What’s New in Medicine

*Rheumatoid Arthritis*

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Disclosure:
Dr. Gardner has no significant financial interest in any of the products or manufacturers mentioned.
Patient Presentation

- **HPI:** A 30 y/o woman comes to clinic complaining of 6 weeks of pain and stiffness in multiple joints including hands, wrists, knees, and feet. She reports 2 hours of AM stiffness and improvement with activity and with ibuprofen 400 mg up to 4 times a day.
- **PMH/SH:** mild scalp psoriasis treated with tar shampoo. Work as elementary school teacher.
- **Exam:** general exam is normal. Has mild fullness and tenderness to MCPs, PIPs, left wrist, both knees and MTPs. CDAI score is 20. Has mild psoriaform lesions on scalp.
Rheumatology Pearl #1
The Three Patterns of Joint Pain

1. Inflammatory
   - AM stiffness > 30 min (often several hrs)
   - Improvement with activity
   - Swelling common
   - Rheumatoid arthritis, polymyalgia rheumatica

2. Mechanical
   - 10-15 minutes of AM stiffness
   - Pain worse with use
   - Osteoarthritis, tendonitis
Three Patterns

3. Fibromyalgia

- AM stiffness significant
- Poor sleep quality
- Afternoon pain and fatigue
- *Exercise intolerance i.e. feeling “wiped out”*
- Other somatic illnesses common i.e. headaches

I use these three patterns in my clinic every day with almost every patient to begin thinking about differential diagnosis
## DDx of Inflammatory Polyarthritis

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parvovirus</strong></td>
<td>Kids-slapped cheeks and fever; adult women- rash and polyarthritis/arthritis lasting a few weeks to years; Dx IgM/IgG antibodies, PCR</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>Rash and polyarthritis/arthritis that may precede the onset of hepatitis</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>Vasculitic rash on legs, polyarthritis/arthritis, <em>rheumatoid factor positive in 50-75%; Dx serology/PCR</em></td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td>Rash and polyarthritis/arthritis; Dx serology</td>
</tr>
<tr>
<td><strong>Chikungunya</strong></td>
<td>Mosquito borne, travelers from endemic area with infected mosquitos now reported in SE US. Fever, polyarthritis/arthritis; rash and myalgia also reported; Dx serology; cases in WA state</td>
</tr>
</tbody>
</table>
## DDx of Inflammatory Polyarthritis

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Inflammatory polyarthritis TBD</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Mono-pauci-polyarthritis, asymmetric, dactylitis, skin involvement, spine involvement; clinical Dx</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Inflammatory polyarthralgias/arthritis, systemic involvement, ANA panel always abnormal</td>
</tr>
</tbody>
</table>
Rheumatoid arthritis demographics

- Autoimmune disease
- Affects 0.5-1% of US population
- 1st degree relative has double the risk
- Women:Men 3:1
- Occurs in two peaks:
  - Women during child bearing years
  - Men and women after age 60
- Genes and environment
  - HLA DR4 plus other genes confer risk
  - Smoking, periodontal disease, etc?
Rheumatoid Arthritis: Pattern of Involvement

Cervical spine
Not T or L spine

Spares DIPs
RA Hands
RA Feet
- Cock up deformities
- Callous formation
- Skin breakdown
Le Moulin de la Galette 1876
Musée d'Orsay
Pierre August Renoir: The arthritis begins
The arthritis progresses
Rheumatoid Factor Pearls

- **Rheumatologic Disease**
  - Rheumatoid arthritis,
  - Sjogren’s syndrome,
  - Mixed connective tissue disease

- **Infectious Disease**
  - Endocarditis,
  - Tuberculosis,
  - Syphilis,
  - Hepatitis B,
  - Hepatitis C

- **Other**
  - Aging,
  - Interstitial lung disease,
  - Liver disease,
  - Sarcoidosis

Points to remember!
- High level; worse prognosis
- Low levels <30 IU rarely meaningful
- 20-30% of RA Pts never develop RF
- Not specific for RA
Anti-CCP: Diagnostic and Prognostic

- Antibodies to Cyclic Citrullinated Peptide (CCP) have a sensitivity of 80% and **specificity of 96%** for RA
- Citrulline is not a normally found amino acid in human tissue but forms from arginine in the presence of inflammation
- 40% of “seronegative RA” are anti-CCP +
- The level of anti-CCP is correlated with joint outcome
- Anti-CCP may be present years (up to 14 years) before the development of arthritis

