Juvenile idiopathic arthritis is a chronic, autoimmune, inflammatory joint disease. It is the most common rheumatic disease in children and adolescents. It is defined as persistent arthritis of unknown etiology that begins before the age of 16 years and persists for at least 6 weeks. It is diagnosed after excluding other causes.

The cause of JIA is unknown. It is suspected that environmental factors such as viral infections may trigger the condition in genetically susceptible children. However, it is unusual for more than one child in a family to have arthritis. The aim of treatment is the induction of remission and control of the disease to minimize pain and function loss, and maximize quality of life. There is currently no cure for JIA. Treatment has altered as a result of recent research into the best practice approach to managing children. This guideline reflects the current evidence based approach to managing children with JIA.

Classification:
Several types of arthritis, all involving chronic (long-term) joint inflammation, fall under the JIA heading. This inflammation begins before patients reach the age of 16, and symptoms last from 6 weeks to 3 months to be called chronic. JIA may involve one or many joints, and cause other symptoms such as fevers, rash and/or eye inflammation.

1- **Systemic onset JIA** affects about 10 percent of children with arthritis. It begins with repeating fevers that can be 103°F or higher, often accompanied by a salmon-colored rash that comes and goes. Systemic onset JIA may cause inflammation of the internal organs as well as the joints, though joint swelling may not appear until months or even years after the fevers begin. Anemia (a low red blood cell count) and elevated white blood cell counts are also typical findings in blood tests ordered to evaluate the fevers and ongoing symptoms. Arthritis may persist even after the fevers and other symptoms have disappeared.

2- **Oligoarticular (Pauciarticular) JIA**, which involves fewer than five joints in its first stages, affects about half of all children with arthritis. Girls are more at risk than boys. Older children with oligoarticular JIA may develop “extended” arthritis that involves multiple joints and lasts into adulthood. Children who develop the oligoarticular form of JIA when they are younger than 7 years old have the best chance of having their joint disease subside with time. They are, however, at increased risk of developing an inflammatory eye problem (iritis or uveitis). Eye inflammation may persist independently of the arthritis. Because iritis usually does not cause symptoms, regular exams by an ophthalmologist (eye doctor) are essential to detect these conditions and identify treatment to prevent vision loss.
3- **Polyarticular JIA** affects five or more joints and can begin at any age. Children diagnosed with polyarticular JIA in their teens may actually have the adult form of rheumatoid arthritis at an earlier-than-usual age.

4- With **Psoriatic Arthritis**, children have both arthritis and a skin disease called psoriasis or a family history of psoriasis in a parent or sibling. Typical signs of psoriatic arthritis include nail changes and widespread swelling of a toe or finger called dactylitis.

5- **Enthesitis-Related Arthritis** is a form of JIA that often involves attachments of ligaments as well as the spine. This form is sometimes called a spondyloarthropathy. These children may have joint pain without obvious swelling and may complain of back pain and stiffness. Some children with arthritis develop uveitis, an inflammation of the eye.

### Features of three of major subtypes of juvenile idiopathic arthritis (JIA)

<table>
<thead>
<tr>
<th></th>
<th>Systemic onset JIA</th>
<th>Pauciarticular onset JIA</th>
<th>Polyarticular onset JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of JIA patients</td>
<td>10 to 15</td>
<td>50</td>
<td>30 to 40</td>
</tr>
<tr>
<td>Sex</td>
<td>F = M</td>
<td>F &gt; M</td>
<td>F &lt; M</td>
</tr>
<tr>
<td>Age</td>
<td>Any &lt; 17 years</td>
<td>Peak 2 to 3 years, rare</td>
<td>Peak 2 to 5, 10 to 14 years</td>
</tr>
<tr>
<td>Joints</td>
<td>any</td>
<td>Large joints but rarely</td>
<td>Any, rare to start in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hip</td>
<td>hip</td>
</tr>
<tr>
<td>Fever, rash, lymphadenopathy, hepatosplenomegaly</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>uveitis</td>
<td>Rare</td>
<td>20%, most common in patients who are ANA positive</td>
<td>Less frequent</td>
</tr>
</tbody>
</table>

