

# Juvenile idiopathic arthritis

A clinicopathologic framework for childhood inflammatory arthritis

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# Learning objectives

- Define JIA and explain why it is a heterogeneous disease group.
- Distinguish major clinical phenotypes and immune mechanisms.
- Relate synovial inflammation to joint damage, extra-articular disease and growth.
- Apply diagnostic, uveitis-screening and treatment principles to cases.

JIA is a clinical umbrella diagnosis

**Arthritis begins before age 16 and persists for at least 6 weeks**

- A group of disorders of unknown cause—not one molecularly uniform condition.
- Requires evaluation for infectious, malignant, mechanical and other inflammatory causes.
- The 6-week threshold is a disease-definition requirement, not permission to delay assessment.

# The diagnosis has three core components

## Childhood onset

First arthritis occurs before  
16 years



## Persistence

Inflammatory arthritis lasts  
≥6 weeks



## Exclusion

No better established  
explanation

# Why a single JIA label is insufficient

## Joint distribution

Oligoarticular or polyarticular disease

## Systemic inflammation

Fever, rash and visceral involvement in systemic disease

## Immune phenotype

RF, ANA and enthesitis patterns vary

## Complications

Uveitis, growth effects or macrophage activation syndrome

# JIA differs from adult rheumatoid arthritis

## Juvenile idiopathic arthritis

- Oligoarthritis and large-joint disease are prominent.
- Systemic manifestations are relatively more common.
- ANA positivity is familiar in subsets; Nodules are usually absent.

## Adult rheumatoid arthritis

- Often symmetric small-joint polyarthritis.
- ACPA/RF and adult RA synovitis inform comparison.
- Rheumatoid nodules can be a feature of established adult RA.

## Textbook epidemiologic context

**30,000–50,000 affected individuals in the United States**

- Estimate quoted by Robbins 11th edition; Not an annual incidence figure.
- JIA subtype frequencies depend on case definitions and population.
- Do not generalize an overall figure to one JIA subtype.

# Historical names do not describe one entity

## Earlier terminology

- Juvenile rheumatoid arthritis (JRA)
- Juvenile chronic arthritis (JCA)
- Different grouping rules hindered comparisons.

## Contemporary umbrella term

- Juvenile idiopathic arthritis (JIA)
- Defined by age, duration and exclusions.
- Subclassification is phenotype-based.

## ILAR classification recognizes seven groups

| Clinical category                   | Defining organizing feature                     |
|-------------------------------------|-------------------------------------------------|
| <b>Oligoarthritis</b>               | 1–4 joints in first 6 months                    |
| <b>Polyarthritis, RF-negative</b>   | ≥5 joints; RF negative                          |
| <b>Polyarthritis, RF-positive</b>   | ≥5 joints; Repeat RF positivity                 |
| <b>Systemic arthritis</b>           | Arthritis plus characteristic systemic syndrome |
| <b>Psoriatic arthritis</b>          | Arthritis with psoriasis-related features       |
| <b>Enthesitis-related arthritis</b> | Arthritis and/or enthesitis pattern             |
| <b>Undifferentiated arthritis</b>   | Does not fit one category exclusively           |

# Classification uses multiple axes

## Joint count

1–4 or  $\geq 5$  during first 6 months



## Clinical phenotype

Systemic, psoriatic or enthesitis features



## Serology and exclusions

RF status; Other required ILAR conditions

## Oligoarthritis: Limited joint count

**One to four joints during the first 6 months**

- Typically affects large joints, especially knee or ankle.
- A lower joint count does not eliminate the risk of vision-threatening uveitis.
- Clinical joint examination, not antibody positivity alone, defines arthritis.

# Persistent versus extended oligoarthritis

## Persistent

- No more than four joints involved throughout the course.
- May remain localized but warrants long-term monitoring.
- Ophthalmic screening remains risk-based.

