Rheumatology Round-up

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The American College of Rheumatology’s Top 5 List of Things Physicians and Patients Should Question

- Do not test antinuclear antibody (ANA) subserologies without a positive ANA
- Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings
- Do not perform magnetic resonance imaging (MRI) of the peripheral joints to routinely monitor inflammatory arthritis
- Do not prescribe biologic agents for RA before a trial of methotrexate (or other conventional nonbiologic DMARD)
- Do not routinely repeat dual x-ray absorptiometry (DXA) scans more often than once every 2 years

Overview and Goals

• Gout: Review the recently released American College of Rheumatology guidelines for management with a particular focus on
  • Goal urate level
  • Evidenced based recommendations for treatment
  • Newer insights into the toxicities of xanthine oxidase inhibitors

• Fibromyalgia: Highlight how recent insights into the pathogenesis impact the clinical utilization of the newer diagnostic criteria (previously classification criteria) and EBM treatment recommendations

• RA: Review the current American College of Rheumatology Recommendations for the use of DMARDs and monitoring for toxicity
Question 1

• Fred is a 44 y.o. with a history of recurrent pain and swelling in his first metatarsal phalangeal joints. He presents today with a painful, swollen ankle.
  – History: Episodes have been going on for approximately five years. Drinks beer and loves organ meats, usually indulging to excess with his friend, Dr. Pearson.
  – Exam: Swollen, erythematous ankle; pain with weight-bearing; pain with range of motion. His ankle is aspirated.
Question 1 cont’d

Question: Which of the following is the **LEAST** best answer?

a) Check routine chemistries and uric acid level; treat with NSAIDs if not contra-indicated

b) Obtain a 24 hour quantitative urine uric acid level and start probenecid if not contra-indicated after resolution of current attack

c) Start febuxostat. It is more effective than allopurinol at lowering uric acid levels to a treatment goal of < 6.

d) Give colchicine. 0.6 mg 2 tablets then follow with one tablet one hour later to a max dose of 1.8 mg in the first 12 hr. period

e) Examine patient further for presence of tophi, with a particular focus on his extensor surface and the auricles of his ears.
Question 2

• Fred returns three weeks after being started on allopurinol 300 mg/day, saying “This medication stinks because I’m now having pain and swelling in multiple joints.”
Question 2 cont’d

Which is the next best thing to do?

a) Tell him that he is a Xanthine-Oxidase inhibitor failure and start the work-up to convert him to an infusible pegloticase
b) Educate him on lifestyle modifications and anticipate a 16-20% decrease in serum uric acid level with compliance
c) Change allopurinol to febuxostat, because it is more effective at getting the uric acid level < 6
d) Decrease allopurinol to 100 mg. and add colchicicine 0.6 mg p.o. b.i.d.
e) Referral to rheumatology for evaluation of refractory gout
Gout
A Review of 2012 American College of Rheumatology Guidelines

The Disease of Kings
The King of Diseases
What You Can Do:
Evaluate for Co-Morbidities (evidence grade C)

- Obesity, dietary factors
- Excessive alcohol intake
- Metabolic syndrome, type 2 DM
- Hypertension
- Hyperlipidemia
- Serum urate – elevating medications
- History of urolithiasis
- Chronic kidney disease
- Aquired causes of uric acid over production
- Lead intoxication

## What They Can Do

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ meats</td>
<td>Serving sizes of meat and seafood</td>
<td>Low fat or non-fat dairy products</td>
</tr>
<tr>
<td>High fructose corn syrup-sweetened products</td>
<td>Naturally sweet fruit juices</td>
<td>Vegetables</td>
</tr>
<tr>
<td></td>
<td>Table sugar</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Table salt and salted food</td>
<td></td>
</tr>
<tr>
<td>Alcohol overuse at all times</td>
<td>Alcohol (particularly beer)</td>
<td></td>
</tr>
<tr>
<td>Any alcohol use during periods of frequent attacks or if under poor control</td>
<td></td>
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</table>
Treatment of the Acute Gouty Arthritis

- Patients should be treated
- Patients do better if treated within 24 hours if possible
- Full dose NSAIDs
- Systemic Corticosteroids
- Colchicine
- Supplement topical Ice

Indications for Chronic ULT

- Tophi
- Frequent attacks (> than 2 attacks per year)
- Gout with CKD stage 2-5 or ESRD and persistent hyperuricemia
- Past urolithiasis