### Laboratory abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Systemic onset JIA</th>
<th>Pauciarticular onset JIA</th>
<th>Polyarticular onset JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis</td>
<td>Marked</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>anemia</td>
<td>Marked</td>
<td>No</td>
<td>Mild</td>
</tr>
<tr>
<td>Elevated ESR</td>
<td>Marked</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>ANA</td>
<td>Absent</td>
<td>Low titer common</td>
<td>Low titer common in younger</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Rare</td>
<td>Rare</td>
<td>10 to 20% in those &gt; 10 years</td>
</tr>
</tbody>
</table>
**Destructive arthritis**  
- > 50%  
- Rare  
- > 50%

<table>
<thead>
<tr>
<th>Disease modifying drugs</th>
<th>Commonly used</th>
<th>Rarely used</th>
<th>Commonly used</th>
</tr>
</thead>
</table>

F: female; M: male; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate.

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**Diagnosis:**

The hallmark of systemic onset JIA is the combination of intermittent daily fevers greater than 38.5°C and arthritis. The fever must be present for at least two weeks in order to make a definitive diagnosis, since many viral and other post infectious forms of arthritis also may be associated with fever. However these infectious illnesses often lack the characteristic intermittent spiking fever pattern of systemic onset JIA. There may be a prolonged delay between the onset of fever and the development of arthritis, but a definitive diagnosis of systemic onset JIA cannot be made until arthritis is present. In the presence of a characteristic fever pattern, rash, and arthritis, a tentative diagnosis of systemic onset JIA can be made and appropriate therapy begun before two weeks have elapsed.

**Treatment:**

**Oligoarticular (Pauciarticular) JIA** treatment:

True pauciarticular onset juvenile idiopathic arthritis (JIA) is usually responsive to nonsteroidal antiinflammatory drugs (NSAIDs) or intraarticular glucocorticoids. Methotrexate and other immunosuppressive drugs are rarely required. Biologic agents are occasionally used in patients with extended pauciartthritis or in those with uveitis.

Several NSAIDs have been approved for use in children with JIA, including naproxen, tolmetin, meloxicam, celecoxib, and ibuprofen. Many other NSAIDs are routinely used by pediatric rheumatologists, but have not been specifically approved for use in children. Concerns regarding potential adverse effects, especially cardiovascular events that may not appear until adulthood, exist for all NSAIDs. Treatment with NSAID therapy is appropriate for patients with low disease activity with assessment for a response within two to three months.
Intraarticular joint injection — Intraarticular injection of glucocorticoids are indicated as a first-line therapy for children with moderate to severe disease. If a patient with moderate to severe disease and poor prognosis does not respond to initial joint injection therapy, a trial of a disease modifying antirheumatic drug (DMARD) is recommended. If the patient responds to intraarticular glucocorticoids but has repeated injections due to disease flares, the patient also becomes a candidate for DMARD therapy.

Most clinicians inject one of the following agents: methylprednisolone acetate (40 mg/mL - Depo-Medrol), triamcinolone hexacetonide (20 mg/mL - Aristospan), or triamcinolone acetate (40 mg/mL - Kenalog) for large joints. For injection of small joints where there is a significant risk of extravasation from the joint resulting in subcutaneous atrophy, a mixture of betamethasone sodium phosphate and betamethasone acetate (6 mg/mL - Celestone soluspan) is preferred. There is no well standardized dosage for intraarticular injection of children. One milliliter of the appropriate glucocorticoid preparation per meter square of body surface area (mL/m²) is a rough guideline. In large children, some clinicians choose to administer 2 mL/m² of glucocorticoid preparation.

