

Juvenile Idiopathic arthritis

Summary

Juvenile idiopathic arthritis (JIA; formerly called juvenile rheumatoid arthritis) is a broad term for childhood rheumatic diseases that begin before the age of 16 and are characterized by joint inflammation that lasts more than 6 weeks. It is classified into various types based on the pattern of joint involvement, the presence of extra-articular manifestations (e.g., uveitis, rash, nail changes, lymphadenopathy, hepatosplenomegaly), laboratory findings, and disease prognosis. Oligoarticular JIA, which is the most common type, presents with asymmetric involvement of up to four joints (with the knee joint most often affected). Nearly half of all cases of oligoarticular JIA are associated with anterior uveitis, which may be diagnosed by slit-lamp examination. Laboratory tests such as ESR, rheumatoid factor (RF), antinuclear antibodies (ANA), and the HLA-B27 antigen test are used to classify and determine the prognosis of JIA. Treatment of JIA is similar to that of adult rheumatoid arthritis and involves the use of NSAIDs, intra-articular steroid injections, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. Systemic glucocorticoid therapy should be avoided because of the risk of growth impairment.

A. **Definition.** JIA is a disorder characterized by chronic joint inflammation in children, with or without extraarticular involvement.

Definition—idiopathic synovitis of peripheral joints associated with soft-tissue swelling and joint effusion

B. Epidemiology

1. **JIA is the most common pediatric rheumatic disease with arthritis** as the distinguishing manifestation.
2. The mean age of onset is **1–3 years**; presentation before 6 months of age is unusual.
3. JIA most commonly occurs in **females**, with two exceptions. **Males are equally likely to have systemic-onset JIA**, and they are much **more likely to have late-onset human leukocyte antigen B27(HLA-B27)–related diseases**.

ETIOLOGY

- The most common chronic rheumatologic disease of childhood is JRA(**juvenile chronic arthritis**), prevalence of **1 : 1000**.
- It is **autoimmune disease** of unknown etiology
- Possible external triggers include viruses (parvovirus B19, rubella, Epstein-Barr virus), host hyperreactivity to specific self antigens (type II collagen), and enhanced T-cell reactivity to bacterial or mycobacterial heat shock proteins.
- The synovitis of JRA is characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the subsynovial tissues.
- The manifestation of this group of illnesses is the presence of chronic **synovitis**.
 - ✓ The synovium becomes thickened and hypervascular with infiltration by lymphocytes
 - ✓ lymphocytes with inflammatory cytokines can be found in the synovial fluid.
 - ✓ The inflammation leads to the production and release of tissue proteases and collagenases.
 - ✓ if left untreated can lead to tissue destruction, particularly of the articular cartilage and eventually the underlying bony structures.
- **Pannus formation**, which is an inflammatory exudate over the synovial lining, occurs in advanced uncontrolled disease and results in progressive erosion of articular cartilage and contiguous bone.
 - Pathophysiology
 - Vascular endothelial hyperplasia and progressive erosion of articular cartilage and contiguous bone
 - Immunogenetic susceptibility and an external trigger
 - **DR8 and DR5**

Sun

Clinical features

For the exact pattern of joint involvement and specific extra-articular symptoms, see “Subtypes and variants” below.

• Arthritic symptoms

- Swollen joints, rarely erythema
- Early morning stiffness
- Limited or painful joint movement

• Extra-articular manifestations ^[1]

- **Fever** (for ≥ 2 weeks)
- **Uveitis**
- **Rash**
- Nail changes
- Lymphadenopathy
- Hepatosplenomegaly

