Chronic Arthritis of Childhood, Juvenile Idiopathic Arthritis

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- No other financial relationship to disclose

Objectives

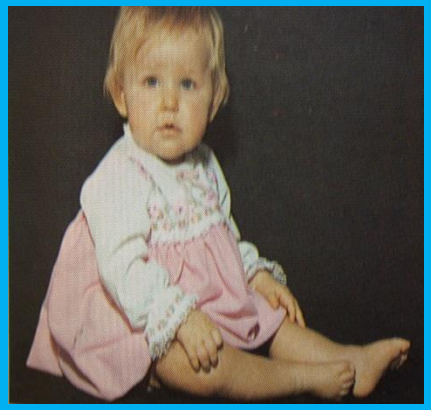
To present an understanding of chronic childhood arthritis

To present the criteria for diagnosis of Juvenile Idiopathic Arthritis (JIA)

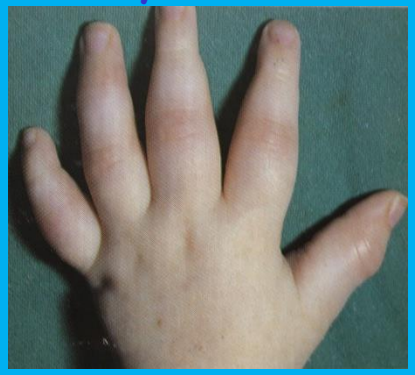
To understand guidelines for the treatment and care of children with JIA

Arthritides of Childhood

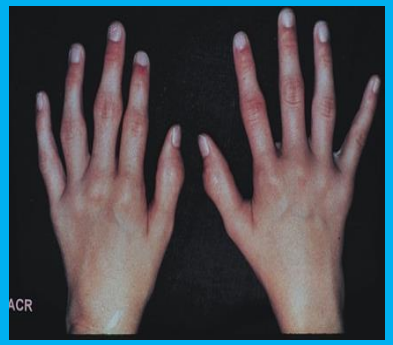
- Infection (viral, bacterial, mycoplasma, TB, Lyme)
- Malignancy (pre B cell ALL)
- Reactive Arthritis (post infectious)
- Associated with Rheumatic Disease (SLE, JDMS, vasculitis)
- Associated with Immunodeficiency (CVID)
- Inflammatory Bowel Disease
- Primary Connective Tissue Disease (Chondroplasia)
- Metabolic (Mucopolysacharidosis, mevalonate kinase deficiency)
- Sarcoidosis (Juvenile onset vs adult type)
- Hypertrophic Osteoarthropathy (Cyanotic Heart Disease, CF)
- Vascular malphormation with secondary inflammation
- Hemarthrosis with secondary inflammation
- Post traumatic (surgical, chronic
- **Idiopathic (Juvenile Idiopathic Arthritis)**



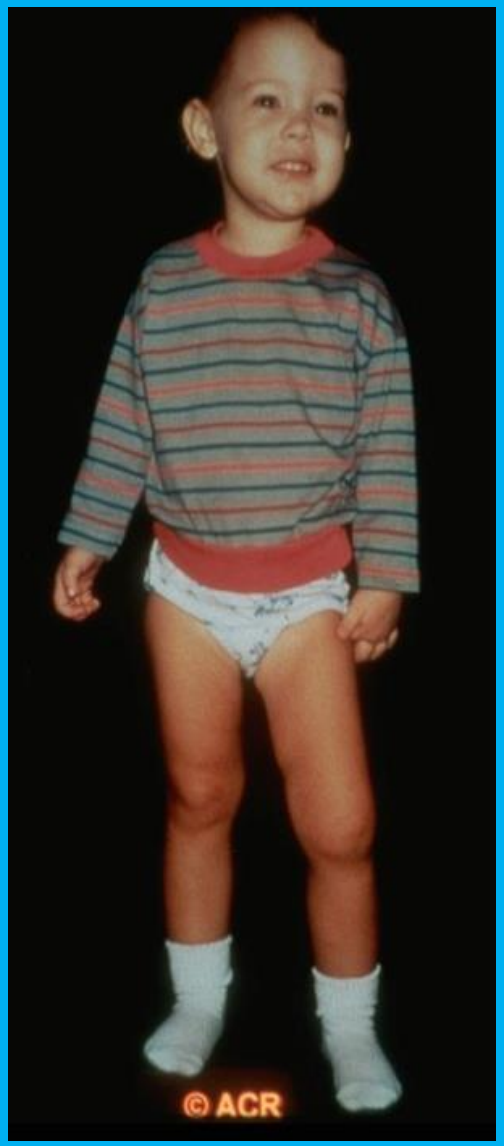
Polyarticular



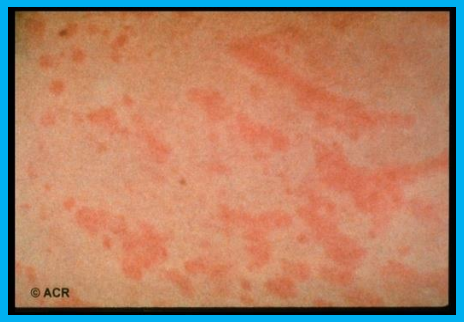
Poly RF -ve



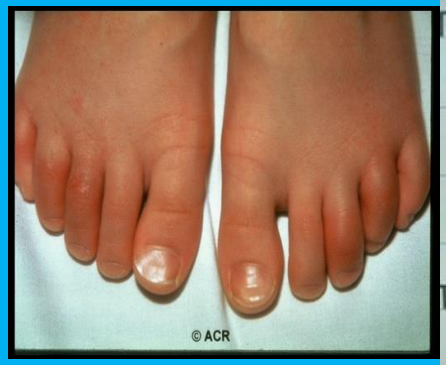
Poly RF +ve



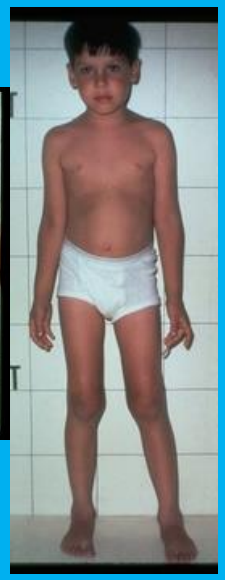
Oligoarticular

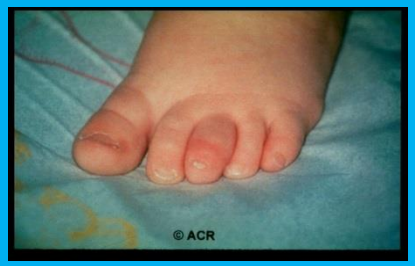


Systemic



ERA





Psoriatic

JIA: General Definition

swelling within a joint

OR

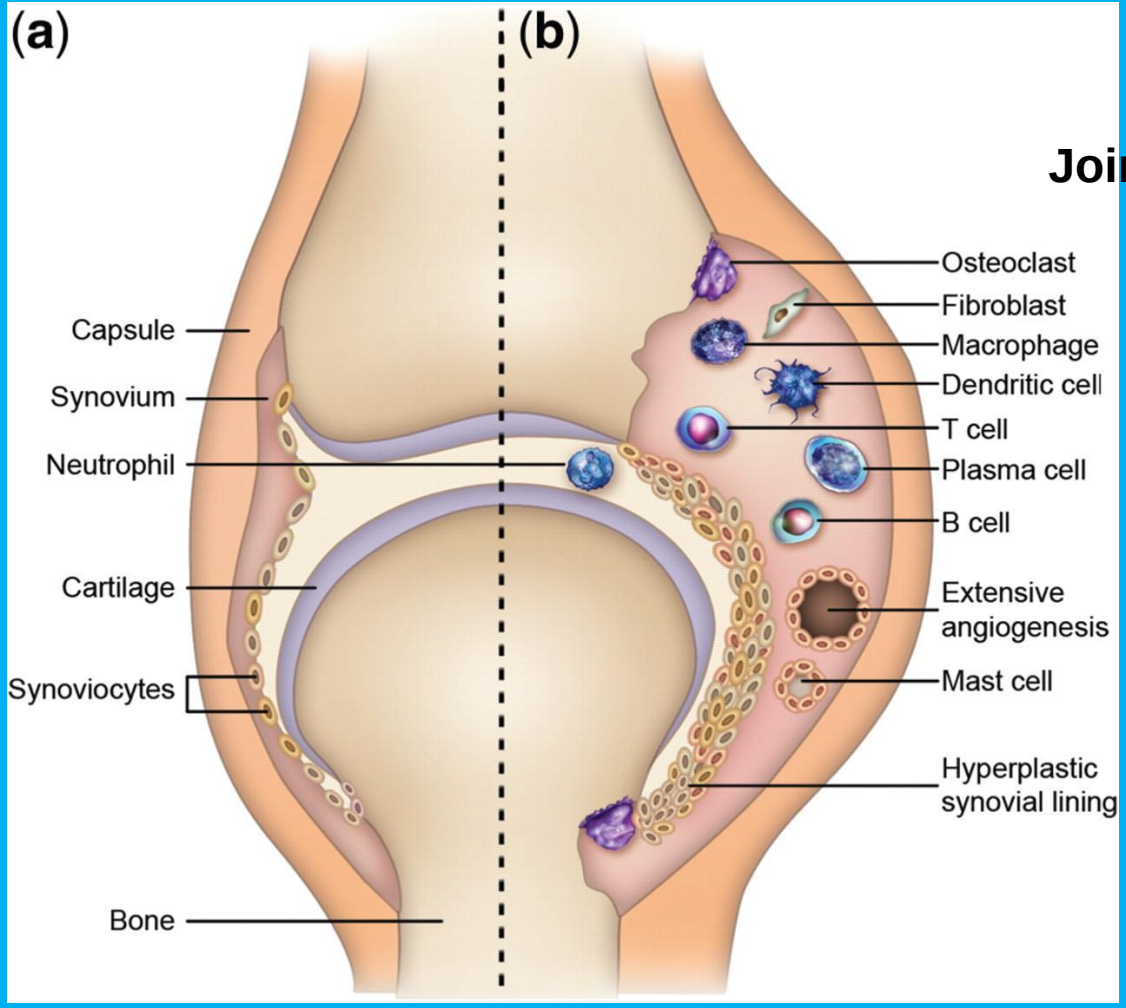
limitation in the range of joint movement with joint pain or tenderness

---

- persists for at least 6 weeks (vs. reactive arthritis)
- Signs/symptoms begin before the 16th birthday
- observed by a physician
- not due to a primary mechanical disorder or other identifiable causes such as
  - Infection (parvovirus, mycoplasma, Lyme)
  - Paraneoplastic (pre-B cell ALL)

normal joint

Joint with active JIA



activated CD4 positive T lymphocytes and monocyte into joint space

activated CD4 T cells, activated monocyte/macrophages secrete pro-inflammatory cytokine (TNFalpha,IL-1,IL-6)

differentiation of osteoclasts over osteoblasts due to inflammatory cytokines
→ destruction and erosion of bone and cartilage → irreversible joint deformity

synovitis (proliferation and inflammation of synovium)

History

"The fundamental difficulty in discussing rheumatism consists in defining what we mean by it."

"Rheumatism and it allies in childhood"

Sir Thomas Barlow, 1883

The Hospital for Sick Children, Great Ormand Street

London, England

Juvenile Arthritis Nomenclature

Juvenile Rheumatoid Arthritis (JRA) 1972

- American College of Rheumatology
  - pauci, poly, systemic JRA

Juvenile Chronic Arthritis (JCA) 1977

- European League Against Rheumatism

Juvenile Idiopathic Arthritis (JIA), 2001

- International League Against Rheumatism
  - 1997, 2001 conferences
    - “to delineate for research purposes, relatively homogenous, mutually exclusive categories of idiopathic childhood arthritis based on predominant clinical and laboratory features.”

ILAR 2nd Revision, Edmonton, 2001. The Journal of Rheumatology 2004; 31:2

Important JIA Descriptors

- age at onset
- descriptions of the arthritis (large vs. small joints, symmetry, upper or lower limb predominance, individual joint involvement)
- disease course (# of joints)
- presence of ANA (effects risk of iritis)
- chronic or acute anterior uveitis
- HLA allelic associations

