BMJ Best Practice

Juvenile idiopathic arthritis

Straight to the point of care

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Summary

Juvenile idiopathic arthritis (JIA) describes a group of chronic pediatric inflammatory arthritides. There are several subtypes, including oligoarticular, polyarticular, and systemic onset.

Affects 1 in 1000 children and can present at any age.

Diagnosis is made clinically. Laboratory and radiographic testing provide classification and prognostic information but are not diagnostic.

The primary goals of treatment are to relieve immediate pain and prevent joint damage and therefore disability. Intra-articular corticosteroids offer good control if only a few joints are affected. Methotrexate is the most commonly used conventional synthetic disease-modifying antirheumatic drug. Physical therapy, occupational therapy, and psychology form an important aspect of management.

Around 10% to 20% of children with JIA are at risk of developing anterior uveitis. All children with a diagnosis of JIA must undergo regular ophthalmologic examinations to detect and manage inflammation.

Definition

A collection of chronic pediatric inflammatory arthritides characterized by onset before 16 years of age and the presence of objective arthritis (in one or more joints) for at least 6 weeks.[1]

Arthritis of joints is defined by swelling or effusion, increased warmth, and/or painful limited movement with or without tenderness.

THEORY

Epidemiology

JIA is the most common chronic rheumatic disorder of childhood.

There are several limitations in the methods applied to study the epidemiology, including the use of different classification criteria. Epidemiological studies focusing on children seen in hospitals and clinics report lower prevalences compared with community-based studies. A population-based study in Rochester, Minnesota demonstrated a prevalence of 86.1 and an incidence of 11.7 per 100,000 children ages under 16 years.[5] A study in Nordic countries found that the incidence was 15 per 100,000 children per year.[6] One meta-analysis reported an incidence of 1.6 to 23 cases per 100,000 children per year and a prevalence of 3.8 to 400 cases per 100,000 children per year in Europe.[7]

JIA is 3 to 6.6 times more common in females than in males.[8] Oligoarticular JIA is the most common subtype (50% to 60% of cases), followed by polyarticular JIA (30% to 35% of cases).[9] Oligoarticular JIA and rheumatoid factor (RF)-negative JIA typically affect young, female children.[8] RF-positive polyarticular JIA is typically seen in teenage girls. Enthesitis-related JIA has male predominance, usually in boys after the age of 6 years.[10] Systemic-onset juvenile idiopathic arthritis comprises 10% to 20% of all JIA and affects boys and girls equally.[9] Black, Indian, and Native American children are more likely to have polyarticular JIA.[11]

Etiology

The exact etiology is unknown. JIA is thought to be an autoimmune disorder, initiated and sustained by environmental factors in genetically susceptible individuals.[12]

Monozygotic twin concordance is 25% to 40%.[13] [14] The prevalence of JIA probands among siblings is 15 to 30 times higher than the population prevalence.[14] [15] [16] Affected sibling pairs have a high concordance of onset age and subtype, which also supports theories of genetic predispositions.[17] [18] There is no association between birth order and JIA.[19]

In one study of 110 families of JIA probands, 74% had at least one relative with autoimmunity compared with only 33% of families of control probands.[20] First- and second-degree relatives of children with JIA have a threefold increase in the prevalence of autoimmunity, particularly autoimmune thyroid disease.[20] This increase appears to be more pronounced in female relatives of mothers compared with that of fathers.[21]

Polymorphisms in the genes encoding human leukocyte antigens have been associated with different JIA subtypes.[12] In the class I human leukocyte antigen (HLA) region, HLA A2 is associated with early-onset JIA.[22] [23] HLA B27 allele is associated with enthesitis-related JIA.[24] Oligoarticular JIA is associated with alleles HLA DRB1*01, DRB1*08, DRB1*11, DRB1*13, DPB1*02, and DQB1*04.[22] [23] [25] [26] [27] [28] Alleles HLA DRB1*04 and DRB1*07 appear to be protective against oligoarticular JIA.[23] [28] Polyarticular rheumatoid factor (RF)-negative JIA is associated with alleles DRB1*08 and DPB1*03.[27] [28] Polyarticular RF-positive JIA, which is phenotypically similar to adult rheumatoid arthritis, is associated with alleles DRB1*04, DQA1*03, and DQB1*03.[27] [28] Fewer confirmed associations between HLA polymorphisms and psoriatic arthritis or systemic-onset juvenile idiopathic arthritis have been reported.

Variants in the genes encoding PTPN22, TNFA, MIF have also been shown to be associated with JIA.[12]

Environmental factors that may influence JIA development include infection in genetically susceptible individuals (no specific infectious agent has been conclusively identified), exposure to antibiotics in

childhood, and maternal smoking during pregnancy (one study suggested an increased risk of inflammatory polyarthritis in female offspring, but this has not been confirmed by other studies).[29] [30] [31]

Pathophysiology

Chronic inflammation of the synovium (manifested by accumulation of synovial fluid and thickening of the synovial lining) is common to all JIA subtypes.

Synovial tissue contains various inflammatory cells including neutrophils, plasma cells, dendritic cells, and a high proportion of activated T-cells.[32] [33] [34] Recruitment of pro-inflammatory cells into the synovium is believed to be mediated by chemokines that selectively attract type 1 helper T cells. This is characterized by the production of pro-inflammatory cytokines such as interleukin (IL)-2, interferon-gamma, and tumor necrosis factor (TNF)-alpha.[35] [36] [37] Several studies have demonstrated that Th1 cytokines also predominate in the synovial tissue and synovial fluid of children with JIA.[38] [39] [40] [41] Pro-inflammatory cytokines, including IL-1beta, IL-6, TNF-alpha, IL-2R, IL-8, and sCD154, are significantly elevated in sera of affected children.[42] These observations support the use of biologic agents directed against TNF-alpha, IL-1, and IL-6 to treat JIA. IL-17 is an inducer of a potent pro-inflammatory cytokine cascade and of the cytokine RANKL. RANKL is present in elevated amounts in the synovium of children with JIA and has been associated with bone resorption and cartilage damage.[43] [44] [45]

Classification

International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis[1]

Seven subtypes are recognized, some of which share clinical and pathological features with other chronic autoimmune disorders:

- Systemic arthritis
- Oligoarthritis
- Polyarthritis (RF-negative)
- Polyarthritis (RF-positive)
- Psoriatic arthritis
- Enthesitis-related arthritis
- Undifferentiated arthritis.

American College of Rheumatology criteria for juvenile rheumatoid arthritis[2]

- Pauciarticular arthritis
- Polyarticular arthritis
- Systemic-onset arthritis.

The European League Against Rheumatism criteria for juvenile chronic arthritis[3]

- Systemic arthritis
- Polyarticular arthritis

- Juvenile rheumatoid arthritis
- Pauciarticular arthritis
- Juvenile ankylosing spondylitis
- Juvenile psoriatic arthritis.

The Pediatric Rheumatology International Trials Organization proposed classification[4]

This classification is proposed as a successor to the ILAR classification.

- A. Systemic JIA
- B. RF-positive JIA
- C. Enthesitis/spondylitis-related JIA
- D. Early-onset antinuclear antibody-positive JIA
- E. Other JIA
- F. Unclassified JIA

Case history

Case history #1

A 3-year-old girl presents with stiffness and limp of several weeks' duration. The onset was insidious and her parents do not recall any specific injury or prior infections. Her parents mention that one of her knees is swollen and cannot be straightened, although it is not especially painful. Her symptoms are particularly bad in the mornings when she wakes, but her gait improves as the day goes on. She has not had any fevers, rashes, or other constitutional symptoms.

Other presentations

Oligoarticular JIA describes arthritis in four or fewer joints and typically affects young children (often younger than 6 years of age and female). It most often affects the large joints such as the knee, ankle, wrist, and/or elbow joints. It can be associated with uveitis, which affects up to 20% of young people with this type of JIA.

Rheumatoid factor (RF)-negative polyarticular JIA typically affects young girls and usually presents with symmetrical stiffness, swelling, and pain in several joints, often involving small joints of the hands and feet.

RF-positive polyarticular JIA typically affects older girls and usually presents with symmetrical symptoms affecting several joints, often involving the small joints of the hands and wrists.

Systemic-onset juvenile idiopathic arthritis may present with arthritis in one or more joints in addition to daily high spiking fevers, and evanescent, truncal, salmon-colored, macular rashes. Arthritis does not need to be present initially for diagnosis.

Enthesitis-related JIA typically (but not exclusively) affects boys over the age of 6 years and usually presents with asymmetrical arthritis, enthesitis, and sacro-iliac joint involvement.

Psoriatic JIA usually presents with arthritis and definite histories or family histories of psoriasis (in first-degree relative), nail changes, and/or dactylitis; psoriatic rash may/may not be present.

Undifferentiated JIA may present with features of more than one subtype.

Approach

Diagnosis is predominantly based on clinical manifestations. Patients with suspected JIA should be referred promptly to a pediatric rheumatologist for further evaluation.

History

Clinicians should elicit the following information:

- Current joint symptoms (e.g., pain, swelling, morning stiffness)
- Which joints are affected
- Whether symptoms are symmetrical or asymmetrical
- Presence of gait abnormality
- Diurnal variation in symptoms
- Presence of fever
- Presence of skin change (rashes, easy bruising)
- Any history of mouth ulcers
- Any history of intercurrent infection, trauma, weight loss, or night sweats
- Any ocular symptoms suggestive of uveitis (although uveitis is often asymptomatic in patients with JIA)
- Family history of JIA, psoriasis, or autoimmunity.

Physical examination

Initial vital signs may reveal pyrexia, and general inspection may reveal macular rashes, psoriatic scales, purpura, or bruising. Nail changes and/or dactylitis may also be evident. Examination of affected limbs may demonstrate symmetrical or asymmetrical edematous and/or tender joints, and gait assessment may show limping.

Laboratory tests

Once clinical diagnosis is made, laboratory tests support subtype classification. They can guide monitoring and treatment and help determine prognosis. Complete blood count is normal in most subtypes except systemic-onset juvenile idiopathic arthritis. Erythrocyte sedimentation rate (ESR) and/or C-reactive protein are often performed and may be elevated to varying levels dependent on JIA subtype. ESR is a component of the juvenile arthritis disease activity score, which informs choice of initial treatment.[46]

Antinuclear antibodies (ANA) are detected in 30% to 60% of children.[47] [48] [49] ANA positivity is a risk factor for the development of uveitis, so this test is routinely performed at diagnosis. Rheumatoid factor (RF) is positive in about 2% to 7% of children with JIA (usually older children with polyarticular JIA).[50] Do not order RF to make a diagnosis of JIA. JIA is a clinical diagnosis and RF should only be ordered to prognosticate severity.[51]

A *Chlamydia* screen may be indicated in teenage patients with monoarticular disease.

Imaging

Radiographic investigations can aid diagnosis but are not specific, and results (particularly from x-rays) may be normal during early stages of disease.

