How to Diagnose a Diagnosis of Exclusion—what the PCP should know about Juvenile Idiopathic Arthritis

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Disclosures

- I have participated in Advisory board for Silvergate pharmaceuticals for Xatmep
- I do not plan to discuss this medication or any unapproved or off-label use of this medication
- I will briefly discuss off-label use of FDA approved medications

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Objectives

- Recognize JIA as a clinical diagnosis
- Learn symptoms/signs of JIA
- Understand association with uveitis
- Identify objectives of treatment in JIA

Case 1

CC: limp

HPI: 2 y/o F - limp x 3m; L knee swelling

- No signs of illness
- Slow to move in AM; ~ 1 hour to walk
- No obvious pain

ROS, PMHx unremarkable

Family Hx: hypothyroid in MGM

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Physical Exam & Labs

Wt: 15 kg; vitals w/nl

Gen: apprehensive at first; participates with games

MSK: tracks toys above neck w/o limitation in ROM

UE: **left elbow-** *decreased* extension, fullness, warmth, tender on passive ROM; digits-full flexion/extension

LE: **L knee** effusion and decrease in ROM; **L ankle** fullness, decrease in passive motion; L leg length > R leg 1 cm; limping noted; other joints w/nl

Labs: CBC/diff, ESR, CRP, CMP, LDH, uric acid w/nl

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Differential Diagnosis?

Infection-related
- Viral synovitis including parvovirus, EBV
- Varicella
- Lyme disease
- Tuberculosis
- *Bartonella,* post-streptococcal arthritis
- Septic arthritis (*Streptococcus, Staphylococcus, Gonococcus, Chlamydia, Kingella kingae)*

Malignancy
- Leukemia/lymphoma*
- Neuroblastoma
- Bone tumor

Hematologic
- Sickle cell disease
- Hemophilia

* eval w/ cbc/diff and consider bone marrow bx esp. prior to corticosteroids

Mechanical
- Trauma
- Benign nocturnal idiopathic leg pain (growing pains)
- Osgood-Schlatter disease
- Avascular necrosis
- Slipped capital femoral epiphysis (knee pain referred from hip)
- Chondromalacia patellae
- Hypermobility syndrome

Genetic/metabolic/storage disease
- Gaucher's disease
- Mucopolysaccharidoses

Other CTD disease-besides JIA
- Systemic lupus erythematosus
- Mixed connective tissue disease
- Vasculitis, polyarteritis nodosa
- Sarcoidosis
- Henoch Schönlein purpura

1.Goldmuntz EA, White PH. Juvenile idiopathic arthritis: A review for the pediatrician. Pediatr Rev 2006;27:e24-32.
2. Rosenberg AM, Oen KJ. Polyarthritis. In: Cassidy JT, Petty RE, Laxer RM, et al, editors. Textbook of Pediatric Rheumatology. Vol 6. 6th ed. Philadephia: Saunders; 2011:249-61.

Patient 1

Dx: **Oligoarticular JIA**

- Referred to PT for stretching, ROM exercises
- Orthotics – shoe lift for right foot
- Naproxen 10 mg/kg/dose BID
- Corticosteroid injection of L elbow, L knee
  Referred to ophthalmology

Case 2

CC: **L ankle** swelling, limp

HPI: 12 y F presents to ER w/ **6 months** L ankle swelling & limp. → dx with fracture

- Ankle stiff/swollen when splint removed
- Pain & swelling in **R ankle** → PCP
- No previous illness, fevers, rashes
- No weight loss or night sweats
- Pain, stiffness in ankles x 45 minutes in AM
- Decrease in physical activity; attends school daily; difficulty writing

Physical Exam

General: well-appearing, NAD; CV, Pulm, Abd, ENT w/nl

MSK: **neck** with decreased extension, flexion, rotation

UE: swelling, tenderness multiple **PIPs**, **MCPs**

- **R wrist:** swelling, limited extension by 45 degrees
- **R elbow:** swelling, limited extension by 15-20 degrees

LE:

- **R knee** w/ effusion, decreased extension by 5 degrees
- b/l **ankles** w/ swelling, decreased rotation
- tenderness of b/l **MTPs**
- **Gait** – limping, unable to fully straighten right knee

