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African recommendations for diagnosis and management of systemic juvenile idiopathic arthritis (sJIA) – a PAFLAR initiative

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Abstract

Objectives To develop evidence-based recommendations for diagnosis and treatment of children and adolescents with systemic juvenile idiopathic arthritis (sJIA), taking into consideration the socioeconomic status and availability of medications in African countries.

Methods A steering group composed of five PAFLAR members formulated questions in PICO format (Patient/Population, Intervention, Comparison, Outcome), conducted a systematic literature review, and identified experts in pediatric rheumatology throughout Africa. The Delphi method was used to reach consensus among the experts on the recommendations for diagnosis and treatment of sJIA patients.

Results The online Delphi questionnaire was sent to the 22 experts selected by the steering committee, who were asked to vote for each statement and to provide their suggestions for modifications or rewording. A 100% response rate was obtained. A minimum agreement of 70% among the voting panel was required. A total of 15 recommendations were formulated, 4 regarding diagnosis and 11 regarding treatment. The percentage of agreement with the recommendations ranged from 72.7% to 95%.

Conclusion We present the first African recommendations for diagnosis and management of sJIA. The feedback about the application of these recommendations in pediatric rheumatology centers will serve as the basis for future revisions in the light of African-specific experiences and insights.

Keywords JIA, sJIA, PAFLAR, Recommendations

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The International League of Associations for Rheumatology (ILAR) define JIA as “arthritis of unknown etiology occurring at less than 16 years of age and persisting for ≥6 week [1].

The objectives of the therapeutic management of JIA are to control disease activity and prevent complications of chronic inflammation. In the past two decades, the development and availability of new effective medications, including biological response modifiers, have made it possible to achieve the goal of a clinically inactive disease in a substantial proportion of patients.

The systemic category of JIA (sJIA) is a distinctive disease entity [2]. It has always represented a challenging problem for practitioners who care for children with this disease. Advances in the understanding of disease mechanisms have led to propose the classification sJIA as a complex autoinflammatory disorder, distinct from the other subtypes of JIA. In recent years, there has been an important advance in the treatment of children with sJIA. New treatments targeting disease-specific pro-inflammatory cytokines, namely IL-1 and IL-6, have radically changed the therapeutic approach and improved the medium- and long-term prognosis [3]. However, the

experience with the use of these medications in Africa is still limited, partly due to their lack of availability or unaffordability.

The aim of this work is to develop evidence-based diagnostic and treatment recommendations for children and adolescents with sJIA, by integrating recently published data, including the new strategy of “treat to target”, taking into account the unique environment of Africa. These recommendations aim to outline the current best practices for diagnosing and managing sJIA in pediatric patients, including those with macrophage activation syndrome (MAS). Additionally, it provides a guide for tapering and discontinuing medications in patients who reach inactive disease.

Methods

The recommendations were developed using the GRADE system and following the 2014 update of the standardized operating procedures (SOP) for EULAR-endorsed recommendations [4, 5]. The steps involved in formulating the recommendations are summarized in Fig. 1:

Developing teams

A Task Force of PAFLAR members was gathered on January 1, 2023, with the aim of providing consensus-based