Juvenile Idiopathic Arthritis Subtypes

1. **Oligoarticular** (persistent, extended) **“oligo”**

2, 3) **Polyarticular, “poly”**

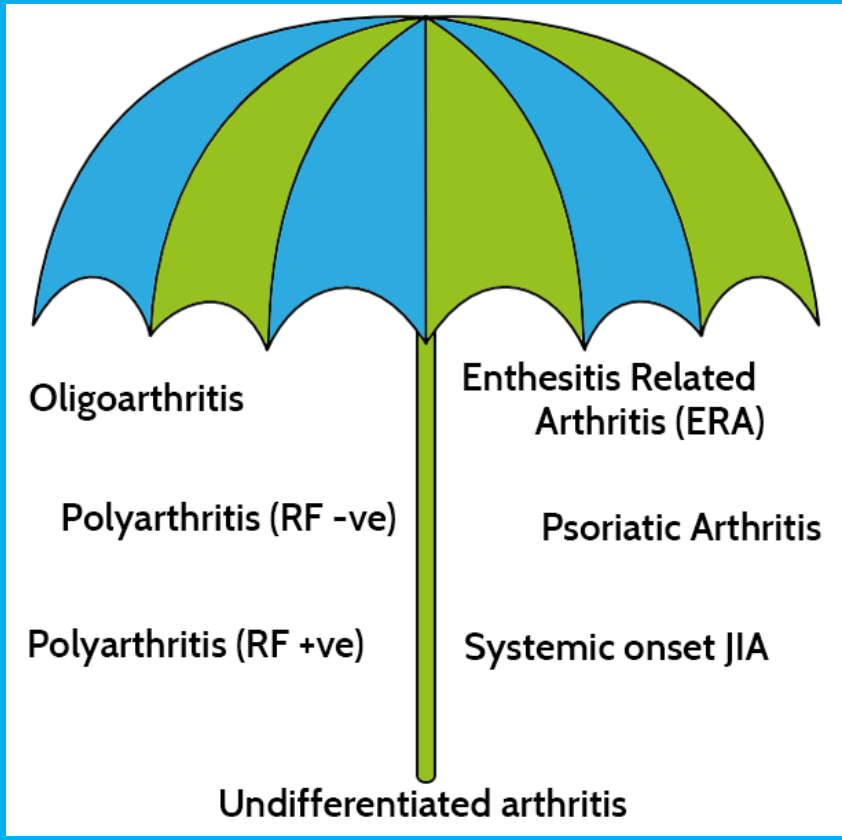
- seronegative
- seropositive

4) **Systemic onset “systemic”**

5) **Enthesitis related (ERA)**

6) **Psoriatic**

7) Other/undifferentiated



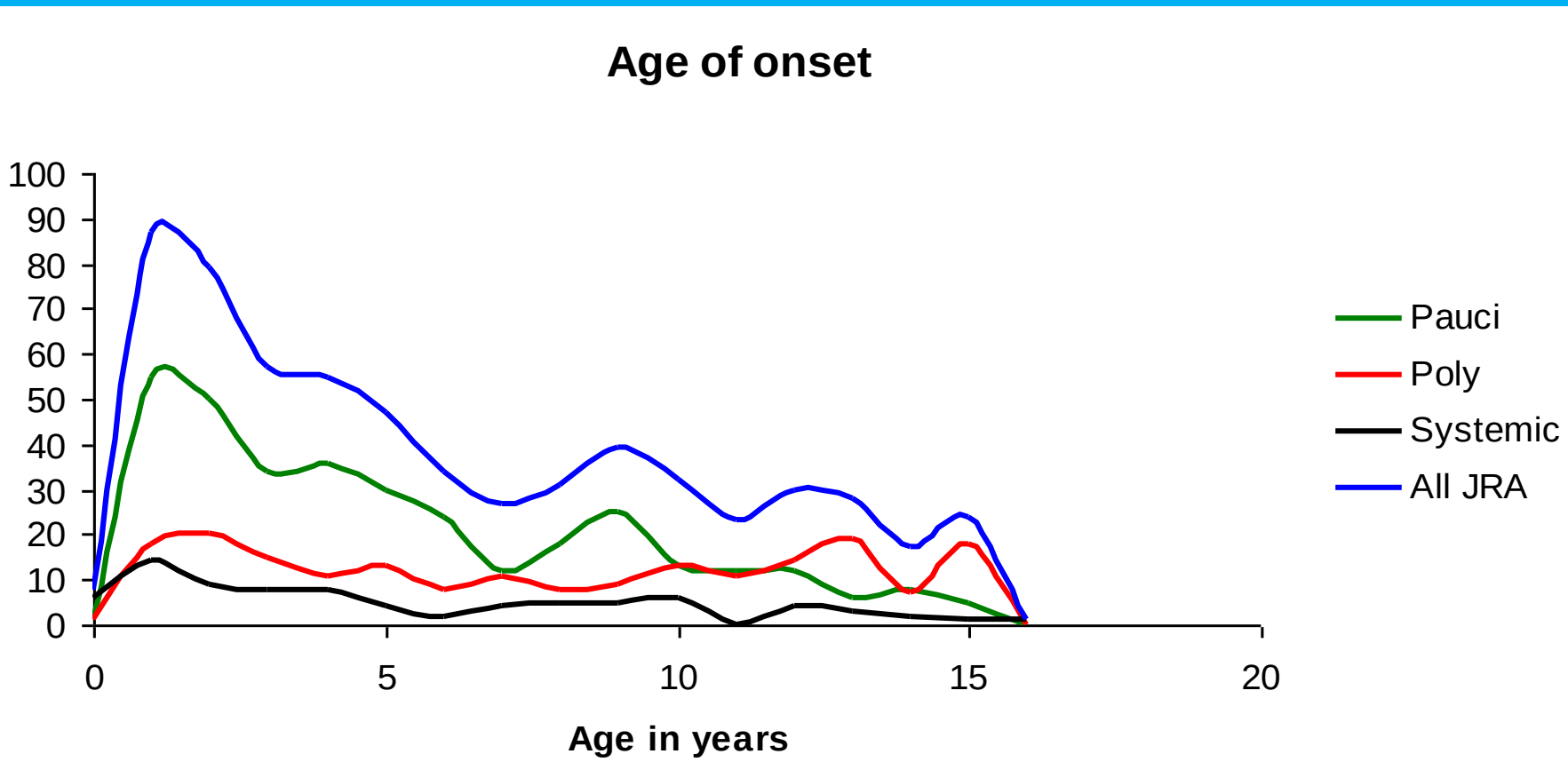
Juvenile Idiopathic Arthritis

Multifactorial etiology

- environmental factors
- genetic risk factors
  - HLA class I & II gene polymorphisms
  - HLA B27 in ERA
  - PTPN22 gene (B&T cell regulator gene)
  - PTPN2 gene
  - IL2RA/CD 25 gene

Epidemiology

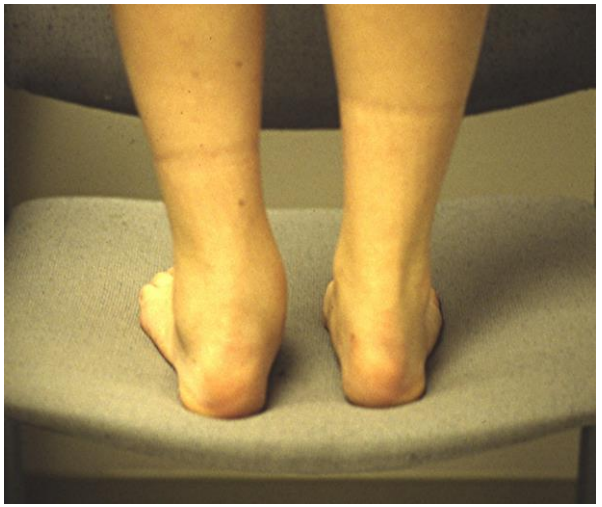
- affects >300,000 children in the United States
- prevalence 1/1,000 children
  - may be more common in Caucasian ethnicity
- age and sex distribution varies depending on JIA subtype


Age of onset
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
Age in years
Pauci
Poly
Systemic
All JRA

Oligoarticular JIA

Pauci Knee Arthritis-3

Pauci Ankle Arthritis - 1



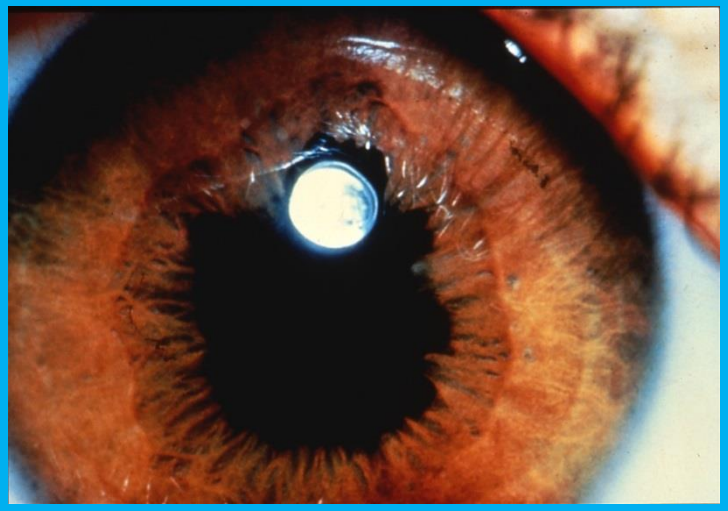
Arthritis affecting 1-4 joints during 1st 6 months of disease

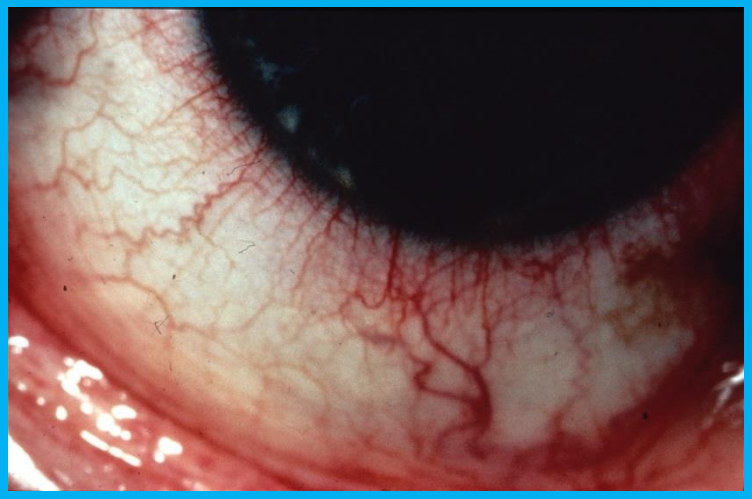
Subcategories:

- Persistent oligoarthritis: <5 joints affected throughout disease course
- Extended oligoarthritis: >4 joints affected after the 1st 6 months of disease

Exclusion of other JIA subtypes

JIA and Iritis / Uveitis





- Up to 20% of ANA+ Oligo (Poly) JIA patients have iritis
- Anterior typically
- Often asymptomatic
  - Screening, schedule
    - ANA status
    - age of onset
    - disease duration

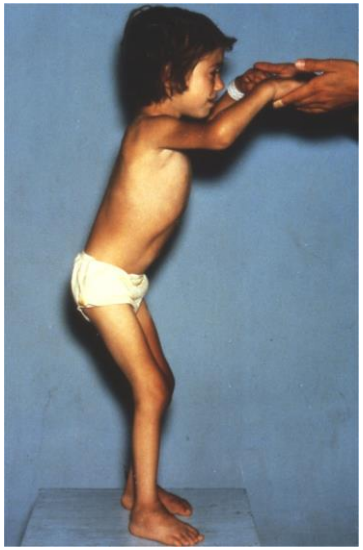
TABLE 1 Frequency of Ophthalmologic Examination in Patients With JRA

Type	ANA	Age at Onset, y	Duration of Disease, y	Risk Category	Eye Examination Frequency, mo
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	−	≤6	≤4	Moderate	6
	−	≤6	>4	Low	12
	−	>6	NA	Low	12
Systemic disease (fever, rash)	NA	NA	NA	Low	12

ANA indicates antinuclear antibodies; NA, not applicable.
Recommendations for follow-up continue through childhood and adolescence.

Polyarticular JIA (RF-)

Poly Patient-1



Arthritis affecting >= 5 joints during the 1st 6 months of disease

Rheumatoid Factor (RF) negative

(Cyclic citrillinated peptid (CCP) negative)

Exclusions

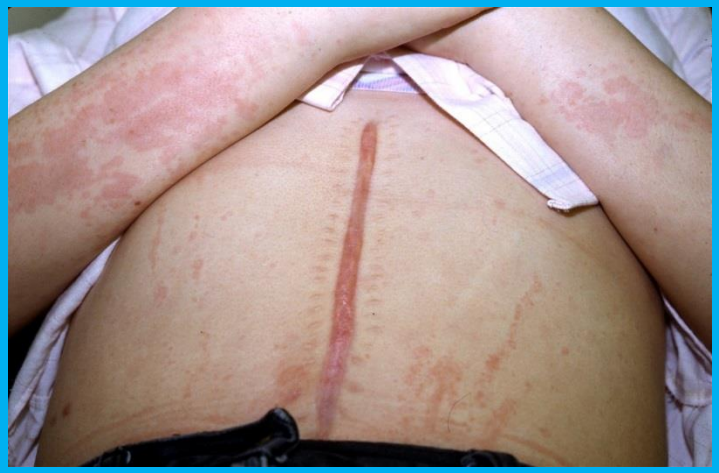
Oligo and RF- Poly exclusions for diagnosis

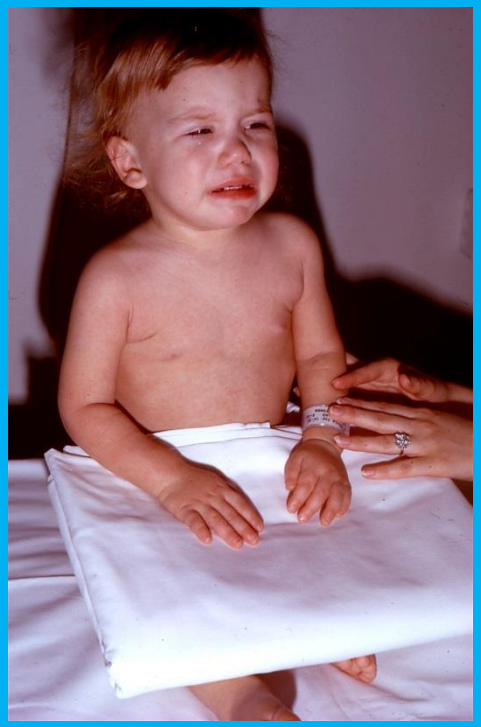
If not,

1. psoriasis in patient or 1st degree relative
2. arthritis in HLAB27+ male beginning after the 6th birthday
3. ankylosing spondylitis, ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis
    - in patient OR 1st degree relative
4. IgM RF > 3 months apart during 1st 6 months of disease
5. meeting diagnostic criteria for systemic onset JIA

and meets criteria for the diagnosis of oligo / poly JIA, **then** make diagnosis

Systemic Juvenile Arthritis



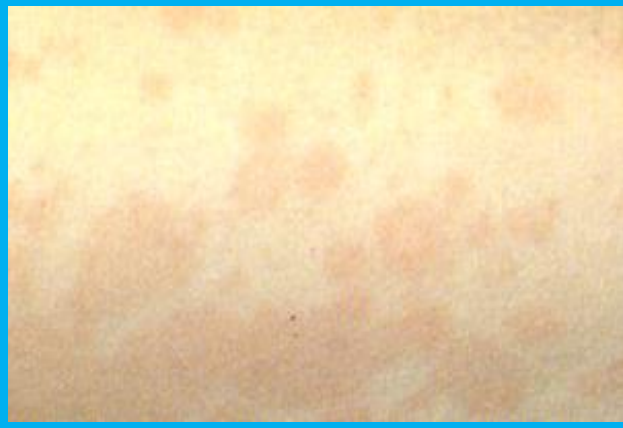


Arthritis or preceded by fever of >2 weeks' duration

- quotidian for at >= 3 days

Plus 2/4 of the following:

1. evanescent (nonfixed) erythematous rash
2. generalized lymph node enlargement
3. hepatomegaly and/or splenomegaly
4. serositis (pericarditis, pleuritis, ascites)



Exclusions

Systemic JIA exclusions for diagnosis

If not,

1. psoriasis in patient or 1st degree relative

2. arthritis in HLAB27+ male beginning after the 6th birthday

3. ankylosing spondylitis, ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis
    - history of or in a 1st degree relative

4. IgM RF > 3 months apart during the 1st 6 months of disease

and meets criteria for the diagnosis of systemic onset JIA, **then** make diagnosis