• Nonspecific features

- Excessive crying
- Lethargy
- Decreased scholastic performance
- Growing pains

• Clinical presentation

- **Morning stiffness**; easy fatigability
- Joint pain later in the day, joint swelling, joints warm with decreased motion, and pain on motion, **but no redness**
- Chronic arthritis typically presents with swelling of the joint and effusion.
- the onset of the arthritis is slow, the actual joint swelling is often noticed by the child or parent acutely, such as after an accident or fall, and can be confused with trauma (although traumatic effusions are rare in children).
- Morning stiffness and gelling also can occur in the joint and, if present, can be followed in response to therapy.
- In children, owing to the presence of an active growth plate, it may be possible to find **bony abnormalities** of the surrounding bone. In a lower extremity joint, a leg length discrepancy may be appreciable if the arthritis is asymmetric.
- All children with chronic arthritis are at risk for chronic **iridocyclitis** (anterior uveitis)
- There is an association with:
 - ✓ HLA-DR5, HLA-DR6, and HLA-DR8 and uveitis.
 - ✓ positive **antinuclear antibody (ANA)** and chronic uveitis.
 - ✓ young girls, with pauciarticular JRA and a positive ANA are at highest risk, with an incidence of uveitis of 80%.
- The uveitis associated with JRA can be asymptomatic until the point of visual loss, so it is an indication for slit- lamp ophthalmic exam.



The affected joints are often stiff in the morning or after longer periods of inactivity (e.g., sitting). Joint stiffness improves with movement and decreases later in the day.

• Criteria for diagnosis

- Age of onset: <16 years
- Arthritis in one or more joints
- Duration: ≥ 6 weeks
- Onset type by disease presentation in first 6 months
- Exclusion of other forms of arthritis, other connective tissue diseases and vasculitides, **Lyme disease**, psoriatic arthritis, inflammatory bowel disease, **lymphoproliferative disease**

Criteria for the Classification of JRA

Age at onset: <16 yr

Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥ 1 joints

Duration of disease: ≥ 6 wk

Onset type defined by type of articular involvement in the 1st 6 mo after onset:

Polyarthritis: ≥ 5 inflamed joints

Oligoarthritis: ≤ 4 inflamed joints

Systemic disease: arthritis with a characteristic intermittent fever

Exclusion of other forms of juvenile arthritis

D. **Classification.** The classification of JIA is determined on the basis of the number and types of joints involved, along with extraarticular manifestations (**Table 16-4**). The categories of JIA include oligoarthritis, polyarthritis, systemic arthritis, enthesitis-related arthritis, and psoriatic arthritis. Regardless of type, all patients have arthritis during their clinical course.

Features of Juvenile Rheumatoid Arthritis Subgroups

Feature	PAUCIARTICULAR	POLYARTICULAR	SYSTEMIC ONSET
No. joints	<5	≥5	Varies, usually ≥5
Types of joints	Medium to large	Small to medium	Small to medium
Gender predominance	F > M (especially in younger children)	F > M	F = M
Systemic features	None	Some constitutional	Prominent
Uveitis	+++	+	+
ANA positivity	++	+	-
RF positivity	-	+	-
Outcomes	Excellent, >90% complete remission	Good, >50% complete remission, some risk for disability	Variable, depends on extent of arthritis

First: Pauciarticular JIA:

1. **Oligoarticular JIA (≤ four joints involved)** accounts for 50% of cases. Patients usually present at 1–5 years of age with a female predominance. A good majority (65–85%) of patients have a **positive antinuclear antibody (ANA)**. These patients are at **high risk for developing chronic uveitis**, which is defined as inflammation of the iris and ciliary body. Uveitis must be monitored by regular slit-lamp evaluations.

- a. **Subtypes.** Subtypes of oligoarticular JIA are recognized on the basis of the presence and timing of joint involvement.

1. **Persistent oligoarthritis** describes patients with one to four joints involved in the first 6 months of disease **who do not develop arthritis in additional joints**.
2. **Extended oligoarthritis** describes patients with one to four joints involved during the first 6 months of disease **who then develop arthritis in greater than four joints**.

- b. **Articular involvement** may present with swelling of one or two joints, not necessarily symmetric. The most common joints involved are the knees and hips.

- Pauciarticular JRA is defined as the presence of arthritis in fewer than five joints within the first 6 months from diagnosis.
- This is the most common form of JRA (approximately 50% of cases)
- The arthritis is found in medium-sized to large joints, with *the knee being the most common joint* involved followed by the ankle and the wrist.
- It is unusual for small joints, such as the fingers or toes, to be involved.
- Involvement of the hip is almost never a presenting sign of JRA.
- Children with pauciarticular JRA not show any evidence of systemic inflammation.

