# Suspecting and treating inflammatory polyarthritis

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# Disclosures

- None

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# Evaluation of Early Inflammatory Arthritis

- Why is this important?
  - Early RA and PMR syndromes present to primary care and generalists first.
  - Appropriate diagnosis, initiation of treatment and referral is paramount in early effective control of RA

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# Learning objectives

- Understand the initial evaluation of a patient with new onset polyarthritis
- Learn the differential diagnosis of patterns of disease presentation
- Understand the initial treatment of newly diagnosed RA and PMR

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# Identification of Early Synovitis

- History is the first clue
  - Morning time symptoms in the hands and forefeet
  - AM stiffness for > 30 minutes
  - Symptoms respond to NSAIDs
- Subtle exam findings


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# Inflammatory Arthritis vs DJD

## Inflammatory

- Sudden onset
- Bilateral symmetric symptoms
- Constitutional symptoms
- Can be erosive
  Marginal erosions (RA)
- Positive inflammatory markers
- Morning stiffness > 30 minutes
- MCP/ MTP squeeze tenderness

## Degenerative

- Gradual onset of scattered symptoms in joints of fingers, knees, spine
- No constitutional symptoms
- Can be erosive!
  Central erosions
- Use related pain with minimal stiffness
- Heberden nodes (DIP), Bouchard nodes (PIP)

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# Case 1

- 32 year old housewife, mother of three school aged children.
- Referred by her family doctor for an acute inflammatory polyarthritis involving the hands, feet and knees.
- ESR is 87 mm/Hr, RF 389 IU/ML, anti-CCP antibody negative, ANA is positive at 6.3 U with a positive ENA panel to SSA, SSB, RNP, Sm, Jo-1 and Scl-70.
- She has been ill for 3 weeks and now is getting better with naproxen 375 mg twice daily

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# Which of the following will most likely confirm the diagnosis?

- A) HLA-B27
- B) Parvovirus B19 antibodies
- C) Serum urate
- D) HIV testing

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# Case 2

- 30-year old man is evaluated for arthritis.
- 3 weeks ago he noticed dysuria without discharge and right eye redness.
- 2 weeks later developed warmth, pain and swelling in the left knee, then right knee, then left heel, then right wrist.
- Dysuria and eye redness have resolved.
- Physical exam: vital signs normal; moderate effusion of the affected joints with tenderness and pain on ROM. Tenderness of Achilles tendon. No rash.

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# Case 2, continued

- Knee x-ray: joint effusion, no bony abnormalities, normal joint space
- Left knee aspiraiton: synovial fluid leukocyte count 5,000/ µL, 65% Neutrophils and 35% mononuclear cells, Gram stain negative, cultures negative, no crystals.

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# Which of the following is the most appropriate diagnostic test to perform next?

- A) Chlamydia nucleic acid amplification urine testing
- B) C-reactive protein
- C) HLA-B27
- D) Interferon gamma release assay

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# Rheumatoid Mimics
# Early Synovitis Patients

- Viral Arthritis
  - Rubella
  - Parvovirus B19
- Reactive Arthritis Syndromes (*Chlamydia trachomatis* – most commonly involved)
- Seronegative Arthritis Syndromes/PMR in the Elderly
- Systemic Lupus Erythematosus
- Atypical crystalline arthritis – CPPD, gout