There is concern that repeated injection of the joint may lead to premature degeneration. In the past, most clinicians would therefore not inject the same joint within six months, or a single joint more than three times. This guideline is currently being reevaluated with careful follow-up studies. Multiple joint injections (eg, both knees or a knee and an ankle) may be performed in children with disease in more than one joint that is resistant to NSAIDs. This approach may be appropriate in children who do not have evidence of systemic inflammation. However, in patients with multiple affected joints who do not respond to NSAIDs and who have significant anemia or elevation of the erythrocyte sedimentation rate, aggressive systemic therapy is more likely to be beneficial.

Methotrexate and other immunosuppressive drugs are required in some children who have disease activity in one or two joints for a prolonged period that do not respond to NSAIDs or intraarticular glucocorticoid injections. These children may benefit from the addition of methotrexate or a tumor necrosis factor (TNF) blocking agent (eg, etanercept or adalimumab). TNF inhibitors are associated with an increased risk of infections and potentially malignancies. Current recommendations include a trial of three to six months with methotrexate therapy before the addition of anti-TNF therapy.

Systemic JIA:

INITIAL THERAPY FOR MILD TO MODERATE DISEASE — Nonsteroidal antiinflammatory drug (NSAID) monotherapy is the preferred initial treatment in children with possible systemic onset juvenile idiopathic arthritis with mild to moderate disease on presentation. While there is no formal definition of disease severity, we would categorize children with possible systemic onset JIA who have white blood cell counts in the range of 20,000 to 30,000 mm³, hemoglobin levels above 10 gm/dL, are not significantly discomforted by their symptoms, and have no evidence of macrophage activation syndrome (MAS), as having mild to moderate disease. In general, a trial of NSAIDs alone should last no more than 6 to 12 weeks; an additional agent is often added within two to four weeks in children who develop or continue to have significant symptoms despite use of NSAIDs.

THERAPY FOR REFRACTORY DISEASE/INITIAL THERAPY FOR SEVERE DISEASE — For patients who have not responded to a trial of an NSAID alone during the acute phase of the illness, or whose initial symptoms include high fevers and painful polyarthritis, options include
Glucocorticoids, nonbiologic disease modifying antirheumatic drugs (DMARDs), such as methotrexate, and biologic DMARDs, such as the IL-1 and IL-6 inhibitors. Glucocorticoids and the biologics are excellent antiinflammatory agents, but they do not directly provide pain relief, unlike NSAIDs. Thus, NSAIDs are often continued in conjunction with other agents for an extended period.

Glucocorticoids provide rapid onset of action and almost uniform efficacy for severely ill children. Thus, historically, most pediatric rheumatologists have used glucocorticoids at this juncture, with methotrexate used as a steroid-sparing agent for longer-term control. However, most anticytokine (biologic) agents (eg, anakinra, canakinumab, tocilizumab) have more favorable side effect profiles than nonbiologic DMARDs (eg, methotrexate) or long-term use of glucocorticoids. In addition, anti-IL-1 and anti-IL-6 agents have shown good efficacy in randomized trials, in which they were primarily used as therapy for refractory disease. Thus, the preferred choice for refractory disease, and in some cases for initial therapy for severe disease, has shifted to the biologics agents (with or without glucocorticoids depending on severity). Inhibitors of IL-1 and IL-6 appear to be the most effective of the anticytokine agents for systemic symptoms (fever and rash), while inhibitors of tumor necrosis factor (TNF)-alpha can be helpful adjuncts for arthritis therapy. In general, a glucocorticoid should be added if there is not a prompt response to a biologic and vice versa, or if there is concern for incipient MAS. Both drugs are often continued until disease control is established and then the clinician may decide to gradually withdraw one or the other.