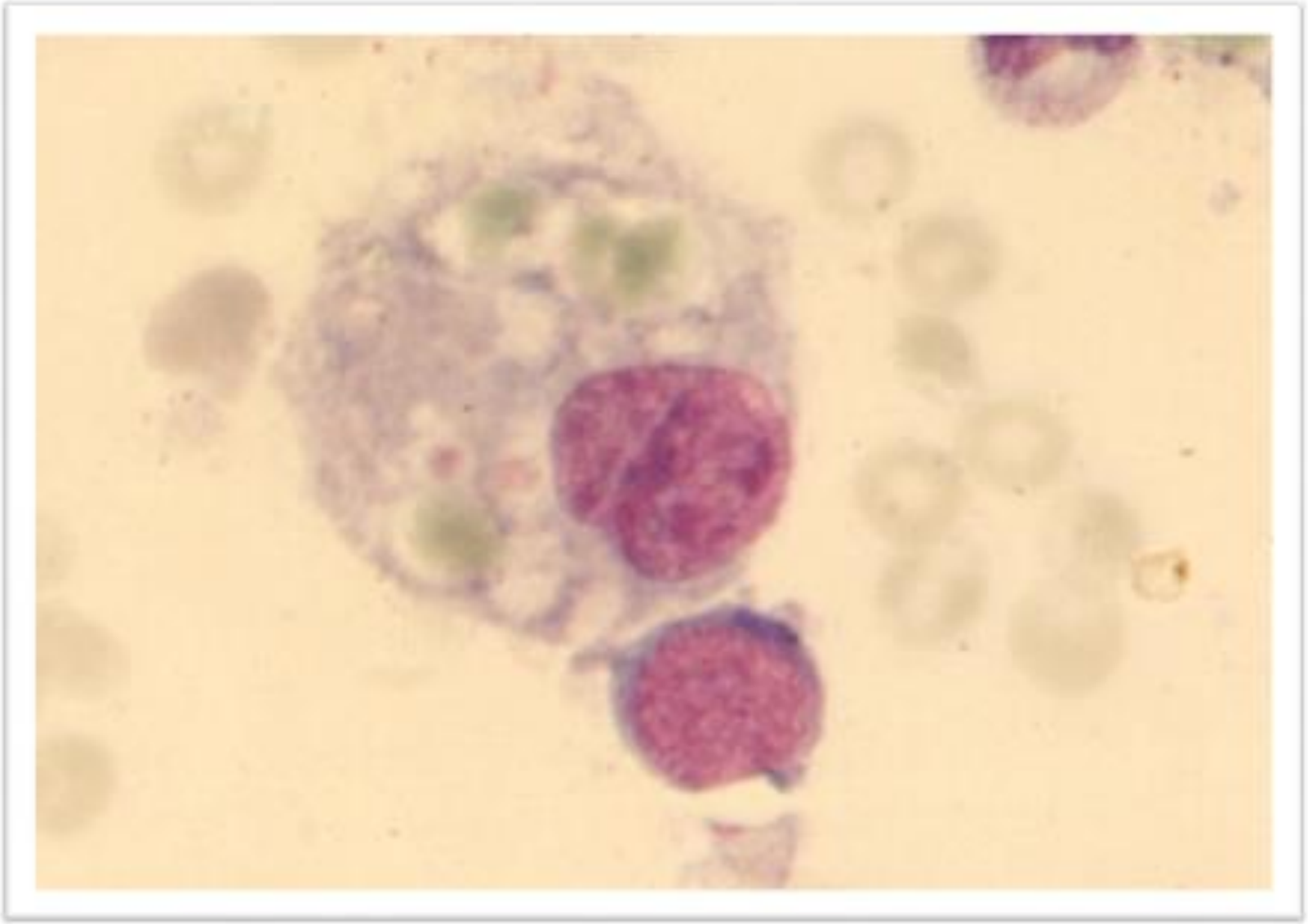
Systemic JIA ← → Macrophage Activation Syndrome

- vs. Reactive Hemophagocytic Lymphohistiocytosis (HLH)
- fever, rash, encephalopathy
- bone marrow or liver bx may or may not reveal hemophagocytosis
- Elevations:
  - ferritin (>3,000), d-dimers, LDH, triglycerides, soluble IL-2 receptor antibodies, transaminases

  Low:
  - fibrinogen, WBC (neutrophils), platelets, albumin, ESR
    - "DIC like picture"

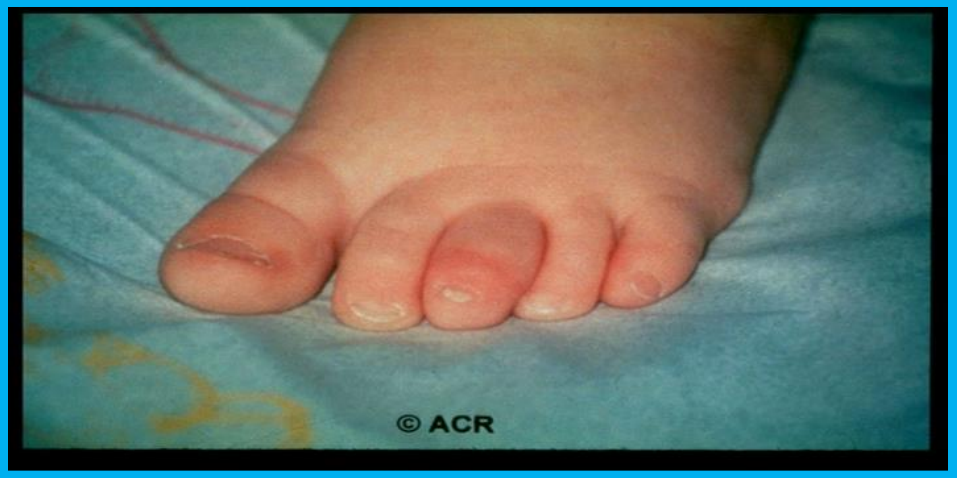
Treat aggressively:

steroids, cyclosporin, anakinra



Histiocyte with hemophagocytosis of platelets and erythrocytes

Psoriatic JIA / Psoriatic Arthritis

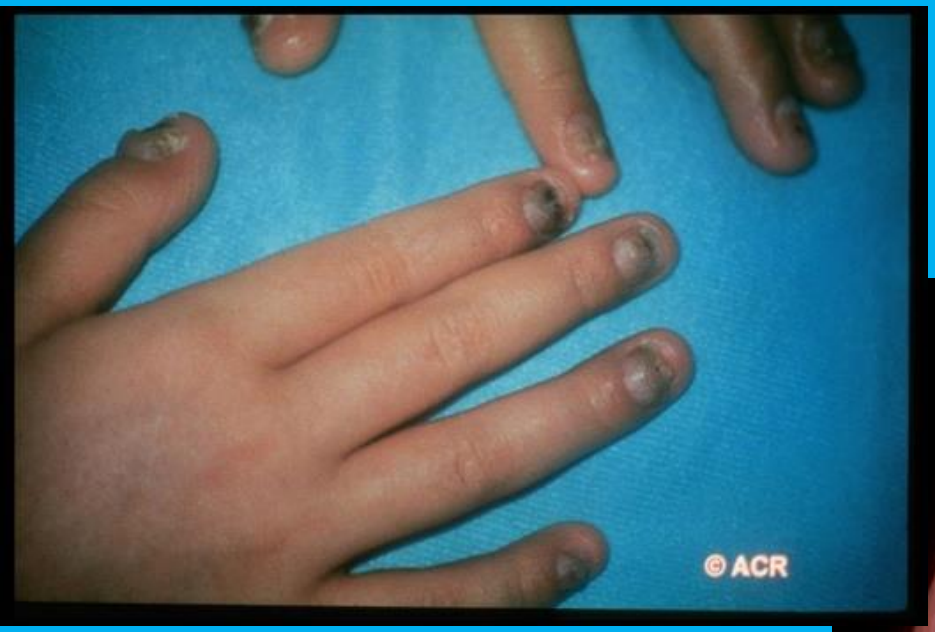


Psoriatic

arthritis <u>and</u> psoriasis (diagnosed by physician (+/- dermatologist))
<u>or</u>
arthritis with 2/3:

1. **dactylitis**
   - swelling of >= 1 digit, usually in an asymmetric distribution
   - extends beyond the joint margin
2. **nail pitting or onycholysis**
   - pitting: minimum of 2 pits on one or more nails at any time
3. psoriasis in a **1st degree relative**

Exclusions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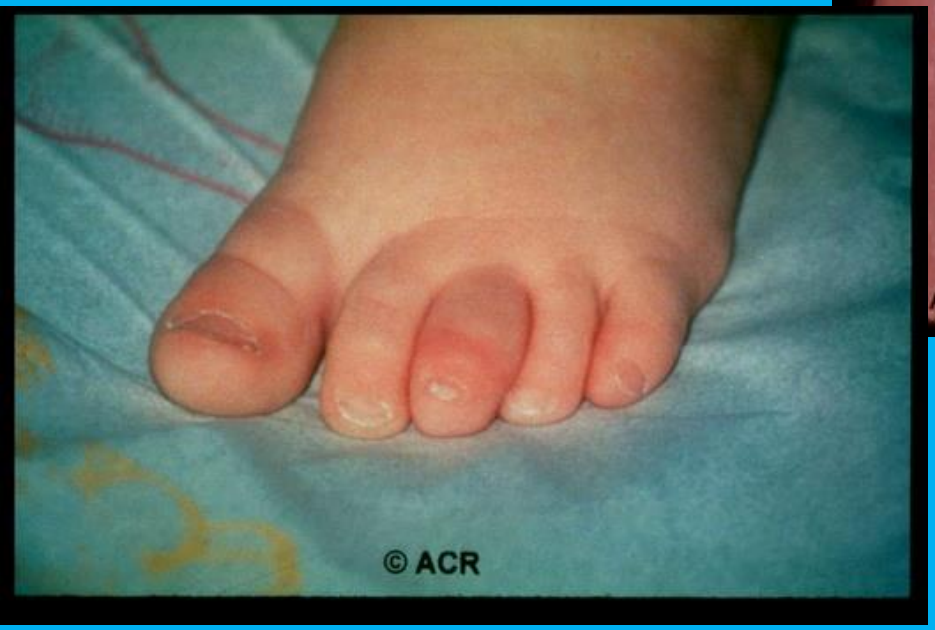
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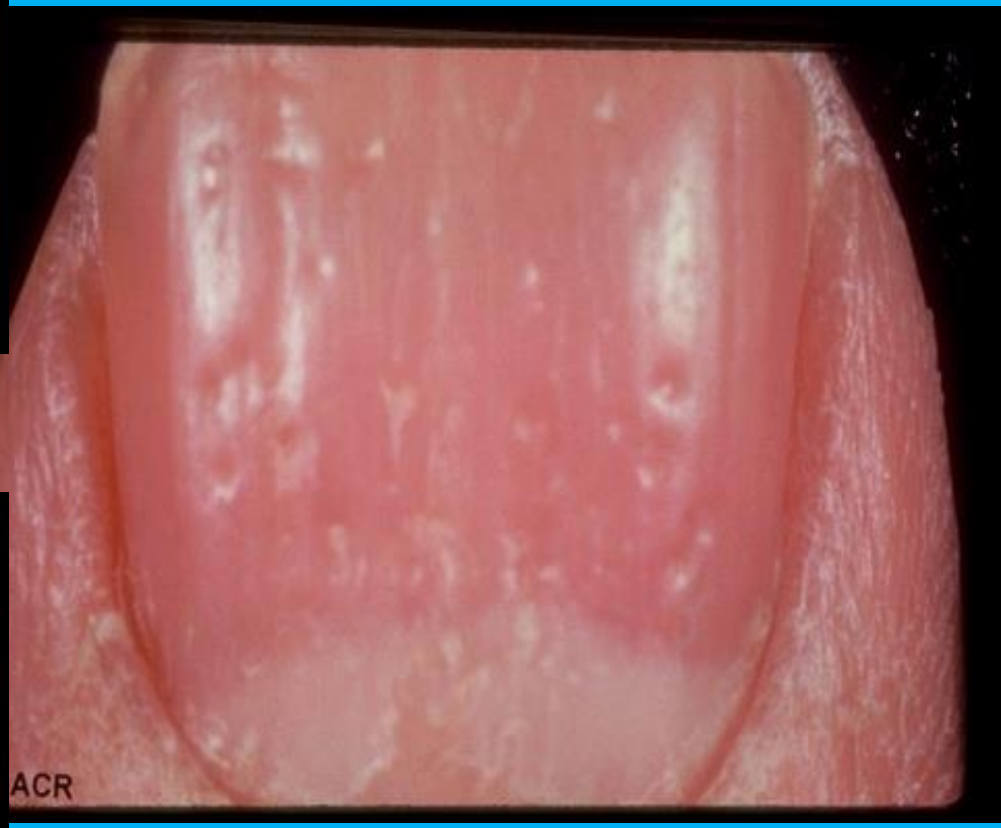
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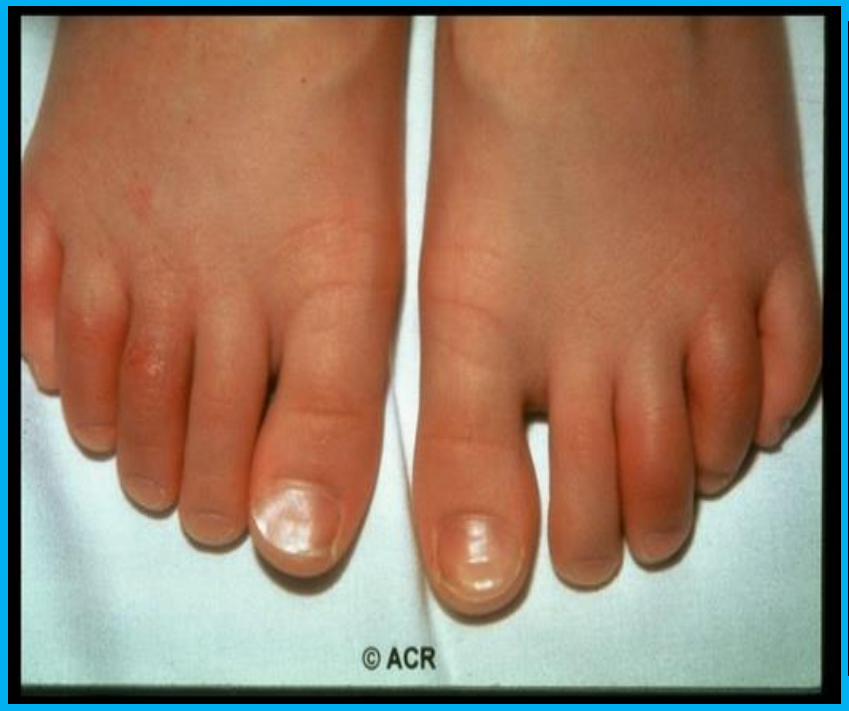
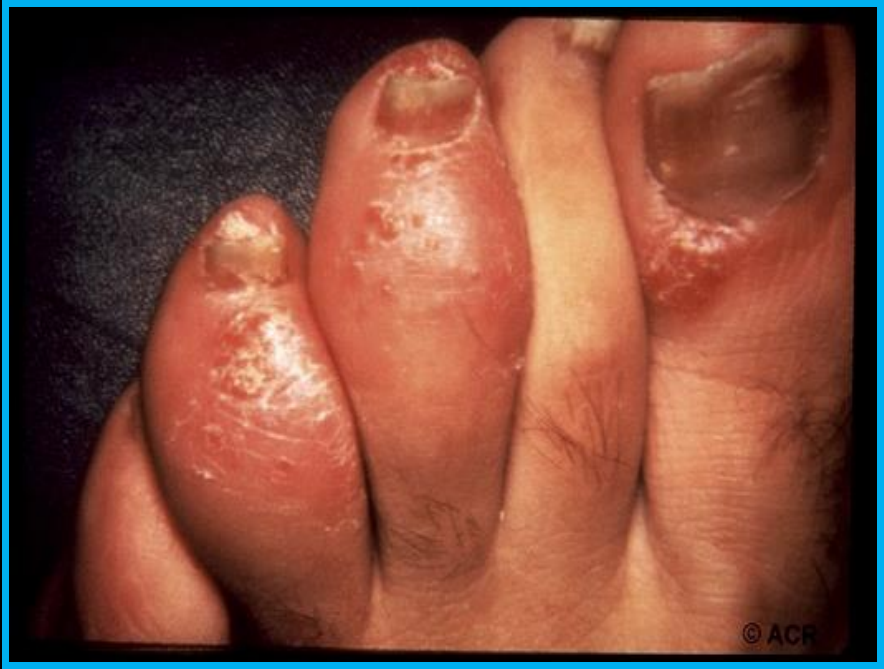
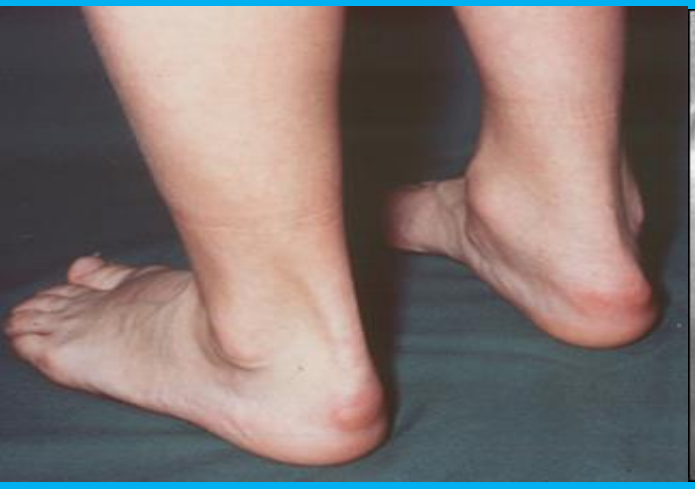
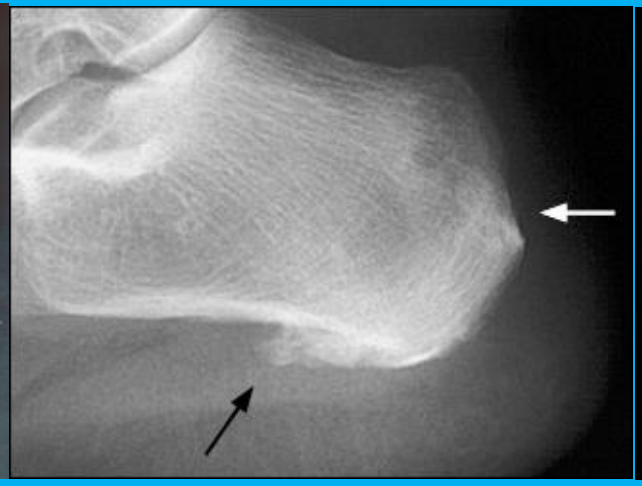
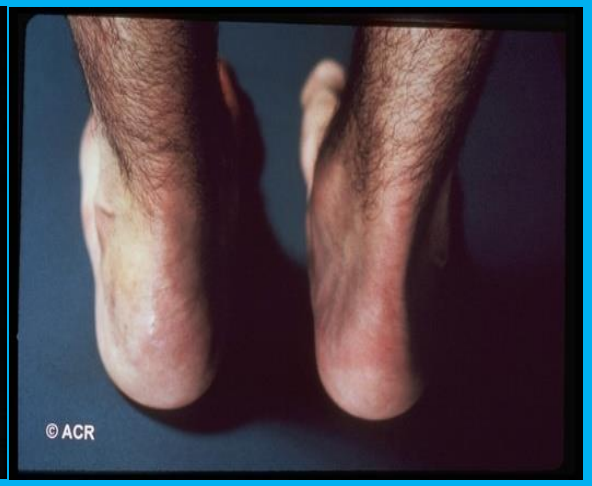
dactylitis, “sausage digit”





