RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

RHAPP NATIONAL CONFERENCE

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Juvenile Idiopathic Arthritis 101

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- The speakers have no relevant financial relationships with any commercial interests.
- The speakers will be discussing off-label medication use.

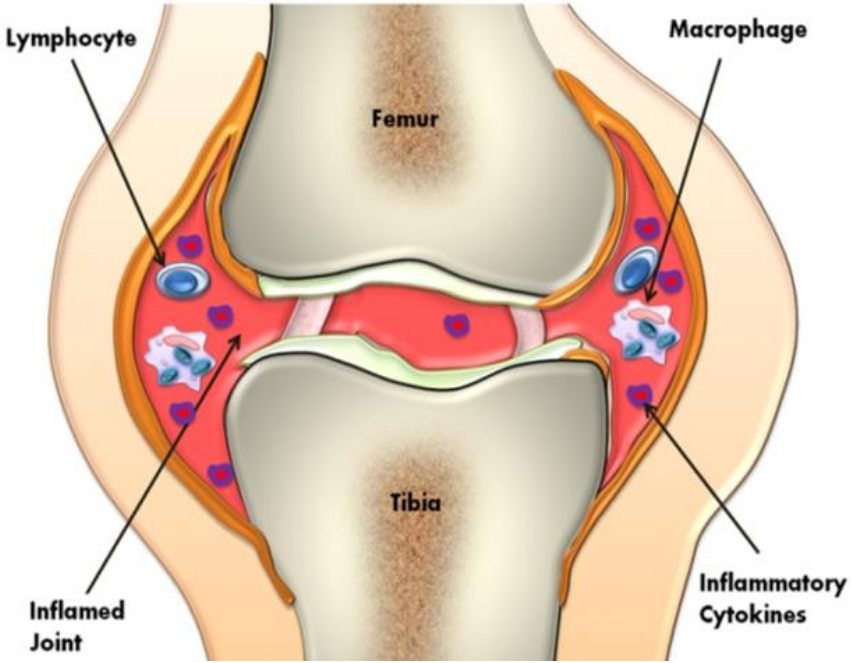
Objectives

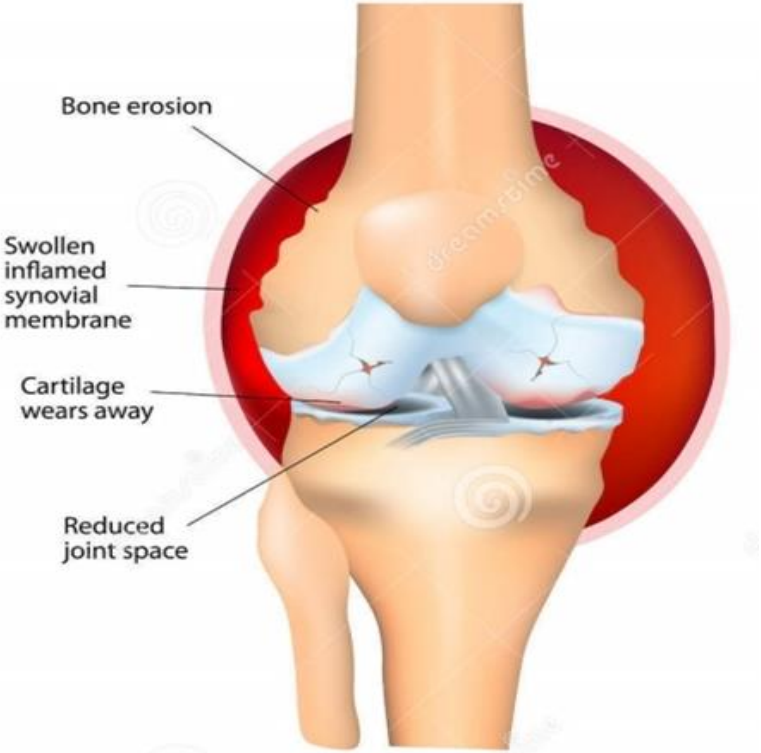
1. Review the epidemiology and clinical presentation of non-systemic Juvenile Idiopathic Arthritis
2. Discuss diagnostics and diagnostic dilemmas specific to non-systemic Juvenile Idiopathic Arthritis
3. Summarize current pharmacologic agents for the treatment of non-systemic Juvenile Idiopathic Arthritis

JIA Epidemiology

- Most common pediatric rheumatologic disease
- Global distribution
- Prevalence: ~300,000 in USA
- Immune mediated inflammatory synovitis

JIA Pathophysiology





JIA Diagnosis

- Onset prior to 16 years of age
- Persistence of symptoms 6 weeks or greater
- No other cause of synovitis identified
- Further specifications for each of the classification types
- Presentation can be different from adults
  - May not complain of pain
  - Stiffness is an abstract concept
  - Irritability in morning, **after naps**
  - Not walking on time, delay in milestones (i.e., pincer grasp), not playing at recess

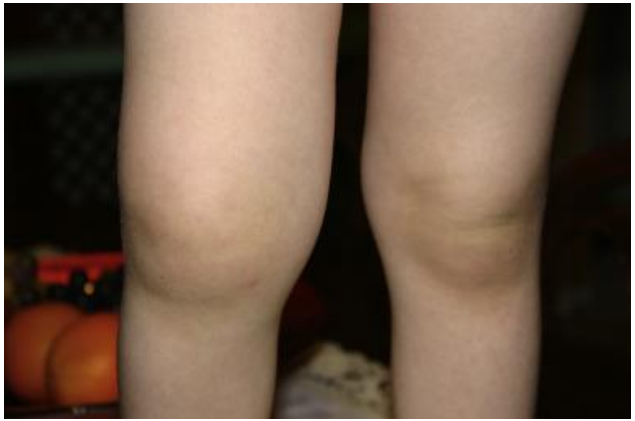
JIA Classification (ILAR)