## Extended

- More than four joints become involved after month six.
- Change is defined by subsequent joint accumulation.
- Can require treatment escalation for additional active joints.

## RF-negative polyarthrititis

- At least five inflamed joints during the first six months.
- Rheumatoid factor is negative under the ILAR category definition.
- Joint distribution and disease activity may vary considerably.
- Negative RF does not exclude chronic erosive inflammatory arthritis.

## RF-positive polyarthrititis

- Five or more affected joints in the initial six months.
- ILAR requires at least two RF-positive tests, three or more months apart.
- Resembles adult seropositive rheumatoid arthritis more than many other JIA groups.
- RF is a classification feature here, not a universal JIA screening diagnosis.

# Systemic JIA is biologically distinct

## **Fever**

Characteristic repeated spikes of systemic inflammation

## **Rash**

Transient erythematous eruption often accompanies fever

## **Visceral findings**

Lymphadenopathy, hepatosplenomegaly or serositis

## **Arthritis**

May develop alongside or after systemic symptoms

## Psoriatic-pattern JIA

- Psoriasis-associated arthritis is a separate ILAR category.
- Nail pitting, onycholysis and dactylitis help establish the phenotype.
- Psoriasis may be absent when other specified features are present.
- Be careful not to classify arthritis from a nonspecific rash alone.

# Enthesitis-related arthritis

## Peripheral phenotype

Arthritis and/or inflammation  
at tendon insertion



## Axial association

Inflammatory back pain or  
sacroiliac disease may  
emerge



## Supportive context

HLA-B27, acute anterior  
uveitis, family history

## Undifferentiated JIA: A real classification result

- Some patients meet no single ILAR category.
- Others fulfill features of two or more categories.
- A classification category is not a measure of severity.
- Phenotype reassessment remains important as disease evolves.

# ILAR and provisional PRINTO frameworks

## ILAR (Edmonton revision)

- Seven named categories.
- Joint count and exclusion rules central.
- Widely used in published JIA studies.

## Provisional PRINTO revisions

- Focus on more biologically coherent groups.
- Emphasize early-onset ANA-positive and Still/enthesitis phenotypes.
- Provisional research classification—not a universal replacement.

## Different patterns imply different surveillance

| Phenotype                         | Priority complication / feature       |
|-----------------------------------|---------------------------------------|
| Early ANA-positive oligoarthritis | Chronic anterior uveitis              |
| Systemic JIA / Still disease      | Macrophage activation syndrome        |
| RF-positive polyarthritis         | Persistently active joint disease     |
| Enthesitis-related arthritis      | Axial disease; Acute anterior uveitis |
| TMJ involvement in any category   | Growth, function and jaw symmetry     |

## JIA pathogenesis remains incompletely defined

**Genetic susceptibility + dysregulated inflammation  $\neq$  a single proven cause**

- Genetic associations and Th1/Th17-related inflammation.
- Mechanisms and importance vary markedly between JIA phenotypes.
- Avoid assuming that all JIA is identical to adult RA.