Enthesitis Related JIA (ERA)

Arthritis and enthesitis

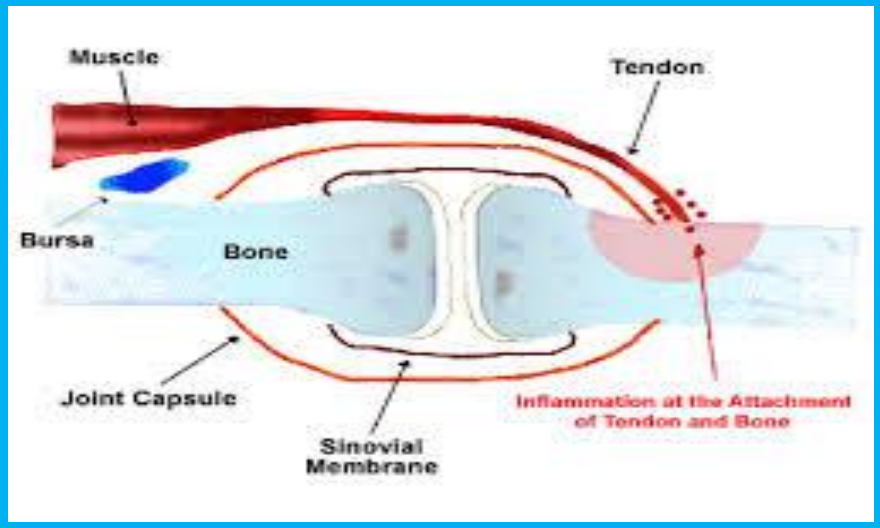
or

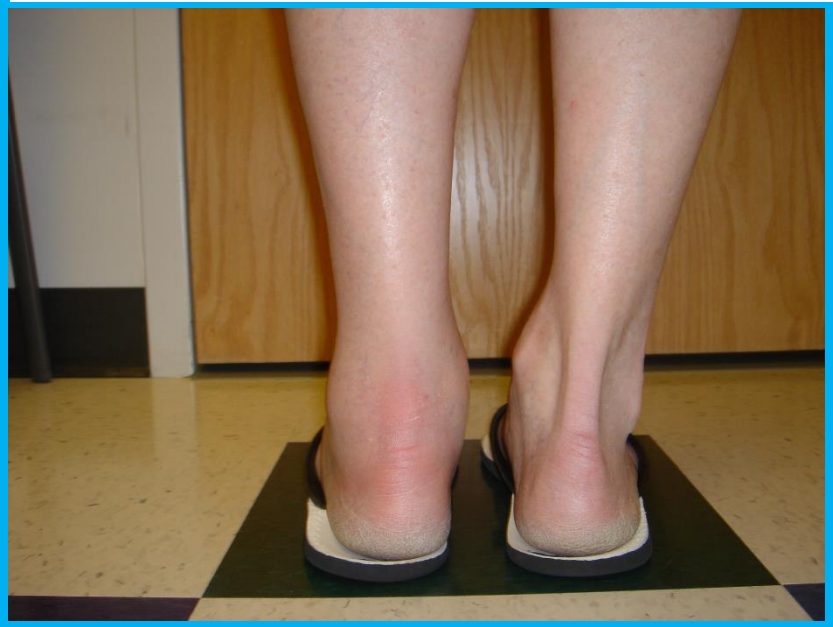
arthritis or enthesitis with >= 2 of the following:

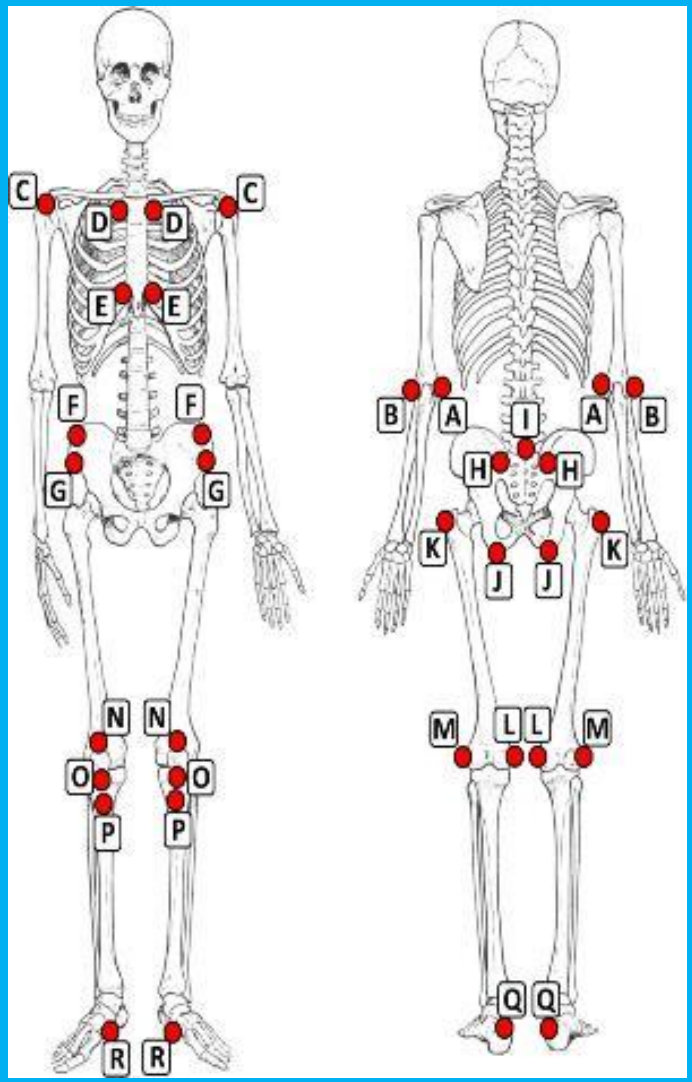
1. history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2. HLA-B27+
3. onset of arthritis in male > 8 years of age
4. acute (symptomatic) anterior uveitis
5. hx of ankylosing spondylitis, sacroiloitis IBD, reactive arthritis, acute anterior uveitis
   - or 1st degree relative

Exclusions

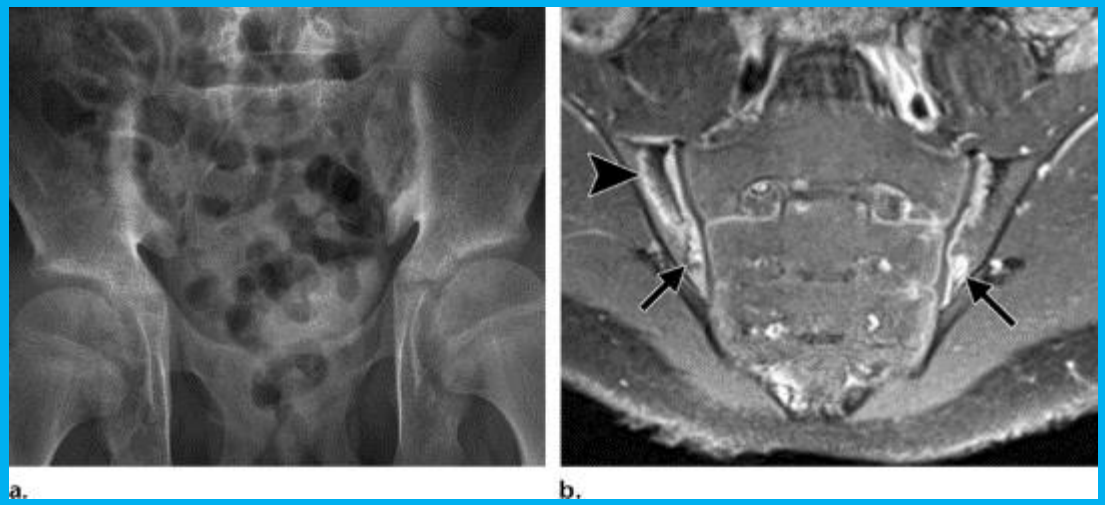
Enthesitis-related arthritis (ERA)







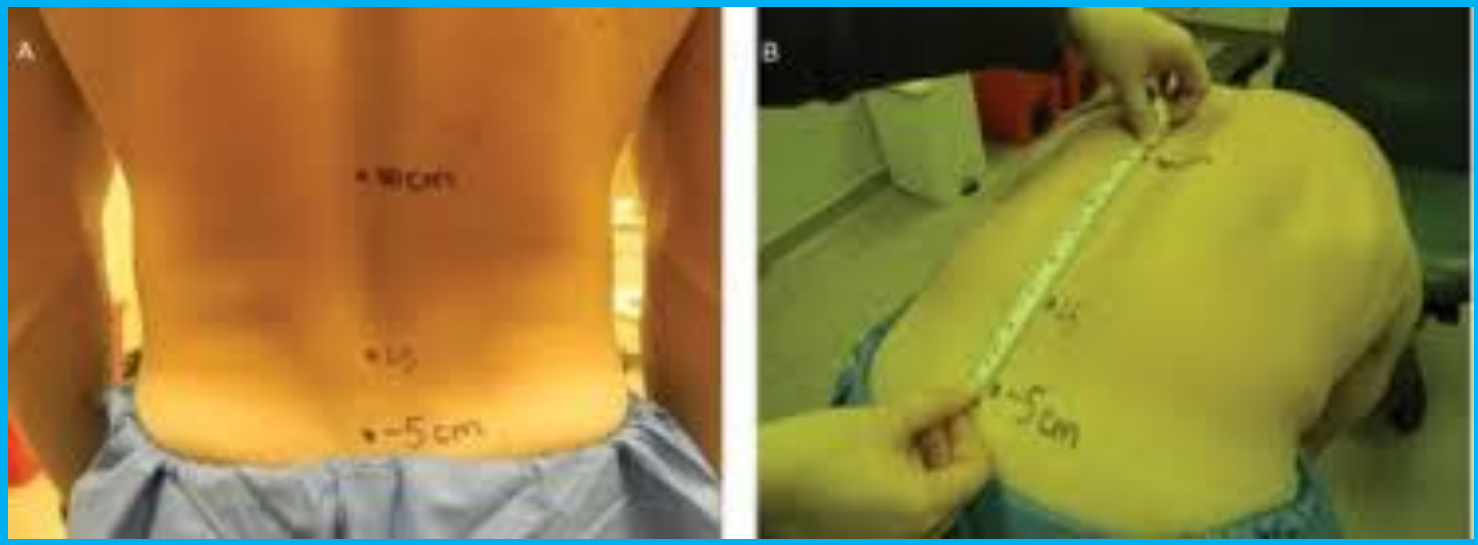
spondyloarthropathy ankylosing spondylitis



spondyloarthropathy, ankylosing spondylitis

physical exam:

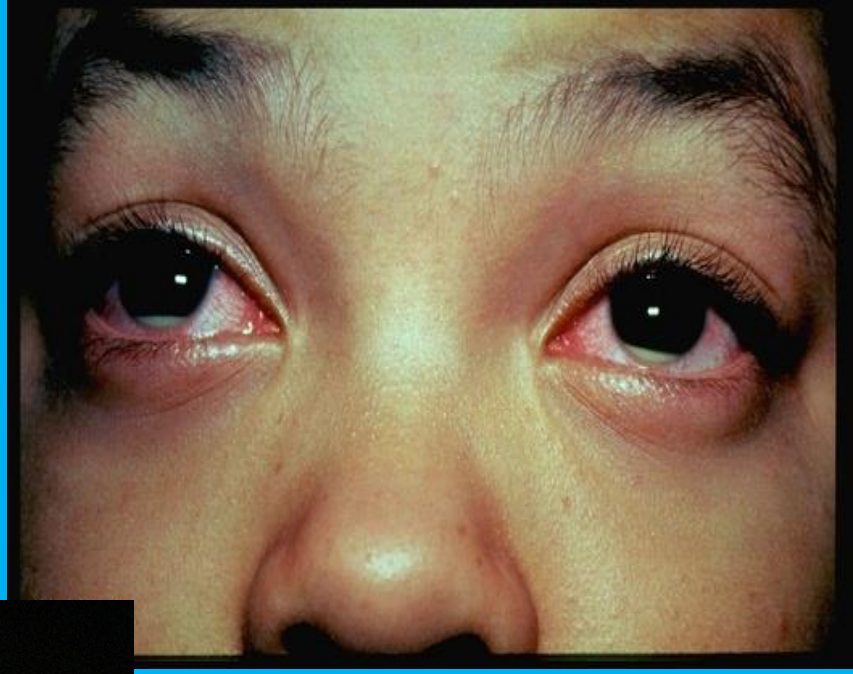
- loss of lumbar lordosis
- decrease lumbar flexion and extension
- **Schober's test:** normal ≥ 21 cm

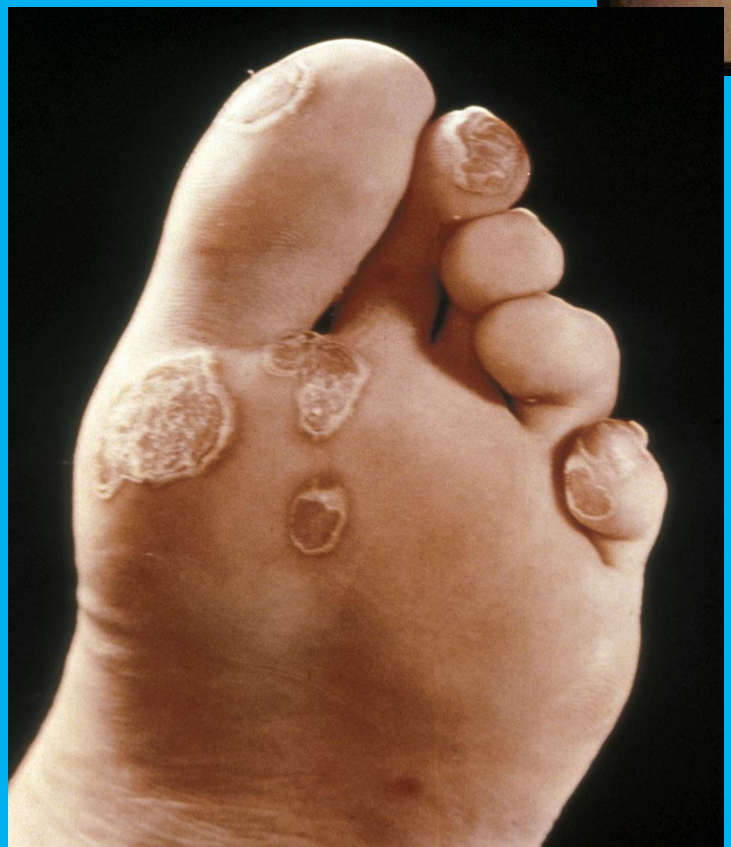


Schober's examination

features of ERA

- Arthritis or enthesitis with at least 2:
  - Sacroiliac tenderness and/or inflammatory spinal pain
  - Presence of HLA B27
  - Family history of confirmed HLA B27 associated disease **(reactive arthritis)**
  - **Acute anterior uveitis (15-25%) with pain, redness, photophobia**
  - Arthritis onset in >8 year old male (80% males)





keratoderma blennorrhagicum

HLA-B27

- HLA Class 1
- 7-10% population (> native American, < AA & Asian)
- 90% of ERA/AS children HLA B27+
- Risk of ERA/AS in HLA B27+ person = 1-3%
- HLA B27 children
  - family hx of AS, risk of ERA/AS x 10 → 10-30%
- Mother or father with AS + HLA B27 +
  - risk male child 5-10%
    - 20% if HLA B27+, <1% if HLA B27 -
  - risk in female children very low

undifferentiated JIA

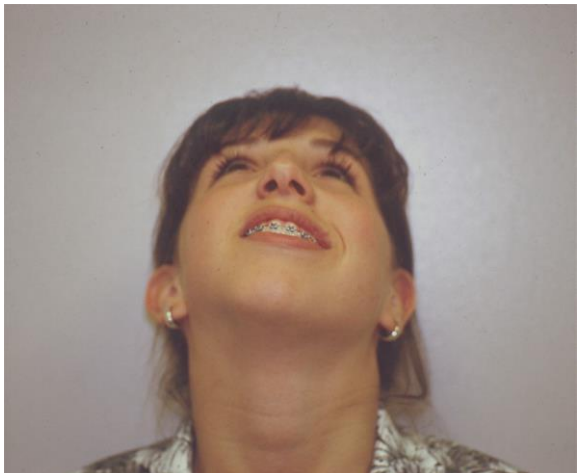
arthritis that fulfills JIA criteria (>6 weeks arthritis, onset prior to 16th birthday) but not fitting into a single JIA diagnostic category

Then diagnosis is “undifferentiated JIA”

TMJ specific joint arthritis

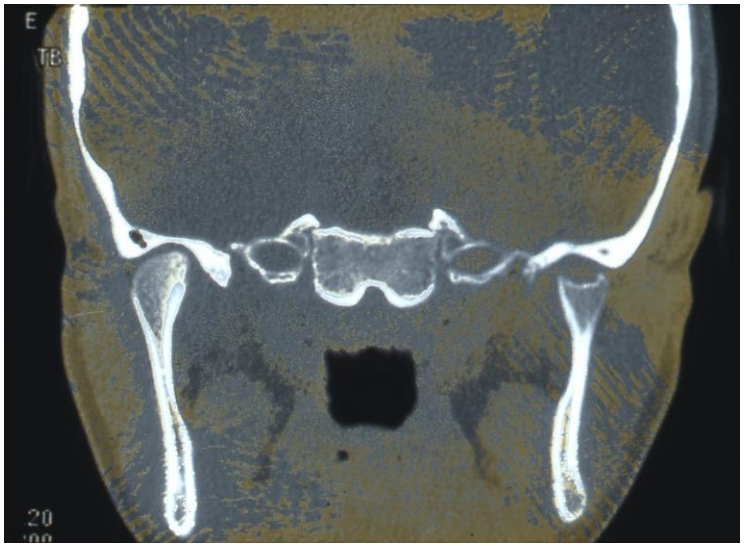
- effects on mandibular condyle
  - condylar joint space narrowing, damage
  - mandible hypoplasia, effect on growth

TMJ-1

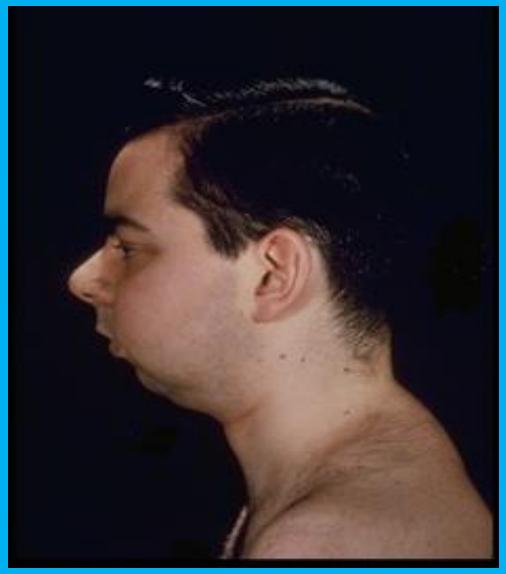


TMJ-5

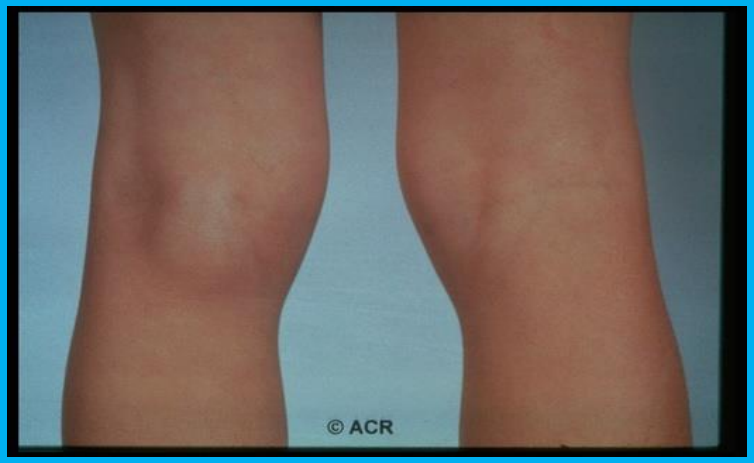
Coronal CT TMJ-3



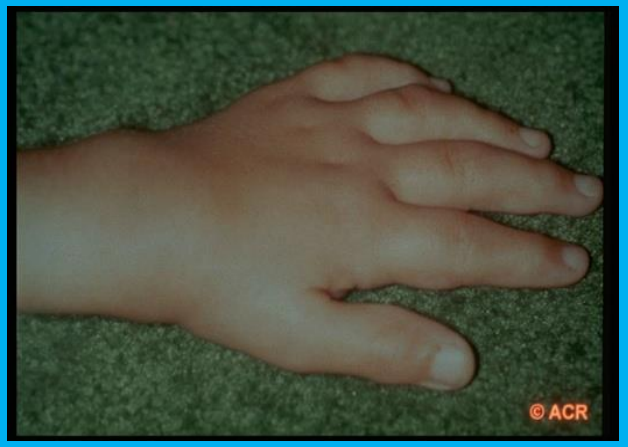
joint, tendon conditions in Juvenile Idiopathic Arthritis (JIA)