PAUCIARTICULAR TYPE I	PAUCIARTICULAR TYPE II
45%	5%
80% females	90% males
Early childhood	Late childhood
Large joints	Large joints
ANA 50%	ANA Neg.
HLA- B27 0%	HLA- B2 75%
Prognosis as spondyloarthritis	Prognosis as spondyloarthritis

Second: Polyarthritis JIA

2. **Polyarticular JIA (five or more joints involved)** accounts for approximately 30–40% of cases, with systemic involvement and extraarticular features generally mild or absent.
- a. **Subtypes.** As in oligoarticular disease, polyarticular JIA can also be divided into two subtypes. Subtypes are based on the absence or presence of **serum rheumatoid factor (RF)**, which is an IgM molecule directed against IgG. Both RF-negative (RF-) and RF-positive (RF+) polyarticular JIA affect **females** more frequently than males.
1. **RF- disease** presents both early and late in childhood.
 2. **RF+ disease** presents in children older than 8 years and is generally **more severe than RF- disease**, with **higher risk of severe arthritis** and rheumatoid nodules.
- b. **Articular involvement** is characterized by a symmetric polyarthritis that typically involves both small joints (hands and feet) and large joints (knees, ankles, and hips).

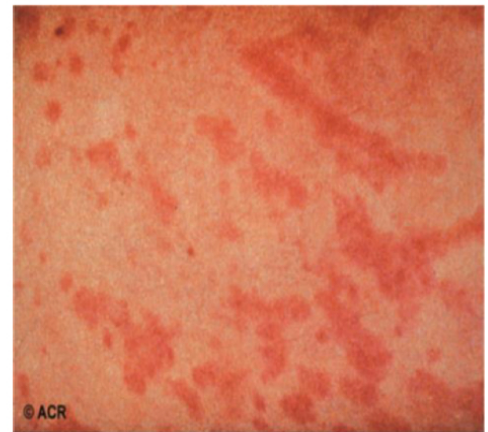
- Polyarticular JRA describes children with arthritis in ≥ 5 joints within the first 6 months of diagnosis and accounts for about 40% of cases.
- As many as 20-40 joints may be affected in the more severely involved child.
- Children with polyarticular JRA tend to have symmetric arthritis, which can affect any joint, but typically involves the small joints of the hands, feet, ankles, wrists, and knees.
- The cervical spine can be involved, leading to fusion of the spine over time. with a risk of atlantoaxial subluxation and potential neurologic sequelae
- **Rheumatoid nodules** on the extensor surfaces of the elbows and over the Achilles tendons, while unusual, are associated with a more severe course.
- **Micrognathia** reflects chronic temporomandibular joint disease.
- polyarticular disease can present with evidence of systemic inflammation, including malaise, low-grade fever, growth retardation, anemia of chronic disease, and elevated markers of inflammation.
- Differ from the other group by the presence of a positive **rheumatoid factor (positive in 15% of JRA)**
- Rheumatoid factor-positive polyarticular JRA most likely represent a subgroup with true adult rheumatoid arthritis.
- Polyarthritis with positive RF have > 50% severe arthritis, more than systemic onset which 30% only.

Sun

Third: Systemic JIA:

3. **Systemic-onset JIA** accounts for 10–15% of cases. At presentation, severe systemic symptoms may overshadow symptoms of arthritis.
 - a. **High spiking fevers** (temperature $> 39^{\circ}\text{C}$ [102.2°F]) occur most commonly in the late afternoon or evening and subsequently return quickly to baseline or subnormal levels (Quotidian fever pattern). **Systemic JIA is typically included in the differential diagnosis of “fever of unknown origin.”**
 - b. **Transient salmon-pink macular rash** is most commonly found on the trunk and proximal extremities, especially during febrile episodes. The rash is **evanescent** (occurs with fever spikes and then fades) and **nonpruritic**.
 - c. **Hepatosplenomegaly**
 - d. **Lymphadenopathy**
 - e. Other features include the following:
 1. **Fatigue, anorexia, weight loss, and failure to thrive** are common.
 2. **Serositis**, including pericarditis and pleuritis, is also common.
 3. **CNS involvement**, including meningitis and encephalopathy, may occasionally be present.
 4. **Myositis and tenosynovitis** can also be seen in addition to the arthritis.