Magnetic resonance imaging (MRI) and ultrasound can provide information about joints that are difficult to examine (including hips, temporomandibular joints, small joints of the feet, etc.).[52] Ultrasound examination of the joints has demonstrated higher sensitivity in assessing synovitis than clinical examination. However, further studies are needed to evaluate the reliability and responsiveness of ultrasound in assessing synovitis changes on follow-up.[53] Subclinical synovitis can be detected by ultrasound and as a result this can be useful at diagnosis and throughout the disease course.[54] [55]

MRI is of particular value in assessing disease activity in patients with longstanding disease and can be used to assess response to treatment.[56] MRI is also helpful in excluding other diagnoses, such as pigmented villonodular synovitis or effusions in joints where effusions are hard to detect clinically or by plain x-ray (e.g., hips). When MRI is indicated, it should be performed with gadolinium, which demonstrates synovial enhancement.

History and exam

Key diagnostic factors

over 6 weeks' duration (common)

- Objective arthritis in joints for at least 6 weeks is necessary for diagnosis.

joint pain (common)

- Affected joints can be painful, especially during motion and on palpation.

joint swelling (common)

- Commonly at the knees in oligoarticular JIA and may be the presenting symptom. Examination of affected joints may reveal edema. Synovial effusions and thickening are frequent findings.

fever (common)

- High-spiking fevers are commonly observed in systemic-onset juvenile idiopathic arthritis (SoJIA) but are not usual in other subtypes. One or two spikes of fever a day interspersed by normal temperatures, occurring daily for at least 2 weeks, is necessary for diagnosis of SoJIA.

Other diagnostic factors

age under 6 years (common)

- The majority of children with JIA present at a young age. However, the condition can occur at any time before the age of 16 years.
- Oligoarticular and rheumatoid factor (RF)-negative polyarticular JIA usually present before the age of 6 years.
- Enthesitis-related and RF-positive polyarticular JIA are usually seen in older children.
- Systemic-onset JIA can occur at any age (including adulthood).

morning stiffness (common)

- Stiffness upon waking or after periods of inactivity is typical of JIA. Parents often describe their children as having stiff gaits in the mornings, which improve after a few hours when lower extremity joints are involved.
- In children wearing nappies, parents may report reluctance for the child to have a nappy change first thing in the morning.

limp (common)

- Often more pronounced in the mornings and may be the presenting symptom when lower extremity joints are involved, or may become evident upon gait assessment.

limited movement (common)

- In active disease, limitation is often secondary to pain. In longstanding disease, limitation can be secondary to joint contractures that are due to ligament/tendon tightening.

rash (common)

- Evanescent, nonpruritic, nonfixed, erythematous rashes frequently occur in systemic-onset juvenile idiopathic arthritis (SoJIA). The rashes are salmon-colored and commonly seen on the trunk and proximal extremities. They are not typically seen on palms, soles, or the face. Rashes often co-occur with fevers. The rash can be elicited by scratching the skin (Koebner phenomenon). Psoriatic rashes may be evident in psoriatic arthritis.
- Rash is a key factor if SoJIA is suspected.

enthesitis (common)

- Inflammation of the entheses (sites of tendon and ligament insertions to bone) is a common feature of enthesitis-related JIA (entheses around the knee and ankle are typically involved).

limb length discrepancy (uncommon)

- Growth disturbances are evident in longstanding, active, asymmetric disease. This is typically observed in oligoarticular JIA with unilateral knee involvement. In these cases, the affected lower extremities tend to be longer than those on the contralateral side.

uveitis (uncommon)

- Chronic nongranulomatous anterior uveitis is seen in about 10% of patients. It is often associated with a subset of patients who are young, female, and have antinuclear antibody positivity. Because uveitis is often asymptomatic, regular ophthalmologic exams are important. Systemic, rheumatoid factor-positive, polyarticular, and enthesitis-related subtypes are not typically associated with chronic anterior uveitis. Patients with enthesitis-related JIA are at risk for acute symptomatic anterior uveitis.

rheumatoid nodules (uncommon)

- Nodules on extensor surfaces of tendons can be seen in rheumatoid factor-positive polyarticular JIA. These nodules are not observed in other subtypes.

Risk factors

Strong

female sex

- Most subtypes are more common in girls.[8] This is pronounced in oligoarticular and polyarticular JIA. Systemic-onset juvenile idiopathic arthritis tends to affect boys and girls equally, while enthesitis-related JIA predominates in males.[9] [10]

human leukocyte antigen (HLA) polymorphism

- Several polymorphisms in the HLA region have demonstrated consistent associations with JIA.[12]

family history of autoimmunity

- Extended multiplex families with JIA are relatively rare. However, positive family history of autoimmune disorders is relatively common.
- In a study of 110 families of JIA probands, 74% had at least one relative with autoimmunity compared with only 33% of families of control probands.[20]
- First- and second-degree relatives of children with JIA have a threefold increase in the prevalence of autoimmunity, particularly autoimmune thyroid disease.[20] This increase appears to be more pronounced in female relatives of mothers compared with that of fathers.[21]
- The prevalence of JIA probands among siblings is 15 to 30 times higher than the population prevalence.[14] [15] [16]

Weak

antibiotic exposure in childhood

- Has been reported as a possible risk factor.[29] [30]

Tests

1st test to order

Test	Result
CBC • Typically normal in oligoarticular JIA. Children with systemic-onset juvenile idiopathic arthritis (SoJIA) often have anemia, thrombocytosis, and leukocytosis. Children with polyarticular and enthesitis-related JIA might have mild anemia and thrombocytosis. • Useful baseline test for all patients. Normal results do not exclude diagnosis. • Important to help exclude differentials such as infection or malignancy.	**normal or reduced hemoglobin and elevated platelets**
erythrocyte sedimentation rate • Elevated to varying levels in different subtypes. Significantly elevated in SoJIA; mildly to moderately elevated in polyarticular JIA; and may be normal or mildly elevated in oligoarticular JIA. • Nonspecific marker that may be elevated due to acute-phase responses from any cause.	**normal or elevated**
C-reactive protein • Elevated to varying levels in different subtypes. • Nonspecific marker that may be elevated due to acute-phase responses from any cause.	**normal or elevated**
antinuclear antibodies#(ANA) • Positive in oligoarticular JIA and to a lesser extent in polyarticular JIA. ANA is generally negative in systemic and enthesitis-related subtypes. • ANA testing should be done as a baseline test. Positive ANA is associated with increased susceptibility to uveitis. Positive ANA alone is not diagnostic of JIA and negative ANA does not rule it out. False-positive ANA tests are frequent.	**positive or negative**
rheumatoid factor (RF) • Positive in RF-positive polyarticular JIA and negative in other subtypes. Two positive test results are required for diagnosis of RF-positive polyarticular JIA. Positive RF is associated with aggressive disease. Do not order RF to make a diagnosis of JIA. JIA is a clinical diagnosis and RF should only be ordered to prognosticate severity.[51]	**positive or negative**

Other tests to consider

Test	Result
anticyclic citrullinated peptide antibody • Positive in rheumatoid factor (RF)-positive polyarticular JIA; negative in other subtypes. May be helpful in older children with polyarticular JIA who have negative tests for RF.	**positive or negative**
chlamydia test • May be indicated in teenage patients with monoarticular disease.	**positive if *Chlamydia* infection**
ferritin levels • Ferritin levels should be measured if SoJIA is suspected.	**may be abnormal**
ultrasound of affected joints • Often abnormal early in the course of disease. Useful in identifying joints for corticosteroid injection in oligoarthritis. Can be an important positive or negative finding if the diagnosis is questionable. • Has demonstrated higher sensitivity in assessing synovitis than clinical examination. However, further studies are needed to evaluate reliability and responsiveness in assessing synovitis changes on follow-up.[53]	**abnormal**
MRI • MRI may be indicated in patients with monoarticular disease to rule out other diagnoses such as pigmented villonodular synovitis or synovial hemangiomas. It can also be used to monitor cartilage injury.	**synovial fluid; synovial thickening and/or synovial enhancement**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Septic arthritis	• Usually presents with single joint involvement, high fevers, severe pain, and/or erythematous joints.	• Synovial fluid analysis demonstrates the presence of bacteria, elevated white blood cells, and positive cultures. • Radionucleotide bone scintigraphy shows increased uptake in the affected joint. • MRI shows synovial enhancement and effusion and marrow edema of the adjacent bone in cases of accompanying osteomyelitis. Significant synovial thickening is more likely to be associated with inflammatory arthritis. • Synovial fluid may be sterile in cases where reactive effusions are present secondary to juxta-articular osteomyelitis.
Osteomyelitis	• Usually presents with high fevers, severe pain, and/or focal tenderness.	• Synovial fluid analysis may demonstrate the presence of bacteria, elevated white blood cells, and positive cultures when there is involvement of the joint. Synovial fluid may be sterile in cases where reactive effusions are present secondary to juxta-articular osteomyelitis. • Radionucleotide bone scintigraphy shows increased uptake in the bone. • MRI shows abnormal diffuse marrow signal, which is best seen on T1-weighted MRI images. However, it should be noted that false-negative MRI results may be observed early in the course of infection.
Malignancy	• Signs and symptoms consistent with bone tumors, leukemias, or neuroblastoma.	• CBC and film, urine catecholamines, and imaging consistent with malignancy.

Condition	Differentiating signs / symptoms	Differentiating tests
Reactive arthritis	• Asymmetrical oligoarticular arthritis, beginning 1 to 4 weeks after genitourinary or gastrointestinal infection. May be associated enthesitis, dactylitis, conjunctivitis, iritis, and rash.	• Stool or genitourinary cultures may detect causative organism, although cultures are often negative by the time arthritis symptoms develop.
Acute rheumatic fever	• Usually presents as an acute, migratory arthritis that responds well to nonsteroidal anti-inflammatory drugs (NSAIDs). Features include continuous fever, cardiac involvement, and/or erythema marginatum rashes.	• Throat cultures positive for group A streptococcus; positive rapid streptococcal antigen test and/or elevated or rising streptococcal antibody titers.
Systemic lupus erythematosus (SLE)	• Usually presents with nonerosive polyarthritis, malar rashes, renal involvement, and/or photosensitivity. Serositis and central nervous system involvement are also suggestive of SLE.	• High-titer antinuclear antibody and other autoantibodies (such as anti ds-DNA, SS-A, SS-B, Smith, ribonucleoprotein) may be present. • Urinalysis may be abnormal, showing blood and/or protein. • Low levels of complements C3 and/or C4. • CBC may show leukopenia, thrombocytopenia, and (autoimmune hemolytic) anemia. • Elevated erythrocyte sedimentation rate in the absence of elevated C-reactive protein.
Juvenile dermatomyositis	• Usually presents with muscle weakness, muscle pain, and/or characteristic rashes such as Gottron papules, linear extensor erythema, or heliotrope rash. • Polyarticular nonerosive arthritis is usually present, especially in early stages of disease. The polyarthritis usually responds to treatment of the underlying myositis.	• Abnormal muscle-derived enzymes such as lactose dehydrogenase, aspartate transaminase, alanine transaminase, creatinine kinase, and aldolase may be present.
Kawasaki disease	• Usually presents with high persistent fevers that do not normalize for	• Demonstration of coronary artery enlargement or

Condition	Differentiating signs / symptoms	Differentiating tests
	several days, polymorphous rash, involvement of lips and conjunctiva, edema of extremities, and/or desquamation.	aneurysms is suggestive of Kawasaki disease.
Pigmented villonodular synovitis	• Usually presents with recurrent, painless swelling in one knee, ankle, or tendon sheath. Usually associated with slow, progressive destruction of cartilage with bone erosion.	• Synovial fluid analysis shows blood-stained, dark brown fluid. • MRI shows low signal density on T1- and T2-weighted studies.
Synovial hemangiomas	• There is usually no morning stiffness and treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) does not result in improvement.	• MRI may show absence of synovial fluid and vascular elements and enhancement.
Osteochondritis dissecans	• Usually presents with activity-related pain, occasional recurrent bland effusions, and/or localized tenderness on examination.	• X-rays may show subchondral fractures. • MRI may demonstrate cartilaginous separation and can also be used in lesion staging.