# Genetic susceptibility is contributory

## HLA variants

Immune recognition and antigen presentation associations



## PTPN22 variants

Association with immune signaling susceptibility



## Inflammatory response

Expression depends on phenotype and other factors

# T-helper-cell pathways in inflammatory JIA

## **Adaptive immune activation**

T-cell responses in susceptible hosts



## **Th1 and Th17 involvement**

Immune-cell recruitment and cytokine signaling



## **Synovial inflammation**

Persistent tissue-level inflammatory response

# Inflammatory mediators named

## **IL-1**

Innate inflammatory signaling; Therapeutically important in systemic JIA

## **IL-17**

Associated with Th17-type immune responses

## **TNF**

Inflammatory signaling; Established therapeutic target in some phenotypes

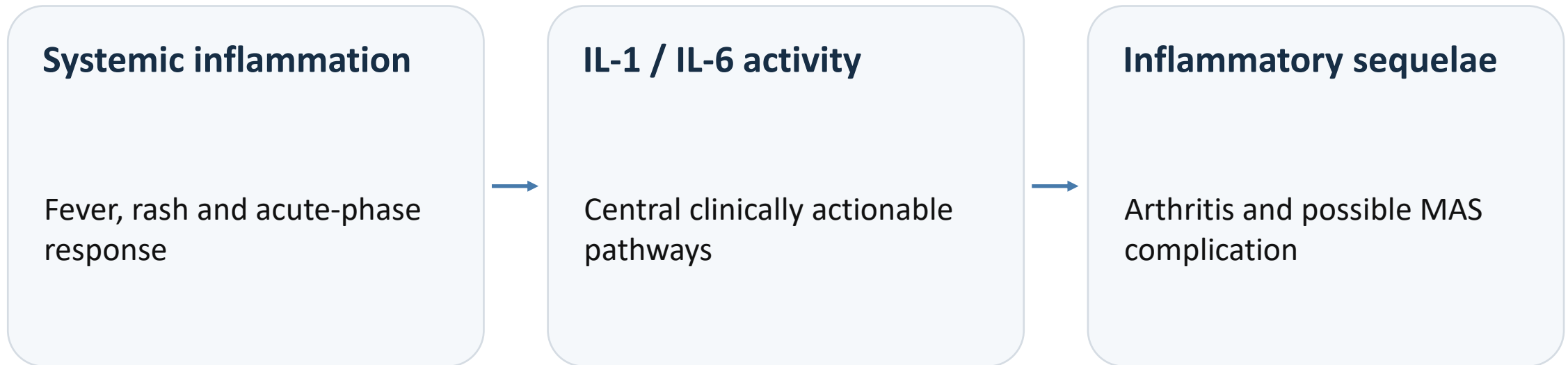
## **IFN- $\gamma$**

Th1-associated mediator; Relevant to inflammatory pathways

## Why IL-6 matters to JIA

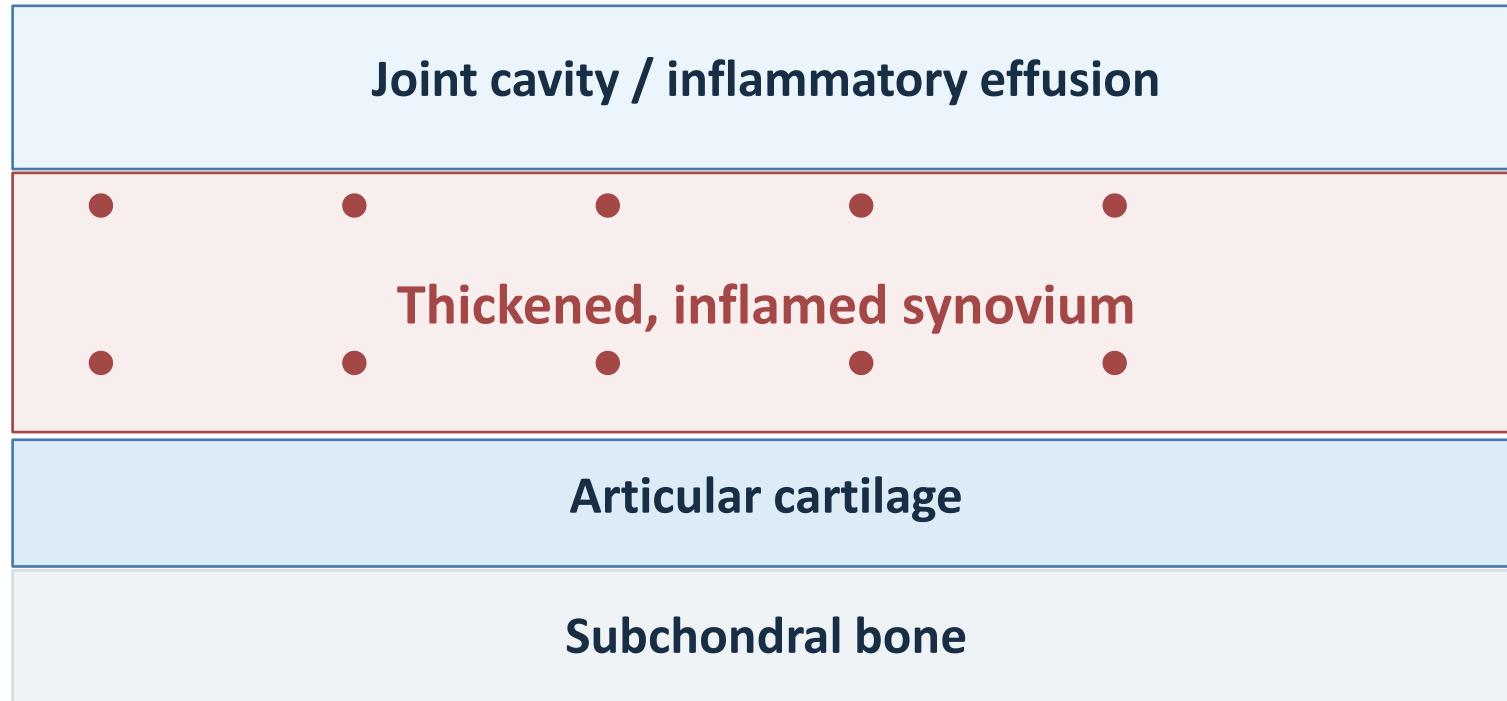
- Successful treatment with an IL-6 receptor antibody.
- Systemic JIA features a major cytokine-driven inflammatory component.
- IL-6 receptor inhibition is a phenotype-specific therapeutic strategy.
- A drug response supports pathway relevance but does not prove a unique cause.