- **Oligoarticular** (40-60%)
- **Polyarticular** (20-35%)
  - RF positive
  - RF negative
- **Enthesitis Related Arthritis (ERA)** (5-10%)
- **Psoriatic** (~5%)
- **Systemic** (10-20%)
- Undifferentiated

ILAR = International League of Associations for Rheumatology

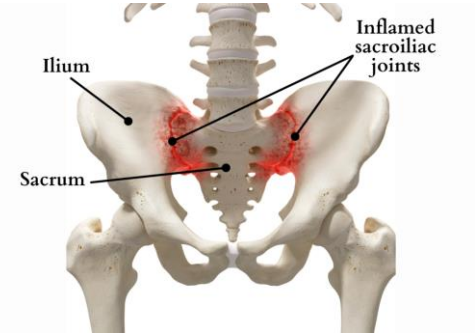
Oligoarticular JIA

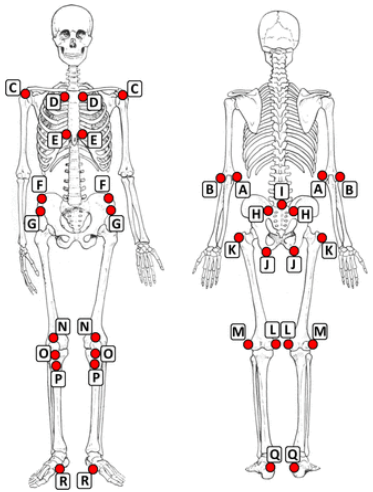
- Arthritis of <5 joints
- Sub-classification:
  - Persistent oligo JIA: never > 4 joints
  - Extended oligo JIA: eventually > 4 joints
- Peak incidence 1 – 3 years old
- Females more affected (3:1)
- Large joints (knees, ankles)
  - **Unilateral hip is rare; look for other cause!**
- Best overall prognosis of all JIA types
- Highest risk of uveitis



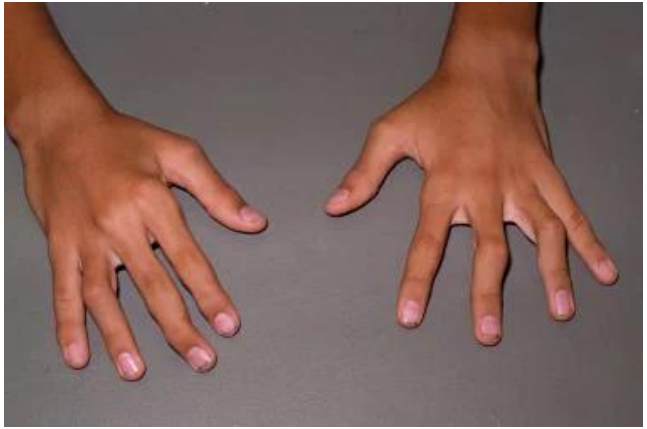
Enthesitis Related Arthritis

- Arthritis *and* Enthesitis
  OR
- Arthritis *or* Enthesitis, plus 2 of following:
  - SI tenderness or inflammatory back pain
  - HLA-B27+
  - Acute anterior uveitis
  - Onset of arthritis in boys > 6 years old
  - 1st degree relative with AS or ERA
- Mean age of diagnosis 10 – 13 years old
- Predominance of males





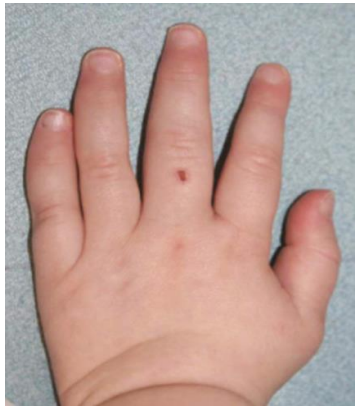
Polyarticular JIA

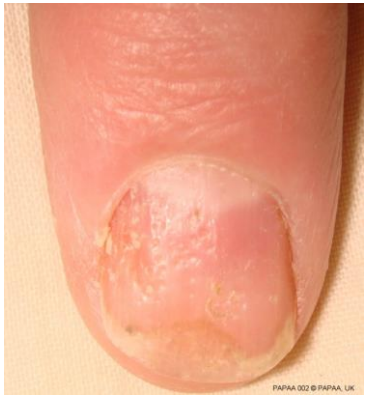


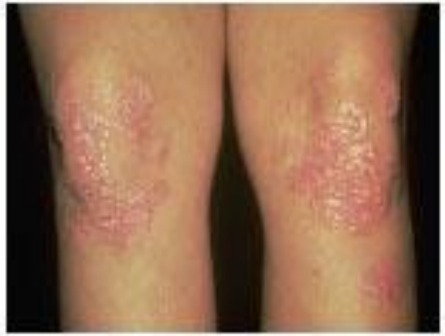
- 5 or more joints affected
- Classified as:
  - **RF positive polyarticular JIA**
    - More severe, erosive
    - Most similar to adult RA
  - **RF negative polyarticular JIA**
    - CCP more specific; historic classifications have not caught up
- Females more affected
- Biphasic peak of onset
  - 1 – 4 years old: F>M
  - Pre-adolescence/adolescence: F >>>M