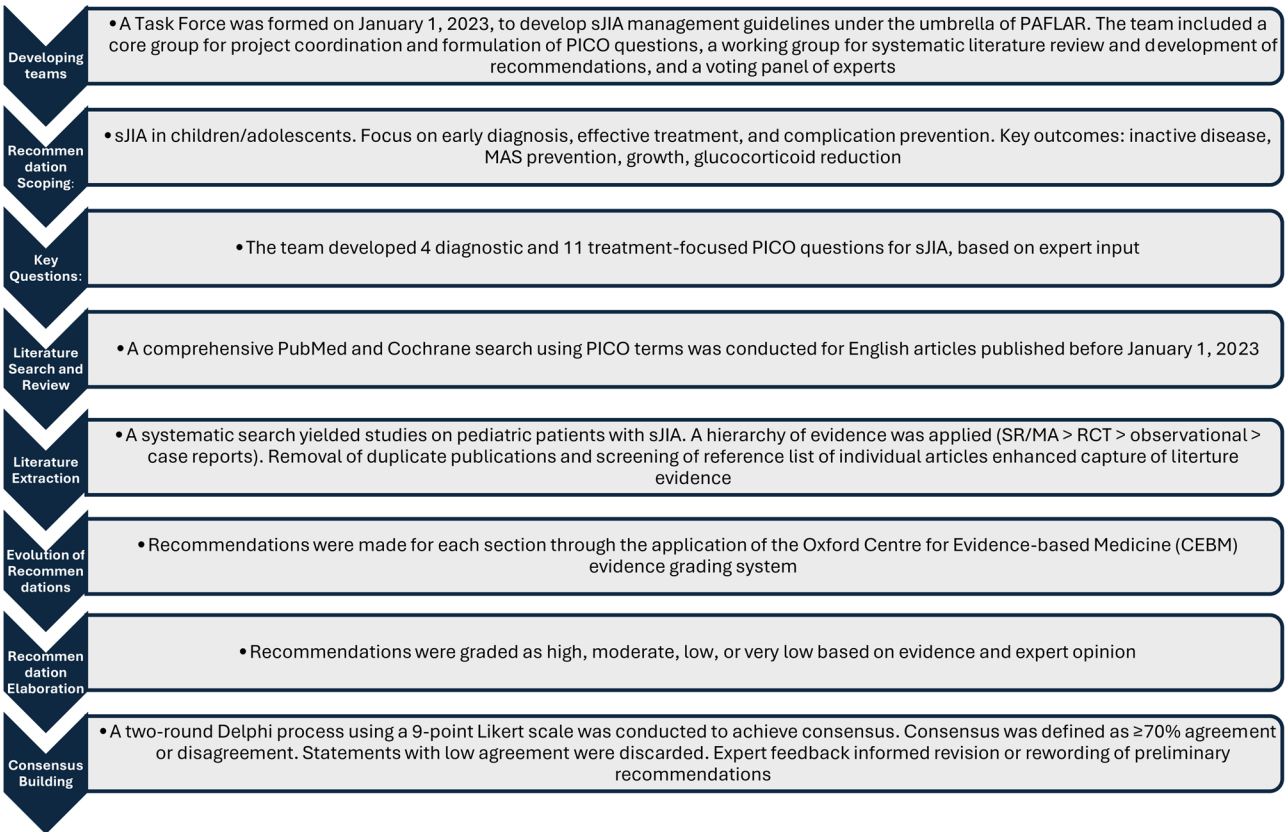


Fig. 1 Recommendations development process

guidance to the management of newly-diagnosed patients with sJIA. The Task Force consisted of the following bodies:

Core team, which assumed a leadership role in project management and coordination. Its members defined the project scope and formulated the Patient/Population, Intervention, Comparison, and Outcomes (PICO) clinical questions. Through discussion, they reached consensus on the key questions to be addressed. The core team was composed of 2 pediatric rheumatologists (convenor and supervisor) and a methodologist.

Working group, composed of 5 pediatric rheumatologists, committed to making the systematic literature review, formulating the preliminary recommendations and rating of the quality of evidence.

Voting Panel: Composed of all members of the two groups above plus a panel of clinical experts involved in voting the recommendations. Collectively, the participating experts provide care for approximately 150 children and adolescents with sJIA across Africa.

Scoping of the recommendations

Scoping is the initial phase of recommendations development, in which the focus and boundaries are defined. It involves identifying the target population, the particular clinical problem, and the desired outcomes. The key components of this step were the following:

a. **Disease**: sJIA

b. **Objective(s)**

- Establish early diagnosis
- Identify treatment modalities for controlling the disease activity and preventing complications (i.e. MAS and interstitial lung disease).

c. **Health/Clinical Question (PICO)**: PICO is a framework that was used to structure clinical questions into four components:

P: Patient (Target Population): Children and Adolescents (Less than 18 years old)

I: Intervention: Diagnosis, Treatment and Prevention of Complications

C: Comparison: What is/are the main alternative(s) to compare with the intervention being considered?

O: Outcomes: Critical outcomes included achievement of inactive disease, avoidance of MAS, resolution of subclinical MAS, prevention of progression to overt MAS, resolution of overt MAS, mortality, response to treatment/inactive disease, growth, ability to taper/discontinue steroids, and prevention of exacerbation of the underlying disease.

Identification of key clinical issues

The following methods were used to search for the evidence that could answer the clinical questions: formulation of questions, structure of questions, literature search, critical evaluation and selection of evidence, presentation of results, and development of recommendations.