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Labs/studies

- CBC/diff: WBC 10,000, hgb 10.6 g/dL, plt 504,000, ESR 47 mm (0-13); CRP w/nl
- ANA negative
- RF negative; anti-CCP negative
- Parvovirus negative
- EBV negative
- Repeat ankle radiographs w/o fracture

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Patient 2

Dx: RF- polyarticular JIA

- Radiographs: osteopenia, joint space narrowing of carpals
- Corticosteroid injection of R wrist, elbow, knee, b/l ankles
- Meloxicam and SQ methotrexate started
- Referral to ophthalmology
- 3m f/up –improvement in ankles, arthritis in wrist, elbow, knee → etanercept initiated

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Juvenile Idiopathic Arthritis

- Jt. swelling or jt. pain w/ limitation in ROM
- Diagnosis of exclusion
- Onset before the age of 16
- Persistent $\geq$ 6 weeks
- 7 categories of JIA

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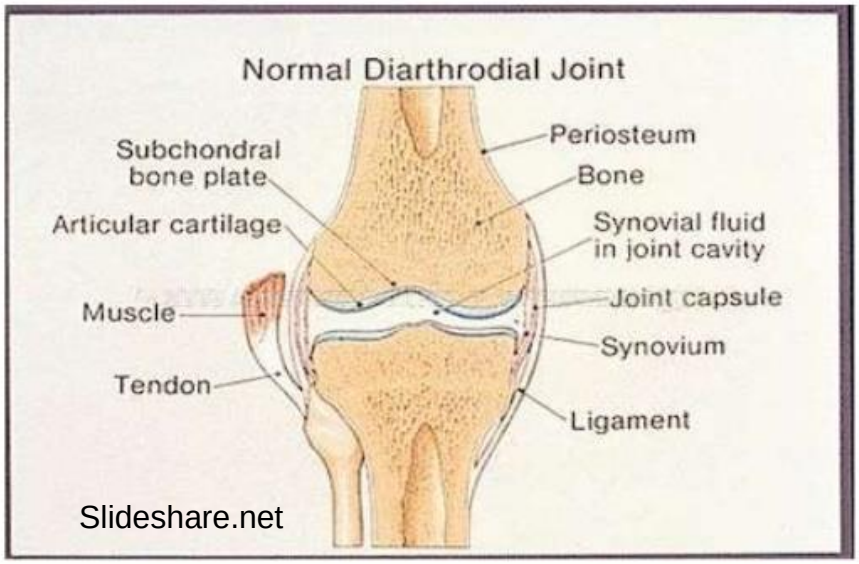
Important connective tissue structures in diarthrodial joints:



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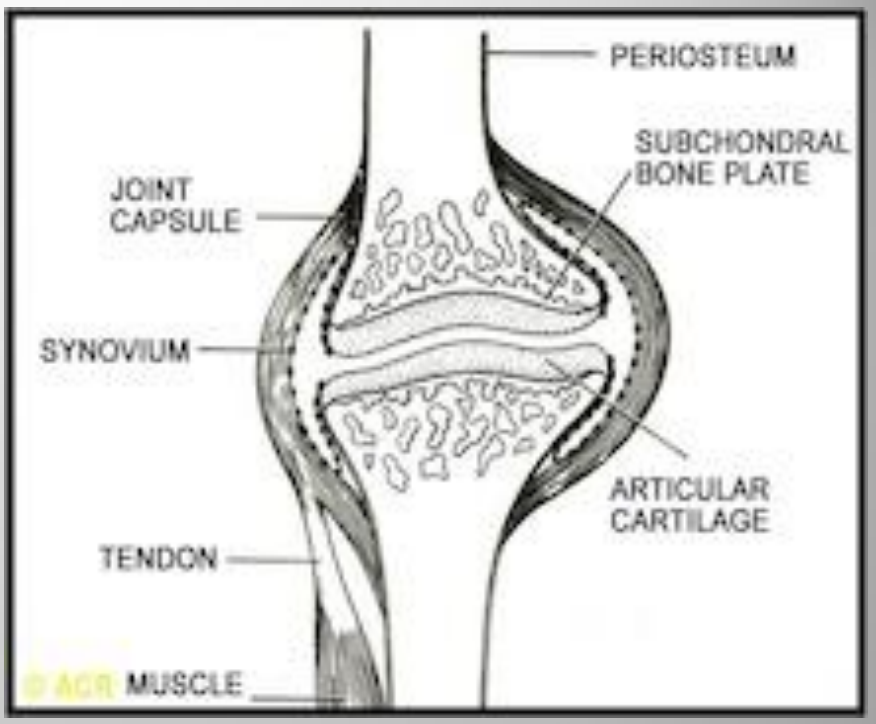