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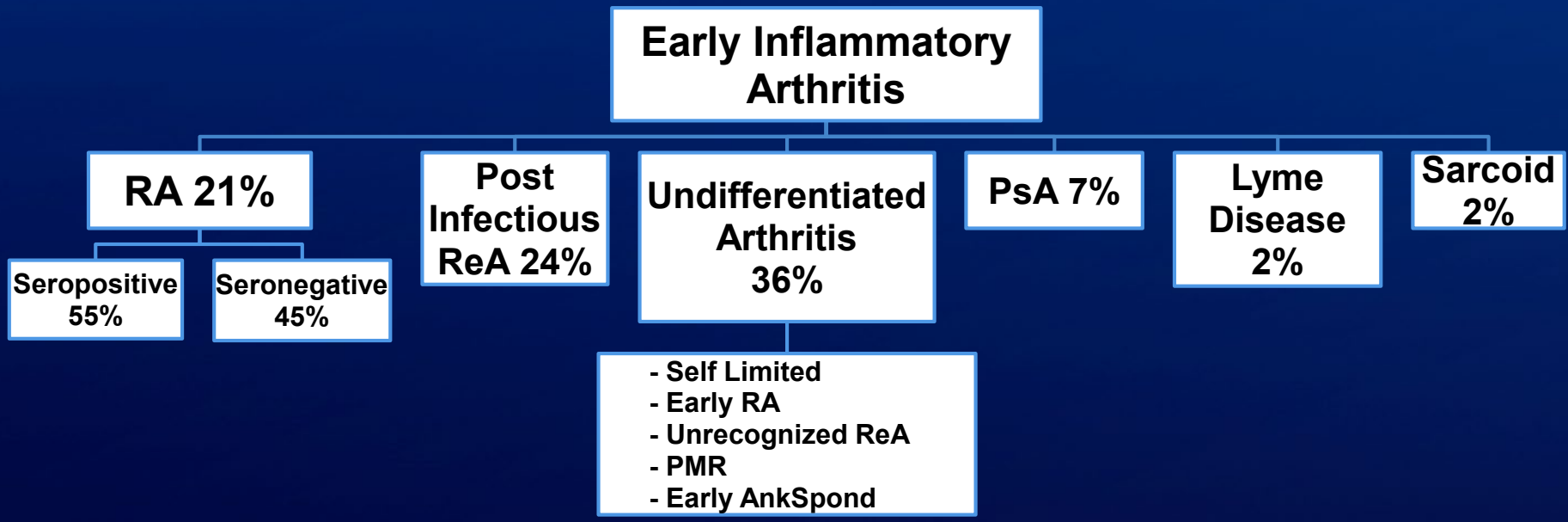
# Early Arthritis Syndromes
# If not RA, what is it?



