Update in Rheumatology
Selected Topics 2017:

Rheumatoid Arthritis
Polymyalgia Rheumatica/Giant Cell Arteritis

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Rheumatoid Arthritis
- Systemic disease whose predominant manifestation involves a chronic, inflammatory, small joint arthritis
- Affects up to 1% of the US population
- Female:Male predominance of 3:1
- Peak incidence: patients in their 30’s-40’s but can occur at any stage of life

Clinical features of RA
- Most often insidious subacute onset
- Small joint, symmetric inflammatory polyarthritis of diarthrodial joints
  - Morning stiffness (hours) prevalent
  - Improves with activity, worse with inactivity (gelling phenomenon)
  - Joint swelling, joint pain are common

RA: Clinical features
- RA is a chronic and progressive disease
- Chronic disease progression leads to permanent joint deformity, destruction, and disability
Rheumatoid arthritis: irreversible damage can occur early in disease course

Radiographic changes in the same joint over time

1 year prior to onset of RA
6 months after onset of symptoms
3 years after onset of symptoms

Early RA: The Window of Opportunity to Intervene

- Chronic disease progression leads to permanent joint deformity, destruction, and disability
- Empirically, RA is a different disease the longer disease activity progresses without effective control
  - More difficult to suppress activity and treat
  - More extra-articular disease?

RA: Chronic Joint Destruction and Disability – What We Try to Prevent

Improving Outcomes in RA

- Improvement in timely and accurate diagnosis and prognosis
- Treating to defined disease activity targets
- Improvements in therapy
ACR Criteria for the Classification of Rheumatoid Arthritis 1987

(≥4 criteria required; 1-4 must be present > 6 wks)
• Morning stiffness > 1 hr
• Arthritis of 3 or more joint areas
• Arthritis of wrists, MCPs, and/or PIPs
• Symmetric arthritis
• Rheumatoid nodules
• Serum rheumatoid factor
• Radiographic changes

Limitations of 1987 ACR Classification Criteria for the diagnosis of early RA

• Developed for the classification of patients with longstanding disease (for clinical studies, not diagnosis)
  – Many of these features (rheumatoid nodules, for ex) are seen with declining frequency

• For early RA, 1987 classification criteria:
  – Specificity: 90%
  – Limited sensitivity: 40-65%

• Relying on criteria to make a diagnosis of RA can lead to delayed or inappropriate diagnosis

• Criteria revised in 2010 to accommodate patients with earlier disease – but not practical to use

Diagnosis of early RA by 1987 ACR criteria

van Gaalen et al. Arth Rheum 50: 709, 2004

936 patients with early inflammatory arthritis

At initial evaluation After 3 years

205 RA by ACR criteria

936

318 “undifferentiated arthritis” ➔ 127 RA

413 other diagnoses

Factors predictive of progression from undifferentiated arthritis to RA

van Gaalen et al. Arth Rheum 50: 709, 2004

At initial evaluation OR (95% CI)

Positive rheumatoid factor 1.7 (0.5-5.6)

Positive anti-CCP antibody 38.6 (9.9-151.0)
Posttranslational modification of proteins: PADI converts arginine to citrulline

RA-associated autoantibodies that recognize peptides containing citrulline

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<thead>
<tr>
<th>Peptide sequence</th>
<th>Antibody recognition</th>
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<tbody>
<tr>
<td>ESSRDGSRHPHSHHD</td>
<td>No</td>
</tr>
<tr>
<td>PADI</td>
<td>Yes</td>
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<tr>
<td>ESSRDGScitPHSHHD</td>
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Actual citrullinated antigen targeted in RA is not known

Antibodies to citrullinated peptides in RA
- Detected by ELISAs using synthetic cyclic citrullinated peptides (CCP)
- Sensitivity for very early RA: 50%
- Sensitivity for early-later RA: 70-80%
- Specificity for RA: 95-98%

Preclinical autoimmunity in RA: appearance of anti-CCP abs and RF prior to onset of arthritis

Nielen et al Arth Rheum 50: 380, 2004
Gene-environment interaction in RA: Is smoking an environmental trigger?