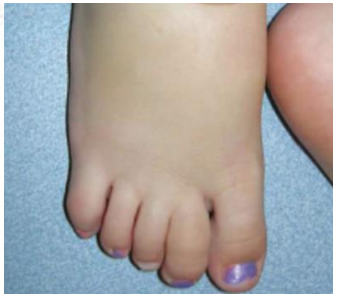
Juvenile Psoriatic Arthritis

- Arthritis *and* Psoriasis
  OR
- Arthritis, plus <u>2 of following</u>:
  - Dactylitis
  - Nail pitting or onycholysis
  - Psoriasis in a first-degree relative
- Age of onset bimodally distributed
  - 1st peak during preschool years
  - 2nd peak during middle to late childhood
- F > M



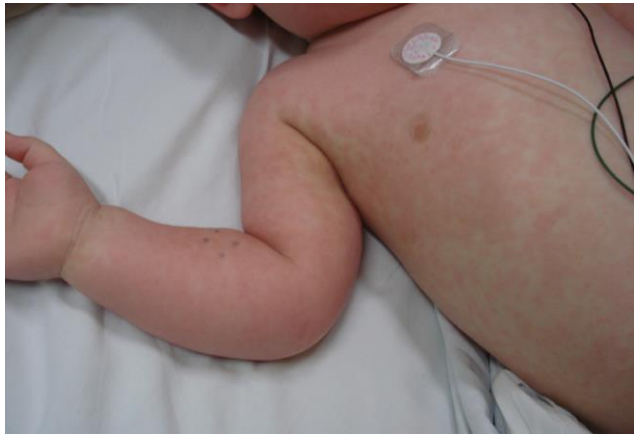






Systemic-Onset JIA

- Most severe JIA classification
- Behaves differently from other forms of JIA
- Autoinflammatory (as opposed to autoimmune)



The Role of Labs in JIA

Diagnosis is <u>not</u> based upon labs

- Labs help us track (sometimes)
  - Inflammatory markers are variable
- Labs help us categorize: RF, CCP, HLA-B27
- Labs help us with prognosis
  - RF/CCP = More erosive disease
  - ANA = Risk of uveitis

Most kids with JIA have normal labs!

ANA plays no diagnostic role

Case Study: J.C.

13-year-old female referred from PCP for chronic bilateral knee pain in July 2019

- 2 – 3 years of knee pain occurring a few times a week
- Family unsure of swelling
- Morning stiffness reported x10 minutes few days a week
- No fevers, rashes, weight loss, mouth sores, abdominal symptoms
- No history of travel outside of Colorado in the past 2 years
- No know preceding illness or injury

<u>At Today's Visit:</u>

- Exam notable for subtle L knee swelling and warmth, full ROM without discomfort
- No notable leg length discrepancy
- Exam otherwise unremarkable
- Normal gait, able to heel and toe walk without difficulty

What would be your next steps?

J.C. (Continued)

MRI obtained August 2021: synovitis, effusion (also L knee medial plica)

<u>Labs</u>

- ANA: 1:640 (ENA negative)
- RF: negative
- CCP: negative
- HLA-B27: negative
- ESR/CRP: normal
- CBC: normal

Based on the information, what is her diagnosis?

Differential Diagnoses

- Growing Pains
- Hypermobility
- Ortho: Trauma, Osgood Schlatter, Sinding-Larsen-Johansson, SCFE, Legg-Calve-Perthes, etc.
- Malignancies (leukemia, lymphoma)
- Infectious
  - Transient Synovitis/Post-viral Reactive Arthritis
  - Post-Streptococcal Reactive Arthritis, Rheumatic Fever
  - Septic Arthritis
  - Osteomyelitis
  - TB, Lyme Arthritis

Differential Diagnoses (Continued)

- GI: IBD, celiac disease
- Coagulopathy (hemophilia)
- PVNS
- Pain with no swelling: Amplified Musculoskeletal Pain Syndrome (AMPS), Vitamin D deficiency, Thyroid Dysfunction
- Rheumatologic disease
  - JIA
  - SLE
  - JDM
  - Vasculitis
  - Sarcoidosis
  - Autoinflammatory diseases

J.C.'s Diagnosis: Oligoarticular JIA

ILAR Classification Criteria for Oligoarthritis *

Definition: Arthritis affecting 1 to 4 joints during the first 6 months of disease

Subcategories:

1. Persistent oligoarthritis: Affects not more than 4 joints throughout disease course
2. Extended oligoarthritis: Affects more than 4 joints after the first 6 months of disease

Exclusions:

- Psoriasis or a history of psoriasis in the patient or first degree relative
- Arthritis in an HLA-B27 positive male beginning after 6th birthday
- Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with IBD, or acute anterior uveitis, or history of one of these disorders in 1st degree relative
- Presence of IgM Rheumatoid Factor on at least 2 occasions at least 3 months apart
- Presence of systemic JIA

** Classification criteria are designed to identify a homogeneous population for research studies and are not diagnostic criteria, although they are often used for diagnosis in practice*

Based on her diagnosis, what would you recommend as initial treatment?