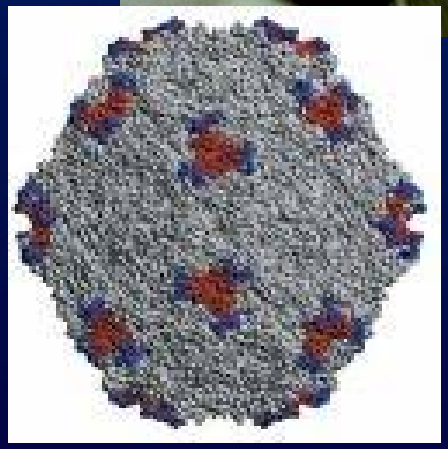

*Soderlin et al. Ann Rheum Dis 2002*



# Parvovirus B19 Arthropathy Epidemiology

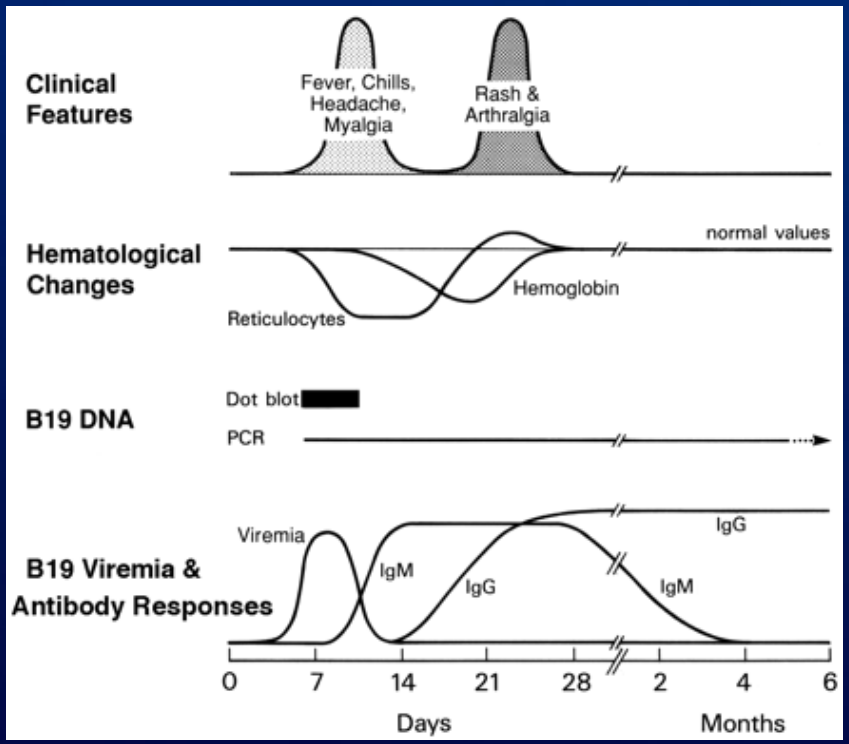
- Single strand DNA virus
- Winter-Spring outbreaks
- Adult risk groups: daycare workers, parents
- Respiratory secretion or pooled blood product transmission
  - Infection most common in young school children
  - 60% of adult blood donors are seropositive (IgG)

# Acute Parvovirus Arthritis

- Females : Males 3:2
- Synovitis in hands, feet, knees, elbows
- 7% of “acute RA” in primary care
  - Always check IgM Parvovirus serology
- Serologically confused as RA or SLE: transient RF and ANAs
- 20% of cases may persist for > 2 months
- Symptomatic management

**Illness Course in Adult Volunteers (Intranasal Inoculation)**



# Case 3

- A 36 year old woman presents with a 2-month history of morning stiffness in her hands, wrists, knees, feet for 1.5 hours. Her only medication is ibuprofen which is helpful.
- Physical exam: normal vital signs. Tenderness and swelling of the 2nd, 3rd and 5th MCPs bilaterally, 2-4th PIPs bilaterally, right wrist, left knee and 2-5th MTPs.

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# What is the most appropriate diagnostic test to perform next?

- A) Anti-cyclic citrullinated peptide antibodies
- B) HLA-B27
- C) Parvovirus IgG antibodies
- D) Serum urate
- E) TSH

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# Rheumatoid arthritis
# Risk factors

- Genetic (60%): HLA-DRB1 and other HLA and non-HLA susceptibility genes
- Environmental (40%): smoking, air pollution
- Other: periodontitis (Porphyromonas gingivalis), hormonal (?)

*Hill JA et al. J Immunol 2003; 171: 538-41*
*Viatte S et al. Arthritis Rheumatol 2016*
*van Beers-Tas MH et al. Best Pract Clin Rheumatol 2015*

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# RA laboratory panel

| | Anti-CCP | RF |
|---|---|---|
| Sensitivity<br>Specificity | 70%<br>95% | 72%<br>80% |
| Utility | - Identifying early inflammatory arthritis patients at risk for erosive disease<br>- Evaluating RF negative inflammatory arthritis patients<br>- Evaluating a positive RF in a person who doesn't seem to have RA<br>- In high titers uniquely specific for potentially erosive rheumatoid arthritis | - Higher likelihood of detection and higher titers in established disease<br>- High titers correlate with more severe disease |
| Impact of other factors | Smoking | Smoking, age |

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# 2010 ACR/EULAR Classification Criteria for RA

| JOINT DISTRIBUTION (0-5) | |
|---|---|
| 1 large joint | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (large joints not counted) | 2 |
| 4-10 small joints (large joints not counted) | 3 |
| >10 joints (at least one small joint) | 5 |
| **SEROLOGY (0-3)** | |
| Negative RF AND negative ACPA | 0 |
| Low positive RF OR low positive ACPA | 2 |
| High positive RF OR high positive ACPA | 3 |
| **SYMPTOM DURATION (0-1)** | |
| <6 weeks | 0 |
| ≥6 weeks | 1 |
| **ACUTE PHASE REACTANTS (0-1)** | |
| Normal CRP AND normal ESR | 0 |
| Abnormal CRP OR abnormal ESR | 1 |