Van de Stadt. Arthritis Rheum 2011;63::3326
### 2010 ACR/EULAR RA Criteria

**Joint involvement**

<table>
<thead>
<tr>
<th>Score</th>
<th>1 large joint</th>
<th>2-10 large joints</th>
<th>1-3 small joints</th>
<th>4-10 small joints</th>
<th>&gt; 10 small joints</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

**Serology**

<table>
<thead>
<tr>
<th>Score</th>
<th>Negative RF ACPA</th>
<th>Low positive RF ACPA</th>
<th>High level RF ACPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Acute phase reactants**

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal CRP or ESR</th>
<th>Abnormal CRP or ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Duration**

<table>
<thead>
<tr>
<th>Score</th>
<th>&lt; 6 weeks</th>
<th>&gt; 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Small joints:**
- MCPs
- PIPs
- Wrists
- 2-5 MTPs

**High RF/ACPA > 3x ULN**

6/10 points Needed for classification
Radiographs in RA

Joint Erosions in RA: From Bad to Worse
Extra-Articular Manifestations of RA

- Eye disease
  - Dry eye/2° Sjogrens syndrome in 11-13%
  - Scleritis in < 5%
    - Most common cause of scleritis beyond idiopathic
    - 2° to vascular inflammation
    - May lead to blindness and globe rupture
  - Corneal melt
    - Severe corneal ulceration that can lead to blindness
Extra-Articular Manifestation of RA

- **Skin**
  - **Nodules**
    - Seen in up to 30%
    - Indicates worse prognosis
    - Form at pressure points
    - Rheumatoid nodulosis
    - Can also form in the lung

- **Vascular**
  - Small vessel disease
  - RA vasculitis
    - PAN like disease
    - Nerve, GI, skin ulcers, livedo
Rheumatoid Arthritis: Extra-Articular Disease

- Lung
  - Pleuritis
  - Single or multiple nodules
    - Handle as would any lung nodule
  - Rheumatoid lung disease
    - Pulmonary fibrosis
    - UIP > NSIP
    - Smoking increases risk
    - 2nd to heart disease as cause of mortality in RA
Extra-Articular Manifestations of RA

- Three types:
  - C1-C2 subluxation
  - Atlantoaxial impaction
  - Subaxial disease

- Who to worry about?
  - All pt undergoing orthopaedic surgery for RA,
  - > 5 yrs of rheumatoid arthritis
  - Any neurologic abnormality

- What to check?
  - Flexion/extension views of C spine
  - MRI if necessary
Options for the anesthesiologist in a patient with a potentially unstable spine who is felt not to need surgical stabilization prior to surgery include regional anesthesia, intubation with fixed neck positioning, fiberoptic intubation, or laryngeal mask.
Extra-Articular Manifestations of RA

- Felty’s syndrome
  - Leukopenia, splenomegaly, RA
  - Infections, leg ulcers
- Septic arthritis
  - Large joints, systemic symptoms
  - Staph > Strep > gram negatives
  - Morbidity/mortality high
- Tendon ruptures
  - Especially ring/little finger extensor tendons
Stages of Rheumatoid Arthritis

- Antibodies, especially CCP, may be present up to 14 years before acute arthritis.
- Immunology changes with time and becomes more difficult to suppress (Bolero effect!)
- Once bone and cartilage are damaged it never returns to normal.

Rx of RA in the 1970’s-1980’s: Go low go slow

- > 90% of RA patients have erosions after 2 yrs

- 5 - 10% of RA patients become disabled each yr
  Kushner I: J Rheumatol 1989;16:1-4

- Only 18% of RA patients achieve a period of remission during the course of their disease.

- Median life expectancy decreased 4 yrs for men and 10 yrs for women with RA
"What we need in RA is a drug for which one does not need a statistician to see the beneficial effects"
Remodeling the Pyramid—a Concept Whose Time Has Come

“Time and comparative observations will be needed to show the optimum combination of drugs and whether step down bridge concept will achieve the sought for and presently unobtainable goal of early and sustained control of inflammation, improved quality of life and prevention of bone and joint damage.”

J Rheumatol. 1989;16:565-7
Changes in Treatment Approaches to RA

- Very early intervention
- Biologics
- Combination therapy
- Early intervention
- Methotrexate
- Treatment pyramid

Single-drug therapy

Timeline:
- 1910
- 1920
- 1930
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
Treating to target critical in the therapy of RA

- Primary care providers used to thinking about treating to target i.e. HTN, DM, lipids
- Various disease activity indices developed for clinical use to measure disease activity
  - Example CDAI or clinical disease activity index
    - Tender joint count (0-28) (no feet/ankles)
    - Swollen joint count (0-28)
    - Patient’s global assessment of status (0-10)
    - Physicians global assessment of Pt (0-10)
  - 0-3 remission; 4-10 low disease activity; 11-22 moderate disease activity; >22 high disease activity
RA Treat to target 2015 for Primary Care

