Topics in Rheumatology - 2013

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Topics for this Talk

- What's new in RA
- New medication for SLE
- New medication for gout
- Adult-onset Still's Disease: diagnosis and therapy

What's new in RA?

- New criteria
- New lab test
  - Anti-CCP
- New risk factor
- New Therapies
- New Treatment Paradigm

Rheumatoid Arthritis

- Most common systemic autoimmune disease
  - Prevalence 1% overall
- Incidence increases throughout life
  - Does not peak in 30-50 range
- Affects women>men 3:1 until menopause, then equal incidence
- It is NOT a benign disease – you die with RA and from RA
- Therapy must be started early, early diagnosis key

What's new in RA?

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- New lab test
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Old "New" RA Criteria

American Rheumatism Association revised criteria for rheumatoid arthritis classification

Criterion	Description
Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.
Arthritis of 3 or more joint areas	At least 3 joint areas (out of 14 possible areas; right or left PIP, MCP, wrist, elbow, knee, ankle, MTP joints) simultaneously have had soft- tissue swelling or fluid (not bony overgrowth alone) as observed by a physician.
Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs, without absolute symmetry is acceptable).
Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician.
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.
Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand or wrist radiographs, which must include erosions or unequivocal bony decalcification localised in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify).

Note: For classification purposes, a patient has RA if at least four of these criteria are satisfied (the first four must have been present for at least six weeks).

Really New Classification of RA:

For patients who have at least 1 joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease

Add score of categories A–D; ≥6/10 classifies patient as having definite RA

A. Joint involvement:

1 large joint	0
2–10 large joints	1
1–3 small joints (with or w/o involvement of large joints)	2
4–10 small joints (with or w/o involvement of large joints)	**3**
>10 joints (at least 1 small joint)	**5**

B. Serology (at least 1 test result is needed for classification)

Negative RF *and* negative ACPA0	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* **high-positive ACPA**	**3**

Really New Classification of RA (2):

For patients who have at least 1 joint with definite clinical synovitis (swelling) with the synovitis not better explained by another disease

Add score of categories A–D; ≥6/10 classifies patient as having definite RA

C. Acute-phase reactants (at least 1 test result needed for classification)

Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1

D. Duration of symptoms

<6 weeks	0
≥6 weeks	1

What's different?

- Old criteria that no longer count toward diagnosis
  - Morning stiffness
  - Symmetry
  - Nodules
  - Radiographic changes
- What's been added?
  - Acute phase reactants
  - Serology
    - Anti-CCP
    - Higher titer of either RF or anti-CCP more significant

Why did they do that?

- Criteria that were removed are seen in late RA
- Criteria that were added can be seen at onset or before onset of clinical disease and/or predict severity of outcome
- Morning stiffness does not discriminate among different inflammatory conditions like RA, SLE, etc.
- The goal of the criteria revision was to identify
  - RA that was likely to persist and
  - have a poor clinical outcome

Why do we want to identify this particular group?

- Early treatment
- Clinical trials

- We sacrifice specificity for sensitivity
- We will probably treat some people who don't need it in exchange for treating many who would not get therapy until damage was done.

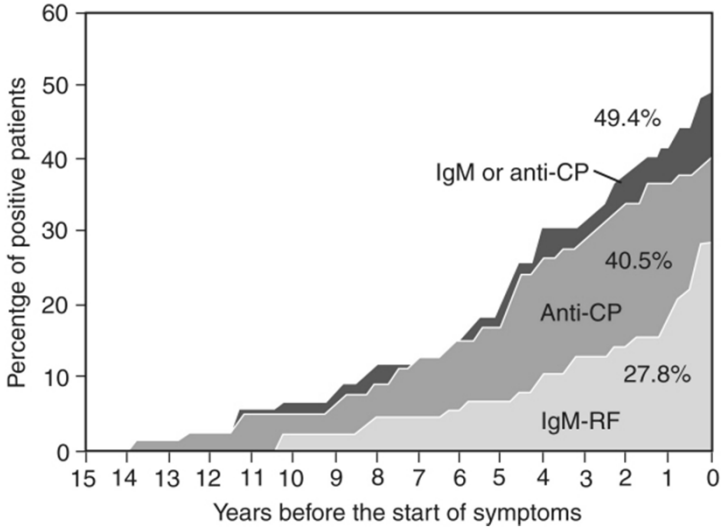
What's new in RA?