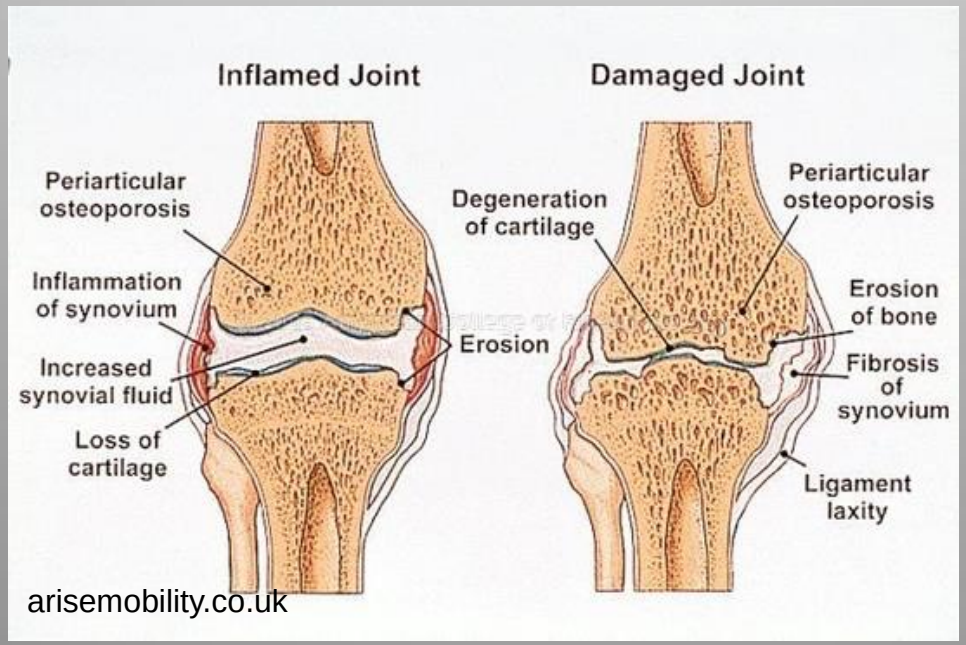

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Clues that NOT JIA

- Pain awakens from sleep and/or low cell counts in 2+ lines – eval for **malignancy**
- GI symptoms: **IBD with MSK** manifestations
- Fevers, rashes, preceding illness → parvovirus, *Bartonella*, EBV, *Streptococcus* (post-strep arthritis)
- One joint w/ severe pain, fever, redness → **septic arthritis**

Systemic symptoms: w/up for malignancy, infection, IBD, SLE or other autoimmune process

vs.

JIA: *AM stiffness*, absence of erythema, unremarkable h/o fever, weight loss, night sweats

****Diagnosis of exclusion!**

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JIA Subtypes

- Oligoarticular
- RF+ polyarticular
- RF – polyarticular
- Enthesitis Related Arthritis
- Psoriatic Arthritis
- Systemic Juvenile Idiopathic Arthritis
- Undifferentiated

Descriptors to aid in subtype

- Age of onset
- Type of joints involved
  - Large vs. small joints or axial vs. peripheral
  - Symmetry
- ANA presence
- HLA allelic associations
- Rheumatoid factor (RF) +/-; cyclic citrullinated peptide Ab (CCP) +/-

Oligoarticular JIA

1-4 joints

- **Persistent**: never more than 4 joints
- **Extended**: more than 4 joints after the first 6 months

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Oligoarthritis

- Most common form of JIA
- Age of onset < 6
- Female predominance
- High incidence of complicating uveitis
- DDx at onset: septic arthritis, osteomyelitis, neoplasia, acute rheumatic fever, Lyme disease.