DIAGNOSIS

Criteria

Diagnostic criteria for juvenile idiopathic arthritis is a complex and changing area that includes debate around the utility of classifying different patient groups by historic, biologic, or phenotypic criteria and the continuum (or otherwise) with adult rheumatologic disease.[57]

International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis[1]

JIA can be diagnosed if age at onset is under 16 years, disease duration is 6 weeks or over, and other known conditions are excluded. The seven different categories are as follows.

- Systemic arthritis is diagnosed if there is arthritis in 1 or more joints with, or preceded by, fever of at least 2 weeks' duration. Signs or symptoms must have been documented daily for at least 3 days and accompanied by 1 or more of the following: evanescent rash, generalized lymphadenopathy, hepato/splenomegaly, serositis. (Exclusions are A, B, C, and D from the exclusion list below.)
- Oligoarthritis is diagnosed if there is arthritis affecting 1 to 4 joints during the first 6 months. Persistent oligoarthritis affects up to 4 joints throughout the course of the disease, and extended oligoarthritis affects more than 4 joints after the first 6 months of disease. (Exclusions are A, B, C, D, and E from the exclusion list below.)

- Polyarthritis (rheumatoid factor [RF]-negative) is diagnosed if there is RF-negative arthritis affecting 5 or more joints during the first 6 months of disease. (Exclusions are A, B, C, D, and E from the exclusion list below.)
- Polyarthritis (RF-positive) is diagnosed if there is RF-positive arthritis affecting 5 or more joints during the first 6 months of disease. Two or more RF tests (taken at least 3 months apart) are positive during the first 6 months of disease. (Exclusions are A, B, C, and E from the exclusion list below.)
- Psoriatic arthritis is diagnosed if there is arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting, onycholysis, and/or family history of psoriasis (in a first-degree relative). (Exclusions are B, C, D, and E from the exclusion list below.)
- Enthesitis-related arthritis is diagnosed if there is arthritis and/or enthesitis with at least 2 of the following: presence or history of sacroiliac joint tenderness with or without inflammatory lumbosacral pain; presence of HLA B27 antigen; onset of arthritis in a male over 6 years of age; acute (symptomatic) anterior uveitis; history of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a first-degree relative. (Exclusions are A, D, and E from the exclusion list below.)
- Undifferentiated arthritis is diagnosed if there is arthritis that does not fulfill criteria in any of the above categories or that fulfills criteria for two or more of the above categories.

Exclusions

- A. Psoriasis or history of psoriasis in patients or first-degree relatives.
- B. Arthritis in HLA B27 positive males beginning after the age of 6 years.
- C. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, acute anterior uveitis, or history of one of these disorders in first-degree relatives.
- D. Presence of IgM rheumatoid factor on at least two occasions at least 3 months apart.
- E. Presence of systemic-onset juvenile idiopathic arthritis (SoJIA) in patients.

American College of Rheumatology criteria for juvenile rheumatoid arthritis (JRA)[2]

JRA can be diagnosed if age at onset is under 16 years; there is arthritis in 1 or more joints; disease duration is 6 or more weeks; and other forms of juvenile arthritis (e.g., psoriatic and inflammatory bowel disease-associated arthritis) have been excluded.

Disease type is defined by the type of disease present in the first 6 months.

- Systemic-onset JRA is daily (quotidian) fever spiking to more than 102.2°F (39°C) for 2 or more weeks in association with arthritis of 1 or more joints.
- Pauciarticular JRA is arthritis in 4 or fewer joints in the first 6 months of disease.
- Polyarticular JRA is arthritis in 5 or more joints in the first 6 months of disease.

The European League Against Rheumatism criteria for juvenile chronic arthritis (JCA)[3]

JCA can be diagnosed if age at onset is under 16 years, there is arthritis in 1 or more joints, and disease duration is ≥3 months.

Diagnostic criteria for specific disease types are outlined below.

- Systemic JCA is arthritis with characteristic fever.
- Pauciarticular JCA is arthritis in fewer than 5 joints.

- Polyarticular JCA is arthritis in more than 4 joints with negative rheumatoid factor.
- Juvenile rheumatoid arthritis is arthritis in more than 4 joints with positive rheumatoid factor.
- Juvenile ankylosing spondylitis is the presence of features of ankylosing spondylitis in a child under 16 years old.
- Juvenile psoriatic arthritis is the presence of psoriatic arthritis in a child under 16 years old.

The Pediatric Rheumatology International Trials Organization proposed classification[4]

This classification is proposed as a successor to the ILAR classification.

- A. Systemic JIA - most closely related to adult-onset Still disease
- B. RF-positive JIA - most closely related to rheumatoid arthritis in adults
- C. Enthesitis/spondylitis-related JIA - most closely related to the spondyloarthropathies
- D. Early-onset antinuclear antibody-positive JIA - a disease course with distinctive clinical features in children
- E. Other JIA
- F. Unclassified JIA

Approach

Patients with JIA, or suspected JIA, should be managed by a specialist pediatric rheumatology multidisciplinary team.[60]

The goals of treatment are:

- Achieving clinically inactive disease
- Excellent symptom control
- Prevention and minimization of of joint damage
- Prevention and minimization of treatment side effects
- Promotion of good physical and mental health.

Prompt initiation of disease-modifying therapy is essential, because active, uncontrolled JIA can cause permanent joint damage.[61]

Specific therapy is indicated by disease phenotype, disease activity, and presence/absence of risk factors.

Phenotypic groups

The treatment of JIA varies according to the predominant clinical features. American College of Rheumatology (ACR) guidelines define treatment groups by clinical phenotype rather than International League of Associations for Rheumatology categories. The patient groups are:[61] [62]

- Oligoarticular arthritis (history of arthritis of 4 or fewer joints)
- Polyarticular arthritis (history of arthritis of 5 or more joints)
- Active sacroiliitis
- Active enthesitis
- Systemic-onset JIA.

Patients with psoriatic arthritis may belong to the polyarticular JIA, sacroiliitis, or enthesitis phenotypic group.[61]

Assessing disease activity

Disease activity is assessed by:

- Patient (or parent) ratings
- Physician ratings
- Measurement of inflammatory markers
- Number of active joints.

Each of these four factors is a component of the Juvenile Arthritis Disease Activity Score.[63] Disease activity scores can help the clinician select an appropriate initial treatment, and recognize a need to escalate treatment.

Physician and patient global assessment of disease activity is performed using a Likert scale. The physician rates the disease activity from 0 (no activity) to 10 (maximum activity). The patient (or parent) rates patient wellbeing from 0 (very good) to 10 (very poor).[64]

A joint is considered active if it is swollen or has limited motion with pain/tenderness.

Low disease activity is not the same as disease remission, and should prompt a re-evaluation of therapy.

Supportive care

All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Physical and occupational therapy are recommended for children with, or at risk of, functional limitations.[61]

Patients should be encouraged to participate in interests, sports, and community life.[60] Inactivity leads to deconditioning and disability.[65] Weight-bearing activity may reduce the risk of low bone mineral density.[66] One Cochrane review found that exercise therapy does not appear to increase quality of life, exercise capacity, functional ability, or pain in patients with JIA; neither is it associated with any adverse effects or exacerbation of arthritis. However, heterogeneous outcome measures were used in the included trials, and the authors suggest that more standardized outcome measures are needed to evaluate the long-term effect of exercise therapy.[67]

Foot orthoses may reduce pain and improve quality of life in children with JIA.[68] [69]

Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

Polyarticular JIA

Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) include methotrexate, sulfasalazine, and leflunomide.

Methotrexate is first-line initial therapy for children with polyarticular JIA.[61] Randomized controlled trials have demonstrated improvement in joint symptoms and a reduction in disease activity with methotrexate.[71] [72] Folic acid is usually given concomitantly to decrease the side effects of methotrexate, and antiemetics may be used to reduce nausea. Patients should be counseled to avoid alcohol and pregnancy while taking methotrexate.

Complete blood count, serum creatinine, and liver enzymes should be checked before starting methotrexate, and every 3 to 4 months during treatment.[73] Patients at risk of hepatitis B or hepatitis C infection should have a screening antibody test before starting methotrexate.[62] Elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 2 times the upper limit justifies temporary suspension of methotrexate, which can be re-started following normalization of serum liver enzyme levels.[62]

Some trials have demonstrated the safety and efficacy of leflunomide as a second-line conventional synthetic DMARD in pediatric patients who are intolerant or unresponsive to methotrexate. Most of the pediatric patients responsive to leflunomide maintained their response in a 2-year open-label extension study.[74] Sulfasalazine may also be used as a second-line option.[61]

Biologic therapies that block the action of inflammatory cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6, are highly effective and have revolutionized the treatment of JIA. These therapies are typically given in addition to a DMARD. They may be given as part of initial therapy in patients with risk factors for a poor prognosis, or started after an inadequate response to a conventional synthetic DMARD.[61]

Risk factors for poor prognosis include:[61]

- Presence of anticyclic citrullinated peptide antibodies
- Presence of rheumatoid factor

- Joint damage at presentation
- High-risk joint involvement (cervical spine, wrist, or hip)
- High disease activity
- Patient judged by physician to be at high risk of disabling joint damage.

A TNF-alpha inhibitor is first-line.[61] Treatment with etanercept or adalimumab is preferred to treatment with infliximab. Infliximab is given by intravenous infusion and carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

Etanercept is a soluble TNF-alpha receptor antagonist. It is approved for polyarticular disease in children 2 years of age and over.[75] An open-label extension trial has demonstrated safety and efficacy for up to 8 years of use.[76]

Adalimumab is a recombinant humanized TNF-alpha inhibitor that is approved for polyarticular disease in children 2 years of age and over.[77] Over 70% of children receiving adalimumab in combination with methotrexate had a 70% improvement in at least three of the ACR core set variables after 16 weeks of therapy.[77] It is also effective in patients with enthesitis.[78] The long-term tolerability and efficacy of adalimumab in JIA has been demonstrated.[79] [80]

Infliximab is a monoclonal, chimeric TNF-alpha inhibitor.[81] Monoclonal antibodies have analogies to murine proteins, meaning premedication with antihistamines, acetaminophen, and corticosteroids is advised to minimize infusion-associated reactions.[82] [83]

TNF-alpha inhibitors should be used with caution in patients with recurrent infections, conditions predisposing to infections, preexisting demyelinating disorders, or hematologic diseases, due to the immunosuppressive nature of these medicines.[84] A study evaluating etanercept and adalimumab showed an increase in number of infections but no clear evidence that the overall malignancy risk was increased.[79] Chronic carriers of tuberculosis and hepatitis B are susceptible to disease reactivation. Tuberculosis skin tests, and viral hepatitis screening for patients with risk factors for infection, are recommended prior to treatment.[62] [84] Live vaccines should be avoided during treatment.[85]

Tocilizumab (an IL-6 inhibitor) or abatacept (a fusion protein) are used if the patient does not respond to a TNF-alpha inhibitor.