1. Start medications as soon as possible
   - Early therapy improves outcome!!!
   - Wait times may be too long where you practice to see rheumatology to delay initial therapy

2. Choose medication(s) based on:
   - Level of disease activity
   - Presence or absence of poor prognostic factors

3. Review disease activity on a regular basis; modify Rx to achieve low disease activity or remission quickly
   - Be familiar with methotrexate and hydroxychloroquine
   - Ok to use LD prednisone in addition to Mtx

Mean DAS Scores Over Time

<table>
<thead>
<tr>
<th>Months</th>
<th>Routine Rx</th>
<th>Intensive Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Total Sharp Score Progression</td>
<td>Routine Rx 8.5</td>
</tr>
</tbody>
</table>

$P < 0.0001$, intensive vs routine after month 3.
TREAT TO TARGET

Remission or low disease activity is the bull’s-eye.
Poor Prognostic Features in RA

- Significant functional limitation
- Extra-articular disease
  - Nodules
  - Eye disease
  - Etc
- High level rheumatoid factor (RF) or cyclic citrullinated peptide (CCP)
- Presence of boney erosions when you first see them
2012 ACR Paradigm for Treating RA of Less Than 6 Months Duration  

Singh et al Arthritis Rheum 2012

Figure 1. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA),
Therapies For RA 2015

- Conventional DMARDs
  - Methotrexate
  - Hydroxychloroquine
  - Leflunomide
  - Sulfasalazine
- Anti-TNF agents
  - Etanercept
  - Adalimumab
  - Infliximab
  - Certolizumab
  - Golimumab
- Anti-B cell agent
  - Rituximab
- Anti-T cell agent
  - Abatacept
- Anti-IL-6 receptor antagonist
  - Tocilizumab
- JAK inhibitor
  - Tofacitinib
- IL-1 receptor antagonist
  - Anakinra
- New agents are on their way!
Methotrexate: The Anchor Drug

- **History:**
  - Developed in 1940’s to treat childhood forms of leukemia
  - First used in 1972 for RA and studied in late 70’s and early 80’s; found to slow the progression of RA

- **Mechanism of action**
  - DHFR inhibitor but anti-inflammatory action is thought to be mediated by methotrexate mediated increases in adenosine

- **Dosage**
  - 7.5 mg to 25 mg SC or PO once weekly
  - Initial dose 7.5-10 mg/wk; increase progressively after 1st mo
  - SC found to be more effective than PO with similar tolerability
  - Onset of activity 3-8 weeks

Methotrexate

- **Toxicity**
  - Liver – minimize ETOH use (1-2 drinks per week?) use folic acid supplementation (1 mg per day)
  - Bone marrow - folic acid use may reduce toxicity
  - GI symptoms – anorexia, nausea especially day after use
  - Teratogen/abortifacient - 3 mo off drug before conception attempted

Methotrexate Monitoring and Immunization

- Initial evaluation and monitoring
  - Baseline CBC, creatinine (decrease in GFR increases Mtx toxicity), chemistry panel, Hepatitis B&C
  - CBC, LFTs monthly for 6 mo then every 1-3 mo; consider intermittent check of albumin and creatinine

- Immunizations
  - UTD influenza & pneumococcal vaccines; can receive zoster if appropriate if methotrexate dose equal or less than 0.4 mg/kg/week
Hydroxychloroquine

- **History**
  - Derivative of quinine which originally came from bark of the cinchona tree is South America
  - Quinine used to treat lupus as early as 1894
  - Hydroxychloroquine developed during WWII and first used to treat RA in 1951

- **Mechanism of action**
  - Raises the pH inside lysosomes of APC and modifies how antigens are presented to T cells
  - Interferes with activation of Toll-like receptors on inflammatory cells

- **Dosage**
  - 200 - 400 mg/day; no more than 6.5 mg/kg/day
Hydroxychloroquine

- Clinical effects (wonder drug in RA & SLE!)
  - Modifies disease course in RA
  - Reduces risk of diabetes in Pts with RA
  - Reduces LDL, VLDL, TG, raises HDL (dec MI risk)

- Potential side effects
  - Ocular: corneal deposits; retinopathy
  - Skin: drug rash, gray skin pigmentation
  - Rare bone marrow toxicity
  - Neuromyopathy/cardio-myopathy (unexplained CHF in older Pt on HCQ?); loss of reflexes

- Monitoring:
  - Baseline eye exam then begin yearly exams in 5 yrs

Kalia & Dutz Dermatologic Therapy 2007
Patient Presentations

- History: 44 y/o woman with 3 months of joint pain in hands and feet. Has 1 hour of AM stiffness and is better with ibuprofen.