Image source: ACR slide deck
TREATMENT

• URATE LOWERING THERAPY

• Allopurinol
  – Starting dose 100mg
    – 50mg in stage 4 CKD
  • Dose titration every 2-5 weeks
  – There is no defined maximum dose other than the FDA max dose of 800mg
    • Dose of 300mg or less daily failed to achieve target in > 50% of subjects

• MONITORING

• Consider checking HLA-B*85801 in selected populations
• Follow up uric acid level 2-5 weeks until goal
  – LFTs for tranaminitis and CBC for eosinophilia
• Uric acid level every 6 months after target level obtained

ALLOPURINOL HYPERSENSITIVITY SYNDROME

• Mortality rates as high as 20-25 % for worse cases
• Frequency estimated as high as 1:1000
  - Spectrum disorder
    - Stevens-Johnson syndrome-TEN -- Eosinophilia
    - Vasculitis -- Fever
  - Over 900 cases described in 320 publications
    - 73% Asian
    - Meta cohort had CKD and HTN as most common chronic conditions
    - No significant association seen between dose >300 and severe cutaneous disease (OR 1.76; CI 0.73-4.22; p=0.23)
    - 90 % of patients developed AHS within the first 60 days
  - Increased risk individuals
    - concurrent use of thiazides and renal impairment
    - HLA-B*5801+ individuals (OR 580; 95%CI 34-9780)
      - Han Chinese, Thai or Korean with stage 3 CKD (allelic frequency up to 8%)

Hung et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. PROC Natl Acad Sci USA. 102(11), Mar 2005
Febuxostat vs Allopurinol

- More likely to reach goal uric acid
- More likely to prevent gout flairs (slight difference)
- Two well documented differences
  - Pathways of excretion
  - Cost difference $154/month vs $17/month

Uricosuric Therapy

- Probenacid is the first line choice
  - will not work in individuals with creatinine clearance less than 50mL/minute

- Losartan and fenofibrate
  - Useful as components of a ULT strategy

- Contraindications
  - History of uric acid stones
  - Elevated uric acid excretion

- Monitoring
  - Urinary uric acid excretion should be measured before initiation of therapy
  - Consider monitoring of urine pH with alkalinization with potassium citrate if there is an ongoing concern for stones

PEGLOTICASE

- Use is recommended in scenarios with severe disease burden and intolerance/refractoriness to appropriately doses ULT
  - 8 mg IV every 2 weeks
    - Goal obtained in 42% of patients
    - Tophi resolution (1 or greater) in 45%
  - Infusion frequency as high as 25%

Indications for Referral

• Refractory signs and or symptoms of gout
• Difficulty reaching target serum urate after and adequate trial of ULT
  – Special considerations for patients with CKD
• Multiple and/or serious adverse events from pharmacologic ULT


Image source: http://blog.mikerendell.com/
Question 3

- Daphne is a 35 y.o. lawyer and mother of two. She presents with insidiously progressive fatigue, arthralgias, myalgias, and transient tingling in her hands and feet.
- ROS: Occasional fleeting chest pain with palpitations, non-restorative sleep, seven pound weight gain, a feeling of full body swelling, occasional light-headedness and vertiginous dizziness, anxiety and occasional feelings of impending doom
- Exam: Completely normal
Question 3 Cont’d

• Which of the following statements best characterizes generally accepted clinical understanding of FMS

a) FMS is a diagnosis of exclusion. A CBC, CPK, TSH, ESR, ANA with full profile, RF, anti-ccp antibodies and lyme titers in endemic areas should be drawn prior to making a diagnosis of FMS.

b) Combination therapy of pregabalin + amitriptyline has been demonstrated in clinical trials to be superior to amitriptyline

c) A diagnosis of FMS requires specialty evaluation and ongoing care.

d) Balneotherapy/heated pool based treatment has shown the strongest treatment effect in multiple meta-analyses.

e) 11/18 tender points are required to make the diagnosis of FMS
Question 4

• Daphne is diagnosed with fibromyalgia syndrome based on the 2010 ACR diagnostic criteria. Interventions:
  
  – amitriptyline at a moderate dose to improve her sleep patterns
  – cognitive behavioral therapy to address work stress management
  – slight decrease in her work hours to just 50 a week to allow for more time for her hobby/passion of throwing glazing traditional Mexican pottery
  – swimming three times per week

• She has a slight improvement in her fatigue, arthralgias, and myalgias, but the tingling in her hands and feet has progressed and is now fixed. Her exam is noted for absence of 10mm fiber sensation feet> hands and diminished light touch discrimination.
Which of the following is your best intervention?

a) Reassure her and add pregabalin
b) Check an A1C, RPR, SPEP and heavy metals
c) Increase amitriptyline q.h.s.
d) Rheumatology referral
e) Order nerve conduction velocities and referral to neurology
FIBROMYALGIA

