

## Juvenile Idiopathic Arthritis (JIA) — Treatment and Prognosis

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**Juvenile idiopathic arthritis is a chronic inflammatory condition that occurs in children and is characterized by the involvement of a single joint (psoriatic type), 1-4 joints (oligoarticular), 5 or more joints (polyarticular), or systemic-onset disease. The exact etiology is unknown, but genetic predisposition is likely to play a significant role in the pathogenesis. The diagnosis is based on clinical criteria which can be supported by laboratory findings. Treatment is dependent on the exact type of the disease and mainly consists of non-steroidal anti-inflammatory drugs, steroids, methotrexate, and tumor necrosis factor-alpha inhibitor. Biologic disease-modifying antirheumatic drugs have recently been approved for use in juvenile idiopathic arthritis.**



### Overview of Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory condition in children and is one of the most common chronic illnesses of childhood. Juvenile rheumatoid arthritis (JRA) is, in fact, **a collective term that includes many disorders which share a common feature “chronic joint inflammation.”**

**Note:** JRA is an autoimmune disorder with evidence in favor of genetic association and predisposition; however, the exact etiology of JRA is still unknown. JIA was formerly known as JRA. The word idiopathic was used instead of rheumatoid because recent evidence has emerged showing significant differences between rheumatoid arthritis and this condition. JIA can be of a polyarticular nature, periarticular nature, or present as a systemic illness with or without the joint disease.

## Definition and Classification of Juvenile Idiopathic Arthritis

In order to diagnose juvenile idiopathic arthritis, the patient must be under 16 years of age and the symptoms should persist for at least six weeks. Per this definition, **JIA can be classified into seven main types:**

- Systemic-onset JIA
- Rheumatoid factor positive polyarthritis
- Persistent or extended oligoarthritis
- Rheumatoid factor negative polyarthritis
- Psoriatic JIA
- Enthesitis arthritis or undifferentiated JIA either does not meet any of the diagnostic criteria for the different types or meets more than one criteria from more than one subtype of JIA
- Oligoarthritis is defined as the involvement of one to four joints. Polyarticular disease is the involvement of five or more joints

## Epidemiology of Juvenile Idiopathic Arthritis

### Occurrence

JIA is the most common chronic inflammatory condition in children with an **estimated annual incidence of 14 new cases per 100,000**. The prevalence of JIA in the United States can range from 1.6 up to 86.1 per 100,000 depending on the diagnostic criteria used to define the patients.

**JIA seems to be more common in Norway and British Columbia.** The prevalence of JIA in Norway is estimated to be 148 per 100,000, while the annual incidence is around 22 new cases per 100,000. The incidence of JIA in Japan is considered low, estimated to be 0.83 cases per 100,000 children.

JIA-related mortality rate in Europe and the United States is quite low and is estimated to range between 0.5 to 1 %. The most common cause of death in the United States is a severe infection, whereas the most common cause of death in Europe appears to be amyloidosis which is a common complication of JIA.

**Note:** The most common form of JIA is the oligoarticular type. The estimated frequency of the oligoarticular JIA type from all JIA cases is around 30 %.

The second most common type is enthesitis-related with a reported frequency of 25 %. Polyarticular rheumatoid factor negative JIA has a frequency of 20 %. **Undifferentiated JIA is diagnosed in 10 % of the cases.** Finally, systemic-onset JIA, rheumatoid factor positive polyarticular JIA, and psoriatic JIA have a 5 % frequency each. Because only 5 % of JIA patients are found to be rheumatoid factor positive, the word "rheumatoid" was removed from the name of the disorder.

## Sex differences

**Sex differences in the frequency of JIA exist and are quite complex.** The female to male ratio of oligoarthritis JIA is 3 to 1. Uveitis, a common complication of JIA, is also found more often in girls with a girls-to-boys' ratio of 6 to 1. Polyarticular disease is also more common in girls with a ratio of 3 to 1. Systemic-onset JIA has an equal frequency in both genders and enthesitis-related JIA is more common in boys.

## Age of diagnosis

**Oligoarthritis and rheumatoid factor negative polyarticular JIA are usually diagnosed within the first 4 years of life.** Rheumatoid factor positive polyarticular JIA typically presents during adolescence. Most cases of enthesitis-related arthritis are diagnosed within the age-group 10 to 12 years. Systemic-onset JIA can be seen at any age during childhood.