**≥6 = definite RA**

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

American College of Rheumatology
Education · Treatment · Research

eular

*Aletaha D et al. Arthritis Rheum 2010; 62: 2569–81*



 

# Making a Diagnosis of Early RA

- Synovitis of at least 3 joints
  - Symmetric, small joint polyarthritis is strongly suggestive
- Positive RF or CCP antibody
- Elevated ESR or CRP
- Exclude other possible mimics
- Persistence > 6 weeks

This is a practical approach that reflects the new ACR/EULAR classification criteria

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# Case 3, continued

- Patient returns with the following results of additional work-up:
  - CRP 36.0 mg/dl
  - Positive CCP antibody >250 U
  - Positive Rheumatoid factor 120 IU
  - Hand x-rays reveal periarticular osteopenia


Magnified view of the left 5th MTP

# Which of the following is the most appropriate treatment at this time?

- A) Continue ibuprofen
- B) Initiate mycophenolate mofetil
- C) Initiate methotrexate
- D) Initiate monotherapy with prednisone

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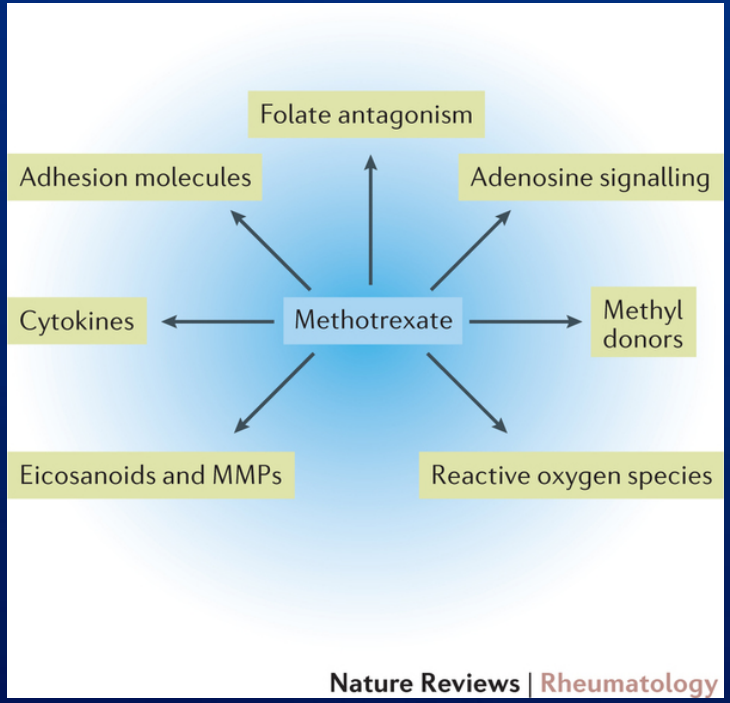
# RA management: Methotrexate

- Methotrexate is the anchor DMARD
- Prevents radiologic progression (disease-modifying!)
- Weekly PO or SQ dosing
- Potential up-titration to max 25 mg/week
- Folic acid supplementation 1 mg/day
- Safety monitoring: CBC, Creatinine, AST, ALT




Adenosine pathway is the likely primary down-regulator of RA inflammation

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# Methotrexate Toxicity

- One of the mechanisms: folate depletion

- Minor: Nausea, stomatitis, hair loss, headache, fatigue
- Serious but rare:
  - Megaloblastic anemia and pancytopenia
    - Increased risk with folate deficiency or azotemia
  - Liver fibrosis
    - Increased risk in NAFL/NASH patients
  - Hypersensitivity pneumonitis
- Teratogenic effect

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# RA treatments

- Treatment goal: Remission or low disease activity
- Synthetic DMARDs: Methotrexate, Sulfasalazine*, Hydroxychloroquine*, Leflunomide
- Biologic DMARDs:

- TNF inhibitors (Infliximab, Adalimumab, Etanercept, Golimumab, Certolizumab*)
- IL6-receptor antagonists (Tocilizumab, Sarilumab)
- T-cell co-stimulator blocker (Abatacept)
- JAK kinase inhibitor (Tofacitinib, Baricitinib, Upadacitinib)
- Rituximab - antibody against CD20 on B-lymphocytes

- * safe in pregnancy and breastfeeding

*Singh JA. Arthritis Care Res (Hoboken). 2016;68:1-25*

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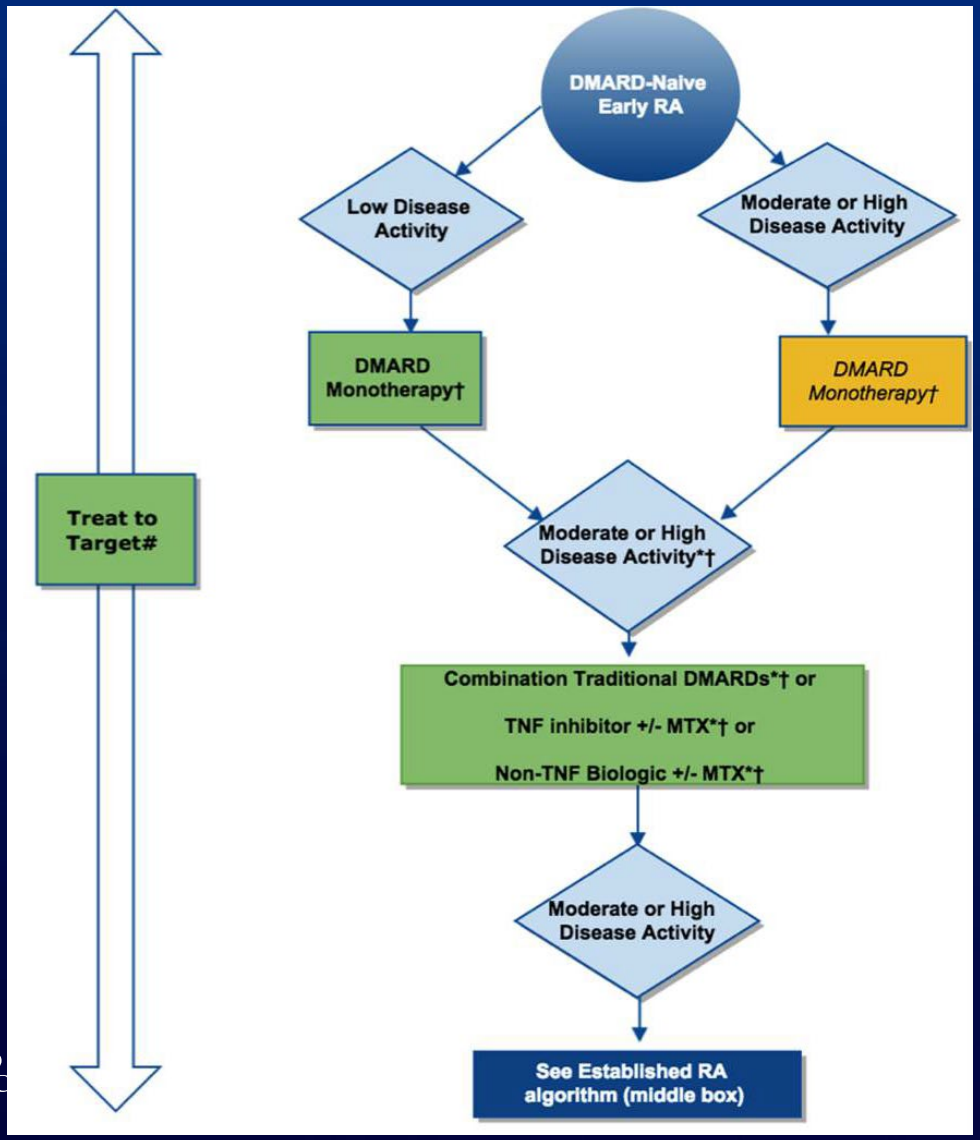
# RA treatment strategies




- Glucocorticoids:
- bridge-therapy,
- management of flares,
- low-moderate doses, limited duration.