- **Formulation of key questions in PICO format**: To leverage the Patient/Population, Intervention, Comparison, and Outcomes (PICO) framework, the scientific committee meticulously gathered the relevant evidence to formulate a comprehensive set of clinical questions. All pharmacological therapeutic procedures and diagnostic approaches were incorporated. They included pharmacological interventions (nonsteroidal anti-inflammatory drugs, NSAIDs, analgesics, glucocorticoids, conventional disease-modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs), intraarticular glucocorticoid injections). Four key questions centered on diagnostic evaluation for patients newly diagnosed with sJIA, and 11 questions aimed to explore various management options were formulated. To ensure that the identified clinical issues were pertinent and addressed the needs of the target population, all questions underwent a rigorous revision process informed by feedback from the entire recommendation development group. The list of PICO questions is provided in the Supplementary Appendix 1.
- **Search and review of the literature**: In adherence to the PICO framework, the PAFLAR sJIA Working Group conducted a systematic literature review to extract pertinent evidence. This search encompassed the entirety of English-language articles indexed within PubMed and Cochrane Libraries, spanning from October 1997 until December 31, 2022. To ensure a focused and rigorous retrieval of the relevant literature, keywords were selected based on various combinations of the predefined PICO elements
- **Literature extraction and preparation of summary tables**: A comprehensive search strategy was adopted to identify relevant articles. Filters were applied to restrict results to human studies with participants between birth and 18 years of age and full abstracts. Publications solely focused on other forms of JIA were excluded. To ensure a methodical approach, the search prioritized the following study types in descending order: systematic reviews/meta-analyses, randomized controlled trials (RCTs), non-randomized/observational studies, and case reports/opinion documents (used only if high-quality RCTs addressing all key elements were unavailable).

An initial screening based on titles and abstracts was conducted.

- Electronic duplicate screening was employed to ensure that the retrieved studies were unique. In addition, a manual search of the reference lists from identified articles was conducted to identify potentially relevant publications not captured by the initial database search. This comprehensive approach aimed to maximize the capture of the pertinent literature that met the pre-defined inclusion criteria
- **Development and wording of recommendations:** following the literature review, preliminary recommendations were created for each section. The Oxford Centre for Evidence-based Medicine (CEBM) approach was used to establish the degree of evidence for each section.

Development of recommendations and article grading: The team defined the strength for each recommendation, based on the combination of literature evidence and expert opinion as high, moderate, low, or very low (A, B, C or D): Every recommendation was categorized according to the level of evidence (Oxford levels of evidence from 1 to 4). An evidence report detailing the retrieved studies was produced (Table 1). A comprehensive bibliography of all included studies, organized by PICO question, was created.

Consensus building

To achieve consensus on recommendation content, a two-round Delphi process was conducted. This structured methodology facilitated the iterative refinement of key aspects. The Delphi technique's strength lies in ensuring equitable consideration of all participant perspectives, making it particularly well-suited for geographically diverse groups. Following the initial round, which identified the core features, the Working Group collaborated with the Core Team to define the elements to be incorporated into the second-round questionnaire.

Rating. Each participant was asked to assess each statement through a five-point Likert scale, with scores ranging from one ("completely disagree") to five ("completely agree"). For analytical purposes, responses were categorized, based on the score obtained, as follows: disagreement [1, 2], uncertainty [3], and agreement [4, 5]. Panelists were given the possibility to abstain from voting on statements deemed outside their domain of expertise. A vote of "uncertainty" signified reservations concerning recommendation accuracy. Submission of comments was actively encouraged for all statements, particularly those receiving a dissenting vote. This procedure facilitated the identification of potential misinterpretations by panelists and empowered the scientific committee to invalidate votes, if necessary

Definition of consensus, a predefined threshold for consensus was established. Consensus on a statement was achieved when at least 70% of participants indicated strong endorsement (4–5). Statements with a mean rating below 3, implying a low level of agreement, were eliminated from further consideration.

External review of the recommendations

Three external reviewers, all renown experts in pediatric rheumatology, reviewed and commented the recommendations, and their feedback, together with that provided by the participants in the Delphi survey, was taken into account in formulating the final set of recommendations.

Results

The members of the expert panel, composed of 22 pediatric rheumatologists with expertise in the clinical management of sJIA were asked to complete the Delphi survey. Based on the results of the survey, a final set of recommendations was developed, which represented the answers to 15 PICO questions (4 regarding diagnosis and 11 regarding management of sJIA) (Table 2). The recommendations outlined are described below.