## Etiology and Pathophysiology of Juvenile Idiopathic Arthritis

The exact etiology of JIA is still unknown, but the disease is **believed to be a complex one with an interplay between environmental exposures and genetic predisposition.** The issue with studying genetic predisposition in JIA is that most of the identified loci overlapped with other autoimmune disorders; hence, none of them were specific for JIA. Regardless, a child with one of some polymorphisms in one of the following genes is at risk of developing JIA and/or other autoimmune disorders.

### **Genes identified with an increased predisposition to JIA:**

- HLA-A(\*)02:06 has been linked to JIA accompanied with uveitis
- HLA-DRB1(\*)04:05 allele is associated with an increased risk of polyarticular JIA
- IL2RA/CD25 gene has been also linked to JIA
- The MHC locus has been also linked to systemic-onset JIA

Regardless of the exact etiology, the pathogenesis of JIA is believed to involve humoral and cell-mediated abnormal immunity responses. **T-cells are usually activated in JIA where they release proinflammatory mediators,** such as tumor necrosis factor-alpha, interleukin 6, and interleukin 1. T-lymphocytes in JIA tend to invade the synovium where they show a non-specific antigen response and activation. B-cells also invade and expand within the inflamed synovium. Macrophages can be also attracted to the synovium.

## Clinical Presentation of Juvenile Idiopathic Arthritis

The signs and symptoms of JIA can be divided as historical findings and physical manifestations.

### **History findings in children with JIA may include the following:**

- Arthritis present for at least 6 weeks before diagnosis
- Psoriasis or more subtle dermatologic manifestations
- Rash on the trunk and extremities
- Fevers occurring once or twice each day at about the same time of day

### Physical manifestations include:

- Arthritis: Examination of the affected joint will reveal intra-articular swelling or limitation of joint motion associated with signs of inflammation, which are: pain, warmth, or erythema of the joint
- Synovitis: Characterized by the proliferation of the synovial membrane and an increase in joint volume; which is held in a position of maximum comfort

**Note:** Children might not complain of pain of a single joint. Instead, they might opt to use that joint less often or in an abnormal way. The most common presentation in that scenario would be a morning limp that disappears as the day goes.

	<b>Oligoarticular</b>	<b>Polyarticular</b>	<b>Systemic</b>
<b>% of JIA cases</b>	50%	35%	10%
<b>Gender</b>	F > M	F > M	F = M
<b>Age</b>	2-3 y, rare > 10 y	2-5 y, 10-14 y	Any < 17 y
<b># joints affected</b>	< 5	> 5	Any
<b>Type of joints affected</b>	<ul style="list-style-type: none"><li>• Medium and large joints</li><li>• Asymmetric</li><li>• Rarely hips</li><li>• Nondestructive arthritis</li></ul>	<ul style="list-style-type: none"><li>• Any</li><li>• Usually symmetric</li><li>• Rarely hips</li><li>• Destructive arthritis</li></ul>	<ul style="list-style-type: none"><li>• Any</li><li>• Destructive arthritis</li></ul>
<b>Systemic features</b>	Asymptomatic 20 % uveitis (if ANA+)	Less frequent uveitis	Daily high fevers, Evanescent salmon-pink rash, HSM, LAD, Heart/lung/liver

## Systemic-Onset JIA

Systemic-onset JIA cannot be diagnosed at presentation. **The definite diagnosis can be made only when the patient develops arthritis** which can happen during the onset period or years after the initial presentation.

The patient is very ill, joint pain is present, muscle pain is common, and a salmon-pink macular rash can be seen. Hepatosplenomegaly, lymphadenopathy and pleural or pericardial effusions are also common findings. Pericarditis and pleuritis might present with chest pain.

## Oligoarticular JIA

Joint involvement is limited to one up to 4 joints. **The most commonly affected joints are the knees and ankles.** In contrast to systemic-onset JIA, children with oligoarticular JIA do not appear ill. Involvement of the small joints of the hands is uncommon.