Tocilizumab can be used as monotherapy or in combination with methotrexate for children with polyarticular JIA. Tocilizumab is relatively well tolerated and has proven efficacy for up to 52 weeks.[86] It is approved in children 2 years of age and older.

Serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) has been identified in eight patients treated with tocilizumab worldwide. Two patients required liver transplantation. Serious liver injury has been reported from 2 weeks to more than 5 years after starting treatment. While liver toxicity occurs rarely and the risk-benefit profile still supports the use of tocilizumab, the ACR recommends monitoring ALT or AST at initiation of treatment, within 4 to 8 weeks of treatment and every 3 to 4 months thereafter.[73] Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the upper limit of normal. If liver enzyme abnormalities are identified, consider a dose modification (reduction, interruption, or discontinuation) according to the manufacturer's recommendations. Advise patients to seek medical help immediately if they experience signs and symptoms of hepatic injury.[87]

Abatacept is a recombinant, fully humanized fusion protein composed of the extracellular domain of human CTLA-4 and a portion of the Fc-domain of human immunoglobulin G-1. It is used in children ages 2 years and older with polyarticular JIA who have had an inadequate response to previous conventional synthetic DMARDs, and has proven efficacy and long-term safety.[88] [89] [90] Improvements in health-related quality of life were observed during a phase 3, double-blind, placebo controlled trial with abatacept, providing real-life, tangible benefits to children with JIA and their parents or caregivers.[91]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as adjunctive therapy to treat pain and stiffness in children with polyarticular JIA while systemic therapies take effect.

Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective medicine for individual patients.

Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

Low-dose oral corticosteroid therapy can be used for up to 3 months to improve symptoms while systemic therapies take effect. This treatment is particularly helpful for children with polyarticular JIA with high or moderate disease activity.[61]

Intra-articular corticosteroid injections can be used alone or as part of a treatment plan involving other systemic treatments. Radiographic assistance may be necessary for injecting some joints. The procedure can be undertaken with the administration of entonox or general anesthetic to the child.

Relief is expected to last for at least 4 months.[62] Injections can be repeated every 4 months as needed. Adverse effects from intra-articular injections are uncommon.

Intra-articular corticosteroid injections may not be a suitable treatment for large numbers of joints that have been injected multiple times. Escalation of systemic therapy may be more appropriate.[61] Duration of relief <4 months may also imply a need to escalate systemic therapy.[62]

Oligoarticular JIA

Corticosteroid injections are first-line treatment for most patients.[62]

Initial NSAID monotherapy may be given for 2 months if the child has low disease activity, no contractures, and no poor prognostic features, to relieve joint pain and swelling.[62]

Poor prognostic features are:[62]

- Arthritis of the hip or cervical spine
- Arthritis of the ankle or wrist plus prolonged or marked inflammatory marker elevation
- Radiographic evidence of erosions or joint space narrowing.

If there is any residual disease activity after 2 months' treatment, therapy should be escalated to intra-articular corticosteroid injections.[62]

Methotrexate is used if a patient has not responded to intra-articular corticosteroids, or as initial treatment for children with high disease activity and adverse prognostic features.[62]

TNF-alpha inhibitors are rarely needed for patients with oligoarticular JIA, but they should be considered in patients with ongoing active disease despite treatment with intra-articular corticosteroids and

methotrexate.[62] When treatment with a TNF-alpha inhibitor is needed, etanercept or adalimumab are preferred to infliximab. Infliximab is given by intravenous infusion and carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

Sacroiliitis

First-line treatment is NSAID monotherapy. Oral corticosteroids may be used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

Treatment should be escalated to a TNF-alpha inhibitor if disease activity is not controlled by NSAID monotherapy. Use of TNF-alpha inhibitors is associated with decreased disease activity, compared with placebo.[93] [94] [95] Treatment with etanercept or adalimumab is preferred to treatment with infliximab. Infliximab is given by intravenous infusion and carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

Sulfasalazine may be used instead of a TNF-alpha inhibitor, particularly for children in whom TNF-alpha inhibitors are contraindicated or not tolerated.[61]

Enthesitis

First-line treatment is NSAID monotherapy. Oral corticosteroids may be used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

Treatment should be escalated if there is active enthesitis despite NSAID monotherapy.[61]

Typically methotrexate or sulfasalazine are used first, with escalation to a TNF-alpha inhibitor if the child doesn't respond.[96] When treatment with a TNF-alpha inhibitor is required, etanercept or adalimumab are preferred to infliximab. Infliximab is given by intravenous infusion and carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

However, the ACR guidelines recommend that children with active enthesitis despite NSAID monotherapy should escalate to TNF-alpha inhibitors, rather than methotrexate or sulfasalazine, and noted that the level of evidence for this recommendation was low.[61] One observational study reported a greater improvement in pain and disease activity after 12 months in children with enthesitis who received a TNF-alpha inhibitor, compared with those who received a DMARD alone.[97]

Systemic-onset JIA

The ACR recommends that the management of systemic JIA is based on a confirmed diagnosis of JIA and whether it has features of macrophage activation syndrome (MAS).[98]

MAS is a life-threatening complication of systemic-onset JIA. Signs and symptoms include:[58]

- Persistent fever
- Elevated and/or rising ferritin or other markers of inflammation/damage
- Inappropriately low or declining hemoglobin, platelet counts or white blood cells (neutrophils and lymphocytes)
- Hepatic dysfunction
- Coagulopathy
- Splenomegaly
- Central nervous system dysfunction

About 10% to 15% of patients with systemic-onset JIA develop life-threatening overt MAS.[99] MAS is present if the following criteria are met in a febrile patient with known or suspected systemic-onset JIA: ferritin >684 ng/mL and any two of platelet count ≤181 x 10^9/L, aspartate aminotransferase >48 U/L, triglycerides >156 mg/dL, or fibrinogen ≤360 mg/dL.[100] If a patient has a normal ferritin level, but there is ongoing clinical suspicion of MAS, serial ferritin testing should be considered.[58]

Consult a pediatric rheumatology specialist urgently if features of MAS are present. Patients with MAS can deteriorate rapidly and may require intensive care admission. For patients with suspected MAS, initiating treatment while diagnostic testing is in progress should be considered.[58]

Monitoring initial treatment response by assessing clinical and laboratory markers of organ involvement should be assessed at least daily, and markers of systemic inflammation at least twice weekly. Worsening or lack of improvement in laboratory parameters of systemic inflammation, particularly ferritin, may indicate disease progression and a need to reassess diagnosis and/or treatment.[58]

The ACR recommends early use of biologic agents in children with systemic JIA due to their proven effectiveness, moving away from former recommendations that focused on corticosteroids and conventional synthetic DMARDs.

Systemic JIA without MAS

Initial treatment is with a biologic agent (i.e., IL-1 or IL-6 inhibitor) and/or an NSAID.[98]

There is some evidence that those with systemic JIA without MAS will respond to NSAIDs alone and even have clinically inactive disease.[98] Patients who undergo an initial trial of NSAID monotherapy should be followed up within 2 weeks for evaluation of a possible need for drug escalation.[101] If a response occurs and inactive disease occurs, then NSAIDs should be tapered and discontinued. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. Several NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective drug for individual patients. Possible adverse effects include renal impairment, gastrointestinal symptoms, headache, and rash.[92]

Biologic agents can be given in combination with an NSAID for initial treatment or after a trial period of an NSAID. The ACR does not recommend any one preferred agent, but indicates that IL-1 inhibitors (e.g., anakinra, canakinumab) and IL-6 inhibitors (e.g., tocilizumab) are extremely effective and well-tolerated options. The choice should be based on discussions between the practitioner and patient as routes of administration and frequency vary. The ACR recommends switching between IL-1 and IL-6 inhibitors when needed due to a lack of efficacy or poor tolerability as individual response varies significantly.[98] [102] [103] [104]

Biologic agents used in systemic JIA appear safe and comparable with respect to adverse effect risk in the short term.[102] Anakinra has a short half-life, meaning its dose can be adjusted or it can be withdrawn quickly. One randomized controlled trial reported a response rate of 66% to 1 month's treatment with anakinra, compared with 8% to placebo, in children with systemic JIA. After 1 month, 83% of the children receiving placebo were switched to anakinra; 90% of children who switched from placebo responded to anakinra.[105] Canakinumab is effective for treating active systemic JIA.[103] [106] Treatment with canakinumab significantly reduces fever and disease activity, compared with placebo.[103] One randomized trial showed a significant reduction in fever and active arthritis in children with systemic JIA refractory to corticosteroids and NSAIDs who were treated with tocilizumab, compared

with placebo.[107] Meta-analysis has shown similar efficacy between tocilizumab, canakinumab, and anakinra.[102] One meta analysis of randomized controlled trials found that canakinumab had the highest probability of being the best treatment, in terms of the modified ACR Pediatric 30 (ACRpedi30) response rate, followed by anakinra and tocilizumab.[108]

Serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) has been identified with tocilizumab. The ACR recommends monitoring ALT or AST at initiation of treatment, within 4 to 8 weeks of treatment and every 3 to 4 months thereafter.[73] Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the upper limit of normal. If liver enzyme abnormalities are identified, consider a dose modification (reduction, interruption, or discontinuation) according to the manufacturer's recommendations.[87]

A range of small-scale trials demonstrated resolution of systemic signs following the use of biologic agents.[105] [107] [109] [110] With prolonged use, some patients suffered from adverse effects (e.g., infection, neutropenia, and increased aminotransferase levels).[107] The ACR recommends considering tapering and discontinuing biologic therapies when the disease is deemed inactive.[98]

Conventional synthetic DMARDs in combination with biologic agents can be considered in people with an inadequate response.