**Glucocorticoids** — there are no randomized trials of glucocorticoids for the treatment of systemic onset JIA, although clinical experience offers general guidelines. As is generally the case, glucocorticoids should be used judiciously in systemic onset JIA to minimize their toxicity. They are typically used during the acute phase of the illness to preserve the ability to carry out activities of daily living, particularly in children who have not responded to NSAIDs.

Every effort must be made to minimize the dosage and duration of therapy. Whenever possible, the dose of glucocorticoids should be kept below 0.5 mg/kg per day of prednisone (or its equivalent) and the duration of therapy should be less than six months. Some clinicians use intermittent high dose intravenous glucocorticoids to reduce the toxicity of daily oral glucocorticoids or to treat severe anemia or pericarditis. However, this dosing regimen may be associated with an increased risk of infection or pancreatitis. It should also be kept in mind that the combination of glucocorticoids and NSAIDs can result in an increased risk of gastrointestinal toxicity due to their additive effect.

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**Polyarticular JIV:**

**Nonsteroidal antiinflammatory drugs** — Nonsteroidal antiinflammatory drugs (NSAIDs) traditionally have been the preferred first-line drugs in patients with mild disease and for symptomatic relief. These medications reach full efficacy within two to three months, but usually start to relieve symptoms within a few days. Those who have not responded to initial NSAID therapy within three weeks should have the initial NSAID discontinued and a second NSAID begun or, if warranted, they should be advanced to a disease modifying antirheumatic drug (DMARD).
The goals of treatment for JIA are to control inflammation, relieve pain, prevent or control joint damage, maximise functional abilities and manage complications.

**Pharmacological treatment**

- **Systemic Juvenile idiopathic arthritis**
  - Fever and other systemic feature
    - NSAID (1)
      - Improve
      - Not improve
      - Observe

  - Arthritis
    - Manage as pauciarticular or polyarticular arthritis
      - Improve

  - Add glucocorticoid
    - Observe

  - Taper corticosteroid
    - Observe

- **Pauciarticular Juvenile idiopathic arthritis**
  - NSAID (1)
    - Improve
    - Not improve
    - Observe
  
    - Intraarticular injection of glucocorticoids (5)
      - Improve
      - Not improve
      - Observe

      - DMARD (6)
        - Improve
        - Not improve
        - Observe

      - Biologic agents: Etanercept, Adalimumab
        - Observe

- **Polyarticular Juvenile idiopathic arthritis**
  - (NSAID) (1)
    - If there is no response to the initial NSAID by three weeks, the first NSAID if discontinued, and a second NSAID may be substituted
  
    - Observe

  - (DMARD) (6)
    - Improve
    - Not improve
    - Observe

  - Individualized therapeutic decisions are necessary. Combination DMARDs or additional biologic agents, is recommended

* Adequate diet including daily calcium and vitamin D intake
  - Calcium supplementation (together with vitamin D when on corticosteroids)
  - Land based exercise programs
  - Aquatic exercise
  - Thermotherapy (heat/ice packs, warm baths)
  - Consider splints
  - Consider foot orthotics

**Non Pharmacological treatment**

- **Systemic Juvenile idiopathic arthritis**
  - Observe

- **Pauciarticular Juvenile idiopathic arthritis**
  - Observe

- **Polyarticular Juvenile idiopathic arthritis**
  - Observe
(1) NSAIDs: non steroidal anti inflammatory drugs; naproxen, tolmetin, meloxicam, celecoxib, and ibuprofen (NSAIDs alone should last no more than 6 to 12 weeks).

(2) The prednisone dose should be limited to 0.5 to 1 mg/kg, if possible, although doses as high as 2 mg/kg, or pulsed dose "bolus therapy" may be required in severe cases. Adding a second line glucocorticoid-sparing agent, such as methotrexate, as soon as the child has stabilized on glucocorticoids and before significant glucocorticoid side effects occur.

(3) Anti-IL-1 agents, anakinra and canakinumab: subcutaneous injection
   Anti-IL-6 agent, tocilizumab, is administered intravenously

(4) HCT: hematopoietic stem cell transplantation.