Evidence for an interaction between smoking and the shared epitope in risk for anti-CCP-positive RA in a European cohort

Periodontitis and the link to RA

Possible culprits

P. Gingivalis can citrullinate proteins directly

Development of better tools to predict disease severity

Is it possible to predict which patients require more aggressive therapy up front?

Aggregatibacter actinomycetemcomitans Exo-toxin causes host neutrophils to auto-citrullinate their proteins
Classic (ABIM!) Predictors of Disease Severity

- More difficult to treat, destructive, extra-articular disease:
  - Rheumatoid factor positive
  - Erosive disease
  - Genetic factors
    - HLA class II DR4 and other molecules that contain "shared epitope"
    - Correlates with number of alleles (homozygous>heterozygous)
    - Not practical to genotype all patients

Progression of joint damage in subgroups of early RA
Huizinga et al Arthritis Research & Therapy 7: 949, 2005

Anti-CCP status

- Anti-CCP positive RA patients are unique compared to anti-CCP negative patients
  - Genetic risk: carry shared epitope
  - More erosive disease
  - More progressive course of disease (radiographically)

Is rheumatoid arthritis a single disease?

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<th>RA #1</th>
<th>RA #2</th>
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<tr>
<td>SE</td>
<td>+</td>
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<tr>
<td>CCP</td>
<td>+</td>
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<tr>
<td>Erosive dz</td>
<td>+</td>
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Improving Outcomes in RA

• Improvement in timely and accurate diagnosis and prognosis

• **Treating to defined disease activity targets**

• Improvements in therapy

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**RA: Chronic Joint Destruction and Disability – What We Try to Prevent**

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**Treatment of early RA**

• **Effective treatment** should be started when the diagnosis is made
  – “Effective treatment” = therapies shown to slow joint destruction

• Goal is to induce and then maintain remission
  – Combination of drugs more effective than monotherapy

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**RA: Traditional Treatment Paradigm**

• Pyramid of therapy
  – Start conservatively
  – Gradually ascend the pyramid in order of potency and toxicity of therapy
  – Only the most severely affected patients receive immunosuppressive, DMARDs
  – DMARD therapy begun only after period of significant delay
Re-Thinking the RA Treatment Pyramid

- Emphasizes earlier diagnosis and initiation of therapy with disease modifying anti-rheumatic drugs

ACR RA Practice Guidelines 2002

- Most patients with Rheumatoid Arthritis should be evaluated expeditiously
- Treatment with DMARD instituted within 3 months of diagnosis
- Goals are to prevent or control joint damage, prevent loss of function, and decrease pain

Tight Control for Rheumatoid Arthritis

- Pre-biologic era study
- Randomly assigned 110 patients to “intensive” vs. usual management
- Every three months, independent blinded metrologist assessed disease activity

TICORA Patients

- Early disease (<2 years)
- Active disease
  - Mean SJC 11-12
  - Mean CRP 38-44 mg/L
What does “Intensive Therapy” Look Like?

**Standard Therapy**
- Follow up visits q 3 mo
- DMARD monotherapy used for active disease
- Intra-articular injections of TAC allowed
- Changes or additions to therapy were made based upon gestalt

**Intensive therapy**
- Follow up visits q 1 mo
- DMARD monotherapy used for active disease
- Intra-articular injections of TAC allowed
- Changes or additions to therapy were based on formal disease activity (score) > moderate

**ACR Treatment Guidelines 2008**
- Building evidence from trials like TICORA suggests better long term outcomes when treating to a defined target early in disease
- ACR guidelines encourages regular, formal assessments of disease activity
  - Similar to hemoglobin A1C for diabetes
  - Several formal disease scores available:
    - DAS28
    - CDAI, SDAI, etc…
    - Vectra-DA biomarker assay
- ACR: Treat to target of mild disease activity or better