Recommendations for diagnosis

1. **When to suspect sJIA and when to refer the patient to a pediatric rheumatologist.** Average score 4.05, agreement percentage 86%, agreement level: high
 - Prolonged fever, $>38.5^{\circ}\text{C}$, for more than 2 weeks, daily for at least 3 days, mainly at night (positive diurnal variation of temperature) associated with maculopapular rash, which tends to be associated with fever spikes. Presence of arthralgia or arthritis in at least one joint. If a pediatric rheumatologist is available, referral should be made as soon as possible. If no pediatric rheumatologist is available, the patient should be referred to a pediatrician with knowledge in pediatric rheumatology, an adult rheumatologist or a pediatric immunologist.
2. **How the diagnosis of systemic JIA should be confirmed?.** Average score 3.77, agreement percentage 81%, agreement level: moderate

(The diagnosis of sJIA) relies on a combination of clinical features and supportive laboratory findings).

Table 1 PICO questions and statements

Questions	statements	LOE	GOR	Source
Questions regarding diagnosis:				
1. a. When to suspect sJIA ?	Prolonged fever, >38.5, for more than 2 weeks, daily for at least 3 days, mainly at night (positive diurnal variation) associated with maculopapular rash which appears with fever. Presence of arthralgia or arthritis at least in one joint.	3	C	[6]
b. When to refer the patient to a pediatric rheumatologist?	• If pediatric rheumatologist is available: Referral once suspected. • If no pediatric rheumatology available refer to general pediatrician with knowledge in pediatric rheumatology, pediatric immunologist, preferably adult rheumatologist.		Expert opinion	
2. How to confirm diagnosis of systemic JIA?	i. High ESR, CRP, Serum ferritin, WBC, PLT, Neutrophils count, S100 if available. ii. Musculoskeletal ultrasound is an important tool to sensitively detect arthritis. • Presence of high inflammatory markers is essential for diagnosis at disease onset.	4	D	[7]
3. What are the Features to consider other diagnosis?	Excluding other diagnosis is essential before considering diagnosis treatment of sJIA. • Hematological malignancies (leukemia, lymphoma, neuroblastoma): Considered if severe joint pain, night pain, bone pain, petechiae, ecchymosis, low to normal platelet count while high ESR, high LDH compared to ferritin. CBC, blood film, BMA, bone marrow biopsy, Ultrasound abdomen, CXR, MRI abdomen should be done. Lymph node biopsy should be done when appropriate. • Infections considered important differential diagnosis for sJIA Fever has no diurnal variation, Persistent rash of any type, History of contact and travel of endemic area. 1. Exclude tuberculosis (TT, QuantiFERON test, HRCT). 2. Malaria (thick blood film) 3. TORCH/Viral screen 4. Brucella/Typhoid serology. 5. Lyme disease • Hereditary autoinflammatory syndromes are rare but important other diagnosis for sJIA: Suspected if disease occur in a very young age, positive family history, No diurnal variation of fever Consider serum amyloid, proceed to genetic testing if available, use PRINTO criteria to help diagnosis and treatment. • Juvenile Systemic Lupus Erythematosus (JSLE), other connective tissue diseases (CTDs), and primary childhood vasculitides • Measurement of specific autoantibodies (RF, ANA, ENA, ANCA, HLAB27) • Urine microscopy, protein: creatinine ratio, MRA, Skin biopsy, other tissue biopsy if needed	4,3,4	D,C,D	[7–9]

Table 1 (continued)

Questions	statements	LOE	GOR	Source
4. A. How to diagnose MAS?	• Daily continuous high grade fever with or without hepatosplenomegaly, Encephalopathy, bleeding tendency, • Lab: - pancytopenia - Hyperferritinemia - High liver enzyme - Dropping ESR/Platelets & WBC count - High D Dimer • BMA: - Typical increased cellularity; increased megakaryocyte counts and the presence of hemophagocytes - if this is normal it does not exclude MAS Change over time in labs parameters is more valuable than absolute number	4,4,1	D,D,A	[10–12]
5. B. how to diagnose pulmonary involvement in sJIA	• Cardiopulmonary symptoms: Dyspnea, shortness of breath, pleurisy. • Ultrasound disclosing pleural irregularities, granularity, thickening, and B-lines, • chest X-ray and HRCT showing pleural thickening, septal thickening, and ground-glass opacities. • pulmonary function tests revealing restrictive lung disease • Echocardiography detecting increased pulmonary artery pressure and signs of right ventricular dysfunction	3,3,4,4	C,C,C,D	[13–16]
Questions regarding treatment:				
1. In children with systemic JIA, what are treatment targets?	• Early treatment goals: - Achieving clinical and laboratory remission during the earlier stages of disease - Prompt recognition and management of MAS and lung involvement - Using the lowest effective dose of glucocorticoids • Late treatment goals - Achieving a full social participation and age-appropriate school attendance. - Complete remission off all therapies.	4	D	[7]
2. In children with systemic JIA, which therapeutic strategy should be adopted as first line management (includes consideration of what is available)?	• Prominent systemic features: - Initial treatment with high dose glucocorticoids (IV pulse therapy or daily oral glucocorticoids with dose reduction subsequently (low resource country) • Low-dose weekly methotrexate (oral or SC) in patients with polyarthritis • NSAIDS may be given in first two weeks when the diagnostic workup is ongoing as adjunctive therapy. • Anakinra can be administered as first-line therapy, especially in patients with prominent systemic features. • Tocilizumab can be used as first-line therapy, especially in patients with predominant arthritis features.	4,4.1A,1A	D,D,A,A	[7, 17, 18, 18, 19]