# Systemic JIA: Innate-immune emphasis



# Synovial architecture: Conceptual map

Simplified architecture, not an observed clinical specimen



## Pathologic link

- Synovial immune activation
- Inflammatory proliferation
- Potential joint injury

# Synovitis produces clinically observable swelling

## **Vascular activation**

Synovial hyperemia and fluid accumulation



## **Synovial proliferation**

Lining thickening and inflammatory infiltration



## **Functional effect**

Warmth, effusion, pain and loss of motion

# What chronic inflammation can do to a joint



# Adult RA pannus: Useful context, not a JIA criterion

## Shared inflammatory concept

- Hyperplastic synovium can become destructive.
- Synovitis can precede cartilage and bone damage.
- Inflammation is an actionable target.

## Important limitation

- Pannus directly for adult RA.
- The JIA excerpt does not establish identical histology.
- Biopsy is not a routine way to assign ILAR subtype.

# Growing joints create pediatric complications

## **Growth plate context**

Inflammation may disturb local growth patterns

## **Joint contracture**

Persistent loss of range restricts function

## **Limb asymmetry**

Asymmetric disease may affect limb growth

## **TMJ growth**

Mandibular growth and facial symmetry warrant attention

## Morphology must answer a clinical question

- Histology may show chronic synovitis, but it is not diagnostic by itself.
- Inflammation is evaluated primarily by clinical examination and selected imaging.
- Tissue sampling is reserved for atypical presentations or suspected mimics.
- Do not interpret a schematic as histologic proof of JIA.

# Clinical arthritis is more than arthralgia

## Inflammatory arthritis

- Objective joint swelling or effusion.
- Restricted range or painful motion.
- Morning stiffness or stiffness after inactivity.

## Isolated pain

- Pain without objective inflammation is nonspecific.
- Consider mechanical, infectious and malignant causes.
- Reassess if symptoms or examination evolve.

## Large-joint involvement is a major clue

- Knee and ankle involvement are characteristic of many oligoarticular presentations.
- Joint distribution should be documented anatomically and longitudinally.
- Asymmetry and a low joint count do not imply a benign course.
- Different distributions direct different differential diagnoses.

