Indian Academy of Pediatrics (IAP)

STANDARD TREATMENT GUIDELINES 2022

Juvenile Idiopathic Arthritis

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Juvenile Idiopathic Arthritis

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Definition

- ☑ Arthritis is diagnosed in the presence of joint effusion or two or more of the following: limited range of movement with joint line tenderness or painful range of movement.
- ☑ Chronic immune-mediated arthritis is previously known as juvenile chronic arthritis or juvenile rheumatoid arthritis. Currently, it is called juvenile idiopathic arthritis (JIA). The exact incidence and prevalence of JIA is unknown and likely varies across the world.

Classification and Categories of Juvenile Idiopathic Arthritis

According to the International League of Associations for Rheumatology (ILAR) criteria, JIA is defined as chronic arthritis (±6 weeks duration) with no known cause occurring in children before the 16th birthday.

The ILAR classification categorizes JIA into seven mutually exclusive categories based on the number of joints involved, extra-articular features, and serology identified in the first 6 months of disease presentation **(Table 1)**.

This categorization attempts to cluster similar JIA presentations into distinct categories to improve research into etiology, disease course, long-term outcomes, response to treatment, and development of future therapies.

This classification system will likely evolve and be refined over the next few decades as knowledge of this disease increases.

TABLE 1: Classification of juvenile idiopathic arthritis as per the International League of Associations for Rheumatology (ILAR).

ILAR category	***ILAR definition***	***Exclusion***
Oligoarthritis	Arthritis affecting one to four joints during the first 6 months of disease *Two subtypes are identified:* 1. *Persistent oligoarthritis*: Affecting not more than four joints throughout the disease course 2. *Extended oligoarthritis*: Affecting a total of more than four joints after the first 6 months of disease	1, 2, 3, 4, and 5
Polyarthritis rheumatoid factor (RF)-negative	Arthritis affecting five or more joints during the first 6 months of disease; a test for RF is negative	1, 2, 3, 4, and 5
Polyarthritis RF-positive	Arthritis affecting five or more joints during the first 6 months of disease Two or more tests for RF at least 3 months apart during the first 6 months of disease are positive	1, 2, 3, and 5
Systemic arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days *Plus one or more:* 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis	1, 2, 3, and 4
Enthesitis-related arthritis (ERA)	Arthritis and enthesitis, or arthritis or enthesitis Plus at least two of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	1, 4, and 5
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative	2, 3, 4, and 5
Undifferentiated arthritis	Arthritis that fulfills criteria for: ☑ No category or ☑ Two or more categories	

- ☑ Psoriasis or a history of psoriasis in the patient or first-degree relative
- ☑ Arthritis in an HLA-B27 positive male beginning after 6th birthday
- ☑ Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease (IBD), or acute anterior uveitis, or history of one of these disorders in first-degree relative
- ☑ Presence of immunoglobulin M (IgM) rheumatoid factor on at least two occasions at least 3 months apart
- ☑ Presence of systemic JIA.

Enthesitis

Enthesitis refers to inflammation at the site where ligaments, tendons, fascia, or capsules attach to bone **(Fig. 1)**. This group includes children most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients from any of the ILAR JIA categories. Active enthesitis is tenderness and/or swelling of the entheses.

Sacroiliitis

This group includes patients with active sacroiliitis who will most likely be classified within the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients in any of the ILAR JIA categories. *Active sacroiliitis* is considered in presence of either prior or current MRI findings consistent with sacroiliitis along with clinical examination suggestive of sacroiliitis and/or associated with inflammatory back pain.