*Singh JA. Arthritis Care Res (Hoboken). 2016;68:1-25*

# Case 4

- A 30-year-old man is evaluated for a 7-year history of intermittent pain and swelling in multiple fingers and toes; 1 hour morning stiffness. Treated with multiple NSAIDs, Ibuprofen most efficacious.
- Physical exam: normal vital signs. Tenderness and swelling of the 4th and 5th PIPs and DIPs bilaterally, swollen right second toe.
- Labs: Uric acid 6.7 mg/dL, RF and CCP-antibody negative.

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# Which of the following is the most likely diagnosis?

- A) Gouty arthritis
- B) Psoriatic arthritis
- C) Reactive arthritis
- D) Rheumatoid arthritis

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# CASPAR – classification criteria for PsA

| | |
|---|---|
| 1. | Evidence of current psoriasis, a personal or family history of psoriasis (in 1st or 2nd degree relative) – score of 1; evidence of current psoriasis – 2 points |
| 2. | Typical psoriatic nail dystrophy on current physical exam – 1 point |
| 3. | Negative RF – 1 point |
| 4. | Dactylitis, either current or in a history recorded by a rheumatologist – 1 point |
| 5. | Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on radiographs of the hand or foot – 1 point |

Diagnosis of PsA requires ≥ 3 points

*Taylor W et al. Arthritis Rheum 2006;54:2665–73*

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# Psoriatic arthritis – Clinical Features

- Oligo/polyarthritis (symmetric or asymmetric); DIP joints
- Arthritis mutilans: deforming and destructive (X-ray: “Pencil-in-cup”)
- Spondyloarthritis: sacroiliitis and spondylitis
- Enthesitis
- Dactylitis: "sausage digit"
- Skin and nail disease
- Lab: elevated uric acid

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# Traditional Classification of the Spondyloarthropathies

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Arthritis associated with IBD

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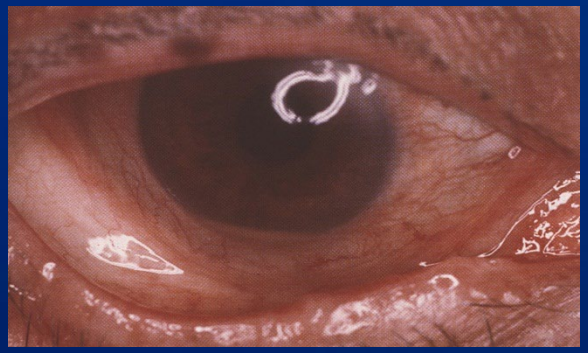
# Clinical characteristics of spondyloarthropathy

- Inflammatory back pain 69%
- Peripheral arthritis 29%
- Enthesitis 29%
- Uveitis 2.5%
- Dactylitis 3.3%
- Positive FHx 32.1%