- A small subgroup of patients (approximately 10%) with juvenile arthritis present with **systemic inflammation** rather than arthritis.
- The arthritis of JRA follows the systemic inflammation by 6 weeks to 6 months.
- characterized by a recurring spiking fever with temperatures to $\geq 39^{\circ}\text{C}$, sometimes followed by mildly hypothermic temperatures for ≥ 2 wk, once or twice a day.
- Each febrile episode is frequently accompanied by evanescent **salmon-colored lesions**
 - ✓ a characteristic faint, erythematous, macular rash
 - ✓ linear or circular
 - ✓ 2-5 mm in size
 - ✓ distributed in groups with a linear distribution
 - ✓ most commonly over the trunk and proximal extremities .
 - ✓ is not pruritic.
 - ✓ Its most diagnostic feature is its transient nature, with a group of lesions usually lasting < 1 hr.
 - ✓ The **Koebner phenomenon** is cutaneous hypersensitivity to superficial trauma resulting in a localized recurrence of the rash, is suggestive, but not diagnostic, of systemic-onset disease.
 - ✓ Heat, such as a warm bath, also evokes a reappearance of the rash.
- Internal organ involvement also occurs.
 - ✓ Serositis, ex. pleuritis and pericarditis (50% of cases)
 - ✓ Hepatosplenomegaly (70% of children)
- Laboratory findings also show the inflammation, with elevated ESR, CRP, WBC count, and platelet counts and anemia.
- The arthritis is typically polyarticular in nature and can be extensive and resistant to treatment, placing these children at highest risk for long-term disability.



Copyright © 2007 by Saunders, an imprint of Elsevier Inc. All rights reserved.

Sun

To Sum Up:

Subtype	Definition	(% of JIA)	Age of Onset	Sex Ratio
Oligoarticular	There are 2 subtypes of oligoarticular JIA: • Persistent oligoarticular arthritis: Never affects more than four joints • Extended oligoarticular arthritis: Affects more than four joints after the first 6 months of disease	50%	Early childhood; peak at 2–4 years	Female > male
Polyarticular	There are 2 subtypes of polyarticular JIA: • RF-negative • RF-positive	30–40% for both subtypes	• RF-negative: Biphasic distribution; early peak 2–4 years and later peak at 6–12 years • RF-positive: Late childhood or adolescence	Female > male
Systemic onset	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("Quotidian") for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, and (4) serositis	10–15%	Throughout childhood	Female = male
Psoriatic	Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, and (3) psoriasis in first-degree relative	2–11%	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	Female > male
Enthesitis related	Arthritis or enthesitis with two or more of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27, (3) onset of arthritis in male >6 years of age, (4) acute anterior uveitis, and (5) family history in a first-degree relative of HLA-B27 associated disease	3–11%	Late childhood or adolescence	Male > female

RF = rheumatoid factor; *Enthesitis* = inflammation of tendinous insertions on bone; HLA-B27 = human leukocyte antigen B27.