NEWER INSIGHTS INTO AN OLD SYNDROME
Fibromyalgia

• Healthcare utilization by patients with FMS adds up to $2000 PPPY
  – Diagnosis and management can reduce utilization
• There are ongoing trials suggesting that despite optimal treatment the patients subjective experience of illness does not improve over time
  – 1555 community patients followed by semiannual surveys up to 11 years
    • 25% had at least moderate improvement
    • Global composite for severity worsened over time in 36%
    • Global composite for pain worsened over time in 39%

Barriers to Diagnosis, Treatment and Management

• 46% of PCPs report some uncertainty when diagnosing FMS
  – Heterogeneity in classification criteria
  – Misperception of a rule out diagnosis
  – Large symptom overlap with other syndromes

• The usual number of visits required to confirm the diagnosis of FMS was 4

• The mean number of office visits over a 12 month period was 4 times higher

Newer Insights into Pathogenesis

• Evidence that small-fiber polyneuropathy underlies some fibromyalgia
  – Skin BX in 41% of subjects with evidence of SFPN
    • Decreased intraepidermal unmyelinated nerve fiber density and regenerating intraepidermal nerve fibers
  – Abnormal quantitative sensory testing and pain-evoked potentials
  – Hyperexcitable C nociceptors in fibromyalgia
    • Mechano-sensitive behave normally
    • Silent nociceptors had spontaneous activity but high activity-dependant slowing

• COMPT gene studies
• Dorsal root ganglia sodium channel polymorphisms

Oaklander et al. Pain. 154(2013): 2310-2316
Sera et al. Ann Neurol. 16 (Nov 2013)
Vargas-Alarcon et al. BMC Musculoskeletal Disorders. 13 (2012)
Changes in Diagnosis

• 1990 Classification Criteria
  – Widespread pain above and below the waist affecting both sides of the body
  – 11/18 tender points
    • 88% sensitivity and 81% specificity

• 2010 ACR preliminary diagnostic criteria
  – Three “conditions” for diagnosis should be met
    – Symptom based
      » Widespread pain index (WPI)
      » Symptom severity scale (ss)
        • Fatigue, sleep and cognitive
        • Somatic burden
    – Temporal based
    – Exclusion of other illness
  • 93% sensitivity and 92% specificity


Wolfe et al. The American College of Rheumatology Preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010; 62;600
# EBM Treatment Guidelines

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Improvement in Pain</th>
<th>Improvement in Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heated pool therapy</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Individually tailored exercise program</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Other psychological support</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Tramadol</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pregabalin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pramipexole</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

SF Carville et al. EULAR evidenced-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;67:536-541
Components of Patient Education

• Reassurance that fibromyalgia is a real syndrome
  – Validation of their subjective experience
  – Confirmation of the benign, non-progressive nature
  – Lack of evidence of correlation to other illnesses
• The interplay between stress and mood disorders
• The relationship between sleep disorder and pain
• The need for exercise
## How Effective Are Medications in the Treatment of FMS

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Medication response rate</th>
<th>Placebo response rate</th>
<th>NNT /RR of drop out</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRI</td>
<td>42%</td>
<td>32%</td>
<td>10/1.83</td>
</tr>
<tr>
<td>SSRI</td>
<td>36%</td>
<td>21%</td>
<td>6.3/1.6</td>
</tr>
<tr>
<td>TCA</td>
<td>48%</td>
<td>27%</td>
<td>4.9/0.84</td>
</tr>
</tbody>
</table>

A meta-analysis of the efficacies of antidepressants in FMS
Inclusion was RTC up to 2010

SF Carville et al. EULAR evidenced-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis 2008;67:536-541

Chronic Opioid use is inappropriate in the treatment of FMS because of the interaction of unique pathophysiology and characteristics of the patients and effects associated with chronic opioid use.

What is the Data for Combination Therapy

• For all comers with chronic pain, <30% respond to monotherapy

• Scare evidence in FMS
  – 10 studies of two drug combinations
  – Cochrane Review 2012 identified 21 trial for neuropathic pain

• Copious expert opinion
  – In routine clinical practice patients with FMS receive a mean of 2 to 3 concomitant drugs

Question 5

• Shaggy is a 54 y.o. with 8 weeks of pain and swelling in his MCPs/PIPs, left wrist, and left knee. He has fatigue and a.m. stiffness that goes back near 5-6 months. His exam is noted for swelling and tenderness in multiple small joints, an effusion in his left knee, and a nodule in his left elbow.