# Extra-articular manifestations are phenotype-specific

## Eye

Chronic or acute anterior uveitis depending on phenotype

## Skin

Psoriatic features or systemic evanescent rash

## Systemic organs

Fever, serositis and reticuloendothelial enlargement

## Growth/function

Limb and mandibular developmental effects

## JIA-associated chronic anterior uveitis

### **Sight-threatening inflammation can be clinically silent**

- Absence of redness, pain or photophobia does not exclude chronic anterior uveitis.
- Screen with slit-lamp examination at a risk-based interval.
- Ocular complications may develop before symptoms become obvious.

# Who needs frequent uveitis screening?

## JIA phenotype

Oligo / RF-negative poly /  
psoriatic / undifferentiated



## Additional risk features

ANA positive; Onset younger  
than 7 years; Disease  $\leq 4$   
years



## High-risk schedule

Eye examination every 3  
months (ACR 2019,  
conditional)

# Do not conflate two uveitis patterns

## Chronic anterior uveitis

- Often asymptomatic at onset.
- Associated with younger, ANA-positive phenotypes.
- Planned slit-lamp screening is essential.

## Acute anterior uveitis

- May cause pain, redness and photophobia.
- Can occur with HLA-B27 / enthesitis-related phenotype.
- Acute symptoms require urgent assessment.

# Macrophage activation syndrome is an emergency

## **A hyperinflammatory complication of systemic JIA / Still disease**

- Consider when systemic disease deteriorates with persistent fever.
- May progress to coagulopathy, organ dysfunction and critical illness.
- Requires urgent specialist evaluation—do not wait for full diagnostic criteria.

# MAS recognition: Discordant laboratory trends

## **Ferritin**

Markedly elevated or rapidly increasing

## **Cell counts**

Falling platelets / cytopenias despite inflammation

## **Coagulation**

Falling fibrinogen and coagulopathy

## **Other markers**

Rising transaminases and triglycerides

## TMJ arthritis may be clinically subtle

- Temporomandibular inflammation can occur without obvious pain.
- Chronic disease may impair mandibular growth and oral function.
- Clinical assessment may be supplemented by targeted imaging.
- Management deserves attention even when other joints are quiet.

# Why disability can outlast active inflammation

## Active arthritis

Pain, effusion and restricted movement



## Secondary consequences

Muscle weakness, contracture, altered growth



## Persistent limitation

Functional difficulty despite reduced inflammation

# JIA is a diagnosis of exclusion

## **Confirm inflammatory joint findings**

History, examination and symptom chronology



## **Look for danger signals**

Infection, malignancy, trauma, multisystem illness



## **Investigate selectively**

Laboratory and imaging tests answer focused questions



## **Classify after evaluation**

Apply clinical phenotype and defined criteria

## Acute hot monoarthritis: Exclude infection first

### **Septic arthritis is a time-critical mimic**

- Fever, severe focal pain, inability to bear weight or marked illness increase concern.
- Obtain urgent evaluation and appropriate joint-fluid studies when indicated.
- A child does not become “JIA” merely because joint swelling persists.

## Malignancy and hematologic disease can mimic JIA

- Leukemia and other marrow disorders may present with limb pain or joint symptoms.
- Night pain, constitutional symptoms, unusual bruising or abnormal blood counts are warnings.
- Inconsistent objective joint findings should prompt reconsideration.
- Do not initiate immunosuppressive treatment before important mimics are addressed.

# Differential diagnosis is pattern dependent

| Presentation                        | Alternatives to consider                                  |
|-------------------------------------|-----------------------------------------------------------|
| Acute monoarthritis                 | Septic arthritis, trauma, osteomyelitis                   |
| Symmetric small-joint polyarthritis | Viral/postinfectious arthritis; Connective tissue disease |
| Persistent fever with joint pain    | Infection, malignancy, autoinflammatory disease           |
| Enthesitis / axial symptoms         | Juvenile spondyloarthritis and infection                  |
| Intermittent isolated pain          | Mechanical and non-inflammatory causes                    |

# What ANA and RF actually contribute

## Antinuclear antibody (ANA)

- Common in important JIA subsets.
- Aids uveitis risk stratification.
- Not diagnostic in isolation.