- New approach to diagnosis, new criteria
- **New lab test**
  - **Anti-CCP**
- New risk factors
- New Therapies
- New treatment Paradigm

Anti-CCP auto-antibodies in RA

- Several autoantibodies found in RA are directed at sites specific to certain proteins.
- These are called antibodies to citrullinated peptides (ACPAs) or anti-CCP in the clinical setting.
- They are present in 50-70% of RA patients, seen in only 2% of the population and generally uncommon in other autoimmune diseases.
- Smoking, gingival bacterium Porphyromonas gingivalis can induce citrullination of proteins
- This may be the mechanism to explain the epidemiology of smoking as a risk factor

Time course of appearance of rheumatoid factors and anti-CCP antibodies in RA patients

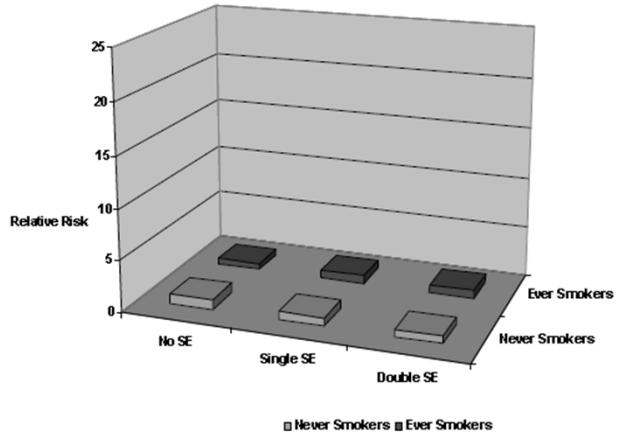


(From Nielen MM, van Schaardenburg D, Reesink HW, et al: Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors. Arthritis Rheum 50:38, 2004.)

What's new in RA?

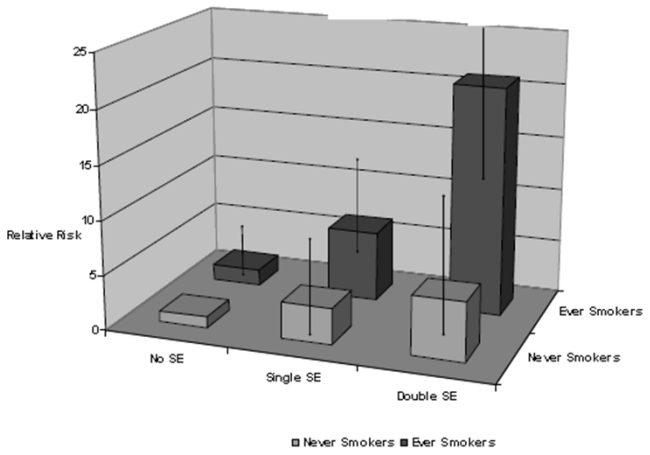
- New criteria
- New lab test
  - Anti-CCP
- **New risk factor**
  - **Smoking**
- New Therapies
- New Treatment Paradigm

No risk from either smoking or HLA-DRB1 SE for ACPA (anti-CCP) negative RA



Klareskog et al, Arthritis Rheum 2006;54:38-46

Interaction between smoking and HLA-DRB1 SE in ACPA (anti-CCP) positive RA



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What's new in RA?

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- New risk factors
- New Therapies
- New Treatment Paradigm
  - Treat to remission/using DAS scores

New Medications in RA

- Abatacept is now available in sc form as well as monthly IV infusion
- Tofacitinib (Xeljanz) approved Nov 2012
  - Blocks Janus kinase, aka Jak-1 inhibitor
  - First of class, oral small-molecule, taken bid
  - Compared to adalimumab (700+ pts) w similar outcomes, to placebo added to non-biologic
  - Inc LDL, LFTs seen, AE profile, role in RA still unknown
- Not so new: Tocilizumab approved Jan 2010
  - IL-6 inhibition
  - IV, drops CRP, AE profile and use not clear

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Treat to remission

- The DAS (Disease Activity Score) is the most accepted measure of RA clinical activity
- Evidence strongly suggests that early, aggressive intervention prevents later damage and disability
- Increasingly, clinical trials are being designed to "Treat to Remission"

Bottom Line:

- Rheumatoid arthritis is not a single disease
  - New criteria focus on early, treatable disease
- Therapies are directed to increasingly specific targets
- Environmental modification of disease risks (ie smoking) are now evidence-based and very important.
- Early therapy and treatment to clinical remission are becoming the standard of care.