Anterior uveitis is found in one-fifth of the cases and patients diagnosed with this type of JIA should receive formal ophthalmological screening to exclude asymptomatic uveitis. Patients who have a positive antinuclear antibody test in addition to the onset of oligoarticular JIA before the age of six years should start screening with a slit-lamp every 3 months for four years. After that, screening should be performed bi-annually for three more years. Finally, screening should be repeated every year for the rest of their life.

## Polyarticular JIA

Polyarticular JIA is characterized by the **involvement of five or more joints within the first five months of onset, but not necessarily at the same time**. Like oligoarticular JIA, the most commonly affected joints are the ankles and knees. Symmetrical involvement of the small joints is common in polyarticular JIA. Arthritis can also involve the temporal-mandibular joint or the cervical vertebral column.

## Psoriatic JIA

**The joint involvement in psoriatic JIA is quite different from the previous two types.** Monoarticular arthritis with the involvement of the distal interphalangeal joints is common. Nail involvement is seen in up to 70% of the cases. Bone growth might be impaired and shortening of the affected limb can ensue. Sacroiliitis is found in one-third of the cases. Half of the cases of psoriatic JIA move on to develop psoriasis later in life.

## Enthesitis-Related Arthritis

This type of JIA is **characterized by the involvement of tendons and ligaments**. Pain and tenderness are common around the affected ligament and tendon insertion points on the bone. Dactylitis can be also seen. The diagnosis of enthesitis-related arthritis can be confirmed when both enthesitis and arthritis are present, or when one of them is present in a patient that meets two of the following criteria:

- Sacroiliitis
- HLA-B27 positive
- The onset of arthritis after the age of 6 years in boys
- Symptomatic anterior uveitis
- Family history of enthesitis-related arthritis, or ankylosing spondylitis

## Diagnostic Workup for Juvenile Idiopathic Arthritis

### Different levels and rates

The erythrocyte sedimentation rate and C-reactive protein levels are usually elevated in systemic-onset JIA and polyarticular JIA. The **levels of these inflammatory markers are typically within a normal range in patients with oligoarticular JIA**.

Thrombocytosis and leukocytosis are also common in patients with JIA in general. More recently, the biomarker S100A12 was found to be elevated in patients with JIA and to be very specific for the prediction of flares.

**Liver function tests are indicated at baseline before starting treatment** to exclude autoimmune hepatitis. Renal function tests including serum creatinine and urine protein should be performed.

**Antinuclear antibodies are positive in up to 70 % of the children with oligoarticular JIA.** A positive antinuclear antibody test in a child with JIA puts the child at an increased risk of acute anterior uveitis.

**Total protein and albumin levels should be checked in patients with systemic-onset JIA.** They are usually decreased when the disease is active. Fibrinogen, D-dimer, and ferritin are usually elevated in systemic-onset JIA. The levels of angiotensin-converting enzyme should be checked to exclude sarcoidosis.

Patients with a falling erythrocyte sedimentation rate, leukopenia, thrombocytopenia, elevated liver enzymes, increased ferritin, high triglycerides, low fibrinogen, fevers and a picture similar to disseminated intravascular coagulation are diagnosed with macrophage activating syndrome.

## Radiography and computed tomography



**Image:** "Rheumatoide Arthritis AP" by Bernd Brägelmann Braegel. License: [CC BY-SA 3.0](#)

**Radiography is indicated to exclude other processes such as septic arthritis,** especially when a single joint is involved.

**Note:** The main features of JIA arthritis are soft tissue swelling, osteopenia, joint-space narrowing, bony erosions, epiphyseal compression fracture, and the presence of synovial cysts on a joint radiograph.

Computed tomography scanning of the affected joints gives a better picture of the nature of the pathology and the degree of bone erosion and involvement. **Magnetic resonance imaging is the best modality for the evaluation of the affected joints, tendons, and ligaments** in patients with JIA. Magnetic resonance imaging is helpful in the evaluation of the sacroiliac joint, the cervical spine, the shoulder, hip, and the temporal-mandibular joint, which are commonly affected in patients with the polyarticular disease.

Bone scanning with positron emission tomography with or without single-photon emission computed tomography might be helpful in the detection of inflamed bones and soft tissue structures when the other imaging modalities are inconclusive.

## Management of Juvenile Idiopathic Arthritis

The main goals of treating JIA in children are **to prevent disability, loss of function, and joint damage**. Pharmacologic treatment should be started as early as possible for optimum results and should be individualized to the patient's needs and subtype of JIA.