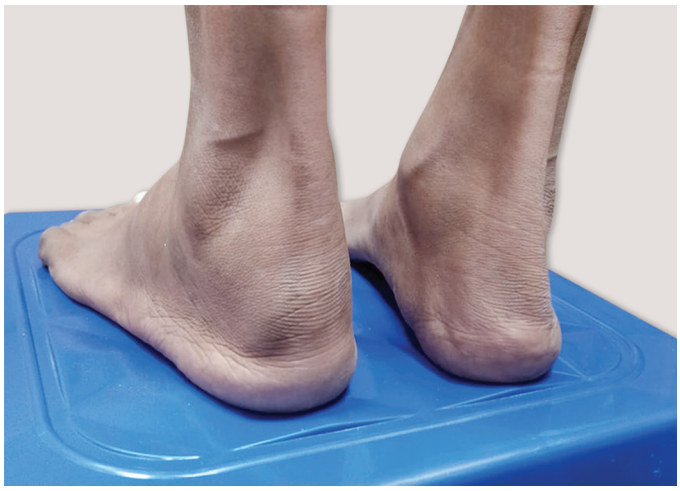
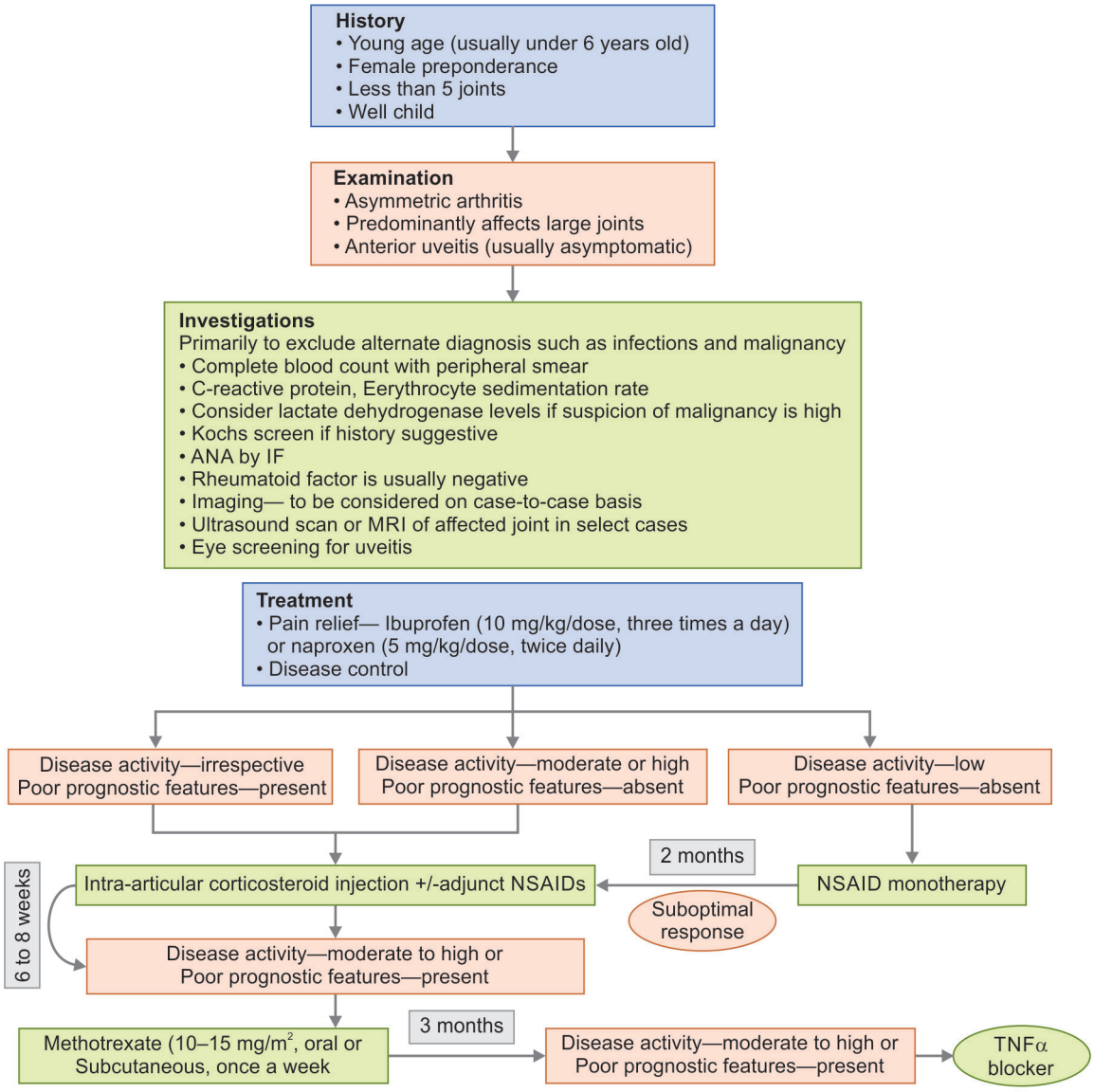