(5) Methylprednisolone acetate (40 mg/mL - Depo-Medrol), triamcinolone hexacetonide (20 mg/mL - Aristospan), or triamcinolone acetate (40 mg/mL - Kenalog) for large joints. For injection of small joints where there is a significant risk of extravasation from the joint resulting in subcutaneous atrophy, a mixture of betamethasone sodium phosphate and betamethasone acetate (6 mg/mL - Celestone soluspan) is preferred.

(6) DMARD: Disease-modifying antirheumatic drugs; Hydroxychloroquine, Cyclosporine, Methotrexate (ineffective in predominantly axial arthritis), Azathioprine, Cyclophosphamide.
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Doses in JIA</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>Children &gt;2 years: Oral: Note: Oral suspension is recommended: 10 mg/kg/day in 2 divided doses (up to 15 mg/kg/day has been tolerated). Do not exceed 15 mg/kg/day</td>
<td>Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, indigestion, nausea, stomatitis, ulcers, vomiting.</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Children ≥2 years: oral; Initial: 20 mg/kg/day in 3-4 divided doses, then 15-30 mg/kg/day in 3-4 divided doses; maximum dose: 30 mg/kg/day in 4 divided doses; do not exceed 1800 mg/day</td>
<td>Abdominal pain, constipation, diarrhea, flatulence, gastritis, heartburn, nausea, peptic ulcer, vomiting, weight gain/loss, hemoglobin/hematocrit decreases (transient), hypertension, edema.</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Children ≥2 years: Oral: 0.125 mg/kg once daily; maximum daily dose: 7.5 mg/day; higher doses (up to 0.375 mg/kg/day) have not demonstrated additional benefit in clinical trials.</td>
<td>Abdominal pain, diarrhea, dyspepsia, flatulence, nausea, cough, pharyngitis, upper respiratory infection.</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Children ≥2 years; Oral: ≥10 kg to ≤25 kg: 50 mg twice daily &gt;25 kg: 100 mg twice daily</td>
<td>Angina, edema, facial edema, hypertension, abdominal pain, anorexia, appetite increased, constipation, diarrhea, bronchitis, bronchospasm, cough,</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Usual: 30-50 mg/kg/day in 3-4 divided doses; start at lower end of dosing range and titrate; patients with milder disease may be treated with 20 mg/kg/day; maximum single dose: 800 mg; maximum daily dose: 2400 mg/day</td>
<td>Edema, dizziness, headache, itching, rash, abdominal pain/cramps/distress, appetite decreased, constipation, diarrhea, dyspepsia, epigastric pain, flatulence, heartburn, nausea, vomiting, Tinnitus.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>I.V.: 10 mg/kg every 2 weeks</td>
<td>Alopecia (reversible; onset: 3-6 weeks after start of treatment), amenorrhea, azoospermia, gonadal suppression, oligospermia, oogenesis impaired, sterility, Abdominal pain, anorexia, diarrhea, mucositis, nausea/vomiting, anemia, leukopenia neutropenia, neutropenic fever, thrombocytopenia</td>
</tr>
<tr>
<td>Anakinra</td>
<td><strong>Systemic onset JIA:</strong> children &gt;1 year. Initial dose: 1 mg/kg once daily; if no response, may increase to 2 mg/kg (maximum dose: 100 mg). <strong>Polyarticular course JIA:</strong> children &lt;2 years: 1 mg/kg once daily (maximum dose: 100 mg).</td>
<td>Fever, headache, diarrhea, nausea, neutropenia arthralgia, nasopharyngitis.</td>
</tr>
<tr>
<td></td>
<td>Children ≥2 years weighing at least 7.5 kg: SubQ: 4</td>
<td>Headache, vertigo, calcium decreased, diarrhea.</td>
</tr>
<tr>