- Examination: Minimal swelling of bilateral 2-3 MCPs, and both 5th MTPs. Rest of the examination is normal including absence of nodules; CDAI score is 10.

- Laboratory examination: CBC normal, ESR and CRP normal, RF is 92, CCP is 86. Xrays of hands and feet without erosions

- Rx?
Figure 1. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA),
Patient Presentations

- History: 52 year old male with 5 month of joint pain comes for evaluation. He has pain, stiffness and swelling in the hands, wrists, elbows, knees, ankles, and feet for 3 hours in the AM. Noted small bump on his left elbow.

- Examination: swelling of MCPs, PIPs, wrists, contractures at both elbows, both knees with moderate effusions, swelling at ankles, and MTPs. Nodule at left elbow; CDAI > 22

- Laboratory examination: CBC shows HCT of 33%, ESR of 55 mm/hr, CRP 32 (nl to 10) ; RF of 800 and CCP >300; several small erosions at MCPs and MTPs
2012 ACR Paradigm for Treating RA of Less Than 6 Months Duration  

Singh et al Arthritis Rheum 2012

Figure 1. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA),
Still Life, Raoul Dufy, 1928
“La Cortisone”

Painted in 1951
Given to Roussel
By Dufy
in gratitude for
making cortisone
available for
his treatment
CAMERA II: MTX +/- 10 mg of prednisone over 2 years in rheumatoid arthritis Bakker et al. Ann Intern Med 2012

- 236 patient with RA of < 1 year duration and methotrexate naïve randomized to:
  - Methotrexate plus 10 mg of prednisone
  - Methotrexate plus placebo
  - All patients given folic acid and bisphosphonate

- Followed 2 years with primary endpoint radiographic outcome

- Methotrexate started at 10 mg/wk and increased monthly based on a computer assisted parameters of improvement to maximum dose of 30 mg/wk. Next step was injectable methotrexate and next step was addition of cyclosporine and later in the trial, adalimumab
Outcomes in CAMERA II

<table>
<thead>
<tr>
<th>Variable</th>
<th>MTX/Prednisone</th>
<th>MTX/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiographic progression at 2 yrs</td>
<td>78%</td>
<td>67% (p = .022)</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ACR 70 response</td>
<td>38%</td>
<td>19% (p=.002)</td>
</tr>
<tr>
<td>Time to remission</td>
<td>6 mo</td>
<td>11 mo</td>
</tr>
<tr>
<td>% Needing more than methotrexate</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>Withdrawal due to SE and overall SE</td>
<td>No reported difference in withdrawal or SE including hyperglycemia, infections; trend to fewer LFT elevations in prednisone group</td>
<td></td>
</tr>
</tbody>
</table>


Conclusions

- Combination of methotrexate and low dose prednisone in RA results in:
  - Better control of inflammation
  - Fewer erosions (MTX alone not too shabby!)
  - No excess toxicity at 2 yrs over placebo
- Do we leave RA patients on 10 mg a day for > 2 years?
- What role did the bisphosphonate play?
  - Trial of methotrexate plus zolendronic acid IV vs methotrexate alone resulted in improved radiographic and MRI joint outcomes at 6 months. Jarrett et al. Arthritis Rheum. 2006 May;54(5):1410-4
**Power of Combination Therapy with TNF agents in RA:**
PREMIER Study: Change in Sharp Score at 2 years

![Graph showing comparison between Adalimumab + MTX and MTX alone in RA pts with < 3 yrs of disease and MTX naïve.](image)

- **ACR < 20**
- **ACR 20-50**
- **ACR 50-70**
- **ACR 70-100**
- **ACR 100**

**RA pts with < 3 yrs of disease and MTX naïve**

<table>
<thead>
<tr>
<th>ACR Category</th>
<th>Adalimumab + MTX</th>
<th>MTX alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR &lt; 20</td>
<td>2.1</td>
<td>0.6</td>
</tr>
<tr>
<td>ACR 20-50</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>ACR 50-70</td>
<td>2.0</td>
<td>11.5</td>
</tr>
<tr>
<td>ACR 70-100</td>
<td>0.6</td>
<td>8.1</td>
</tr>
<tr>
<td>ACR 100</td>
<td>0.5</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Summary

- Exciting changes in the treatment of RA over the last 20 years; most patients will never know how sick they could be!

- Remember themes
  - Early recognition, early therapy
  - Treat to target – low disease activity/remission
  - Early institution of biologics/combination therapy

1980s 2014