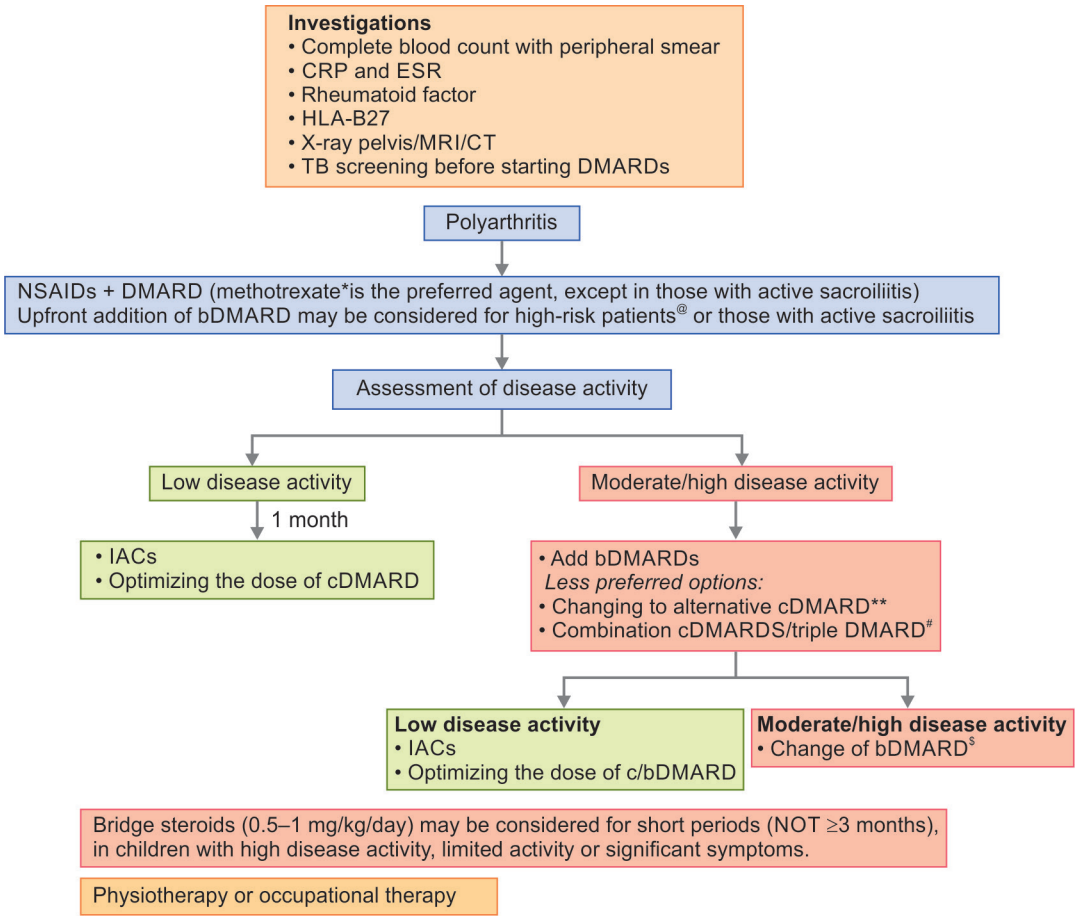
Fig. 1: Enthesitis of left tendo-Achilles.

