Methotrexate, hydroxychloroquine, and sulfasalazine
- Superior to any one or two alone for ACR 50% improvement response and maintenance of the response
- Side effects no worse

Monitoring Treatment With DMARDs

- DMARDs require frequent monitoring
- Blood, liver, lung, and kidney are frequent sites of adverse effects
- Interval of laboratory testing varies with the drug
  - 4- to 12-week intervals are commonly needed
- Most patients need to be seen 2 to 6 times a year for physical exam
  - Monitor for lung disease, lymphoma, rash

Biologic Agents for RA Treatment

- Biologics only treatments that STOP damage
- Infliximab (Remicade) 3-10mg/kg IV q4-8 wks
  - FDA approved 8/24/1998
  - Chimeric monoclonal antibody that binds to TNFα, interferes with endogenous TNFα activity
  - Due to murine portion, can cause formation of neutralizing antibodies- given with MTX to prevent
  - Typically used in Medicare patients since infusion covered under part B
  - Largely replaced by SQ biologics
Sub-Q Biologics modulating TNFα

- Etanercept (Enbrel) 25mg biw or 50mg qweek
  - TNFα receptor linked to Fc human IgG1
  - FDA approved for RA 11/1998
- Human monoclonal antibodies vs TNFα
  - Adalimumab (Humira) 40mg once weekly (12/02)
  - Certolizumab pegol (Cimzia) 400mg qmonth (5/09)
  - Golimumab (Simponi) 50mg qmonth (7/13)

Other Biologics with different MOAs

- Abatacept (Orencia) CD80/86 T cell blocker
  - SQ 125mg qweek (12/2005 IV then 7/2011 SQ)
- Rituximab (Rituxan) anti-CD20 Anti-B cell (1/2006)
  - IV Infusion 1000mg x2 then PRN q16-24 weeks
  - Check for Hep B prior to infusion, CBC with diff
- Tocilizumab (Actemra) IL6 receptor antagonist
  - SQ 162mg qweek or qoweek (1/2010 IV then 10/2013 SQ)
  - CBC with diff, LFTs, lipids
- Tofacitinib (Xeljanz) JAK inhibitor (11/2012)
  - Oral 5mg twice daily
  - CBC with diff, lipids

Conclusions

- Inflammatory Arthritis-proximal fingers/toes, monoarticular redness, warmth, swelling
- No Lyme in Tennessee
- RF, ANA, B27 not specific, CCP is for RA
- Treat gout flares ASAP
- Maintain sUA levels at least <6mg/dL
- At least 6 months prophylaxis when starting ULT
- RA - start with NSAIDs/steroids and DMARDs
- Biologics: TNF, IL6, JAK, CD20, CD80/86
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