Topics for this Talk

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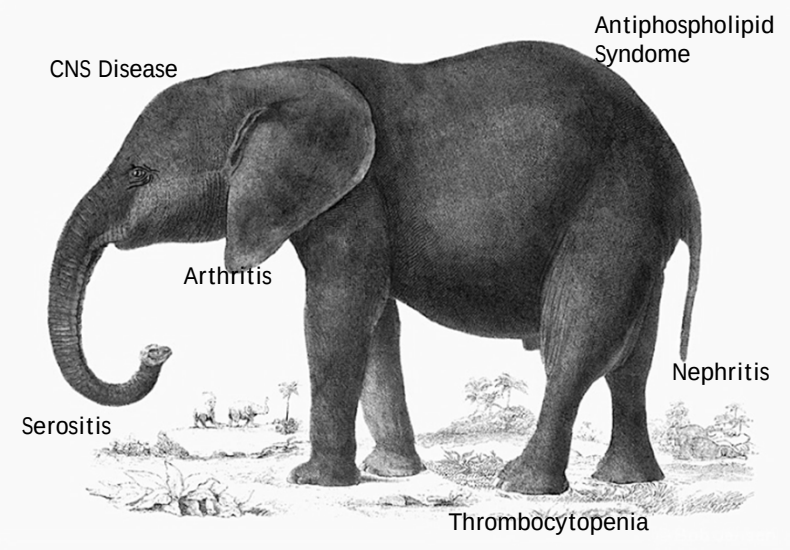
- New medication for SLE
- New medication for gout
- Adult-onset Still's Disease: diagnosis and therapy

The Blind Men and the SLE Elephant



Systemic Lupus Erythematosus: a disease of young women of color

Demographics

- 40-150 cases/100,000
  - Compare to RA ~1% prevalence
  - Incidence has tripled in the last 40 years, perhaps due to detection of mild cases
  - Urban >> rural risk
- African American > Hispanic, Asian > Caucasian
  - SLE appears to be rare in Africans in Africa
- 90% of patients are female
  - Will this continue to be true?
- Mean age of patients at onset is 33 yrs
  - 65% onset between 16 and 55

SLE in 2013

- Changing management of renal disease
  - Mycophenolate for sure
- Other agents for SLE?
  - Abatacept?
- Changing management of Raynaud's
  - Sildenafil
- Increasing attention to surveillance of infection, immunization, ASCVD. Next - unusual cancers?
- No news
  - Neuropsychiatric SLE
  - Pregnancy
  - Antiphospholipid syndrome

New Medication Approved in Systemic Lupus: Belimumab

- Fully human monoclonal antibody
- Blocks B-lymphocyte stimulator (aka Blys)
  - Discovered by searching gene databases, a true "designer drug"
- Given as a monthly IV infusion
- Can be given with MTX, azathioprine
- Not to be used with other biologics

Belimumab (Benlysta)

- Approved in March 2011
- First new SLE drug in 50 years
- For mild SLE, not nephritis or CNS disease
- Unclear if effective in African-Americans because numbers were too small
- Clinically, seems useful esp for cytopenias

Borrego Springs, CA

Gout

- Biggest (bad) news is the high cost of colchicine
  - Was an orphan drug, FDA approved sole rights if a company would do a double-blind RCT
  - Price went from 10 cents to $5 per pill
  - Exclusivity for acute gout for 3 years, should end in 2013.

Gout – Pegloticase Therapy

- Pegylated recombinant form of urate-oxidase enzyme, also know as uricase, which converts uric acid to an inactive, water-soluble form (allantoin)
  - Reserved for refractory gout which needs rapid remediation such as tophus breakdown, renal disease, uncontrollable flares
  - Hypersensitivity reactions a concern, must premedicate.
  - 8 mg IV q 2 wks
  - Does not need adjustment for renal function
  - Recommend rheum consult before using

Heading for the finish

Adult-onset Still's Disease (AOSD)

- There are several categories of immune/autoimmune febrile illnesses. This is one of the more common
- Adults with joint pains and recurrent fever who do not meet criteria for RA, do not have infections
- Uncommon but not rare
- "Salmon-colored" rash seen on trunk and extremities in classic cases
- Ferritin: Characteristic lab test is very high ferritin, often > 3,000

Yamaguchi Criteria for AOSD

4 major Yamaguchi criteria:

- Fever of at least 39ºC (102.2ºF) lasting at least one week
- Arthralgias or arthritis lasting two weeks or longer
- A nonpruritic macular or maculopapular skin rash that is salmon-colored in appearance and that is usually found over the trunk or extremities during febrile episodes
- Leukocytosis (10,000/microL or greater), with at least 80 percent granulocytes

Adult-onset Still's Disease

The minor Yamaguchi criteria include:

- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal LFTs, particularly elevations in AST, ALT and LDH concentrations
- Negative tests for antinuclear antibody and rheumatoid factor

Treatment for AOSD

- Anakinra
  - Recombinant IL-1 receptor antagonist, approved for RA but not a standard therapy due to inefficacy
  - Daily 100 mg/d
  - Dramatic resolution of fever and joint symptoms in 2-3 days
- Anakinra is also used in refractory gout
  - Usually in hospitalized patients
- Canakinumab, IL-1 inhibitor, recently approved for Cryopyrin-associated periodic syndrome