**Mean Disease Activity**

**Disease Activity Score 28 Joints**
1. Tender Joint count
2. Swollen Joint Count
3. Patient global disease assessment (visual analog scale from 0-100mm)
4. Serum measure of inflammation (ESR/CRP)
**DAS: Treating to target**

- **DAS28 disease activity cutoffs:**
  - DAS28 < 2.6: Remission
  - DAS28 2.6-3.2: Mild Activity
  - DAS28 3.21-5.1: Moderate Activity
  - DAS28 > 5.1: High Disease Activity

**Improving Outcomes in RA**

- Improvement in timely and accurate diagnosis and prognosis
- Treating to defined disease activity targets
- **Improvements in therapy**

**DMARD Therapies**

- Methotrexate
- Leflunomide (Arava)
- Sulfasalazine
- Azathioprine
- Mycophenolate Mofetil
- “Corticosteroids”
- “Hydroxychloroquine”
- “Minocycline”

**Families of Biologic Therapies**

- Anti-TNF medications (5 total)
  - Etanercept (TNF decoy receptor fusion protein)
  - Infliximab, Adalimumab, certolizumab, golimumab (variations of anti-TNF antibodies or Fab’)
- B-cell depleting agents
  - Rituximab
- T-cell costimulation inhibitors (receptor-ligand)
  - Abatacept
- Inhibitors of Il-6 signaling
  - Tocilizumab (anti Il-6 receptor antibody)
- Il-1 Inhibitors (Il-1 cytokine receptor decoy)
  - Anakinra
RA: Targeted Therapy Approach

- Start with traditional DMARD (usually methotrexate)
- Check to see if low disease activity or better has been attained
- Advance therapy (dose), switch from oral to SQ MTX, or add combination
- Good data that combination DMARDs or combination DMARD + biologic both effective (TEAR & CSP 551 RACAT)

Why Move Towards Combination Regimens with Biologics?? Klareskog L. et al. TEMPO Lancet 2004

The Current Pyramid Paradigm

- Early initiation and titration of DMARD
- If incomplete response to DMARD alone, after reasonable titration, addition of combination therapy recommended

Black Hole

- Rare
- Poorly understood mystery of universe
- Gravity prevents light from escaping
- If suspected - refer to astrophysicist

Vasculitis

- Rare
- Poorly understood mysteries of medicine
- Complexity prevents knowledge from escaping
- Suspected cases referred to rheumatologists
How common is vasculitis??

Giant Cell Arteritis

- Annual incidence approx 18/100,000 (Minn) 22/100,000 (UK) in individuals > 50 years of age
- Higher incidence in northern latitudes
- Prevalence of GCA 200/100,000 in individuals > 50 years of age (0.2%)  
- Females > Males 3.7:1
- Age > 50 years but incidence increases with age (mean approx 75 years)

Clinical Manifestations

Demographics

Same as PMR (May be part of spectrum of same disease)

40-50% develop PMR (may precede, follow, or occur concomitantly)

70% female

Rare before age 50.

Increases in prevalence with each decade with peak 70-80
Giant Cell Arteritis
Clinical Manifestations

- Headache (70-80% at one time or another)
  - Commonly dull, aching, often over the temporal area but can be anywhere
  - Scalp tenderness may be present

- Visual Changes
  - Present in up to a third of patients
  - Blurred vision, diplopia, amaurosis fugax often presage blindness
  - Monocular blindness can be abrupt without warning
  - Can be permanent

- Jaw Claudication
  - Most specific symptom for GCA
  - Classic presentation is discomfort over masseter muscles with protracted chewing
  - This is not pain at temporal mandibular joint