## Rheumatoid factor (RF)

- Repeated positivity helps classify RF-positive polyarthritis.
- Negative result does not exclude JIA.
- Not a universal disease activity measure.

## Inflammatory laboratory results need context

- ESR and CRP may support active inflammation but do not confirm JIA.
- CBC can reveal inflammation—or signals pointing to infection, malignancy or MAS.
- Normal inflammatory markers do not exclude all JIA phenotypes.
- Use laboratory results with examination and trajectory, not as a stand-alone verdict.

# Choosing imaging for the clinical question

| Modality             | Best teaching role                                   |
|----------------------|------------------------------------------------------|
| Ultrasound           | Detect synovitis/effusion; Guide selected injections |
| MRI                  | Evaluate deep synovitis, marrow and complex joints   |
| Radiographs          | Identify structural damage or alternative diagnosis  |
| Targeted TMJ imaging | Evaluate a potentially occult high-impact joint      |

A normal radiograph does not exclude synovitis

**Plain films are insensitive for early inflammation**

- ACR 2021 recommends against obligatory radiography before advanced imaging to find active synovitis or enthesitis.
- Use radiographs for structural damage or differential diagnosis when appropriate.
- Unnecessary imaging requirements can delay care.

# A practical diagnostic pathway

## **Inflammatory arthritis suspected**

Joint examination and chronology



## **Red flags?**

Urgent assessment for infection / malignancy / MAS



## **Exclusion and targeted testing**

CBC, inflammatory markers, serology, imaging as indicated



## **Longitudinal phenotype**

Joint count, systemic signs and extra-articular surveillance

# Clinical risk changes initial treatment planning

## High-risk joint

Hip, wrist, ankle, sacroiliac or TMJ

## Structural damage

Erosion or progressive limitation

## Burden of disease

Many active joints, high inflammatory activity

## Delayed diagnosis

Long untreated inflammatory course

# Treatment targets inflammation and function

## **Suppress active inflammation**

Minimize pain and prevent ongoing injury



## **Preserve joint structure**

Avoid erosive and growth-related damage



## **Protect participation**

Mobility, school activity, vision and well-being

# Oligoarthritis: Staged pharmacologic care



# Polyarticular disease needs early control

- Persistent multiple-joint inflammation risks progressive structural and functional consequences.
- Conventional DMARDs such as methotrexate are widely used.
- Biologic agents target inflammatory mediators or lymphocyte signaling.
- Therapy is phenotype- and response-dependent, not determined by joint count alone.

# Systemic JIA: Targeted cytokine blockade

## Recognize systemic phenotype

Fever, rash, systemic inflammation with or without arthritis



## Choose targeted therapy

IL-1 or IL-6 blockade is central in current guidance



## Evaluate for complications

Ongoing surveillance for MAS and lung involvement

## Systemic corticosteroid exposure matters

- Glucocorticoids can rapidly reduce severe systemic inflammation.
- Chronic exposure creates important pediatric toxicity and growth concerns.
- Current Still-disease guidance prioritizes early IL-1/IL-6 blockade to limit prolonged systemic steroids.
- Individualize treatment during severe illness or macrophage activation syndrome.