Table 1 (continued)

Questions	statements	LOE	GOR	Source
3. In children with sJIA what is the 2nd line therapy and third line therapy?	1. 2nd line therapy: • IL-1 blockade may be introduced in patients with predominant systemic features with persistent disease activity or experience a disease flare after 1st line therapy • IL-6 blockade can be introduced in patients with predominant arthritis features who respond inadequately to MTX, with or without low-dose glucocorticoids • In patients at high risk for poor outcome who show an inadequate response to IL-1 blockade as first-line, increase in the dose of anakinra. • Inadequate response to IL-6 blockade as first-line: addition of MTX, with or without low-dose glucocorticoids. 2. 3rd line therapy • In case of inadequate efficacy of IL-1 blockade, switch to IL-6 blockade should be considered. • In case of inadequate efficacy of IL-6 blockade, switch to IL-1 blockade should be considered. Refractory JIA treatment: • Abatacept, JAK inhibitors (tofacitinib) and rituximab can be used in patients with incomplete response to IL-1 and IL-6 inhibitors.	4,2A,1A,1A,3,3,2A,4,2A,3,4,4,2B,1A,3	D,B,A,A,C,C,B,D,B,D,B,C,D,D,B,A,C	[7, 18, 18–33]
4. in children with sJIA what is the role of steroids oral and IAI?	• Systemic high-dose glucocorticoids are effective in the short term in treating sJIA symptoms. • Intra-articular glucocorticoids may be used for treating residual arthritis.	1A,1A,3	A,A,C	[34–36]
5. What is the role of cyclosporine in sJIA?	• Patients without MAS: cyclosporine at therapeutic dose of 3–5 mg/kg/day can be used in frequently relapsing, glucocorticoid-dependent disease in resource-limited settings with no access to biologic DMARDs. • Patients with MAS: cyclosporine at 3–5 mg/kg/day can be effective. • Measurement of blood level is required to monitor toxicity.	1,2A	A,B	[30, 37]
6. in children with sJIA which biologics approved and available	• IL-1 inhibitors (anakinra and canakinumab), and the IL-6 inhibitor tocilizumab are approved.	1A	A	[34]
7. in child with sJIA what is the management of MAS?	• High-dose glucocorticoids (IV or oral) • IL-1/IL-6 inhibitors for resolution of MAS (IL-1 blockade is the preferred approach) • Cyclosporine at the dose of 3–5 mg/kg/day should be considered in resource-limited settings with no access to biologic DMARDs. • Emapalumab and MAS825 (bispecific anti-IL-1β and IL-18 monoclonal antibody) can be used in refractory cases, whenever available	1A,1A	A,A	[19, 32]
8. In a child with sJIA how should pulmonary complications be managed?	- Tofacitinib (JAK inhibitor). - Ruxolitinib (JAK inhibitor). - MAS825 - Mycophenolate mofetil (MMF)	4,3,4	D,C,D	[25, 33, 38, 38]

Table 1 (continued)