J.C.'s Treatment Course

August 2019

- Started scheduled NSAIDs
- Left knee steroid injection

December 2019

- Uveitis diagnosis
- Treated with Pred Forte® drops

May 2020

- Returned to care: found to have active arthritis in both knees
- Bilateral knee steroid joint injections

J.C.'s Treatment Course

January 2021

- Worsening uveitis
- Started on oral methotrexate

August 2021

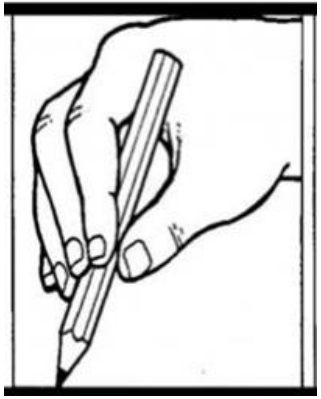
- Ongoing mild active left knee arthritis
- Switched from oral to SC methotrexate

April 2022

- Doing well on current treatment plan: arthritis and uveitis quiet

JIA Complications Unique from RA

- Impact on development
- Social / emotional / bullying
- Leg length discrepancy
- Flexion Contractures
- Uveitis
- TMJ arthritis



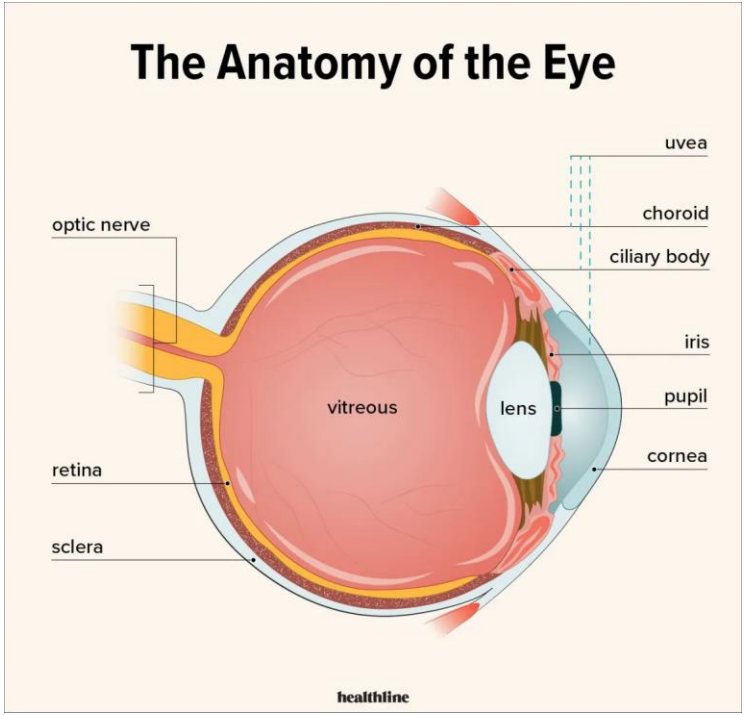
JIA Associated Uveitis

What does it look like?

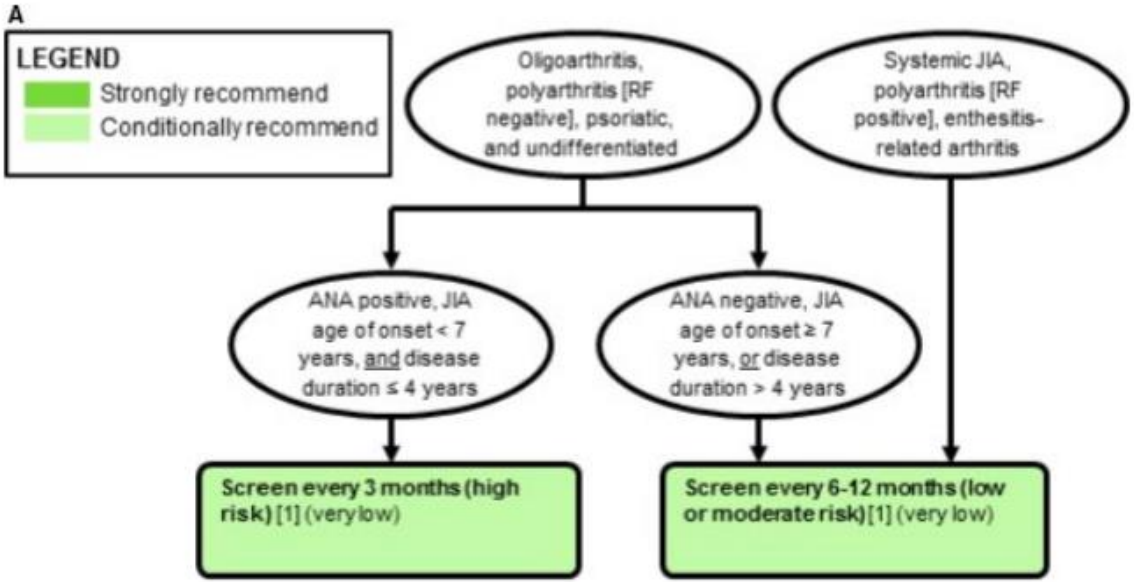
- **ERA/HLA-B27+:** Acute anterior
  - Symptomatic (painful red eyes, blurry vision)
- **Oligoarticular (& sometimes polyarticular):** Chronic anterior