# Uveitis treatment follows ocular activity

## Initial ocular control

Topical glucocorticoid for active anterior uveitis



## Steroid dependence / persistence

Systemic methotrexate when indicated



## Refractory/high-risk course

Monoclonal anti-TNF therapy in selected patients

# Medication safety and immunizations

## Monitoring

CBC, liver function and renal tests according to drug

## Infection risk

Screen for tuberculosis before biologic DMARDs

## Vaccines

Keep inactivated immunizations current

## Coordination

Plan live vaccines around immunosuppression

# Rehabilitation is not optional

- Physical therapy helps maintain range of motion, strength and mobility.
- Occupational therapy supports daily activities and school participation.
- Monitor pain, fatigue, growth, function and quality of life.
- Individualize activity while controlling active synovitis.

## Longitudinal follow-up has several targets

| Domain      | What changes clinical decisions?                       |
|-------------|--------------------------------------------------------|
| Articular   | Active/swollen joints, range of motion and function    |
| Ocular      | Slit-lamp screening findings and uveitis treatment     |
| Systemic    | Fever pattern, rash, serositis, MAS laboratory signals |
| Medication  | Efficacy, toxicity and infection prevention            |
| Development | Growth, jaw/limb symmetry, school participation        |

Prognosis is heterogeneous

**Serious functional disability occurs in ~10%**

- The figure is the 11th-edition textbook estimate, not an individual risk prediction.
- Chronic disease persists in many patients; Others achieve sustained inactivity.
- Phenotype, joint damage, extra-articular disease and treatment response matter.

# Case 1: Painless swollen knee

Illustrative vignette — not patient data

- A 5-year-old has a persistently swollen knee and morning limping for 9 weeks.
- No major systemic illness; Inflammatory arthritis is confirmed on examination.
- ANA is positive; RF is negative.
- Question: Which classification pattern and associated screening need are suggested?

# Case 1: Interpretation

## Most likely working phenotype

- Oligoarticular JIA if mimics are excluded.
- Joint count in the first six months determines initial class.
- The positive ANA is supportive, not diagnostic.

## Critical next action

- Arrange ophthalmic slit-lamp screening.
- Younger ANA-positive onset is high-risk for chronic anterior uveitis.
- Use a risk-based follow-up interval.

## Case 2: Fever, arthritis and falling platelets

Illustrative vignette — not patient data

- A child with systemic JIA develops persistent fever and worsening illness.
- Ferritin rises rapidly; Platelets and fibrinogen fall.
- Transaminases and triglycerides increase.
- Question: What complication must be addressed urgently?

## Case 2: Interpretation

**Suspect macrophage activation syndrome immediately**

- Converging clinical deterioration and abnormal laboratory trends are high-risk.
- Seek urgent specialist and inpatient assessment; Do not await a solitary confirmatory test.
- Treat the underlying hyperinflammation using an expert-directed approach.

# Three recurring diagnostic mistakes

## Premature labeling

Not excluding septic arthritis or malignancy

## Antibody overreach

Treating ANA or RF as a definitive JIA diagnostic test

## Ocular omission

Assuming asymptomatic children cannot have uveitis

## Phenotype conflation

Applying one immune model or treatment to every subgroup

# Integrating phenotype, pathology and consequence

| Disease feature                       | Mechanistic / practical implication              |
|---------------------------------------|--------------------------------------------------|
| <b>Oligoarticular, ANA-associated</b> | Immune-mediated synovitis; Eye screening         |
| <b>RF-positive polyarticular</b>      | RA-like inflammatory phenotype; Joint protection |
| <b>Systemic JIA</b>                   | Cytokine-driven inflammation; MAS vigilance      |
| <b>Enthesitis-related</b>             | Insertions / axial pattern; Uveitis phenotype    |
| <b>TMJ arthritis</b>                  | Potential growth and functional damage           |

## Five concepts to retain

- JIA begins before 16 years and persists for at least 6 weeks after exclusion of alternatives.
- Subtypes are clinically heterogeneous; ANA/RF are contextual markers.
- Th1/Th17 and cytokines contribute, but no universal causal pathway is established.
- Quiet uveitis and fulminant MAS demand different surveillance strategies.
- Early individualized inflammation control aims to protect joints, growth and function.

# Core readings and clinical frameworks

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