Systemic JIA with MAS

Initial treatment includes a biologic agent and/or corticosteroid.[98] Biologic agent monotherapy may not be sufficient for severely sick patients. Biologic agents combined with a corticosteroid and a conventional synthetic DMARD may be necessary to control MAS in some patients.[98] If a combination is used, then it is typically continued until disease control is established. If a patient is receiving both a biologic agent or conventional synthetic DMARD and a corticosteroid, the corticosteroid should be tapered and discontinued first before attempting to taper the biologic agent or the conventional synthetic DMARD. It is unclear how soon or rapidly these can be safely discontinued in patients with inactive systemic JIA.[98]

Although there are potential effects on bone health and growth, corticosteroids are conditionally recommended by the ACR as part of the initial treatment of acute systemic JIA with MAS.[98] [111] Glucocorticoid therapy should be limited to the lowest effective dose for the shortest duration possible, although treatment with high-dose corticosteroids may be required for initial disease control.[98] Long-term corticosteroid therapy in children is not appropriate because of its potential side effects on bone health and growth.[111]

Treatment with biologic agents may mask some MAS features and lead to limitations in diagnosis.[112] In children with systemic JIA whose disease is inactive, it may be possible to maintain this inactive disease state with lower doses of, or discontinuation of, biologic agents.[113] [114]

Conventional synthetic DMARDs are strongly recommended over long-term corticosteroids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors.[98] There is no preferred agent.[98] The primary conventional synthetic DMARD used for the treatment of systemic JIA is methotrexate. Methotrexate has been commonly used in children with systemic JIA due to its corticosteroid-sparing effect.[115] Although it is used less frequently, it can be given alone or alongside a biologic agent to control symptoms. Leflunomide is another conventional synthetic DMARD that can be used in JIA to manage the inflammatory response when methotrexate is not tolerated.[74] [116] Tacrolimus,

cyclosporine, cyclophosphamide, etoposide, chlorambucil, and azathioprine have been used in the treatment of systemic JIA, but are used less frequently due to the introduction of biologic agents.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
polyarticular JIA: 5 or more joints ever involved		
	1st	conventional synthetic disease-modifying antirheumatic drug (DMARD)
	plus	supportive care
	adjunct	biologic agent
	adjunct	nonsteroidal anti-inflammatory drug (NSAID)
	adjunct	intra-articular corticosteroid
	adjunct	oral corticosteroid
oligoarticular JIA: 4 or fewer joints ever involved		
	1st	intra-articular corticosteroid
	plus	supportive care
	adjunct	NSAID
	adjunct	methotrexate
	2nd	tumor necrosis factor (TNF)-alpha inhibitor
	plus	supportive care
	adjunct	intra-articular corticosteroid
	adjunct	NSAID
active sacroiliitis		
	1st	NSAID
	plus	supportive care
	adjunct	oral corticosteroid
	2nd	TNF-alpha inhibitor or sulfasalazine
	plus	supportive care
	adjunct	oral corticosteroid
active enthesitis		
	1st	NSAID
	plus	supportive care

Ongoing (summary)

	adjunct	oral corticosteroid
	2nd	methotrexate or sulfasalazine or TNF-alpha inhibitor
	plus	supportive care
	adjunct	oral corticosteroid
systemic-onset JIA		
▪ without macrophage activation syndrome (MAS)	1st	brief trial of NSAID
	plus	supportive care
	adjunct	biologic agent
	adjunct	conventional synthetic DMARD
▪ with MAS	1st	biologic agent
	plus	supportive care
	adjunct	systemic corticosteroid
	adjunct	conventional synthetic DMARD

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

polyarticular JIA: 5 or more joints ever involved

1st **conventional synthetic disease-modifying antirheumatic drug (DMARD)**

Primary options

» methotrexate: children ≥2 years of age and adolescents: 10-15 mg/square meter of body surface area orally/subcutaneously/intramuscularly once weekly on the same day of each week, adjust dose according to response, maximum 25 mg/week
Alternative dose regimens may be recommended.

Secondary options

» leflunomide: children and adolescents: consult specialist for guidance on dose

OR

» sulfasalazine: children ≥6 years of age and adolescents: 30-50 mg/kg/day orally given in 2 divided doses, maximum 2000 mg/day

» Patients with JIA should be managed by a specialist pediatric rheumatology multidisciplinary team.[60]

» Synthetic DMARDs are used as initial therapy for children with polyarticular JIA.[61]

» Methotrexate is first-line and can be given orally, subcutaneously, or intramuscularly. Randomized controlled trials have demonstrated improvement in joint symptoms and a reduction in disease activity with methotrexate.[71] [72] Folic acid is usually given concomitantly to decrease the side effects of methotrexate, and antiemetics may be used to reduce nausea. Patients should be counseled to avoid alcohol and pregnancy while taking methotrexate.

» Before starting methotrexate, a complete blood count, serum creatinine, and liver enzymes should be checked. Measurements should be repeated every 3 to 4 months during treatment.[73] Patients at risk of hepatitis B or hepatitis C infection should have a screening

Ongoing

antibody test before starting methotrexate.[62] Elevation of aspartate aminotransferase or alanine aminotransferase above 2 times the upper limit justifies temporary suspension of methotrexate, which can be re-started following normalization of serum liver enzyme levels.[62]

» Some trials have demonstrated the safety and efficacy of leflunomide as a second-line conventional synthetic DMARD in pediatric patients who are intolerant or unresponsive to methotrexate. Most of the pediatric patients responsive to leflunomide maintained their response in a 2-year open-label extension study.[74]

» Sulfasalazine may also be used as a second-line option.[61]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **biologic agent**

Treatment recommended for SOME patients in selected patient group

Primary options

» adalimumab: children ≥2 years of age and adolescents (10-14 kg body weight): 10 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (15-29 kg body weight): 20 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 40 mg subcutaneously every 2 weeks

OR

» etanercept: children ≥2 years of age and adolescents (<63 kg body weight): 0.8 mg/kg subcutaneously once weekly, maximum 50 mg/week; children ≥2 years of age and adolescents (≥63 kg body weight): 50 mg subcutaneously once weekly

Ongoing

Secondary options

» tocilizumab: children ≥2 years of age and adolescents (<30 kg body weight): 10 mg/kg intravenously every 4 weeks, or 162 mg subcutaneously every 3 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 8 mg/kg intravenously every 4 weeks, or 162 mg subcutaneously every 2 weeks

OR

» abatacept: children and adolescents: consult specialist for guidance on dose

OR

» infliximab: children and adolescents: consult specialist for guidance on dose

» This therapy is typically given in addition to a conventional synthetic DMARD. It may be given as part of initial therapy in patients with risk factors for a poor prognosis, or started after an inadequate response to a conventional synthetic DMARD.[61] Risk factors for poor prognosis include: presence of anticyclic citrullinated peptide antibodies, presence of rheumatoid factor, joint damage at presentation, high-risk joint involvement (cervical spine, wrist, or hip), high disease activity, or patient judged by physician to be at high risk of disabling joint damage.[61]

» A tumor necrosis factor (TNF)-alpha inhibitor is first-line. Treatment with etanercept or adalimumab is preferred to treatment with infliximab. Infliximab carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

» Tocilizumab (an interleukin-6 inhibitor) or abatacept (a fusion protein) are used if the patient does not respond to a TNF-alpha inhibitor.

» Caution is advised in patients with recurrent infections, conditions predisposing to infections, preexisting demyelinating disorders, or hematologic diseases, due to the immunosuppressive nature of these medicines.[84] One study evaluating etanercept and adalimumab showed an increase in number of infections but no clear evidence that the overall malignancy risk was increased.[79]

Ongoing

Chronic carriers of tuberculosis and hepatitis B are susceptible to disease reactivation. Tuberculosis skin tests, and viral hepatitis screening for patients with risk factors for infection, are recommended prior to treatment.[62] [84] Live vaccines should be avoided during treatment.[85]

» Serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) has been identified with tocilizumab. The American College of Rheumatology recommends monitoring alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, within 4 to 8 weeks of treatment and every 3 to 4 months thereafter.[73] Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the upper limit of normal. If liver enzyme abnormalities are identified, consider a dose modification (reduction, interruption, or discontinuation) according to the manufacturer's recommendations.[87]

adjunct **nonsteroidal anti-inflammatory drug (NSAID)**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» NSAIDs are used to control pain and stiffness in children with polyarticular JIA while systemic therapies take effect.

» Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential

Ongoing

trials of different NSAIDs are used to identify the most effective medicine for individual patients.

» Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

adjunct **intra-articular corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» triamcinolone acetonide: children and adolescents: consult specialist for guidance on intra-articular dose

OR

» methylprednisolone acetate: children and adolescents: consult specialist for guidance on intra-articular dose

» Intra-articular corticosteroid injections are used to relieve pain and/or swelling while systemic therapies take effect.[61]

» Radiographic assistance may be necessary for injecting some joints. The procedure can be undertaken with the administration of entonox or general anesthetic to the child. Adverse effects from intra-articular injections are uncommon.

» Relief is expected to last for at least 4 months.[62] Injections can be repeated every 4 months as needed. A shorter duration of relief may imply a need to escalate systemic therapy.[62]

» Intra-articular corticosteroid injections may not be a suitable treatment for large numbers of joints that have been injected multiple times. Escalation of systemic therapy may be more appropriate.[61]

adjunct **oral corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisone: children and adolescents: 0.05 to 2 mg/kg/day orally given in 1-4 divided doses

» Used to relieve symptoms for up to 3 months in patients with high or moderate disease activity,

Ongoing

while disease-modifying antirheumatic drugs or biologic therapies take effect.[61]

oligoarticular JIA: 4 or fewer joints ever involved

1st **intra-articular corticosteroid**

Primary options

» triamcinolone acetonide: children and adolescents: consult specialist for guidance on intra-articular dose

OR

» methylprednisolone acetate: children and adolescents: consult specialist for guidance on intra-articular dose

» Patients with JIA should be managed by a specialist pediatric rheumatology multidisciplinary team.[60]

» Corticosteroid injections alone may be appropriate for children with oligoarticular arthritis.[62]

» Radiographic assistance may be necessary for injecting some joints. The procedure can be undertaken with the administration of entonox or general anesthetic to the child. Adverse effects from intra-articular injections are uncommon.

» Relief is expected to last for at least 4 months.[62] Injections can be repeated every 4 months as needed. A shorter duration of relief may imply a need to escalate systemic therapy.[62]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **NSAID**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» Used for relief of joint pain and/or swelling. NSAID monotherapy may be given for 2 months if the child has low disease activity, no contractures, and no poor prognostic features.[62] Poor prognostic features are: arthritis of the hip or cervical spine, arthritis of the ankle or wrist plus prolonged or marked inflammatory marker elevation, or radiographic evidence of erosions or joint space narrowing.[62] If there is any residual disease activity after 2 months' treatment, therapy should be escalated to intra-articular corticosteroid injections.[62]

» Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective medicine for individual patients.

» Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

adjunct **methotrexate**

Treatment recommended for SOME patients in selected patient group

Primary options

» methotrexate: children ≥2 years of age and adolescents: 10-15 mg/square meter of body surface area orally/subcutaneously/intramuscularly once weekly on the same day of each week, adjust dose according to response, maximum 25 mg/week

Ongoing

Alternative dose regimens may be recommended.

» Started initially for patients who have high disease activity and poor prognostic features.[62] Poor prognostic features are: arthritis of the hip or cervical spine, arthritis of the ankle or wrist plus prolonged or marked inflammatory marker elevation, or radiographic evidence of erosions or joint space narrowing.[62]

» Recommended after initial corticosteroid injections for patients with high disease activity but without poor prognostic features, and patients with moderate disease activity and poor prognostic features.[62] Also recommended after repeated corticosteroid injections for patients with moderate disease activity but no poor prognostic features, and patients with low disease activity and poor prognostic features.[62]

» Folic acid is usually given concomitantly to decrease the side effects of methotrexate, and antiemetics may be used to reduce nausea. Patients should be counseled to avoid alcohol and pregnancy while taking methotrexate.