- Constitutional signs are common in this SYSTEMIC disease (lots of pro-inflammatory cytokines)
  - Weight loss, Malaise
  - Low grade fever in up to half of patients
  - Cause of FUO in elderly
  - Signature IL-6 driven disease (high CRPs)

Retinal Ischemia

Blood supply to the optic nerve
Giant Cell Arteritis

**Work-up**

- Establish pre-test probability of GCA using demographics, history, physical exam

- **Laboratory Evaluation**
  - ESR
    - >90% patients have an ESR >50; frequently >100
    - C-reactive protein may be more sensitive and be elevated in patients with normal ESR
  - CBC
    - Normocytic anemia, thrombocytosis

**Giant Cell Arteritis: Diagnosis**

**Temporal artery biopsy**

- If elect to pursue biopsy, initiate prednisone 1 mg/kg/day
- Request 3-5 CM segment of artery.
- Unilateral biopsy is >90% sensitive
- 2 weeks of empiric prednisone does not significantly affect the sensitivity.

**Diagnosing GCA**

- Currently – much rests on empiricism
  - Practice is to place patients with suspected GCA based upon history/physical exam on high dose prednisone and arrange for a biopsy
  - Cutoff can be as low as 10% pre-test clinical suspicion to trigger above algorithm given potential morbidity of disease
  - Biopsy is invasive and difficult to diagnose
    - Often segmental (skip lesions can be missed)
    - Negative biopsy raises problems about continuing long term morbidity therapy

**GCA Diagnosis: Ultrasound**

- In the right hands, classic ultrasound findings of GCA include a periluminal “halo sign” of hypoechoic edema in the vessel wall
- Also can see stenoses and occlusion
- Operator dependent and not reliably reproduced
**GCA: Large Vessel Involvement**

- Large vessel involvement is more common than once thought
- 25% of patients have large vessel arteritis (often can be symptomatic)
- When great vessel dz is suspected, MRI/MRA or CTA are reliable diagnostic tools for visualizing intramural edema (inflammation), thickening, stenoses, aneurisms
- FDG-PET/CT might be more sensitive: can detect inflammation in vessel wall in over 50% of GCA pts.
- Use of FDG-PET/CT to quantify inflammation in GCA is not standardized and can be nonspecific (atherosclerosis also can look “inflammatory”)


**GCA: Treatment**

- Treat with large, long-term corticosteroids (1 mg/kg) and with expectation of long-term therapy (and morbidity)
- No proven steroid-sparing regimen, but baby ASA usually given as adjuvant therapy to reduce thrombotic complications
- Majority of patients will experience a durable remission but a substantial minority (40%) will relapse
- Relapse can be usually treated with increases of 10-20% prednisone dosage and are rarely associated with ischemic complications
- Persistent elevations in inflammatory markers (ESR/CRP) and more rapid tapers of corticosteroids associated with higher risk of relapse

**GCA: Future Therapies**

- Long term corticosteroid exposure associated with significant morbidity
- Search for steroid-sparing agents generally underwhelming
  - Methotrexate
  - Azathioprine
  - Infliximab and other anti-TNF therapies
Tocilizumab (Actemra)

- Antibody to the IL-6 receptor complex
- By inhibiting IL-6 signaling, markedly reduces acute phase inflammatory response
- Inflammation in GCA is thought of as a prototypically IL-6 driven disease

Tocilizumab for induction and maintenance of remission GCA

- Randomised, double-blind, placebo-controlled trial
- Tocilizumab (2:1) or placebo
- 13 IV infusions were given q 4 wks
- Prednisilone taper to 0 mg according to a standard schedule,
- Primary outcome: Wk 12 proportion of patients complete remission of at a prednisolone dose of 0-1 mg/kg/day

Villiger et al. Lancet May 2016

Tocilizumab for GCA

Villiger et al. Lancet 7-13 May 2016, Pages 1921–1927

Relapse-free survival through to week 52

Time to taper down pred to 0 mg/day