*Rudwaleit M et al. A&R 2004. 50(suppl):S617*

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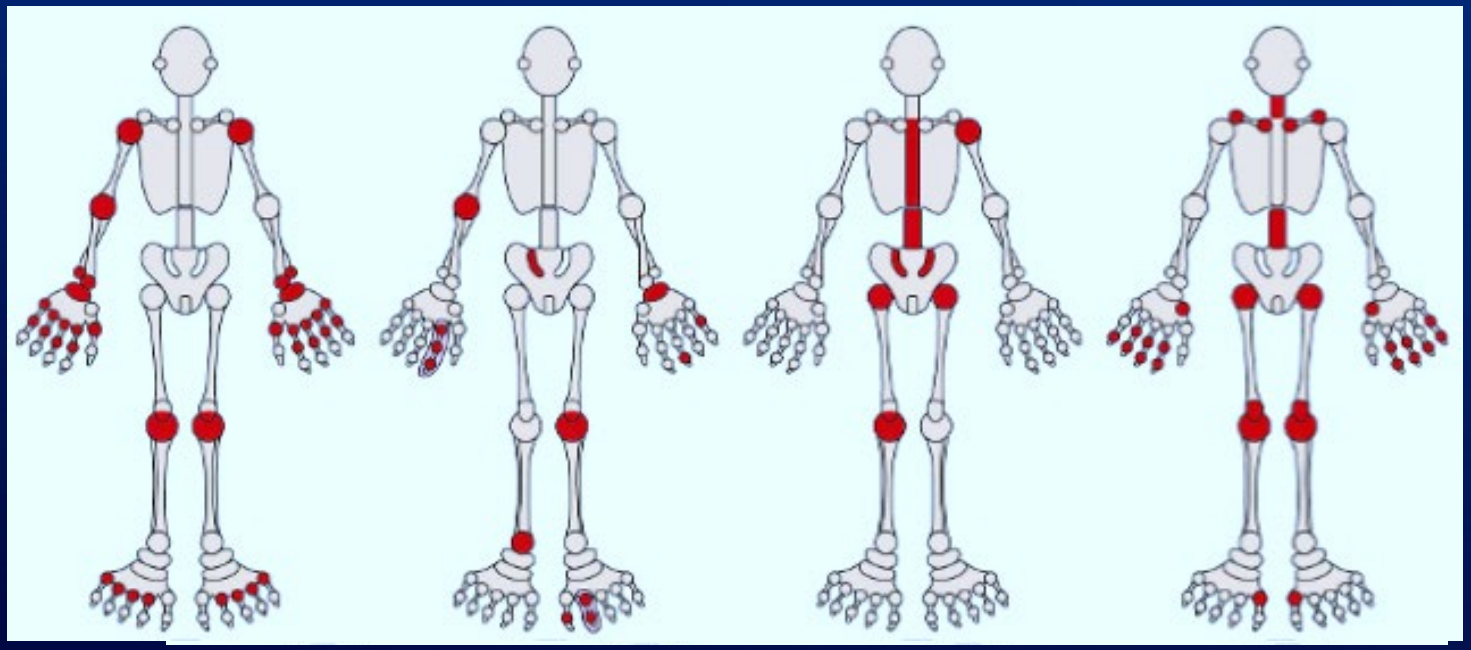
# Patterns are Important

RA PsA Ank Spond OA



# Polymyalgia Rheumatica

At Initial Presentation Think of PMR as a Syndrome

- Review for symptoms of GCA
- Elderly onset RA or a spondyloarthropathy
- Malignancy
  - Paraneoplastic syndrome
  - Myeloma or bone metastases
- Infectious endocarditis

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# Diagnosis of PMR

- > Age 50 years (reality >> 60 years)
- Bilateral shoulder pain
- Morning stiffness > 45 minutes
- Elevated C-reactive protein and/or ESR
  - A small number of patients may have normal acute phase response
- New hip pain
- Negative RF or CCP antibody

*Dasgupta B et al. Arthritis & Rheum 2012; 67:943-54*

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# Some pearls about PMR

- A disease of Vikings
  - Don’t consider it in one of your clinic patients from Somalia
- If a patient is < 60 years old, think of an alternative diagnosis
  - Late onset spondyloarthropathy is the closest mimic
- If patient’s feet and ankles are involved, it’s another condition, likely RA

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# Case 5

- A 75 year old woman presents with 2-week history of worsening shoulder and hip pain.
- No headache, jaw claudication, or vision changes.
- Dx of PMR 3 months ago, Rx Prednisone 15 mg/day down taper with substantial improvement. Was asymptomatic on 10 mg/day. Current dose 8 mg/day (started 1 month ago).
- Physical exam: normal vital signs. BP identical on both arms. No TA tenderness/ induration. Painful ROM in shoulder and hips.

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# Which of the following is the most appropriate management?