• Labs: RF of 320; CCP > 250; ESR = 72.
Question 5, Cont’d

Which of the following is the **LEAST** best treatment approach?

a) Start naproxen 500 mg. b.i.d. and recheck for efficacy in 6 weeks

b) Check radiographs of hands and feet

c) Start prednisone for symptom relief and request a priority consult with the rheumatology

d) Screen for causes of occult liver disease and start methotrexate 10 mg./week

e) Answer d) plus sulfasalazine and hydroxychloroquine
Question 6

- Shaggy’s younger sister, Velma, is 39 and just moved to town. After hearing what a great doctor you are, she decides to come to your practice. She has R.A. and has been treated with methotrexate for 2 years. She feels that she is doing pretty well now that she can walk and play with her dog and 5 kids again.
  - Current morning stiffness 60 minutes
  - Exam: 6 swollen and 3 tender joints
  - Radiology – slight increase in number of erosions in hands and feet
Besides routine monitoring labs for her methotrexate, which should include liver function, serum creatinine, and a CBC, which of the following next steps should be included?

a) Start prednisone, 5 mg/day
b) Check hepatitis B serologies, LTBI screen with intent to start biologics vs. triple therapy or referral for consultation with rheumatology
c) Insure appropriate contraceptive planning, bring vaccines up to date, check lipids, and tobacco screen
d) All of the above
e) B and C only
RHEUMATOID ARTHRITIS

MORE IS MORE
Rheumatoid Arthritis

• It is a ‘good time’ to have RA
  – The treatment options are broad
  – Treatments are well tolerated
  – Newer understandings into treatment combinations are leading to increased likelihood of obtaining a treatment associated remission

• Toxicities associated with therapy require enhanced monitoring and vigilance from Rheumatologists and Primary care providers alike
### Treatment Options

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-metabolite DMARD</td>
<td>Methotrexate</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Leflunamide</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib</td>
<td>$$$$</td>
</tr>
<tr>
<td>&quot;Anti-biotic&quot; DMARD</td>
<td>Sulfasalazine</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td>$</td>
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<tr>
<td>Anti-TNF Biologic</td>
<td>Adalimumumab</td>
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</tr>
<tr>
<td></td>
<td>Certolizumab pegol</td>
<td>$$$$</td>
</tr>
<tr>
<td></td>
<td>Etnercept</td>
<td>$$$$</td>
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<tr>
<td></td>
<td>Golimumab</td>
<td>$$$$</td>
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<tr>
<td></td>
<td>Infliximab</td>
<td>$$$$</td>
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<tr>
<td>Non-TNFi</td>
<td>Abatacepts</td>
<td>$$$$</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>$$$$</td>
</tr>
<tr>
<td></td>
<td>Tocilizumab</td>
<td>$$$$</td>
</tr>
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</table>
DMARDs

• Monotherapy vs. combination therapy in early RA
  – Negative prognostic indicators

• Switching therapy
  – Lack of efficacy, loss of therapy or intolerance
    • 3 months with additive therapy
    • Triple therapy

• Established disease
  – Earlier conversion to combination therapy for patients with poor prognostic factors

Features of Poor Prognosis

• Functional limitations
  – As measured by a validated tool
• Extra articular disease
  – Nodules
  – Vasculitis
  – Eye or lung disease
• High titer RF/CCP
• Presence of boney erosions
• Greater than 10 swollen or tender joints at the time of diagnosis

## Biologic Therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Comorbidity</th>
<th>Agents</th>
<th>Evidence strength</th>
</tr>
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<tbody>
<tr>
<td>AVOID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>All biologic therapy</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>NYHA class III/IV CHF with an EF ≤ 50%</td>
<td>Any Anti-TNF biologic</td>
<td>C</td>
</tr>
<tr>
<td>Accepted therapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treated solid Malignancy &gt; 5 years ago (exception melanoma)</td>
<td>Any biologic</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Treated solid Malignancy &lt; 5 years ago and melanoma</td>
<td>Rituximab</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C</td>
<td>Etanercept</td>
<td>C</td>
</tr>
</tbody>
</table>

Treatment Prescreening and Treatment Monitoring

• Latent TB Infection
  – All patients being considered for therapy of biologic agents
    • TST or interferon-gamma release assays

• Vaccines
  – Pneumococcal, Influenza, Hepatitis B
  – HPV- Recombinant
  – Herpes Zoster

• Medication Specific
  – CBC, sCreat, LFT’s

• Co morbidity based
  – Lipids and cardiovascular maximization
  – Bone and Vit D