**Note:** The main goal of treatment that we should aim for is to induce remission.

Remission in JIA can be defined as having no inflammatory joint pain, no morning stiffness, no fatigue, no inflammation of the synovium, no progressive damage of the joint

on subsequent radiographs, and normal inflammatory markers.

The American College of Rheumatology chose to classify the treatment options for JIA in five main groups based on the type of JIA the child has.

## Treatment of Oligoarticular JIA or Psoriatic JIA

**Patients should be started on non-steroidal anti-inflammatory drugs followed by intra-articular steroid therapy.** Patients who do not respond to this regimen should be started on methotrexate. Additionally, patients with severe oligoarticular JIA with positive inflammatory markers might better off being started on methotrexate. After 6 months of methotrexate therapy, the patients who fail to show any sustainable and significant response might benefit from tumor-necrosis factor-alpha inhibitor treatment.

## Treatment of Polyarticular JIA

Non-steroidal anti-inflammatory drugs should be used for one month only. If the patient does not show a good response, methotrexate should be started. **Non-steroidal anti-inflammatory drugs might be used as adjunctive therapy** when needed while the patient is receiving methotrexate. Patients with severe polyarticular JIA and multiple positive inflammatory and bad prognostic factors should be started on methotrexate from the beginning. Patients who do not tolerate methotrexate should receive leflunomide.

Tocilizumab, an interleukin-6 inhibitor antibody, has been recently approved for monotherapy and as adjunctive therapy for the treatment of polyarticular JIA. **Tumor necrosis factor-alpha inhibitor should be started in patients who do not show a good response** after six months of methotrexate or leflunomide treatment.

## Treatment of Active Sacroiliac Arthritis

Patients should be given non-steroidal anti-inflammatory drugs for three to six months. If they show no response, they should be switched to tumor-necrosis factor-alpha inhibitor.

## Treatment of Systemic-Onset JIA without Active Arthritis

Patients with systemic-onset JIA who do not have active arthritis and who have mild to moderate serositis should be started on a two-week trial of non-steroidal anti-inflammatory drugs. If no response is seen after two weeks, the patient should receive systemic corticosteroids.

**Patients with severe serositis should be started on systemic steroids** from the beginning. Tocilizumab can be also used for the management of this type of JIA. Canakinumab, an interleukin-1 beta inhibitor, has been also used with success in the management of systemic-onset JIA without active arthritis.

## Treatment of Systemic-Onset JIA with Active Arthritis

This group of patients should also be started on non-steroidal anti-inflammatory drugs for one month. After that, they should start receiving methotrexate. After three months of methotrexate, patients who still have the active and significant disease should be started on anakinra or tumor-necrosis factor-alpha inhibitor.

## Treatment of Macrophage Activation Syndrome

**Macrophage activation syndrome is a life-threatening rare complication of JIA.**

The treatment of macrophage activation syndrome depends mainly on cyclosporine A which should be administered as early as possible. Anakinra can be also used.

## Treatment of Acute Anterior Uveitis

Most JIA patients with anterior uveitis are asymptomatic. Regardless, this condition, if recognized by a slit-lamp exam should be treated with topical corticosteroids and a mydriatic agent. **Methotrexate and cyclosporine have been used in the treatment of chronic anterior uveitis** with good results. Patients who do not respond to steroids, methotrexate, or cyclosporine should receive infliximab.

## Prognosis of Juvenile Idiopathic Arthritis

Due to advances in treatment, there has been an improved prognosis for children with JIA. Most children can lead normal lives.

**The American College of Rheumatology criteria for complete remission include:**

- No inflammatory joint pain
- No fatigue
- No synovitis
- No morning stiffness
- No elevation of ESR and CRP levels
- No progression of damage

## References

[Juvenile Arthritis](#) via [rheumatology.org](http://rheumatology.org)

[Juvenile Idiopathic Arthritis](#) via [emedicine.medscape.com](http://emedicine.medscape.com)

[Juvenile rheumatoid arthritis](#) via [mayoclinic.org](http://mayoclinic.org)

[What is Juvenile Idiopathic Arthritis?](#) via [arthritis.org](http://arthritis.org)

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