Chronic anterior uveitis

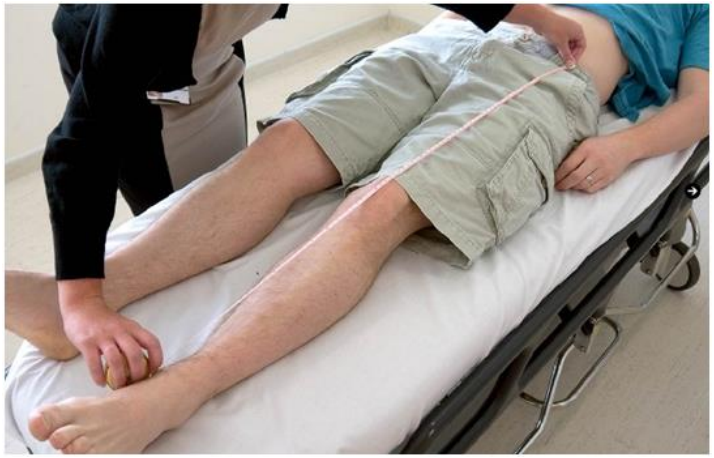
- Most are asymptomatic
- 4th leading cause of blindness in children
- Positive ANA significantly increases risk
- 20% of ANA+ oligoarticular JIA

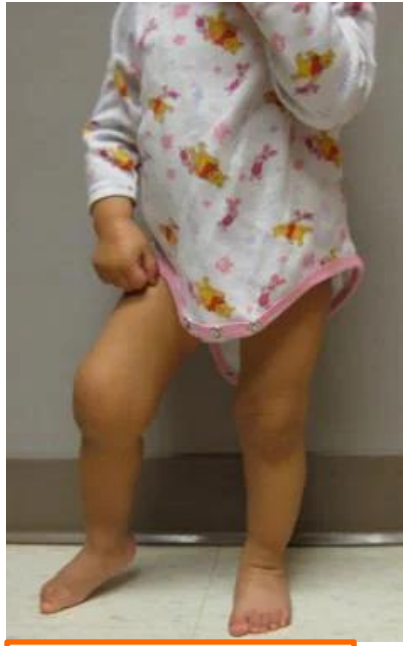


2019 ACR/AF Guidelines: Ophthalmic Screening Examination for Uveitis



Other Complications of JIA: Leg Length Discrepancy

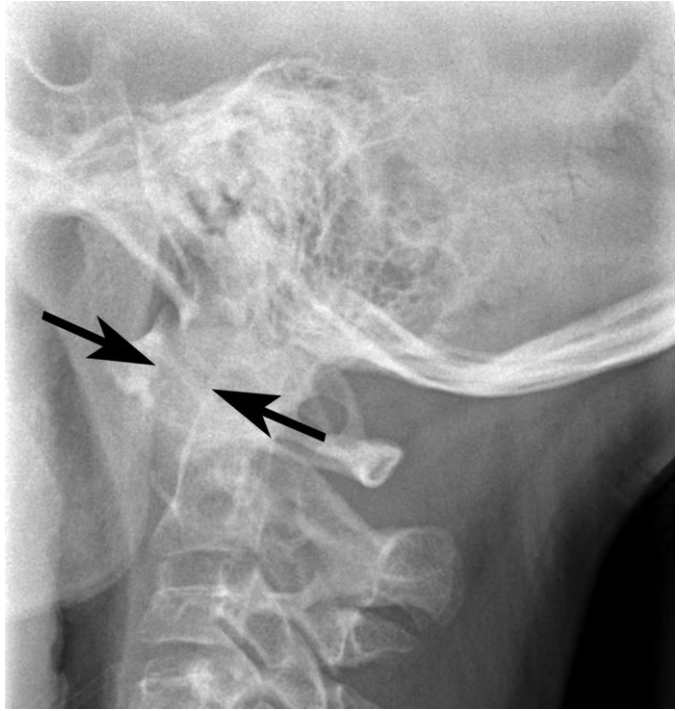




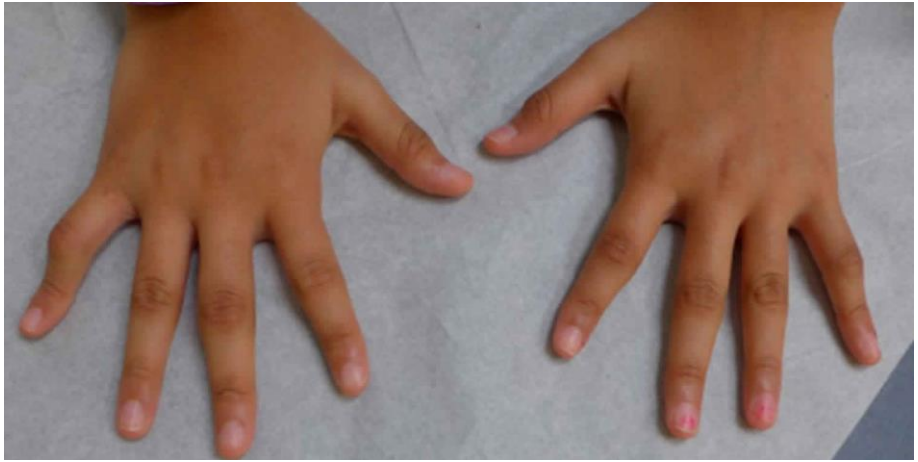
>1 cm difference: Refer to PT for shoe lift