» Before starting methotrexate, a complete blood count, serum creatinine, and liver enzymes should be checked. Measurements should be repeated every 3 to 4 months during treatment.[73] Patients at risk of hepatitis B or hepatitis C infection should have a screening antibody test before starting methotrexate.[62] Elevation of aspartate aminotransferase or alanine aminotransferase above 2 times the upper limit justifies temporary suspension of methotrexate, which can be re-started following normalization of serum liver enzyme levels.[62]

2nd **tumor necrosis factor (TNF)-alpha inhibitor**

Primary options

» adalimumab: children ≥2 years of age and adolescents (10-14 kg body weight): 10 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (15-29 kg body weight): 20 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 40 mg subcutaneously every 2 weeks

OR

MANAGEMENT

Ongoing

» etanercept: children ≥2 years of age and adolescents (<63 kg body weight): 0.8 mg/kg subcutaneously once weekly, maximum 50 mg/week; children ≥2 years of age and adolescents (≥63 kg body weight): 50 mg subcutaneously once weekly

Secondary options

» infliximab: children and adolescents: consult specialist for guidance on dose

» TNF-alpha inhibitors are rarely needed for patients with oligoarticular JIA. They should be considered in patients with moderate or high disease activity and poor prognostic features after 3 months' treatment with methotrexate at maximum tolerated dose and intra-articular corticosteroids, and in patients with high disease activity but without poor prognostic features after 6 months' treatment with methotrexate and intra-articular corticosteroids.[62] Poor prognostic features are: arthritis of the hip or cervical spine, arthritis of the ankle or wrist plus prolonged or marked inflammatory marker elevation, or radiographic evidence of erosions or joint space narrowing.[62]

» If the patient has had a partial clinical response to methotrexate, this should be continued after initiating a TNF-alpha inhibitor.[62]

» When treatment with a TNF-alpha inhibitor is needed, etanercept or adalimumab are preferred to infliximab. Infliximab carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

» Caution is advised in patients with recurrent infections, conditions predisposing to infections, preexisting demyelinating disorders, or hematologic diseases, due to the immunosuppressive nature of these medicines.[84] A study evaluating etanercept and adalimumab showed an increase in number of infections but no clear evidence that the overall malignancy risk was increased.[79] Chronic carriers of tuberculosis and hepatitis B are susceptible to disease reactivation. Tuberculosis skin tests, and viral hepatitis screening for patients with risk factors for infection, are recommended prior to treatment.[62] [84] Live vaccines should be avoided during treatment.[85]

plus **supportive care**

Ongoing

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **intra-articular corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» triamcinolone acetonide: children and adolescents: consult specialist for guidance on intra-articular dose

OR

» methylprednisolone acetate: children and adolescents: consult specialist for guidance on intra-articular dose

» Injection of corticosteroids into the affected joints is recommended for all patients with active arthritis, in addition to any systemic therapy.[62]

» Radiographic assistance may be necessary for injecting some joints. The procedure can be undertaken with the administration of entonox or general anesthetic to the child. Adverse effects from intra-articular injections are uncommon.

» Relief is expected to last for at least 4 months.[62] A shorter duration of relief may imply a need to escalate therapy.[62]

adjunct **NSAID**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

Ongoing

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» Used for relief of joint pain and/or swelling.

» Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective medicine for individual patients.

» Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

active sacroiliitis

1st **NSAID**

Primary options

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» Patients with JIA should be managed by a specialist pediatric rheumatology multidisciplinary team.[60]

» NSAIDs are first-line for children and adolescents with active sacroiliitis.[61]

» Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective medicine for individual patients.

Ongoing

» Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **oral corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisone: children and adolescents: 0.05 to 2 mg/kg/day orally given in 1-4 divided doses

» Used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

2nd **TNF-alpha inhibitor or sulfasalazine**

Primary options

» adalimumab: children ≥2 years of age and adolescents (10-14 kg body weight): 10 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (15-29 kg body weight): 20 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 40 mg subcutaneously every 2 weeks

OR

» etanercept: children ≥2 years of age and adolescents (<63 kg body weight): 0.8 mg/kg subcutaneously once weekly, maximum 50 mg/week; children ≥2 years of age and adolescents (≥63 kg body weight): 50 mg subcutaneously once weekly

Secondary options

Ongoing

» sulfasalazine: children ≥6 years of age and adolescents: 30-50 mg/kg/day orally given in 2 divided doses, maximum 2000 mg/day

OR

» infliximab: children and adolescents: consult specialist for guidance on dose

» Treatment should be escalated if there is active sacroiliitis despite NSAID monotherapy. Use of TNF-alpha inhibitors is associated with decreased disease activity, compared with placebo.[93] [94] [95] Treatment with etanercept or adalimumab is preferred to treatment with infliximab. Infliximab carries a risk of infusion-associated reactions and is not approved for the treatment of any form of JIA.

» Sulfasalazine may also be used, particularly for children in whom TNF-alpha inhibitors are contraindicated or not tolerated.[61]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **oral corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisone: children and adolescents: 0.05 to 2 mg/kg/day orally given in 1-4 divided doses

» Used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

active enthesitis

1st **NSAID**

Primary options

Ongoing

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» Patients with JIA should be managed by a specialist pediatric rheumatology multidisciplinary team.[60]

» NSAIDs are first-line for children and adolescents with active enthesitis.[61]

» Specific NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective medicine for individual patients.

» Possible adverse effects include renal impairment, gastrointestinal symptoms (nausea, constipation, diarrhea, abdominal pain), headache, and rash.[92]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **oral corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisone: children and adolescents: 0.05 to 2 mg/kg/day orally given in 1-4 divided doses

MANAGEMENT

Ongoing

» Used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

2nd **methotrexate or sulfasalazine or TNF-alpha inhibitor**

Primary options

» methotrexate: children ≥2 years of age and adolescents: 10-15 mg/square meter of body surface area orally/subcutaneously/intramuscularly once weekly on the same day of each week, maximum 25 mg/week Alternative dose regimens may be recommended.

OR

» sulfasalazine: children ≥6 years of age and adolescents: 30-50 mg/kg/day orally given in 2 divided doses, maximum 2000 mg/day

OR

» adalimumab: children ≥2 years of age and adolescents (10-14 kg body weight): 10 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (15-29 kg body weight): 20 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 40 mg subcutaneously every 2 weeks

OR

» etanercept: children ≥2 years of age and adolescents (<63 kg body weight): 0.8 mg/kg subcutaneously once weekly, maximum 50 mg/week; children ≥2 years of age and adolescents (≥63 kg body weight): 50 mg subcutaneously once weekly

Secondary options

» infliximab: children and adolescents: consult specialist for guidance on dose

» Treatment should be escalated if there is active enthesitis despite NSAID monotherapy.[61]

» Typically methotrexate or sulfasalazine are used first, with escalation to a TNF-alpha inhibitor if the child doesn't respond.[96] When treatment with a TNF-alpha inhibitor is required, etanercept or adalimumab are preferred to infliximab. Infliximab carries a risk of infusion-

Ongoing

associated reactions and is not approved for the treatment of any form of JIA.

» However, American College of Rheumatology guidelines recommend that children with active enthesitis despite NSAID monotherapy should escalate to TNF-alpha inhibitors, rather than methotrexate or sulfasalazine, and noted that the level of evidence for this recommendation was low.[61] One observational study reported a greater improvement in pain and disease activity after 12 months in children with enthesitis who received a TNF-alpha inhibitor, compared with those who received a disease-modifying antirheumatic drug alone.[97]

» Before starting methotrexate, a complete blood count, serum creatinine, and liver enzymes should be checked. Measurements should be repeated every 3 to 4 months during treatment.[73] Patients at risk of hepatitis B or hepatitis C infection should have a screening antibody test before starting methotrexate.[62] Elevation of aspartate aminotransferase or alanine aminotransferase above 2 times the upper limit justifies temporary suspension of methotrexate, which can be re-started following normalization of serum liver enzyme levels.[62] Folic acid is usually given concomitantly to decrease the side effects of methotrexate, and antiemetics may be used to reduce nausea.

» For TNF-alpha inhibitors, caution is advised in patients with recurrent infections, conditions predisposing to infections, preexisting demyelinating disorders, or hematologic diseases, due to the immunosuppressive nature of these medicines.[84] A study evaluating etanercept and adalimumab showed an increase in number of infections but no clear evidence that the overall malignancy risk was increased.[79] Chronic carriers of tuberculosis and hepatitis B are susceptible to disease reactivation. Tuberculosis skin tests, and viral hepatitis screening for patients with risk factors for infection, are recommended prior to treatment.[62] [84] Live vaccines should be avoided during treatment.[85]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

MANAGEMENT

Ongoing

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **oral corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» prednisone: children and adolescents: 0.05 to 2 mg/kg/day orally given in 1-4 divided doses

» Used to relieve symptoms for up to 3 months during initiation or escalation of systemic therapy.[61]

systemic-onset JIA

without macrophage activation syndrome (MAS)

1st **brief trial of NSAID**

Primary options

» ibuprofen: children and adolescents: 30-50 mg/kg/day orally given in 3-4 divided doses, maximum 3200 mg/day

OR

» naproxen: children ≥2 years of age and adolescents: 5 mg/kg orally twice daily, maximum 1000 mg/day

OR

» meloxicam: children and adolescents (≥60 kg body weight): 7.5 mg orally once daily

» An initial trial of NSAID monotherapy is a first-line option.[98]

» There is some evidence that those with systemic JIA without MAS will respond to NSAIDs alone and even have clinically inactive disease.[98]

» Patients who undergo an initial trial of NSAID monotherapy should be followed up within 2 weeks for evaluation of a possible need for drug escalation.[101] If a response occurs and inactive disease occurs, then NSAIDs should be tapered and discontinued. If clinical response is not rapid and complete, rapid escalation of therapy is recommended.

Ongoing

» Several NSAIDs are approved for children with JIA (e.g., ibuprofen, naproxen, meloxicam). Others are commonly used off-label. No specific NSAID is superior to another.[92] Sequential trials of different NSAIDs are used to identify the most effective drug for individual patients.

» Possible adverse effects include renal impairment, gastrointestinal symptoms, headache, and rash.[92]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **biologic agent**

Treatment recommended for SOME patients in selected patient group

Primary options

» tocilizumab: children ≥2 years of age and adolescents (<30 kg body weight): 12 mg/kg intravenously every 2 weeks, or 162 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg body weight): 8 mg/kg intravenously every 2 weeks, or 162 mg subcutaneously once weekly

OR

» canakinumab: children ≥2 years of age and adolescents (≥7.5 kg body weight): 4 mg/kg subcutaneously every 4 weeks, maximum 300 mg/dose

OR

» anakinra: children and adolescents: consult specialist for guidance on dose

» Biologic agents can be given in combination with an NSAID for initial treatment or after a trial period of an NSAID.[98] Biologic agents can also be used as monotherapy (i.e., interleukin [IL]-1 or IL-6 inhibitor) first-line option.