- A) Prednisone, 10 mg/d
- B) Prednisone, 30 mg/d
- C) Prednisone, 60 mg/d
- D) Prednisone, 20 mg/d, and methotrexate

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# Prednisone Dosing in PMR

- Excessive dosing will obscure your assessment of treatment response
  - Polymyalgia is a syndrome
    - Malignancy, endocarditis, systemic vasculitis
      - Many fatal diseases feel better on steroids for a while
- Treatment response to prednisone 15 mg daily should be rapid – a day or two
  - Persons > 75 Kg may require 20 mg daily
  - CRP should be normal within days

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*Dejaco C et al. Arthritis & Rheum 2015; 67:2569-80*

 

# Prednisone Dosing in PMR relapse

- Increase prednisone to the last pre-relapse dose, at which patient was doing well
- Gradual reduction within 4-8 weeks back to the relapse dose
- Taper below 10 mg/day by 1 mg every 4 weeks
- Methotrexate can be added if recurrent relapses/ significant glucocorticoid toxicity

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*Dejaco C et al. Arthritis & Rheum 2015; 67:2569-80*

 

# Case 6

- A 78 year old man presents with 2-week history of pain and swelling in his left knee.
- He had 2 similar episodes over the past 6 months in his knees, ankles and wrists, each resolving after 3 weeks
- Physical exam: normal vital signs. Swollen left knee, left ankle and wrists, with tenderness and decreased ROM
- Labs: ESR 53 mm/h, uric acid 3.8 mg/dL
- Knee radiograph:

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# Which of the following is the most likely diagnosis?

- A) Gout
- B) Acute CPPD arthritis
- C) Infectious arthritis
- D) Palindromic rheumatism

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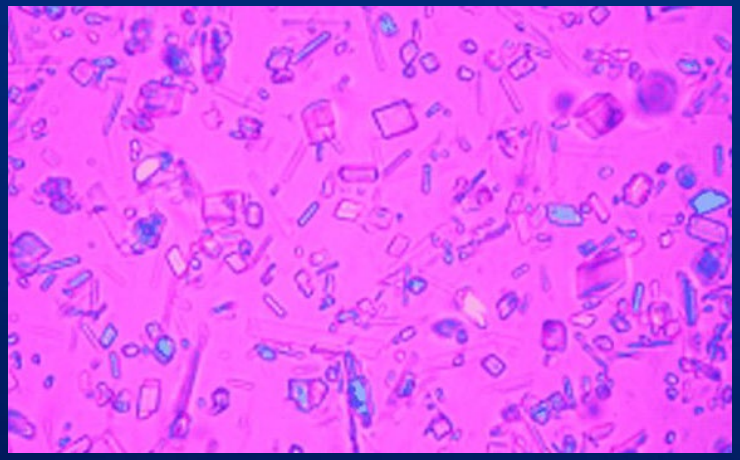
# Acute CPPD arthritis (Pseudogout)

- Most common form of calcium pyrophosphate disease
- Mono-oligoarticular, most commonly in the elderly
  - DDx acute gout versus septic arthritis
  - Fever and delirium in the elderly
  - Slower resolution than acute gout
- Knee > Wrist > MCP>>>>1st MTP



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# Acute Pseudogout, treatment

- Treat like acute gout but modify for the elderly
  - Intra-articular steroid, short course prednisone, short dosing colchicine, preferable to NSAIDs
- No way to remove CPPD from the joints, unlike intra-articular urate
  - Screen all patients for hyperparathyroidism and hypomagnesaemia

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# Take home points

- Arthritis: Inflammatory or degenerative?
- Remember patterns of joint involvement
- Understand the approach to identification of poor prognosis polyarthritis
- Know the serious complications of MTX therapy
- Recognize PMR but always think of it as an inflammatory syndrome first
- Do not over treat PMR

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# Helpful resources

- https://www.acponline.org/featured-products/mksap-18
- https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines
- https://www.rheumatology.org/Learning-Center/Medication-Guides
- https://www.uptodate.com/contents/search

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# Questions & Discussion