Sun

LABORATORY AND IMAGING STUDIES

- Most children with pauciarticular JRA may have no laboratory abnormalities.
 - Children with polyarticular and systemic-onset disease commonly show Laboratory abnormalities characteristic of inflammation include:
 - ✓ elevated erythrocyte sedimentation rate (ESR)
 - ✓ elevated C-reactive protein (CRP)
 - ✓ Leukocytosis
 - ✓ Thrombocytosis
 - ✓ anemia of chronic disease,
 - indicators for leukemia include a low WBC count or platelet count, instead of elevated values, or significantly lower hemoglobin than would be expected with anemia of chronic disease alone.
 - Elevated ANA titers are present in 40-85% of children with oligoarticular or polyarticular JRA, but are unusual in children with systemic-onset disease.
 - All patients with pauciarticular JRA should have an **ANA** to help identify patients at higher risk for uveitis.
 - Rheumatoid-factor (RF) seropositivity may be associated with:
 - ✓ onset of polyarticular involvement in an older child (≈8%)
 - ✓ development of rheumatoid nodules
 - ✓ poor overall prognosis with eventual functional disability.
 - Both ANA and RF seropositivity occur in association with viral infections, particularly Epstein-Barr virus.
 - Older children and adolescents with polyarticular disease should have a **rheumatoid factor** performed to identify children with early onset adult rheumatoid arthritis.
 - Diagnostic **arthrocentesis** may be necessary to exclude suppurative arthritis in children who present with acute onset of monarticular symptoms.
 - ✓ The synovial fluid WBC count less than 50,000 to 100,000/mm³
 - ✓ predominantly lymphocytes, not neutrophils as in suppurative arthritis
 - ✓ negative Gram stain and culture .
 - **The most common radiologic finding in the early stages of JRA is a normal bone x-ray.**
 - **periarticular osteopenia is most commonly found.**
 - Erosions of bony articular surfaces may be a late finding.
 - Abnormalities of skeletal growth become most prominent during the pubertal growth spurt and in postpubertal children (Tanner stages IV-V) and lead osteopenia.
1. **Anemia** is usually **microcytic and hypochromic**, consistent with anemia of chronic disease.
 2. **Acute-phase reactants** are **elevated**, including ESR, CRP, and platelet count.
 3. **Rheumatoid markers**
 - a. **RF** is negative in most patients with JIA. RF positivity is not diagnostic but can help determine prognosis for patients with polyarticular disease.
 - b. **ANA** is present in 65–85% of patients with oligoarticular JIA and in 50% of patients with polyarticular JIA. An ANA is not a diagnostic test for JIA but can help determine the risk of uveitis. *ANA is rare in children with systemic-onset JIA.*

DIFFERENTIAL DIAGNOSIS

- Although a presumptive diagnosis of systemic-onset JRA can be established for a child during the systemic phase, a definitive diagnosis is not possible until arthritis develops.
- Children must be younger than 16 years old at time of onset of disease; the diagnosis of JRA does not change when the child becomes an adult.
- Because there are so many other causes of arthritis, these disorders need to be excluded before providing a definitive diagnosis of JRA.
- The acute arthritides can affect the same joints as JRA, but have a shorter time course.
- All of the pediatric spondyloarthropathies (associated with spinal involvement and enthesitis) can present with peripheral arthritis before other manifestations and initially may be diagnosed as JRA.

Sun

TREATMENT

- **NSAIDs** are the first choice in the treatment of JRA. Naproxen^{Rx}, sulindac^{Rx}, ibuprofen^{Rx}, indomethacin^{Rx}.
- Aspirin^{Rx} products, the mainstay of arthritis treatment in the past because of concerns about Reye syndrome, and the convenience of twice daily rather than four times daily dosing.
- **Systemic corticosteroid medications**, it is used as **bridging therapy** until other medications take effect in:
 - ✓ severe systemic-onset JRA with internal organ involvement
 - ✓ active arthritis leading to inability to ambulate.
- **Second-line medications**, such as **hydroxychloroquine** and **sulfasalazine^{Rx}**.
- **Methotrexate**, orally or SC, safest, most efficacious, and least toxic of the currently available second-line agents for initial adjunctive therapy with an NSAID. Methotrexate can cause bone marrow suppression and hepatotoxicity; regular monitoring can minimize these risks.
- For patients who do not respond to NSAIDs, second-line medications, or methotrexate, can use agents that control arthritis by blocking the cytokine TNF- α . **etanercept^{Rx}** and **infliximab^{Rx}**,