Flowchart 1: Management of oligoarticular juvenile idiopathic arthritis.



(ANA: antinuclear antibody; IF: immunofluorescence; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor)

Flowchart 2: Management of polyarticular course of juvenile idiopathic arthritis (JIA).



Choice of bDMARD in order of preference: TNFi >> abatacept or tocilizumab > rituximab (only in RF positive polyarticular JIA)

@ Involvement of high-risk joints cervical spine, wrist or hip or those with high disease activity

* Sulfasalazine may be preferred in those with active sacroiliitis
Methotrexate: Subcutaneous route is preferred particularly at higher doses (>12.5 mg)

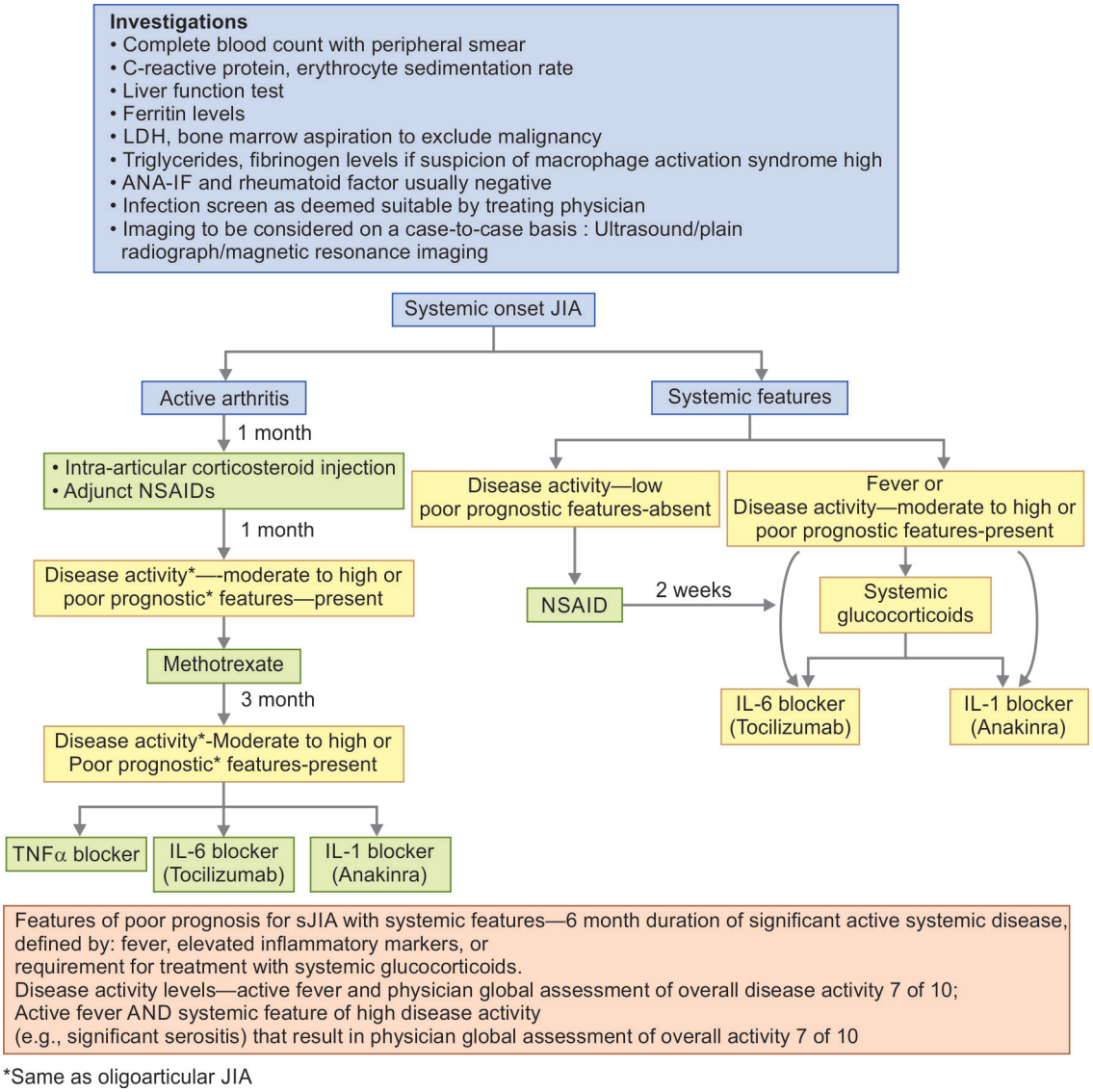
** Changing to another DMARD or combination DMARD seems a pragmatic approach in resource poor setting