C-spine & TMJ involvement



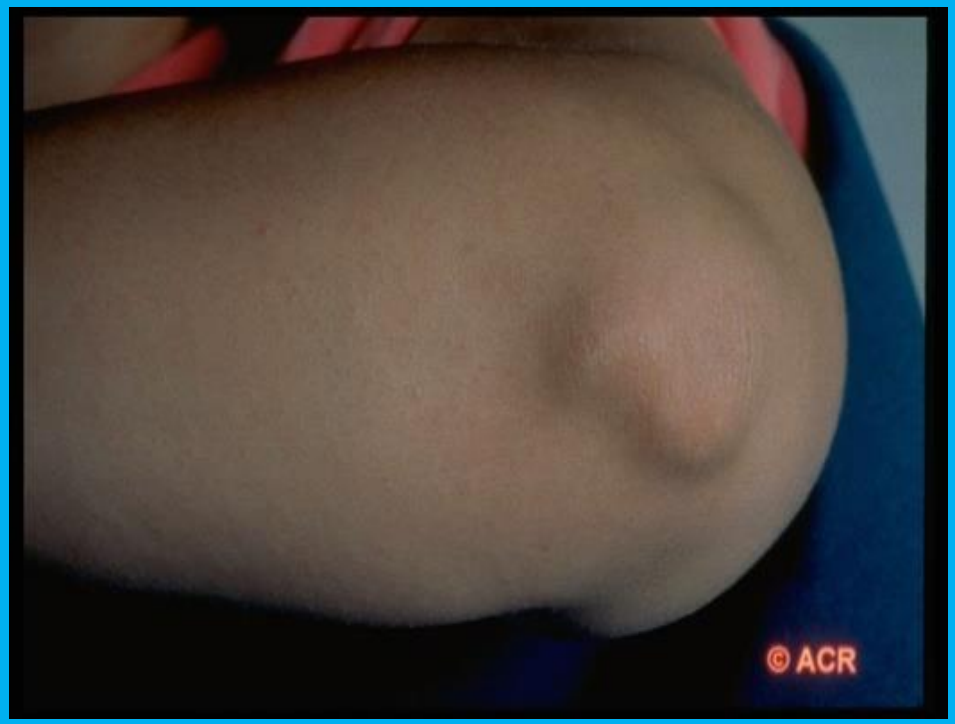
Baker’s cyst

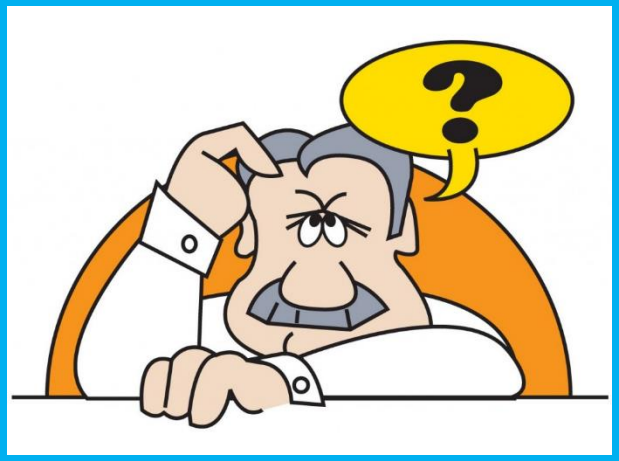


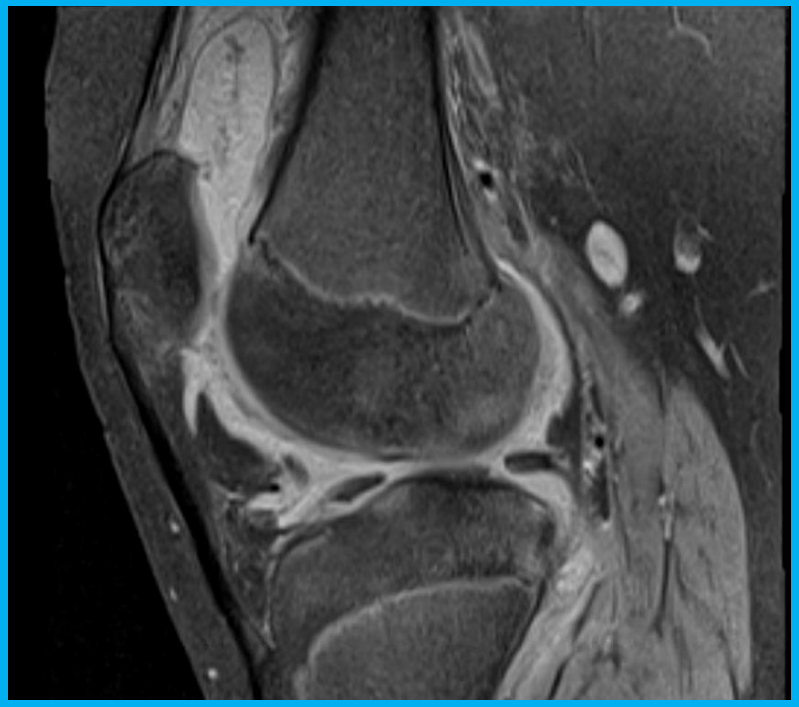
tenosynovial cyst

extra articular manifestations of polyarticular JIA (RF+)

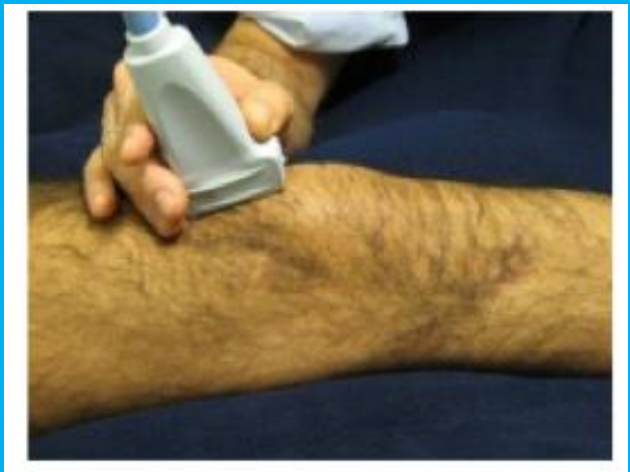
- rheumatoid nodules
  - granuloma annulare
- vasculitis
- Felty's syndrome
  - splenomegaly
  - neutropenia

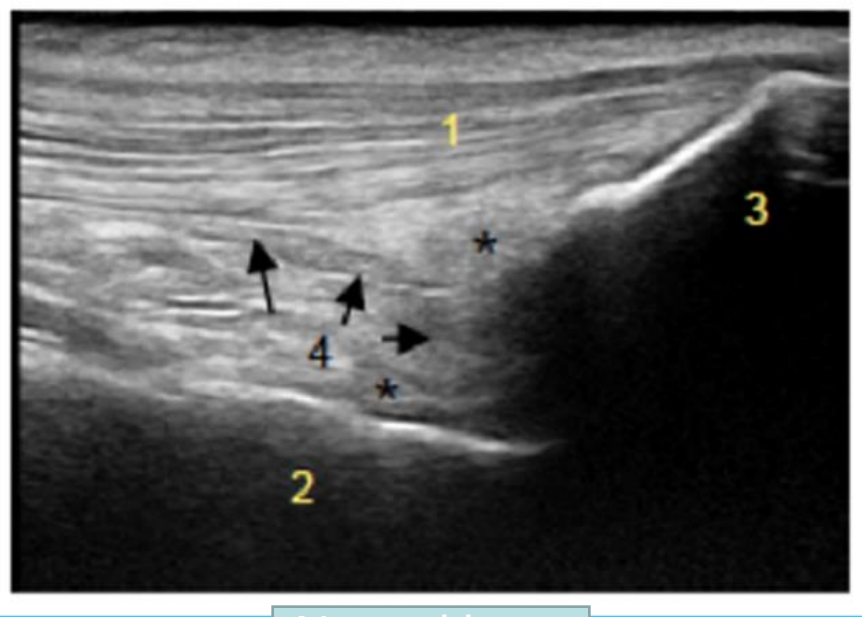




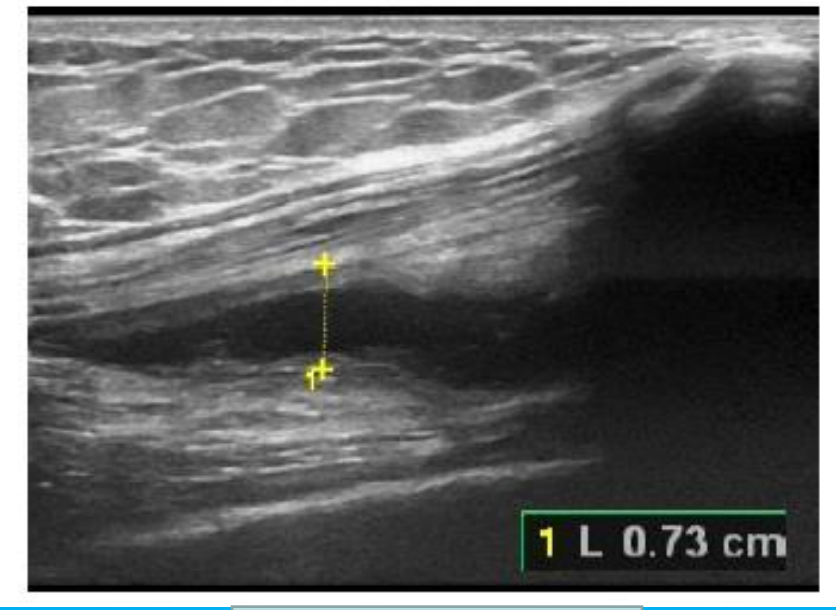


Arthritis
- joint fluid
- synovial tissue thickening
- increased blood flow via doppler signal



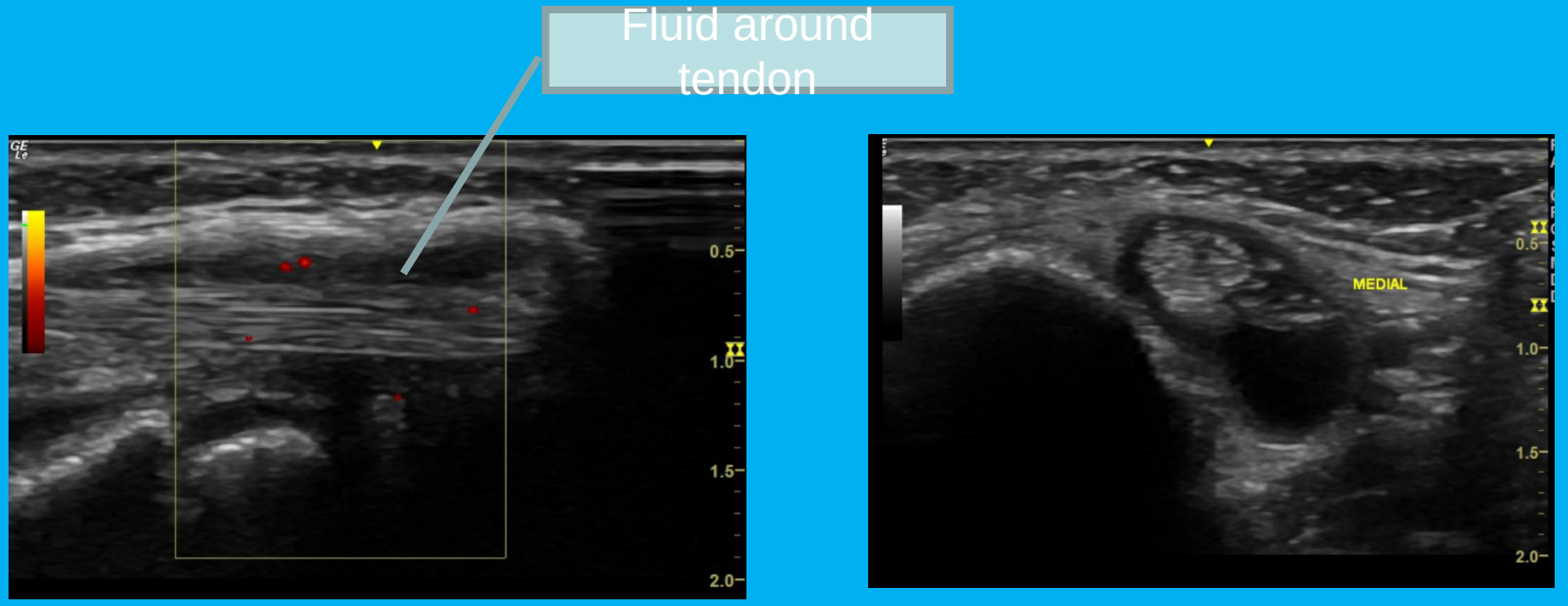


Normal knee

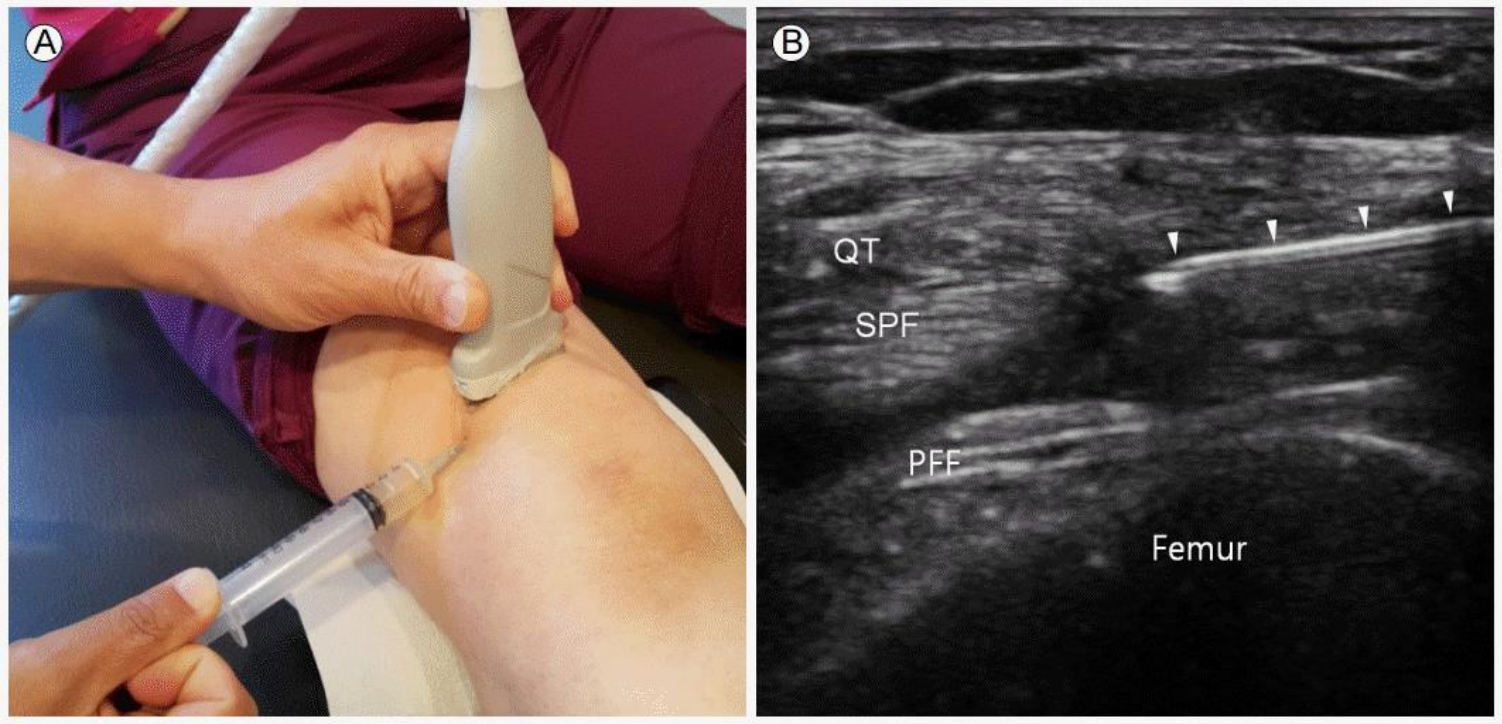


Arthritis knee with fluid

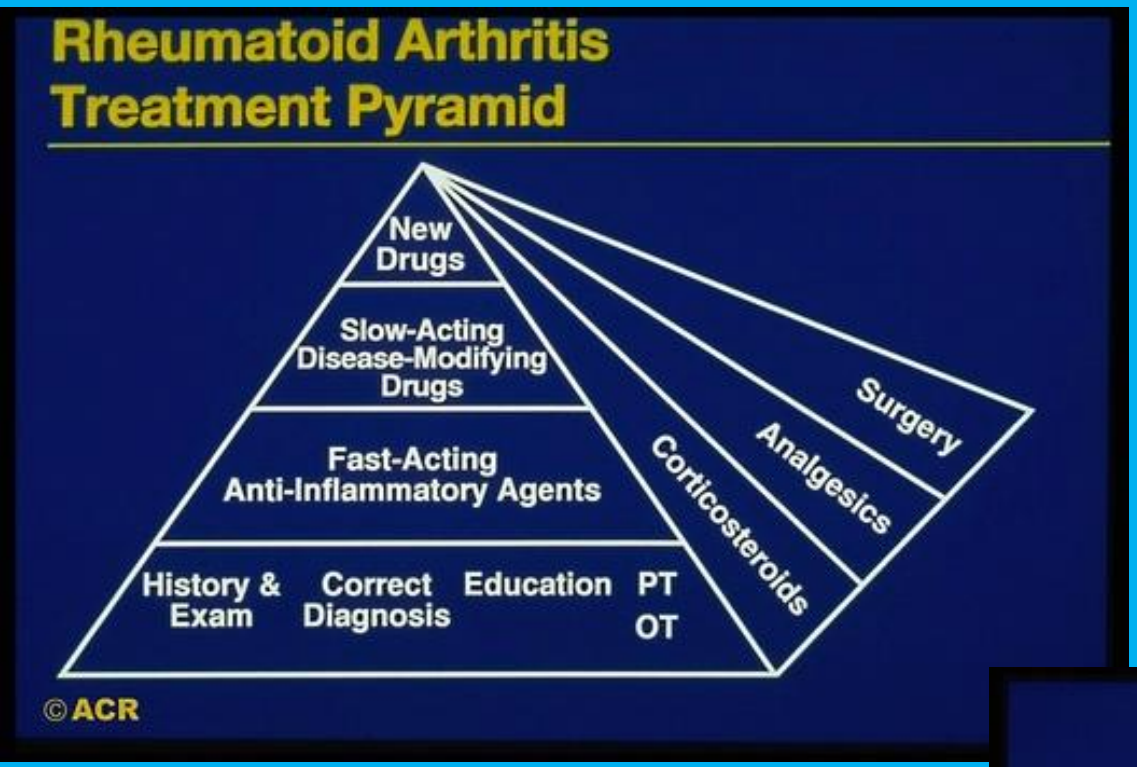
Tenosynovitis



improved accuracy of steroid joint injection procedure



Treatment Philosophy



Inverted pyramid

Aggressive therapy

window of opportunity

- disease may continue into adulthood

Medication Treatments

NSAIDs (pain control)