COMPLICATIONS

- Complications with JRA result primarily from the **loss of function of an involved joint** secondary to joint contractures or bony fusion or loss of joint space.
 - anterior uveitis result in posterior synechiae, cataracts, and band keratopathy, and result in blindness.
 - **macrophage activation syndrome**, a rare and occasionally fatal complication of systemic JRA
- 
- ✓ The acute development of a profound anemia associated with thrombocytopenia ($\leq 262 \times 10^9/L$) or leukopenia ($\leq 4.0 \times 10^9/L$), Elevated levels of aspartate aminotransferase (>59 U/L), Hypofibrinogenemia (≤ 2.5 g/L), with a high, spiking fever, lymphadenopathy, and hepatosplenomegaly
 - ✓ Other abnormal laboratory findings in S-JIA-associated MAS: erythrocyte sedimentation rate fall, increased bilirubin, presence of fibrin degradation products, hypertriglyceridemia, low sodium levels, decreased albumin, and hyperferritinemia.
 - ✓ bone marrow biopsy demonstrating hemophagocytosis
 - ✓ Emergency treatment with high-dose intravenous pulse methylprednisolone, cyclosporine.

PROGNOSIS

- The prognosis of JRA is **excellent**, with an overall 85% complete remission rate.
- poorer prognosis:
 1. Systemic-onset disease
 2. positive rheumatoid factor
 3. poor response to therapy
 4. the presence of erosions on x-ray .
- Children with pauciarticular JRA uniformly tend to do well, whereas children with polyarticular disease and systemic-onset disease constitute most children with functional disability.

To Sum Up:

يلا خلصنا على الـ Sum up جرائي 🦋🦋🦋

A 7-year-old girl complains of pain and swelling of the left wrist and right knee off and on for the past 3 months. She has been previously healthy. The pain is worse in the morning and improves throughout the day. Physical examination is remarkable for swelling and effusion of the right knee, with decreased range of motion.

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis	
Clinical features	• Symmetric arthritis for at least 6 weeks ◦ Polyarticular: ≥ 5 joints involved ◦ Oligoarticular: < 5 joints involved
Laboratory findings	• Elevated inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) • Hyperferritinemia • Hypergammaglobulinemia • Thrombocytosis • Anemia

1. Autoimmune disorder of childhood marked by **SYMMETRIC** arthritis of **≥ 1 JOINTS** within first 6 months of symptom onset
2. Presentation:
 - a. Joint swelling
 - b. Minimal pain
3. Large joints (eg, knees, ankles) are most commonly affected; however, hip involvement is rare
4. Anemia is seen due to chronic inflammation and iron deficiency
 - a. Improves with anti-inflammatories (eg, methotrexate)
5. Uveitis is also a serious complication:
 - a. **Ophthalmologic screening** is performed regularly because untreated uveitis is often asymptomatic and can lead to irreversible vision loss
6. Treatment:
 - a. NSAIDs (first-line)
 - b. Intraarticular glucocorticoids
 - c. DMARDs (eg, methotrexate)

TYPES OF JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis				
Subtype	Frequency	Age of onset	Clinical features	Sex ratio
Systemic	10%	Age <18	- Arthritis in ≥ 1 joint for ≥ 6 weeks - Quotidian fever for ≥ 2 weeks - Evanescent rash - Hepatosplenomegaly - Lymphadenopathy	F = M
Polyarticular	40%	Age 2-5 or 10-14	- Arthritis in ≥ 5 joints - May be complicated by uveitis	F > M
Oligoarticular	50%	Age 2-4	- Arthritis in <5 joints - May be complicated by uveitis	F > M

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

- Clinical features
 - Chronic oligoarthritis
 - Joint pain worse in morning
 - Daily fever
 - Rash
- Look for:
 - ≥ 2 weeks of fever occurring once a day (quotidian fever)
 - Arthritis of ≥ 1 joint
 - Pink macular rash that worsens during fever
- Lab findings
 - Leukocytosis
 - Thrombocytosis
 - $\uparrow$ inflammatory markers
 - Anemia
- Treatment
 - NSAIDs
 - Glucocorticoids
 - Anti-inflammatory Biologic agents

Sun