Triple DMARDs: Methotrexate, hydroxychloroquine, and sulfasalazine

$ Switching to a non-TNFi (abatacept/tocilizumab) agent is preferred over switching to second anti-TNF. An alternative second anti-TNF agent may be appropriate for patients with good initial response to first anti-TNF.

(bDMARD: biological disease modifying anti-rheumatic drug; cDMARD: conventional disease modifying anti-rheumatic drug; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IACs: intra-articular corticosteroids, triamcinolone acetonide is used in India due to nonavailability of triamcinolone hexacetonide; NSAIDs: nonsteroidal anti-inflammatory drugs, naprosyn is the preferred agent; TB: tuberculosis; TNF: tumor necrosis factor)

Flowchart 3: Management of systemic arthritis.



*Same as oligoarticular JIA

(ANA: antinuclear antibody; IF: immunofluorescence; IL: interleukin; JIA: juvenile idiopathic arthritis; LDH: lactate dehydrogenase; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor)

Assessment of Disease Activity

The disease activity is assessed using clinical JIA score. The CJADAS-10 is a sum of total active joint count (to a maximum of 10), physician global assessment of disease activity (0–10), and parent/patient global assessment of well-being (0–10).

Low disease activity: CJADAS 10–25 and 1 active joint

Moderate-to-high disease activity: CJADAS > 2.5

Management of Enthesitis

In children with persistent enthesitis despite treatment with NSAIDs, TNFi is considered over methotrexate or sulfasalazine. However, in our settings DMARDs can be considered if TNFi is not feasible due to cost constrains. A short course of bridge steroids may also considered for significant symptoms.

Bridge Steroids

Short course (<3 months) of oral glucocorticoid intended to control disease activity quickly during escalation of DMARD or biologic therapy, using the shortest possible duration *(not >3 months)* and the lowest dose needed to control symptoms. The usual starting dose for this is 0.5–1 mg/kg/day in divided doses which is gradually tapered and stopped over 3 months. This may be considered during initiation or escalation of therapy in children with moderate or high disease activity.

Intra-articular glucocorticoid injections (triamcinolone acetonide) can be used for ameliorating the symptoms in limited number of joints in any of the JIA subtype.

Physiotherapy

In addition to drugs, physiotherapy is an integral part of JIA management to curtail the joint deformity and disability.

TABLE 2: Common drugs used to treat JIA.