Other Complications of JIA

C-Spine Subluxation



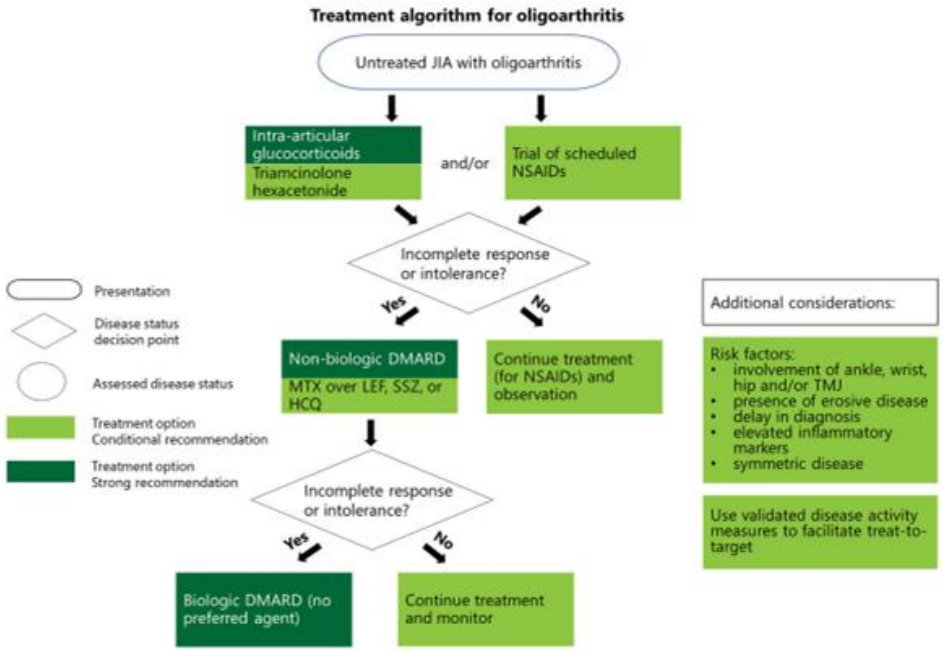
Finger Deformities



TREATMENT GOAL:

REDUCE PAIN, IMPROVE FUNCTION, PREVENT DAMAGE / DISABILITY

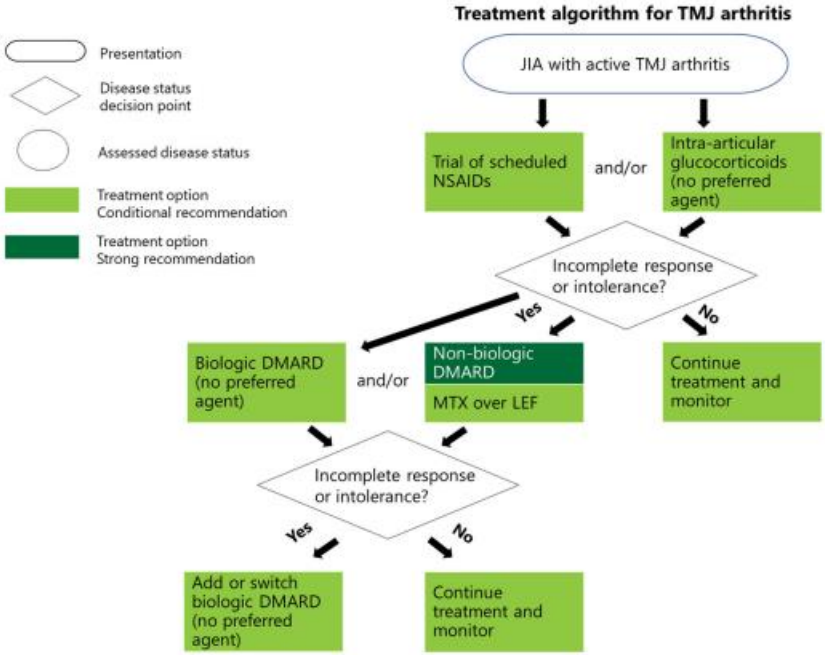
2021 ACR/AF Guidelines for the Treatment of Oligoarticular JIA



DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, SSZ = sulfasalazine, TMJ = temporomandibular joint

Figure 1. Treatment algorithm for oligoarthritis.

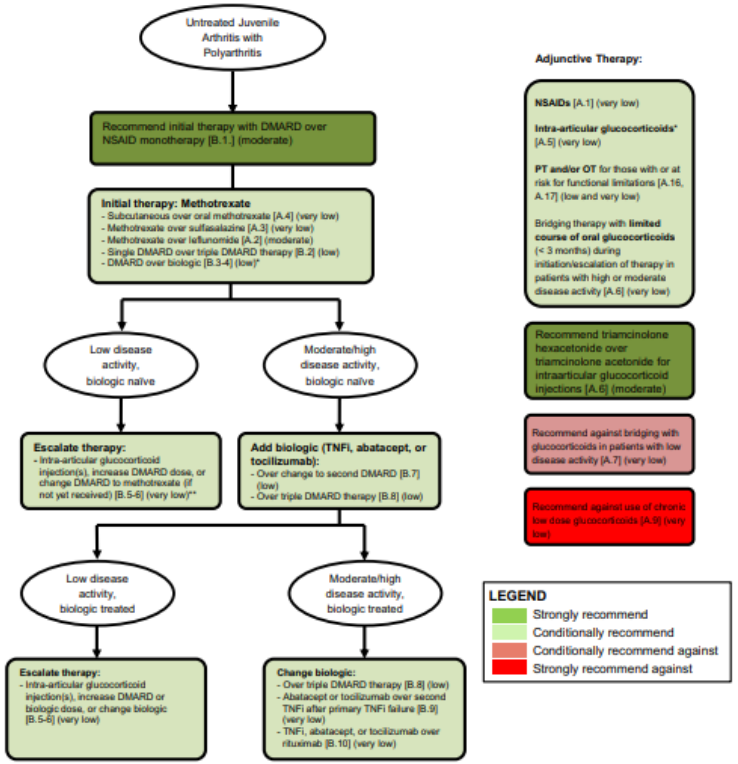
2021 ACR/AF Guidelines for the Treatment of TMJ Arthritis