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- methotrexate, leflunomide,sulfasalazine, hyroxychloroquine

Corticosteroids

- intra-articular: aristospan, kenalog, celestone
- systemic (pill, liquid, IV)

Biologics

- Anti-tumor-necrosis factor (polyarticular & “extended” oligoarticular)
  - etanercept, adalimumab
- T-cell co-stimulator signal inhibitor (polyarticular)
  - abatacept
- Antagonists to IL-1 (systemic)
  - canakinumab
- Antagonists to IL-6 (systemic JIA, polyarticular)
  - tocalizumab

facets of JIA care and management

- multidisciplinary care, consultation
  - ophthalmology, orthopedics, radiology, dermatology, cardiopulmonary, gastroenterology
- specialty pharmacy
- physical and occupational therapy
- surgery: synovectomy, joint replacement
- psychological, education
- compliance issues
- nutrition

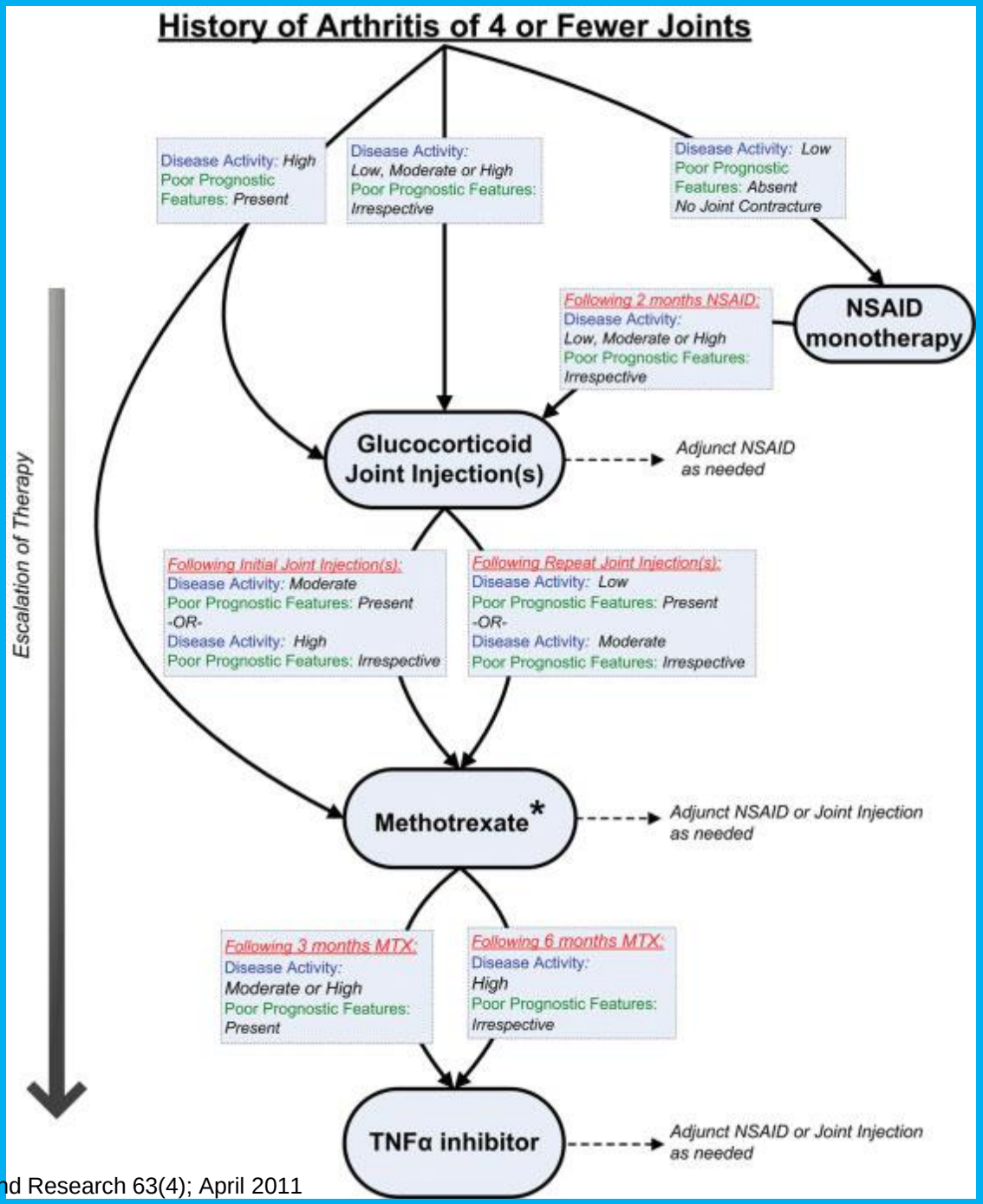
JIA Guidelines

2011 ACR Recommendations for the Treatment of JIA: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features

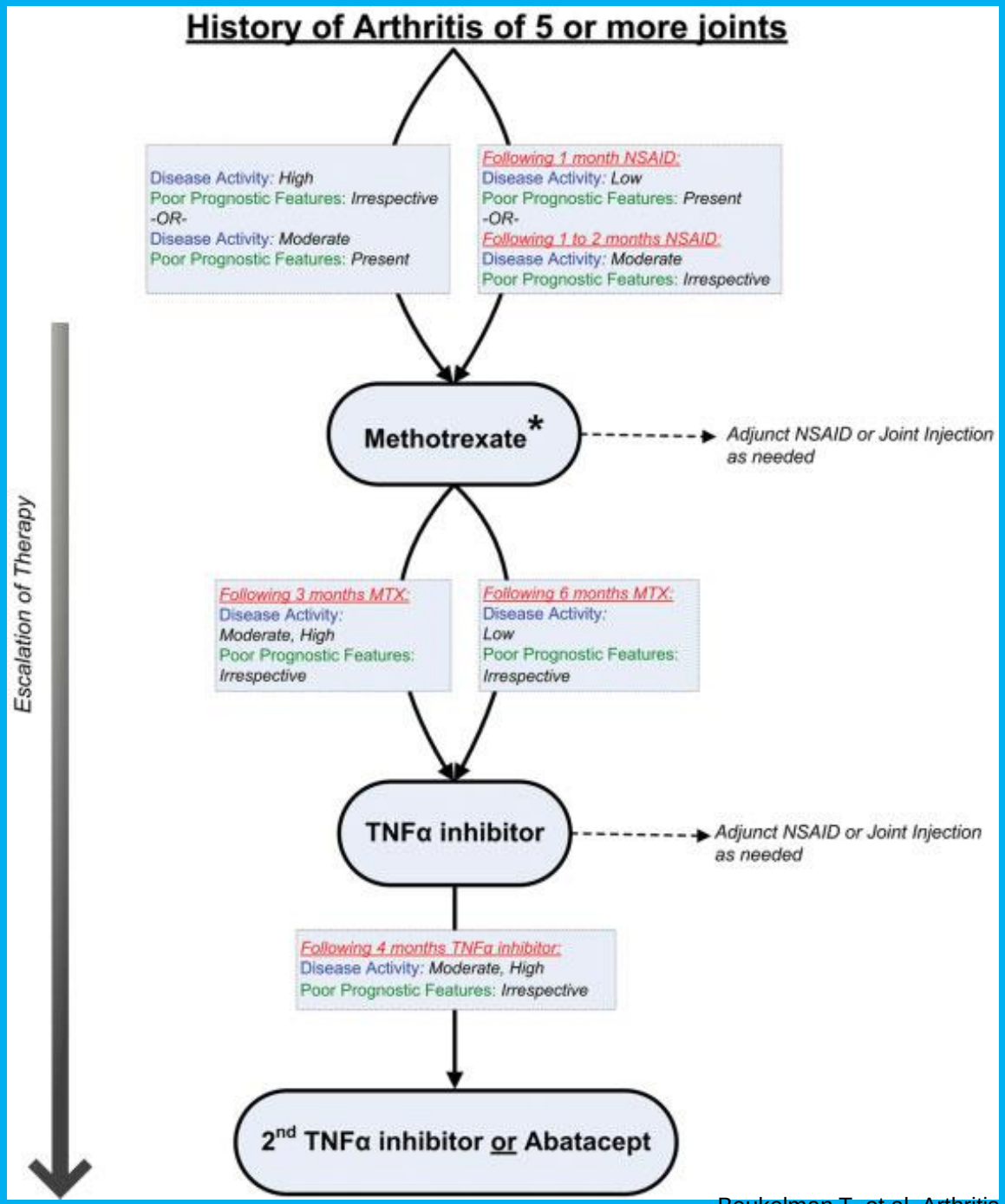
Beukelman T, et al. Arthritis Care and Research 63(4); April 2011

Five Treatment Groups

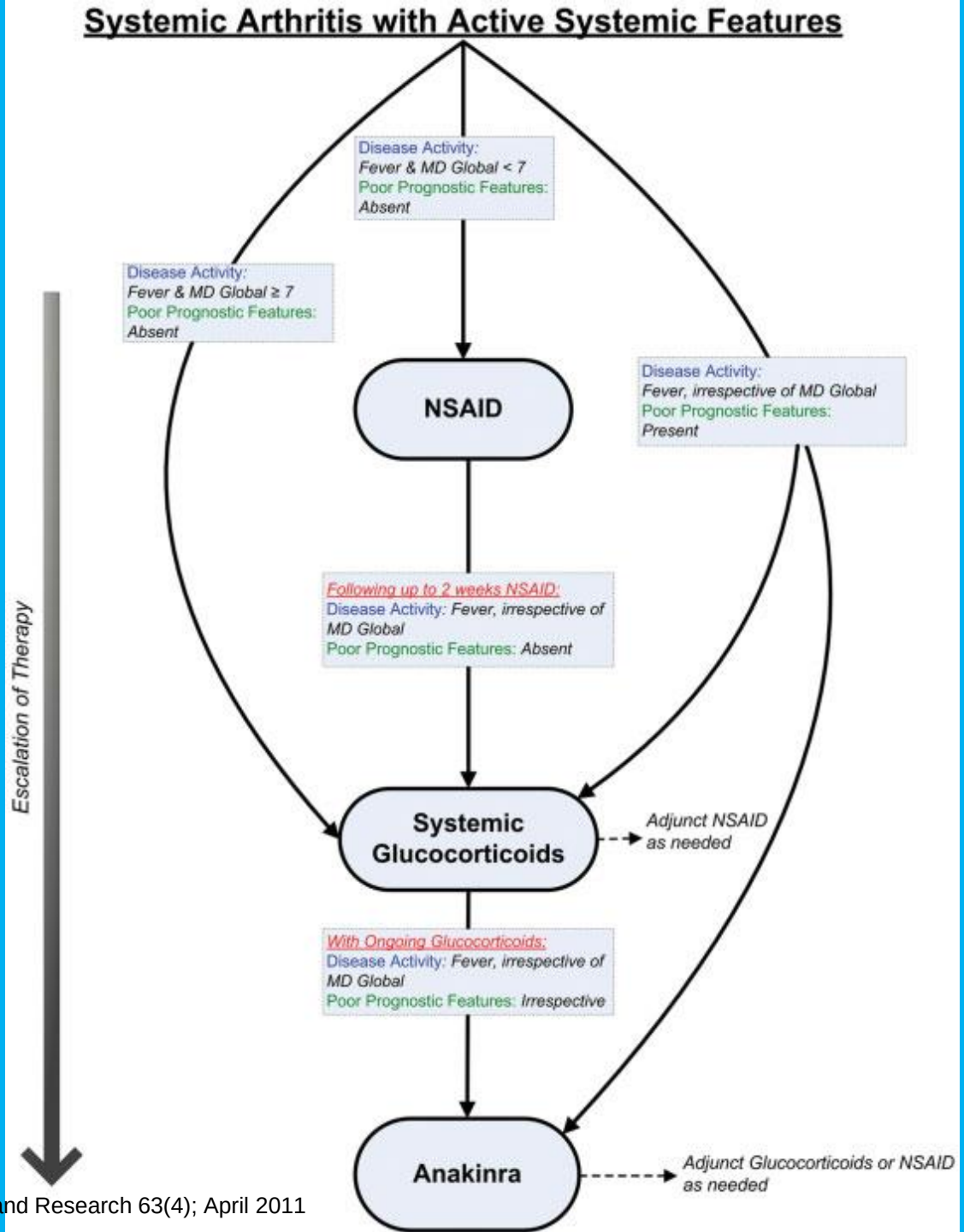
1. history of arthritis of 4 or fewer joints
2. history of arthritis of 5 or more joints
3. active sacroiliac arthritis
4. systemic arthritis with active systemic features (without active arthritis)
5. systemic arthritis with active arthritis (without active systemic features)