Ongoing

» The American College of Rheumatology (ACR) does not recommend any one preferred agent, but indicates that IL-1 inhibitors (e.g., anakinra, canakinumab) and IL-6 inhibitors (e.g., tocilizumab) are extremely effective and well-tolerated options. The choice should be based on discussions between the practitioner and patient as routes of administration and frequency vary. The ACR recommends switching between IL-1 and IL-6 inhibitors when needed due to a lack of efficacy or poor tolerability as individual response varies significantly.[98] [102] [103] [104]

» Biologic agents used in systemic JIA appear safe and comparable with respect to adverse effect risk in the short term.[102] Anakinra has a short half-life, meaning its dose can be adjusted or it can be withdrawn quickly. One randomized controlled trial reported a response rate of 66% to 1 month's treatment with anakinra, compared with 8% to placebo, in children with systemic JIA. After 1 month, 83% of the children receiving placebo were switched to anakinra; 90% of children who switched from placebo responded to anakinra.[105] Canakinumab is effective for treating active systemic JIA.[103] [106] Treatment with canakinumab significantly reduces fever and disease activity, compared with placebo.[103] One randomized trial showed a significant reduction in fever and active arthritis in children with systemic JIA refractory to corticosteroids and NSAIDs who were treated with tocilizumab, compared with placebo.[107] Meta-analysis has shown similar efficacy between tocilizumab, canakinumab, and anakinra.[102] One meta analysis of randomized controlled trials found that canakinumab had the highest probability of being the best treatment, in terms of the modified ACR Pediatric 30 (ACRpedi30) response rate, followed by anakinra and tocilizumab.[108]

» Serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) has been identified with tocilizumab. The ACR recommends monitoring alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, within 4 to 8 weeks of treatment and every 3 to 4 months thereafter.[73] Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the upper limit of normal. If liver enzyme abnormalities are identified,

Ongoing

consider a dose modification (reduction, interruption, or discontinuation) according to the manufacturer's recommendations.[87]

» A range of small-scale trials demonstrated resolution of systemic signs following the use of biologic agents.[105] [107] [109] [110] With prolonged use, some patients suffered from adverse effects (e.g., infection, neutropenia, and increased aminotransferase levels).[107]

» The ACR recommends considering tapering and discontinuing biologic therapies when the disease is deemed inactive.[98]

adjunct **conventional synthetic DMARD**

Treatment recommended for SOME patients in selected patient group

Primary options

» methotrexate: children ≥2 years of age and adolescents: 10-15 mg/square meter of body surface area orally/subcutaneously/intramuscularly once weekly on the same day of each week, maximum 25 mg/week Alternative dose regimens may be recommended.

Secondary options

» leflunomide: consult specialist for guidance on dose

» A conventional synthetic DMARD may be added if there is residual arthritis after initial treatment.[98] There is no preferred agent.

» The primary conventional synthetic DMARD used for the treatment of systemic JIA is methotrexate. Methotrexate has been commonly used in children with systemic JIA due to its corticosteroid-sparing effect.[115] Although it is used less frequently, it can be given alone or alongside a biologic agent to control symptoms. Leflunomide is another conventional synthetic DMARD that can be used in JIA to manage the inflammatory response when methotrexate is not tolerated.[74] [116]

with MAS **1st** **biologic agent**

Primary options

» tocilizumab: children ≥2 years of age and adolescents (<30 kg body weight): 12 mg/kg intravenously every 2 weeks, or 162 mg subcutaneously every 2 weeks; children ≥2 years of age and adolescents (≥30 kg

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body weight): 8 mg/kg intravenously every 2 weeks, or 162 mg subcutaneously once weekly

OR

» canakinumab: children ≥2 years of age and adolescents (≥7.5 kg body weight): 4 mg/kg subcutaneously every 4 weeks, maximum 300 mg/dose

OR

» anakinra: children and adolescents: consult specialist for guidance on dose

» MAS is a life-threatening complication of systemic-onset JIA. MAS is present if the following criteria are met in a febrile patient with known or suspected systemic-onset JIA: ferritin >684 ng/mL and any two of platelet count ≤181 x 10^9/L, aspartate aminotransferase >48 U/L, triglycerides >156 mg/dL, or fibrinogen ≤360 mg/dL.[100] If a patient has a normal ferritin level, but there is ongoing clinical suspicion of MAS, serial ferritin testing should be considered.[58]

» Consult a pediatric rheumatology specialist urgently if features of MAS are present. Patients with MAS can deteriorate rapidly and may require intensive care admission. For patients with suspected MAS, initiating treatment while diagnostic testing is in progress should be considered.[58] Monitoring initial treatment response by assessing clinical and laboratory markers of organ involvement should be assessed at least daily, and markers of systemic inflammation at least twice weekly. Worsening or lack of improvement in laboratory parameters of systemic inflammation, particularly ferritin, may indicate disease progression and a need to reassess diagnosis and/or treatment.[58]

» Biologic agent monotherapy (i.e., interleukin [IL]-1 or IL-6 inhibitor) is a first-line option.[98]

» The American College of Rheumatology (ACR) does not recommend any one preferred agent, but indicates that IL-1 inhibitors (e.g., anakinra, canakinumab) and IL-6 inhibitors (e.g., tocilizumab) are extremely effective and well-tolerated options. The choice should be based on discussions between the practitioner and patient as routes of administration and frequency vary. The ACR recommends switching between IL-1 and IL-6 inhibitors when needed due to a lack of efficacy or poor tolerability as individual

Ongoing

response varies significantly.[98] [102] [103] [104]

» Biologic agents used in systemic JIA appear safe and comparable with respect to adverse effect risk in the short term.[102] Anakinra has a short half-life, meaning its dose can be adjusted or it can be withdrawn quickly. One randomized controlled trial reported a response rate of 66% to 1 month's treatment with anakinra, compared with 8% to placebo, in children with systemic JIA. After 1 month, 83% of the children receiving placebo were switched to anakinra; 90% of children who switched from placebo responded to anakinra.[105] Canakinumab is effective for treating active systemic JIA.[103] [106] Treatment with canakinumab significantly reduces fever and disease activity, compared with placebo.[103] One randomized trial showed a significant reduction in fever and active arthritis in children with systemic JIA refractory to corticosteroids and NSAIDs who were treated with tocilizumab, compared with placebo.[107] Meta-analysis has shown similar efficacy between tocilizumab, canakinumab, and anakinra.[102] One meta analysis of randomized controlled trials found that canakinumab had the highest probability of being the best treatment, in terms of the modified ACR Pediatric 30 (ACRpedi30) response rate, followed by anakinra and tocilizumab.[108]

» Serious hepatotoxicity (including acute liver failure, hepatitis, and jaundice) has been identified with tocilizumab. The ACR recommends monitoring alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at initiation of treatment, within 4 to 8 weeks of treatment and every 3 to 4 months thereafter.[73] Be cautious when considering starting tocilizumab treatment in patients with ALT or AST levels higher than 1.5 times the upper limit of normal. Tocilizumab is not recommended if ALT or AST levels are higher than 5 times the upper limit of normal. If liver enzyme abnormalities are identified, consider a dose modification (reduction, interruption, or discontinuation) according to the manufacturer's recommendations.[87]

» A range of small-scale trials demonstrated resolution of systemic signs following the use of biologic agents.[105] [107] [109] [110] With prolonged use, some patients suffered from adverse effects (e.g., infection, neutropenia, and increased aminotransferase levels).[107]

Ongoing

» In children with systemic JIA whose disease is inactive, it may be possible to maintain this inactive disease state with lower doses of, or discontinuation of, biologic agents.[113] [114] It is unclear how soon after achievement of inactive disease these can be tapered.[98]

»

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All aspects of the child's physical and psychological health should be evaluated and addressed by the multidisciplinary team.[60] Ongoing input from physical therapists and occupational therapists is required.[60]

» Patients with JIA have an increased risk of psychiatric morbidity.[70] Support and strategies for managing any difficulties should be provided.[60]

adjunct **systemic corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» methylprednisolone sodium succinate: children and adolescents: consult specialist for guidance on intravenous dose

OR

» prednisone: children and adolescents: consult specialist for guidance on oral dose

» Corticosteroids may be used in combination with a biologic agent. Biologic agent monotherapy may not be sufficient for severely sick patients.[98]

» Glucocorticoid therapy should be limited to the lowest effective dose for the shortest duration possible, although treatment with high-dose corticosteroids may be required for initial disease control.[98] Long-term corticosteroid therapy in children is not appropriate because of its potential side effects on bone health and growth.[111] Tapering and discontinuing corticosteroids is strongly recommended after inactive disease has been attained in systemic JIA.[98]

adjunct **conventional synthetic DMARD**

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» methotrexate: children ≥2 years of age and adolescents: 10-15 mg/square meter of body surface area orally/subcutaneously/intramuscularly once weekly on the same day of each week, maximum 25 mg/week Alternative dose regimens may be recommended.

Secondary options

» leflunomide: consult specialist for guidance on dose

» Biologic agents combined with a corticosteroid and a conventional synthetic DMARD may be necessary to control MAS in some patients.[98]

» A conventional synthetic DMARD may be added if there is residual arthritis after initial treatment.[98] There is no preferred agent.[98]

» The primary conventional synthetic DMARD used for the treatment of systemic JIA is methotrexate. Methotrexate has been commonly used in children with systemic JIA due to its corticosteroid-sparing effect.[115] Although it is used less frequently, it can be given alone or alongside a biologic agent to control symptoms. Leflunomide is another conventional synthetic DMARD that can be used in JIA to manage the inflammatory response when methotrexate is not tolerated.[74] [116]

» If a patient is receiving both a biologic agent and a corticosteroid, the corticosteroid should be tapered and discontinued first before attempting to taper the biologic agent. It is unclear how soon or rapidly these can be safely discontinued in patients with inactive systemic JIA.[98]

Emerging

Baricitinib

Baricitinib is a Janus kinase (JAK) inhibitor. It is approved for the treatment of juvenile idiopathic arthritis by the European Medicines Agency (EMA), in children 2 years and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic disease-modifying antirheumatic drugs (DMARDs).[117] It may be used as monotherapy or in combination with methotrexate. Baricitinib is not currently approved in the US for this indication. Further guidance on its use is expected by late 2023.

Tofacitinib

Tofacitinib is another JAK inhibitor. One phase 3 study has demonstrated that tofacitinib significantly reduces disease flares in patients with polyarticular JIA, compared with placebo.[118] Tofacitinib is approved in the US and Europe for use in children ages 2 years and older with active polyarticular JIA.

Golimumab

Golimumab is a recombinant human monoclonal antibody against tumor necrosis factor alpha.[119] In Europe, it is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children in combination with methotrexate. It has been approved by the US Food and Drug Administration for children ages 2 years and older with polyarticular JIA.

Rilonacept

An interleukin-1 inhibitor that has demonstrated efficacy in active systemic JIA.[120] In one small study, rilonacept was shown to be well tolerated and demonstrated improvements in articular and systemic manifestations of JIA in >50% of patients over 2 years.[110]

Primary prevention

There are no known primary preventive measures.

Secondary prevention

Regular physical activity can help prevent deconditioning.[65] Physical therapy and occupational therapy are also recommended.[60]

Patients should be vaccinated, but shared decision-making with patients should be encouraged regarding holding immunosuppressive medications or delaying vaccination to maximize vaccine efficacy. Individual risk for vaccine-preventable illness and disease flare should be considered if immunosuppressive medications are withheld for vaccination.[121] Annual influenza vaccinations, especially for those on immunosuppressive agents, can help prevent the development of concurrent infection and/or infection triggering a flare. For those on immunosuppressive agents, varicella prophylaxis following contact is advised.

Patient discussions

Patients require regular follow-up, although those with oligoarticular JIA need less frequent follow-up once their disease is controlled. Children with polyarticular or systemic subtypes need more frequent follow-up (initially monthly or bi-monthly).