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Presentation

- Insidious – child does not usually c/o pain
- Limp; joint swelling, stiff esp. in AM, after nap etc.
- Young child may stop walking, standing.

Exam: joint effusion, swollen synovial tissue, warmth, mild or moderate tenderness. Little objection to palpation of the joint but pain on extremes of ROM.

Presentation cont…

- Antalgic gait
- Common joints: knees, ankles; small joints of hands and feet < 10%. Wrists and elbows may predict extension to polyarticular disease.
- Hips, TMJ's, cervical spine rare .

Acute onset with redness, tenderness, fever and refusal to bear weight = r/o infection or neoplasm.

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Labs in oligoarthritis

- CBC/D, ESR, CRP usu. normal or mildly elevated
- ANA + in 70-80% of young girls with oligo=risk factor for uveitis.
- Radiographs should be obtained to r/o other diagnoses but usu. normal. (early=soft tissue swelling or effusion w/o bony abnormality).

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Oligoarthritis

- Asymmetrical growth and muscle atrophy esp. in legs
- Involved joints grow faster
- TMJ involvement later in course usu. unilateral- feel the mandibular condyle
- Complications: overgrowth of bone and cartilage; destruction of cartilaginous surfaces slower than in other forms

Prognosis

- ~50% of children with oligo at onset will have ongoing disease or functional joint problems 10 or more yrs. after onset
- Long term psychological effects

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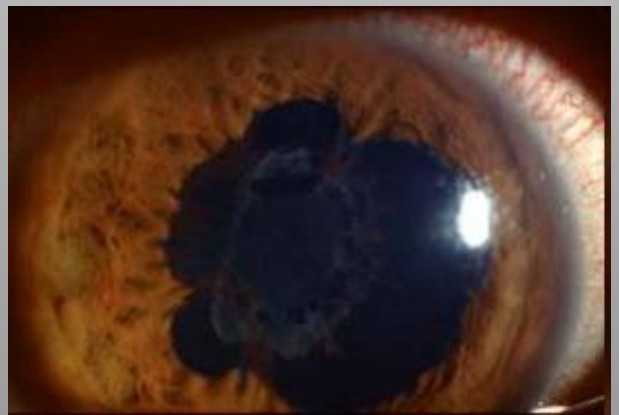
Uveitis

- Most serious complication for all children with oligo is potential blindness
- Incidence ~ 30% of patients with oligo
- Insidious onset and usu. painless
- Slit lamp exam necessary for diagnosis



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Frequency of Eye Exams

JIA Category	< 7 years	>= 7 years
ANA + polyarticular or oligoarticular	Every 3-4 months x 4 yrs Every 6 months x 3 yrs then yearly	Every 6 months x 4 yrs then yearly
ANA – polyarticular or oligoarticular	Every 6 months x 4 yrs then yearly	Every 6 months x 4 yrs then yearly
Systemic JIA (ANA+/-)	yearly	yearly

ANA is useful for assessing increased risk of uveitis in patients with JIA

(Adapted from reference: Goldmuntz EA, White PH. Juvenile idiopathic arthritis: A review for the pediatrician. Pediatr Rev 2006;27:e24-32.)

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Polyarthritis

- Symmetric or asymmetric
- Large and small joints
- Hip involvement may be a later feature
- PIP > MCP joints at first
- Tenosynovitis of wrists, ankles, flexor tendons of hands

Polyarthritis (RF negative)

- 5+ joints during first 6 months of disease; RF negative
- ~ ¼ of patients with JIA have Poly at onset (most RF -).
- 2 peaks: toddler-preschool, pre-adolescent]
- Most classic = symmetric; age 7-9
- Female:Male=3:1

Polyarthritis (RF positive)

- 5 or more joints during first 6 months
- Tests for RF positive in 2+ blood tests at least 3 months apart

RF+ polyarthritis

- Smallest category (~5% of cases)
- Most common in teenage girls
- Poor prognosis
- Symmetric, small and large joints: wrists, MCPs, PIPs.
- Erosion can be seen 6 m from onset