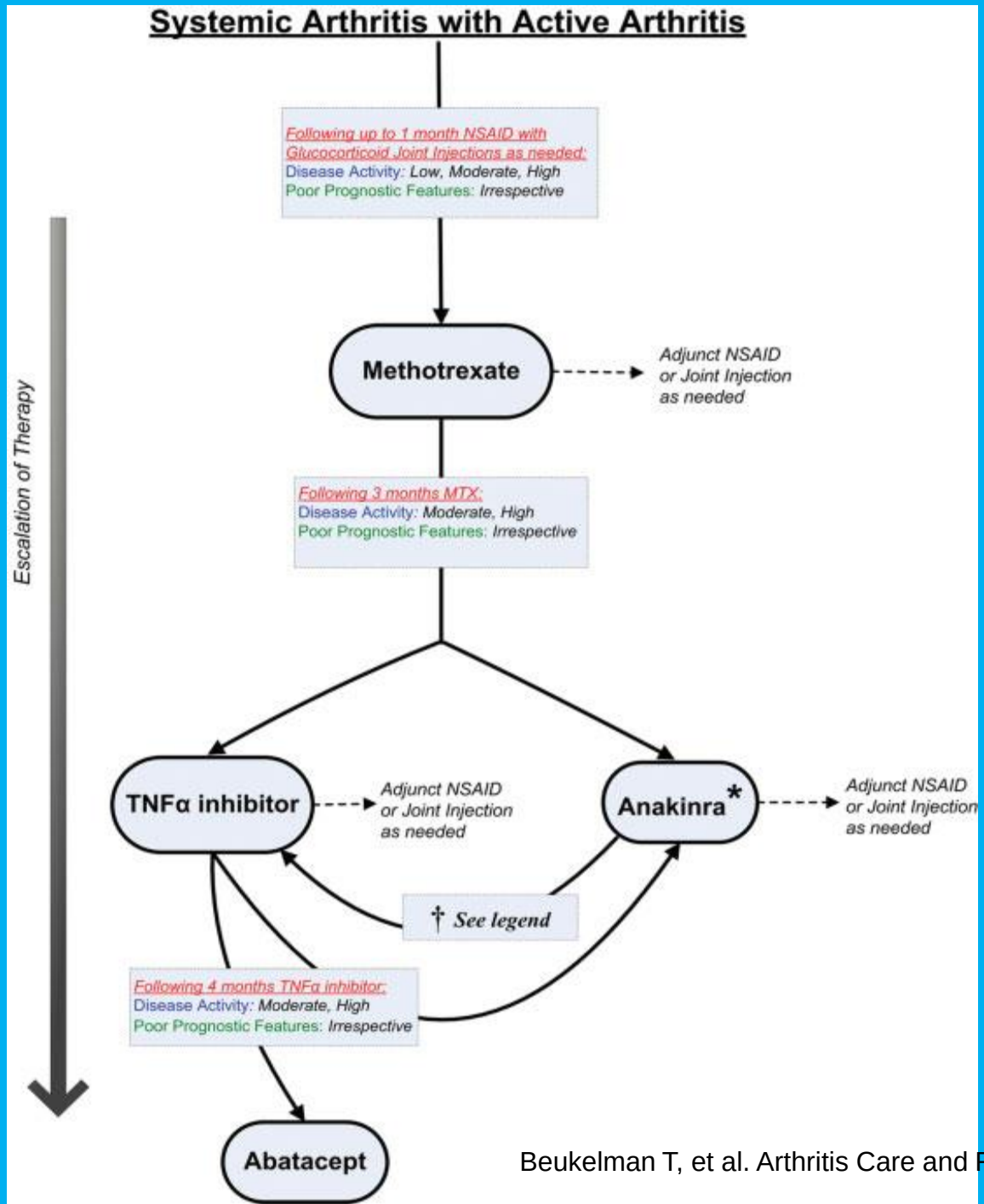
Beukelman T, et al. Arthritis Care and Research 63(4); April 2011



Beukelman T, et al. Arthritis Care and Research 63(4); April 2011



Beukelman T, et al. Arthritis Care and Research 63(4); April 2011



Beukelman T, et al. Arthritis Care and Research 63(4); April 2011

Treatment guidelines


2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications†

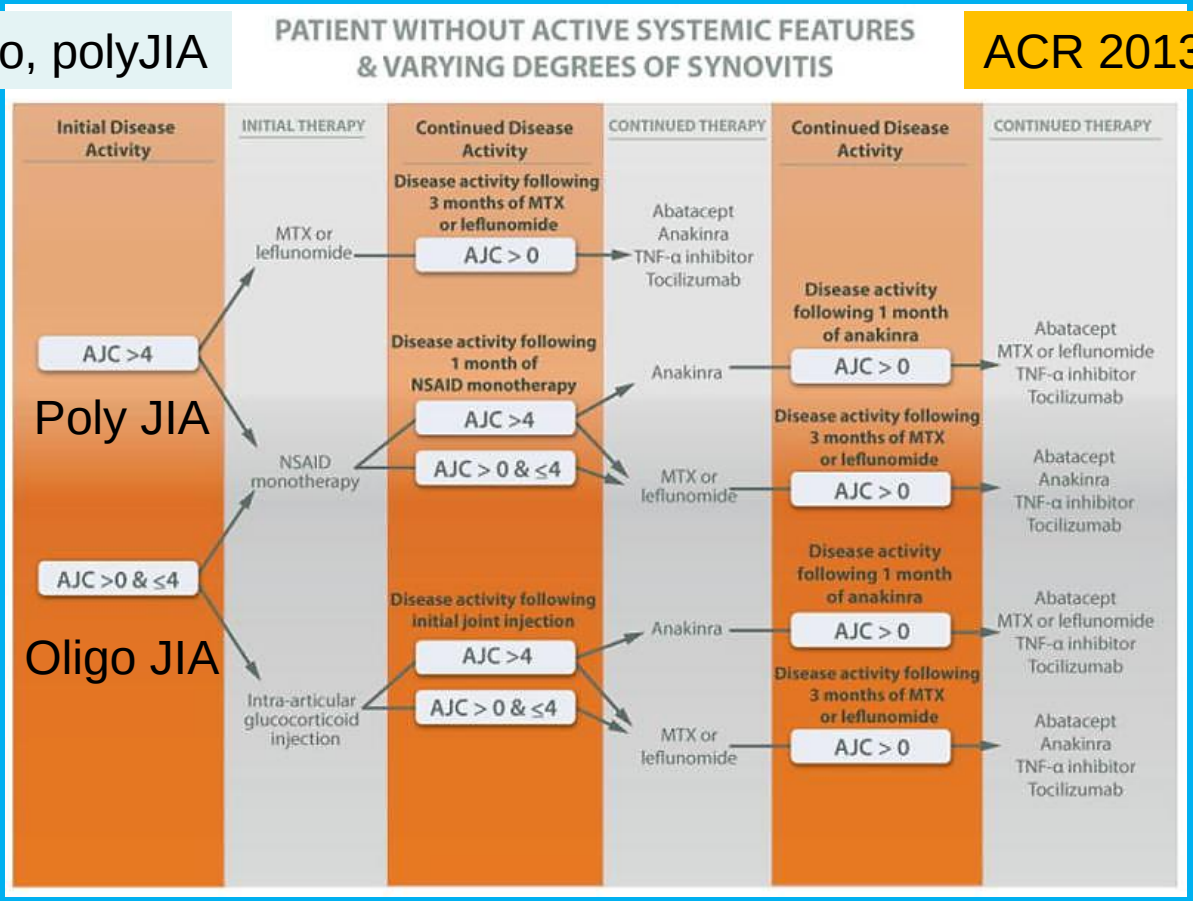
Sarah Ringold, Pamela F. Weiss, Timothy Beukelman, Esi Morgan DeWitt, Norman T. Ilowite, Yukiko Kimura, Ronald M. Laxer, Daniel J. Lovell, Peter A. Nigrovic, Angela Byun Robinson, Richard K. Vehe ... See fewer authors

Pediatric JIA Guidelines

- **1. American College of Rheumatology**
  - JIA Beukelman T, et al. Arthritis Care and Research 63(4); April 2011
  - Systemic JIA (Ringold S et al, Arthritis & Rheumatism; October 2013)
- **2. Childhood Arthritis Research Rheumatology Alliance (CARRA)**
  - Systemic JIA (DeWitt EM et al, Arthritis Care Research; July 2012)
  - Polyarticular JIA (Ringold S et al, Arthritis Care Research; July 2014)
  - JIA associated uveitis (Angeles-Han ET et al, Arthritis Care Research; May 2018)

Oligo, polyJIA

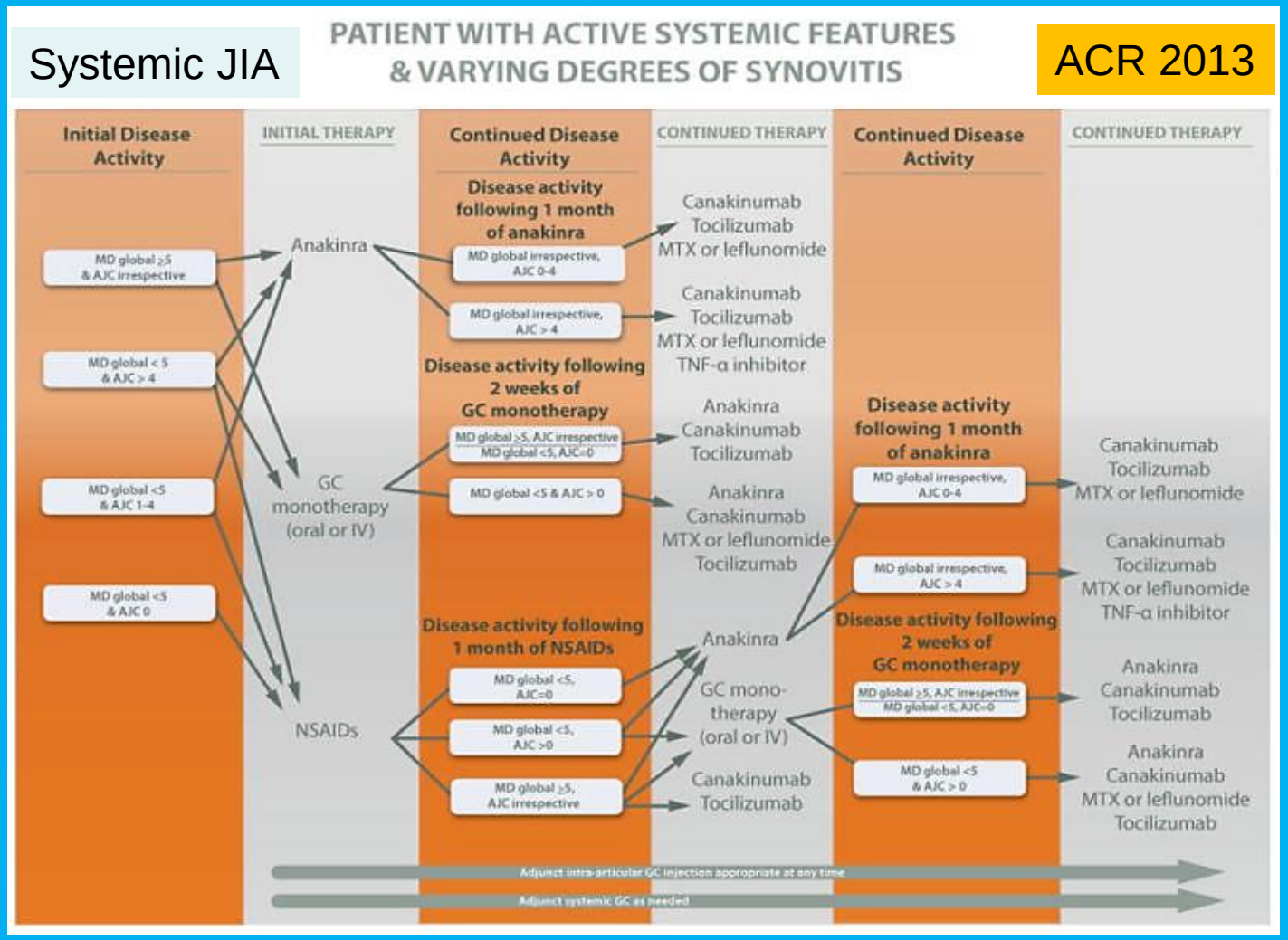
ACR 2013



Ringold S et al, Arthritis & Rheumatism; October 2013

Systemic JIA

ACR 2013



Ringold S et al, Arthritis & Rheumatism; October 2013

Recommendations for medication safety monitoring

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

- Complete blood count, liver enzymes, serum creatinine
- Prior to or soon after initiation of routine use
- Repeat approximately twice yearly for chronic daily use
- Repeat approximately once yearly for routine use(3–4 days per week)

METHOTREXATE

- Complete blood count, liver enzymes, serum creatinine
- Prior to initiation
- Approximately 1 month after initiation
- Approximately 1–2 months after increase in dose
- Repeat approximately every 3–4 months if prior
- results normal and dose stable

TUMOR NECROSIS FACTOR INHIBITORS

- Complete blood count, liver enzymes, serum creatinine
- Prior to initiation
- Repeat approximately every 3–6 months
- Tuberculosis screening
- Prior to initiation
- Repeat approximately once yearly

Beukelman T, et al. Arthritis Care and Research 63(4); April 2011

- **Transition of care program for adolescent patients with rheumatologic diagnosis**

- Balancing 3 sides of the Wellness triangle, overlap for children with amplified pain syndromes (CRPS, RSD)

- **Dedicated musculoskeletal ultrasound and joint injection clinic**

- **Rheumatology Dermatology Combined Clinic**

Cleveland Clinic Center for Pediatric Rheumatology

- Care of children and young adults with childhood onset autoimmune disorders
- Research
- Education

<u>Clinic Locations (far West and West)</u>

Firelands Regional Medical Center – Sandusky, Ohio

Cleveland Clinic Avon Richard E. Jacobs Family Health Center - Avon, Ohio

Cleveland Clinic Strongsville Family Health Center – Strongsville, Ohio

Cleveland Clinic Children’s Outpatient Center (main campus, R Building)

- **Thank you!**
- **Questions**

Cleveland Clinic Center for Pediatric Rheumatology

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zefta@ccf.org