<td><strong>Canakinumab</strong></td>
<td>mg/kg/dose every 4 weeks; maximum dose: 300 mg</td>
<td>gastroenteritis, nausea, upper abdominal pain, weight gain, decreased platelet count, decreased white blood cell count, increased susceptibility to infection, creatinine clearance decreased, proteinuria, bronchitis, nasopharyngitis, pharyngitis, rhinitis</td>
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<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>Polyarticular juvenile idiopathic arthritis: Children ≥2 years: &lt;30 kg: I.V.: 10 mg/kg every 4 weeks, ≥30 kg: I.V.: 8 mg/kg every 4 weeks; maximum single dose: 800 mg</td>
<td>Hypertension, peripheral edema, dizziness, headache, skin rash, hypothyroidism, increased LDL cholesterol, abdominal pain, diarrhea, gastric ulcer, gastritis, oral mucosa ulcer, stomatitis, weight gain, Leukopenia, neutropenia, Herpes simplex infection, conjunctivitis, cough, dyspnea.</td>
</tr>
<tr>
<td></td>
<td>Systemic juvenile idiopathic arthritis: Children ≥2 years: &lt;30 kg: I.V.: 12 mg/kg/dose every 2 weeks, ≥30 kg: I.V.: 8 mg/kg/dose every 2 weeks; maximum dose: 800 mg.</td>
<td></td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>3-5 mg/kg/day (as sulfate) divided 1-2 times/day to a maximum of 400 mg/day (as sulfate); not to exceed 7 mg/kg/day</td>
<td>Cardiomyopathy, ataxia, dizziness, emotional changes, headache, irritability, alopecia, angioedema, pigmentation changes, abdominal cramping, anorexia, diarrhea, nausea, vomiting, weight loss, agranulocytosis, aplastic anemia, hemolysis, Abnormal color vision, abnormal retinal pigmentation, deafness, tinnitus.</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>Oral: Cyclosporine (modified): Initial: 2.5 mg/kg/day divided every 12 hours; may increase dose by 0.5-0.75 mg/kg/day if insufficient response is seen after 8 weeks of treatment; maximum dose: 4 mg/kg/day</td>
<td>Edema, hypertension, headache, paresthesia, Female genital tract disease, hirsutism, increased serum triglycerides, abdominal distress, diarrhea, dyspepsia, gingival hyperplasia, nausea, increased susceptibility to infection, upper respiratory tract infection</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>Oral: 2-2.5 mg/kg/dose once daily</td>
<td>Malaise, diarrhea, nausea/vomiting, leukopenia, thrombocytopenia, hepatotoxicity, increased alkaline phosphatase, increased serum bilirubin, increased serum transaminases</td>
</tr>
<tr>
<td></td>
<td>BSA-directed dosing: Children 2-16 years: Oral, I.M.,</td>
<td>Vasculitis, severe headache, nuchal rigidity, vomiting,</td>
</tr>
</tbody>
</table>

**BSA-directed dosing: Children 2-16 years:** Oral, I.M.,
**Methotrexate**

SubQ: Initial: 10 mg/m2 once weekly, adjust gradually up to 20-30 mg/m2 once weekly; usual maximum dose: 25 mg; to reduce GI side effects, consider parenteral administration (I.M., SubQ) of higher doses (20-30 mg/m2).

Weight-directed dosing: Oral, SubQ: Initial: 0.5 mg/kg once weekly; maximum initial dose: 15 mg; if symptoms worsen or unchanged after 4 weeks, may increase to SubQ: 1 mg/kg; maximum dose: 30 mg.

and fever; may be alleviated by reducing the dose, alopecia, burning sensation of skin, diabetes mellitus, hyperuricemia, anorexia, aphthous stomatitis, diarrhea, gingivitis, glossitis, intestinal perforation, mucositis, nausea, periportal fibrosis, hemorrhage, leukopenia, pancytopenia, thrombocytopenia, immunosuppression, infection.

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