DMARD = disease-modifying antirheumatic drug, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, TMJ = temporomandibular joint

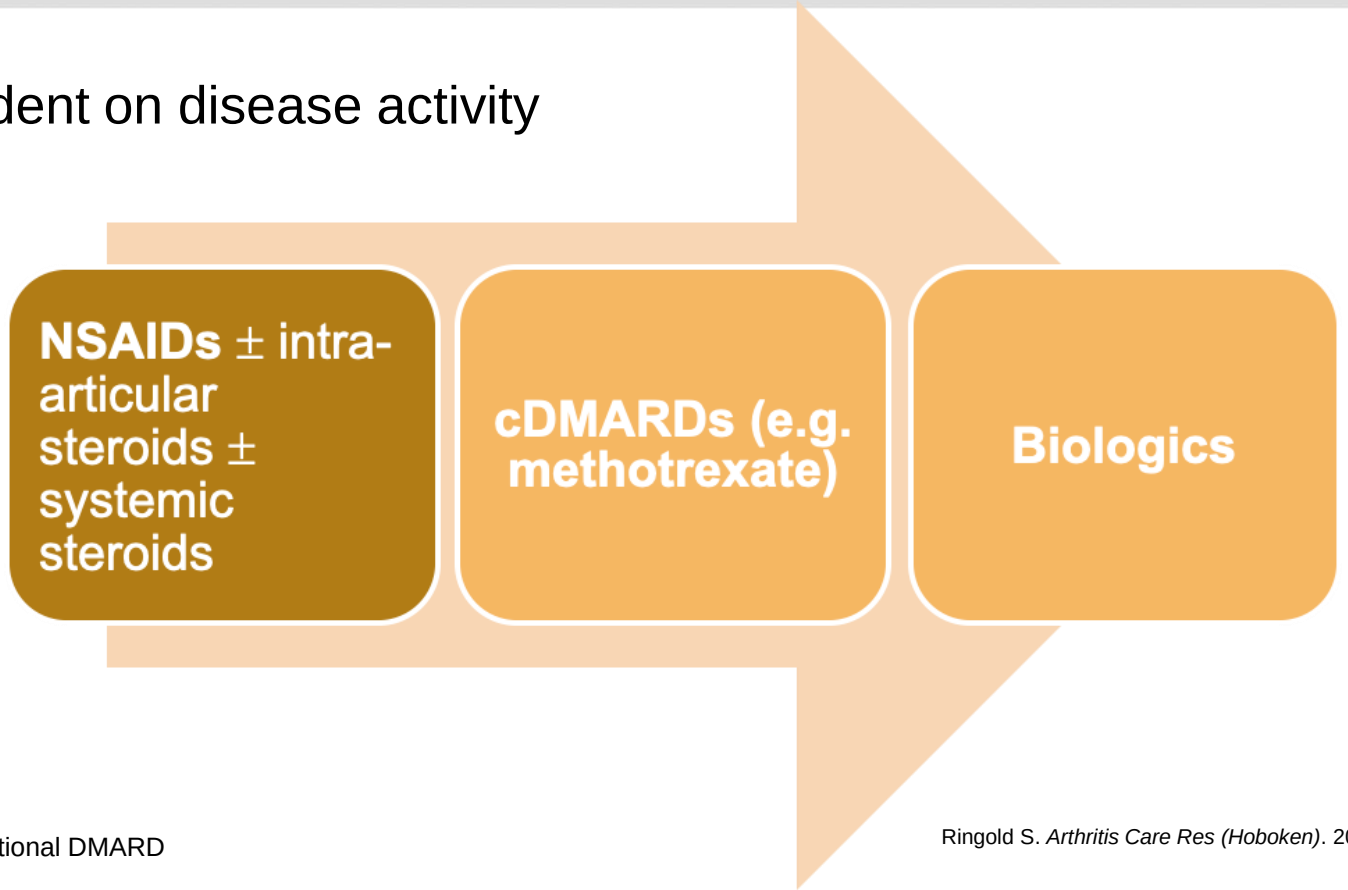
Figure 2. Treatment algorithm for temporomandibular joint arthritis.

2019 ACR/AF Guidelines for the Treatment of Polyarthritis



Therapy Escalation

Dependent on disease activity



cDMARD = conventional DMARD

Ringold S. *Arthritis Care Res (Hoboken)*. 2019 Jun;71(6):717-734.