Drug name	***Dosage (mg/kg/day)***	***Doses/day***	***Maximum dose (mg/day)***
	NSAIDs		
Naproxen	10–20	2	1,000
Indomethacin	1.5–3	3	150
Ibuprofen	30–40	3–4	2,400
	Conventional DMARDs		
	Dosage and route	*Clinical monitoring*	*Laboratory monitoring*
Methotrexate	10–15 mg/m^2, once weekly, oral (preferably on empty stomach) or subcutaneous Administer with folic acid or folinic acid	Improvement seen in 6–12 weeks Initial evaluation in 2–4 weeks, then monitor every 3–6 months	CBC with WBC count, differential and platelets; MCV; AST, ALT, albumin, baseline and in 4–8 weeks initially and with dose adjustments, then every 12 weeks once clinically stable
Sulfasalazine	30–50 mg/kg/day in two divided doses (maximum 2 g/day)	Improvement seen in 4–8 weeks Initial evaluation in 2–4 weeks, then every 2–4 months Discontinue if rash appears	CBC with WBC count, differential and platelets; AST, ALT, creatinine, baseline and every 1–2 weeks with dose increases, then every 3 months while on maintenance doses
Leflunomide	<20 kg: 10 mg every other day 20–40 kg: 10 mg daily >40 kg: 20 mg daily, oral	Improvement seen in 6–12 weeks Initial evaluation in 2–4 weeks then every 3–6 months	CBC with WBC count, differential and platelets; AST, ALT, creatinine (± urine pregnancy screening, if appropriate) baseline and in 2–4 weeks with dose adjustments, then every 3 months while on maintenance doses

(ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; DMARDs: disease modifying anti-rheumatic drugs; JIA: juvenile idiopathic arthritis; MCV: mean corpuscular volume; NSAIDs: nonsteroidal anti-inflammatory drugs; WBC: white blood cell)

TABLE 3: Biologic DMARDs used to treat JIA.

Agent	*Mechanism*	*Major use(s)*	*Dose*
Etanercept	TNF soluble receptor	Polyarticular-course JIA, enthesitis-related JIA	0.8 mg/kg weekly, 0.4 mg/kg twice weekly, to a maximum of 50 mg; administered by subcutaneous injection
Infliximab	Chimeric (mouse–human) anti-TNF antibody	Polyarticular-course JIA, enthesitis-related JIA, uveitis	6 mg/kg administered intravenously at weeks 0, 2, and 6 and every 8 weeks thereafter
Adalimumab	Humanized anti-TNF antibody	Polyarticular-course JIA, enthesitis-related JIA, uveitis	If patients <30 kg, 20 mg by subcutaneous injection every other week; if patient ≥30 kg, 40 mg by subcutaneous injection every other week
Abatacept	T-cell costimulation inhibitor	Polyarticular-course JIA, in cases that do not respond to anti-TNF therapy	10 mg/kg (maximum 1,000 mg) administered intravenously at weeks 0, 2, and 4 and every 4 weeks thereafter
Anakinra	IL-1 receptor antagonist	Systemic JIA, cryopyrin-associated periodic syndrome (CAPS)	1–2 mg/kg daily (maximum 100 mg) administered by subcutaneous injection
Rilonacept	IL-1 soluble receptor	Systemic JIA, CAPS	2.2 mg/kg weekly (maximum 160 mg), with a loading dose of 4.4 mg/kg loading dose at week 1, administered by subcutaneous injection
Canakinumab	Humanized anti-IL-1 antibody	Systemic JIA, CAPS	4 mg/kg (maximum 300 mg) administered by subcutaneous injection once monthly
Tocilizumab	Anti-IL-6-receptor antibody	Systemic JIA	If patient <20 kg, 12 mg/kg, administered intravenously every 2 weeks; If patient ≥20 kg, 8 mg/kg, administered intravenously every 2 weeks
Rituximab	Anti-CD20 antibody	Rheumatoid-factor positive polyarthritis JIA, cases that do not respond to anti-TNF therapy	Two doses of 750 mg/m^2 (maximum 1,000 mg) administered intravenously 2 weeks apart

(DMARDs: disease modifying anti-rheumatic drugs; IL: interleukin; JIA: juvenile idiopathic arthritis; TNF: tumor necrosis factor)

Further Reading

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- ☑ Onel KB, Horton DB, Lovell DJ, Shenoi S, Cuello CA, Angeles-Han ST, et al. 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. Arthritis Care Res (Hoboken). 2022;74(4):521-37.
- ☑ Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.
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