Patient and family education is an important aspect of therapy and helps to ensure concordance with treatment regimens. Concordance with home exercise programs should also be encouraged to preserve and improve range of motion. However, the long-term benefit of exercise is uncertain.[67] Psychological

support for patients and their families can be helpful in promoting adherence to treatment and should be considered for all patients with long-term illness.[130]

Careful monitoring for drug side effects is crucial. Patients should be advised to inform their healthcare provider immediately if there are any signs of infection, especially persistent fevers.

Live viral vaccines are not recommended for patients on certain medicines, although killed vaccines are safe and annual influenza vaccination is recommended. Due to concerns about the safety of vaccines in JIA, clinicians must discuss with families the evidence that strongly supports their benefits and safety, ensuring where possible that local scheduled immunizations are adhered to.[73]

There is evidence that children with JIA and flat feet may benefit from custom-made foot orthoses.[69] [131] [132]

Patient information is available from the Arthritis Foundation and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. [Arthritis Foundation: juvenile idiopathic arthritis] (http://www.arthritis.org/about-arthritis/types/juvenile-idiopathic-arthritis-jia) [National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): juvenile arthritis] (http://www.niams.nih.gov/Health_Info/Juv_Arthritis/default.asp)

Physical and occupational therapy are encouraged in conjunction with medications.

Monitoring

Monitoring

The American College of Rheumatology (ACR) recommends infection surveillance of tuberculosis (TB) screening prior to starting a biologic therapy and when there is a concern for TB exposure. Exposure is broad and includes contact with someone with active TB, travel to locations where TB is endemic, contact with high-risk individuals (e.g., prisoners, visitors from TB-endemic areas), or living in communities with a higher frequency of TB. However, in an urgent clinical scenario (i.e., in active systemic JIA and macrophage activation syndrome), it would be appropriate to initiate treatment without delay.[73]

Patients are usually actively managed by pediatric rheumatologists until their disease achieves remission. Once in remission, they can be followed up by their primary care providers.

Diet should be optimized and where necessary, a calcium and vitamin D supplement should be used, particularly if patients are on long-term corticosteroids.[129]

Complete blood count (CBC), serum creatinine, and liver enzymes should be checked every 3 to 4 months during treatment with methotrexate.[73] Elevation of aspartate aminotransferase or alanine aminotransferase above 2 times the upper limit justifies temporary suspension of methotrexate, which can be re-started following normalization of serum liver enzyme levels.[62]

Ultrasound and MRIs are useful to monitor activity in joints that are clinically difficult to assess in the early stages (temporomandibular joints, subtalar joints, hips). Subtle growth abnormalities can occur insidiously over time, so it is important to monitor for leg length discrepancy, scoliosis, and temporomandibular joint asymmetry.

Regular ophthalmic exams for signs of anterior uveitis are essential. The ACR recommends screening every 3 months for children at high risk of uveitis, and screening every 6 to 12 months for children at lower risk.[126] High-risk features are oligoarticular JIA, rheumatoid factor-negative polyarticular JIA, psoriatic arthritis, undifferentiated arthritis with positive antinuclear antibodies, age younger than 7 years at JIA onset, and duration of JIA 4 years or less.[126]

The British Society for Paediatric and Adolescent Rheumatology guidelines state initial screening must be within 6 weeks of diagnosis, and for those most at risk every 2 months thereafter for 6 months. When patients go into remission and stop immunosuppressive treatment, screening should be re-started at 2-monthly intervals for 6 months before reverting to previous screening arrangements.[60]

The ACR recommends baseline laboratory testing prior to treatment initiation, for all medications.[73] This should include CBC with differential cell count and liver function tests (e.g., alanine aminotransferase and aspartate aminotransferase), plus renal function tests (e.g., blood urea nitrogen, creatinine, and urinalysis) for patients being treated with methotrexate, sulfasalazine, or nonsteroidal anti-inflammatory drugs (NSAIDs) and lipid profiles for patients being treated with tocilizumab and tofacitinib. It provides recommendations for regular laboratory monitoring to detect medication toxicity, and the risk of adverse events pertaining to specific medications or medication classes. If a child is receiving >1 medication, a more frequent schedule for laboratory testing is recommended.[73]

Complications

Complications	Timeframe	Likelihood
leg length discrepancy, micrognathia	**long term**	**medium**
Can occur with ongoing inflammation and poor disease control.		
joint erosion	**long term**	**medium**
Can occur with poor disease control and lead to the need for joint replacement.		
C-spine fusion and C1-C2 subluxation	**long term**	**low**
Can occur with ongoing inflammation and poor disease control, especially in systemic and polyarticular subtypes.		
sacro-iliac joint and spine ankylosis	**long term**	**low**
Can occur with ongoing inflammation and poor disease control in children with enthesitis-related JIA.		
uveitis	**variable**	**medium**
JIA-associated uveitis is one of the most devastating complications. It is predominantly chronic, anterior, nongranulomatous inflammation affecting the iris and ciliary body. Onset of chronic uveitis is usually insidious and often asymptomatic; therefore, screening and close monitoring by a pediatric ophthalmologist with a slit lamp is essential for diagnosis. The American College of Rheumatology recommends screening every 3 months for children at high risk of uveitis, and screening every 6 to 12 months for children at lower risk.[126] High-risk features are: oligoarticular JIA, rheumatoid factor-negative polyarticular JIA, psoriatic arthritis, undifferentiated arthritis with positive antinuclear antibodies, age younger than 7 years at JIA onset, and duration of JIA 4 years or less.[126] Further complications such as glaucoma, cataracts, band keratopathy, synechiae, and blindness may occur. Topical corticosteroids should be used initially to treat active anterior uveitis. Topical and systemic nonsteroidal anti-inflammatory drugs should not be used alone to treat active anterior uveitis. Systemic immunosuppression is recommended if inactivity is not achieved within 3 months or inflammation is reactivating during corticosteroid dose reduction. Systemic immunosuppression in active uveitis is recommended if poor prognostic factors (uveitis antedating arthritis, posterior synechia, male sex, band keratopathy, glaucoma and cataract, poor initial vision, hypotony, macular edema, and dense vitreous body opacification) are present at the first visit. Lack of remission later on during the disease course also requires systemic immunosuppression.[127] Methotrexate is the first choice for systemic immunosuppression. If methotrexate is ineffective or not tolerated, adding or switching to biologic treatment is recommended. The use of anti-tumor necrosis factor treatment strategies is recommended in patients with uveitis refractory/resistant to disease-modifying antirheumatic drugs, principally methotrexate.[127]		

Complications	Timeframe	Likelihood
macrophage activation syndrome (MAS)	**variable**	**medium**
MAS is a life-threatening complication of systemic-onset JIA. Signs and symptoms include persistent fever; elevated and/or rising ferritin or other markers of inflammation/damage; inappropriately low or declining hemoglobin, platelet counts or white blood cells (neutrophils and lymphocytes); hepatic dysfunction; coagulopathy; splenomegaly; central nervous system dysfunction.[58] Laboratory abnormalities include pancytopenia, decreased erythrocyte sedimentation rate, elevated liver function tests, and disseminated intravascular coagulation-like coagulopathy. MAS is present if the following criteria are met in a febrile patient with known or suspected systemic juvenile idiopathic arthritis: ferritin >684 ng/mL and any two of platelet count ≤181 x 10^9/L, aspartate aminotransferase >48 U/L, triglycerides >156 mg/dL, or fibrinogen ≤360 mg/dL.[100] Consult a pediatric rheumatology specialist urgently if features of MAS are present. Patients with MAS can deteriorate rapidly and may require intensive care admission. Initial treatment is with high-dose intravenous corticosteroids. The management of patients with MAS is covered in this topic's Treatment algorithm .		
highly fatal lung disease	**variable**	**low**
Highly fatal lung disease has been observed in some children with systemic JIA, the majority of whom were treated with biologic therapy. Risk factors include macrophage activation syndrome (MAS), younger age with MAS, previous reactions to tocilizumab and trisomy 21. Affected children often present with acute digital clubbing.[98] [128]		

Prognosis

Reports suggest that approximately two-thirds of patients achieve remission or inactive disease.[122] However, outcome is variable depending on disease subtype, and long-term outcome is best predicted by disease characteristics at 5 years follow-up than at onset.[123] Generally speaking, there have been vast improvements in the past decade as a result of novel and highly effective therapeutic modalities.

Shorter disease duration prior to treatment, good initial response to therapy, and aggressive therapy result in a higher likelihood and longer duration of clinically inactive disease in patients with polyarticular JIA.[124] Unfortunately, some patients do not respond to treatment and experience moderate to severe disabilities.

Oligoarticular disease appears to have the best prognosis, with better functional outcomes, and a greater proportion of patients achieve remission.[125] A greater proportion of patients with rheumatoid factor-positive and systemic-onset subtypes continue to have active disease after several years.

Juvenile idiopathic onset-associated uveitis is the most common extra-articular manifestation and can lead to visual impairment if disease is poorly controlled. Although most patients have good outcomes when properly monitored and treated, 25% to 50% of children with uveitis develop cataracts, glaucoma, or synechiae, and 10% to 20% develop visual loss.[126]

Diagnostic guidelines

International

EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/ macrophage activation syndrome (https://www.eular.org/recommendations-eular-acr) [58]

Published by: European League against Rheumatism; American College of Rheumatology **Last published:** 2023

International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision (https://pubmed.ncbi.nlm.nih.gov/14760812) [1]

Published by: International League of Associations for Rheumatology **Last published:** 2004

EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice (https://www.eular.org/recommendations_management.cfm) [59]

Published by: European League against Rheumatism; Paediatric Rheumatology European Society **Last published:** 2015

Treatment guidelines

International

2022 American College of Rheumatology guideline for vaccinations in patients with rheumatic and musculoskeletal diseases (https://rheumatology.org/vaccinations-guideline) [121]

Published by: American College of Rheumatology **Last published:** 2023

2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) [98]

Published by: American College of Rheumatology **Last published:** 2022

2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) [73]

Published by: American College of Rheumatology **Last published:** 2022

American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) [61]

Published by: American College of Rheumatology; Arthritis Foundation **Last published:** 2019

EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (https://www.eular.org/recommendations-eular-acr) [58]

Published by: European League against Rheumatism; American College of Rheumatology **Last published:** 2023

BSPAR standards of care for children and young people with juvenile idiopathic arthritis (https://academic.oup.com/rheumatology/article/49/7/1406/1785261/BSPAR-Standards-of-Care-for-children-and-young) [60]

Published by: British Society of Paediatric and Adolescent Rheumatology **Last published:** 2010

Online resources

1. Arthritis Foundation: juvenile idiopathic arthritis (http://www.arthritis.org/about-arthritis/types/juvenile-idiopathic-arthritis-jia) *(external link)*

2. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): juvenile arthritis (http://www.niams.nih.gov/Health_Info/Juv_Arthritis/default.asp) *(external link)*

Key articles

- Davies K, Cleary G, Foster H, et al. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2010 Jul;49(7):1406-8. Full text (https://academic.oup.com/rheumatology/article/49/7/1406/1785261/BSPAR-Standards-of-Care-for-children-and-young) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20173199?tool=bestpractice.bmj.com)

- Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011 Apr;63(4):465-82. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222233) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21452260?tool=bestpractice.bmj.com)

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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