NSAIDs

- Role: mostly for symptomatic relief
- Mechanism of action: COX inhibition
- Clinical pearls
  - Celecoxib: only FDA-approved NSAID in pediatrics
  - Naproxen: available as oral suspension, but rarely covered by insurance
  - Drug-drug interaction with methotrexate: not clinically significant with rheumatologic ”low-dose” of methotrexate used
  - Avoid aspirin due to Reye’s Syndrome, excluding Kawasaki Disease

NSAIDs

1. Intra-articular steroid injections
   - Role: symptomatic relief
   - Agents: Triamcinolone acetonide, triamcinolone hexacetonide
   - Joint injections can be due either without or with sedation depending on patient's age and number of joints requiring injections
   - Duration of effect: 3-6 months, up to 12 months

2. Systemic steroids
   - Role: quick control of initial disease presentation, disease flare
   - Goal is to always minimize long-term exposure given established short-term and long-term consequences of chronic corticosteroid exposure in pediatric population

Topical Treatments

1. Topical diclofenac gel 1%
   - Available OTC
   - No specific pediatric dosing – no current literature available for use in patients < 13 years old

2. Lidocaine
   - 5% patch: up to 3 on a time (adult-sized)
   - 2% gel: up to QID
   - Tiger Balm: anecdotal use; not routinely recommended

Conventional DMARDs: Clinical Pearls

1. Methotrexate: first-line DMARD
    a. Preferred route of administration: Subcutaneous
    b. Supportive care
        i. Oral sores, GI side effects: folic acid
        ii. Nausea: folic acid, antiemetic
        iii. Major surgeries: Hold 1 week before and 2 weeks after
2. Leflunomide
    a. Typically used if patient is intolerant to methotrexate
    b. No specific pediatric dosing
3. Sulfasalazine
    a. Minimal evidence for use in JIA
    b. Used in spondyloarthritis/ERA

Biologic DMARDs

Drug Class	Clinical Pearls
TNF inhibitors • Adalimumab (Humira®) • Etanercept (Enbrel®) • Infliximab (Remicade®) and biosimilars	• Adalimumab: FDA approved indications for polyarticular JIA and uveitis • Infliximab: additional role in treatment of uveitis • Adalimumab and infliximab: commercially available method to measure drug level and development of antidrug antibodies • Warnings and precautions (select): malignancies, new-onset or worsening heart failure, new-onset or worsening of CNS demyelinating disease • Can cause pustular and palmoplantar psoriasis
Tocilizumab (Actemra®)	• Additional role in treatment of uveitis • Dose adjustments necessary in the setting of neutropenia, thrombocytopenia, and hepatotoxicity • Dyslipidemia: no current guidance in pediatric patients
Abatacept (Orencia®)	• Intravenous route of administration requires a loading dose period vs. subcutaneous • Post marketing adverse effects: new or worsening psoriasis, angioedema reactions, vasculitis, non-melanoma skin cancers

Humira. Package insert. AbbVie Inc; 2021.
Enbrel. Package insert. Amgen; 2022.
Remicade. Package insert. Janssen Pharmaceutical Companies; 2021.
Actemra. Package insert. Genentech, Inc.; 2022.
Orencia. Package insert. Bristol-Myers Squibb Company; 2022.
Klein A. *ACR Open Rheumatol.* 2020 Jan;2(1):37-47.

New Kids on the Block

Medication Name	FDA-Approved Indication(s)	Pivotal Study
Golimumab (Simponi Aria®)	Polyarticular and psoriatic JIA ≥ 2 years old	Ruperto N et al. Open-label phase 3 study of intravenous golimumab in patients with polyarticular juvenile idiopathic arthritis. *Rheumatology (Oxford).* 2021 Oct 2;60(10):4495-4507.
Tofacitinib (Xeljanz®)	Polyarticular-course Juvenile Idiopathic Arthritis ≥ 2 years old	Ruperto N et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. *Lancet*. 2021 Nov 27;398(10315):1984-1996.
Secukinumab (Cosentyx®)	Psoriatic arthritis ≥ 2 years old and enthesitis-related arthritis ≥ 4 years old	JUNIPERA

Simponi Aria. Package insert. Janssen Pharmaceutical Companies; 2021.
Xeljanz. Package insert. Pfizer Laboratories Div Pfizer Inc; 2022.
Cosentyx. Package insert. Novartis Pharmaceuticals Corporation; 2021.

New Kids on the Block

Medication Name	Dosing	Clinical Pearls
Golimumab (Simponi Aria®)	80 mg/m2 IV at Week 0 and 4, then every 8 weeks	• No maximum dose • Antidrug antibodies were found to not be clinically significant • Off-label use for non-infectious uveitis
Tofacitinib (Xeljanz®)	• 10 - < 20 kg: 3.2 mg PO twice daily • 20 kg - < 40 kg: 4 mg PO twice daily • ≥ 40 kg: 5 mg PO twice daily	• Available as oral solution and tablet • Black Box Warning of cardiovascular risk • Numerous drug-drug interactions • Dose adjustments necessary in the setting of neutropenia, lymphopenia, and anemia
Secukinumab (Cosentyx®)	• 15 - < 50 kg: 75 mg SC at Week 0, 1, 2, 3, and 4, then every 4 weeks • ≥ 50 kg: 150 mg SC at Week 0, 1, 2, 3, and 4, then every 4 weeks	• FDA-approved age for use is different based on types of JIA • Auto-injector (Sensoready pen) is only available in 150 mg strength and takes ˜15 seconds for total administration

Simponi Aria. Package insert. Janssen Pharmaceutical Companies; 2021.
Xeljanz. Package insert. Pfizer Laboratories Div Pfizer Inc; 2022.
Cosentyx. Package insert. Novartis Pharmaceuticals Corporation; 2021.

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