RF+ Polyarthritis

- Rheumatoid nodules often present
- Mean onset 9-12 years (2-4 yrs higher than RF-)
- Non-Caucasian populations – more common
  - Native North American, Canadian Aboriginal, AA, Caribbean, Black and Ind. South African children and Latin American
  - Nodules more often present

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Complications and Prognosis of Polyarticular JIA

- Growth retardation proportional to degree and duration of inflammation
- Eye complications in ANA+ (similar to oligo)
- Outcome varies (remission over time to progressive joint damage)
- Symmetric arthritis & early wrist involvement predicts poorer outcome
- Prognosis worse than oligo; worse with RF +

Psoriatic Arthritis

- Arthritis + psoriasis *or*
- Arthritis + at least 2 of the following:
  - Dactylitis
  - Nail pitting or onycholysis
  - Psoriasis in a first degree relative

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Enthesitis Related Arthritis

- **Enthesitis** = inflammation of attachment of a ligament, tendon, joint capsule, or fascia to bone.
- Previously called juvenile ankylosing spondylitis, seronegative enthesitis, spondyloarthropathy
- Prototype: inflammation of entheses, SI joints, L-S spine.
- More common in males & older children (uncommon before age 7)
- Strong association with **HLA-B27**

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ERA presentation

- Insidious or abrupt onset
- Symptomatic enthesitis around foot and knee
  - Calcaneal insertions of Achilles tendon, plantar fascia
  - Plantar fascia to base of 5^{th} metatarsal and heads of 1^{st}-5^{th} metatarsal
  - Patellar ligament attachment to tibia and inferior pole of patella and insertions of quad muscles on patella

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Systemic Arthritis

- Arthritis + daily fever x min 2 weeks documented as *quotidian** at least 3 days + one or more of following:
  - Evanescent, non-fixed, erythematous rash
  - Generalized LN enlargement
  - Hepatomegaly and/or splenomegaly
  - Serositis
- ***quotidian**: daily recurrent fever of 39℃ or above once/day; returns to normal between fever peaks.
- Appear sick
- Treatment escalation different than other JIA types

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Course/Prognosis of JIA in general

- No cure
- Treatment induces remission, prevents joint destruction and disability
- Remission rate variable: 15 – 70%
- Delay in referral & initiation of appropriate therapy → worse prognosis

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Treatment

- ***Goal***: quick, complete suppression of arthritis to prevent/lessen permanent damage to joint.
- NSAIDS
- Intra-articular corticosteroid injections
- DMARDS (MTX, sulfasalazine) – cbc/diff, LFTs every 4-12 weeks
- Anti-TNF agents (Etanercept, Adalimumab, Infliximab)
- Other: Abatacept, Tocilizumab, Anakinra, Canakinumab
- Corticosteroids –AFTER all other causes excluded

NSAIDS

NSAID	Dose	Max dose/day	FDA- approved age for use in JIA
Naproxen	10 mg/kg BID	1000 mg	2 and older
Ibuprofen	30-50 mg/kg/day in 3-4 doses	2400 mg	12 and older
Indomethacin	1-2 mg/kg/day divided in 3 doses	200 mg	> 14 years
Diclofenac	50-100 mg BID IR: 50 mg 3-4 x/day 75 mg BID	200 mg	N/A
Meloxicam	0.125 – 0.25 mg/kg/day	15 mg	2 and older
Celecoxib (COX-2)	10-25 kg: 50 mg BID >25 kg: 100 mg BID	100 mg 200 mg	2 and older

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3. Clinical Pharmacology Database. Tampa, FL:Elsevier/Gold Standard; 2013. http://clinicalpharmacology-ip.com. Accessed 3 September 2017.

Biologics – anti-TNF agents

- Increased risk of infection & TB reactivation
- **Live** vaccinations contraindicated
- Injection site reactions
- Adverse reactions: optic neuritis, demyelinating events, lupus-like syndrome, autoantibody formation, psoriaform rash
- Administered w/ or w/o MTX
- CBC/D, LFTs every 3-6 months

Summary

- Heterogeneous group of diseases
- CHRONIC
- Diagnosis is made by history and physical
- **No specific laboratory findings diagnostic**
- **Autoantibodies not helpful diagnostically**
- Refer to Ophthalmology
- Start NSAIDs, avoid Steroids

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