Questions	statements	LOE	GOR	Source
9. In children with systemic JIA, how to assess the disease activity and how often?	• Disease activity should be assessed with a validated composite score at every visit, with the preferred tool being the systemic JADAS (sJADAS) • Patients with active systemic features should be admitted to the hospital until resolution. • Monthly visits are if the patient has moderate–high disease activity • Evaluations every 3 to 6 months in patients in clinical remission	3	C	[39]
10. In children with sJIA when can be medication be stopped or withdrawn?	1. Tapering of steroid/discontinuation • In patients with sJIA treated with steroid tapering and discontinuation of glucocorticoids is strongly recommended when the disease is inactive (definition of inactive disease***). 2. In patient treated with biologics monotherapy • B DMARD is conditionally tapered and discontinued after inactive disease achieved • Tapering by decreasing the dose is superior to increase dose interval to prevent disease relapse • Clinically inactive disease should be monitored for 6–12 months • Once the treatment target achieved ongoing monitoring is recommended to ensure maintaining of the target.	1A,3,2A, 1A	A,C,B, A	[19, 40–42]
11. In children with systemic JIA, what non pharmacological management is recommended?	1. Physical and occupational therapy (PT/OT). 2. Nutrition • Healthy, age-appropriate diet is strongly recommended, with consideration for specific nutritional requirements (e.g., fat, calcium) • Use of a specific diet to treat sJIA is strongly recommended against. 3. Immunization • Annual inactivated influenza immunization • Live-attenuated and inactivated vaccines are recommended for children who are not receiving immunosuppressive drugs. • Inactivated vaccines are strongly recommended for children with sJIA who are receiving immunosuppressive drugs. • Children who are taking immunosuppressive drugs should receive the 23-valent pneumococcal polysaccharide vaccine in addition to the 13-valent pneumococcal conjugate vaccine. • Vaccines are strongly recommended for household contacts of children with JIA who are taking immunosuppressive drugs. 4. Imaging: X-ray imaging to assess JIA-associated damage or to rule out alternative diagnoses.	4,2B	D,B	[43, 44]

Table 2 PICO questions**Key questions (diagnosis)**

1. When to suspect sJIA and to refer the patient to a pediatric rheumatologist?
2. How the diagnosis of sJIA should be confirmed?
3. What are the features that should lead to consider alternative diagnoses?
4. How to diagnose MAS and pulmonary involvement in sJIA?

Key questions (management)

In children with sJIA:

1. What are the optimal treatment targets?
2. Which therapeutic strategy should be adopted as first line management (including consideration of which medications are available)?
3. Which are the best second-line and third line therapies. What are the characteristics of high-risk patients who should proceed immediately to second- or third line therapy?
4. What is the role of glucocorticoids (oral and intra-articular)?
5. What is the role of cyclosporine?
6. Which biologic DMARD are approved/available?
7. What is the optimal management of MAS?
8. How should pulmonary complications be managed?
9. How should disease activity be assessed and how often?
10. When can medication be stopped/withdrawn after the achievement of disease remission?
11. What are the non-pharmacological management recommendations?

- Increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum ferritin, white blood cell count (WBC), platelet count (PLT), neutrophils count and S100 (if available) are all relevant for diagnosis.
- Musculoskeletal ultrasound can improve the accuracy of arthritis detection.

3. **What are the features that should lead to consider alternative diagnoses?** Average score 3.77, agreement percentage 81%, agreement level: moderate

(Excluding other diagnosis is essential before starting treatment of sJIA).

- Hematological malignancies (leukemia, lymphoma, neuroblastoma) are main differential diagnoses. They should be considered in case of severe joint pain, night pain, bone pain, and should be excluded before initiating corticosteroid treatment by assessing complete blood count, blood smear, bone marrow aspirate and, whenever needed, bone marrow biopsy and lymph node biopsy. Additional clues are lactate dehydrogenase (LDH) disproportionally high compared with ferritin, normal white blood cell count "WBC" and platelet "PLT" count in the context of high ESR.

- Infections are important differential diagnosis of sJIA in the presence of prolonged fever with absence of diurnal variation, History of contact with affected individuals and travel to endemic areas are useful clues. Recommended investigations are thick blood film (for malaria), tuberculin test "TT", quantiferon test, pulmonary high-resolution computed tomography (HRCT) for tuberculosis, brucella/typhoid serology and viral screening.
- Hereditary autoinflammatory syndromes are rare but important differential diagnosis of sJIA. They should be suspected if the illness occurs at a very young age, there is a positive family history, or fever does not display diurnal variation. Check serum amyloid and proceed to genetic testing, if available.
- In case of prolonged fever, juvenile systemic lupus erythematosus (JSLE), other connective tissue diseases (CTDs), and primary childhood vasculitides should be considered as potential mimics. Search for specific autoantibodies (antinuclear antibodies, ANA, anti-extractable nuclear antigen antibodies, ENA and anti-neutrophil cytoplasmic antibodies, ANCA), Angio MRI (MRA), skin biopsy, and additional tissue biopsies, when clinically indicated, can aid in establishing the diagnosis.

4. **How to diagnose MAS and pulmonary involvement in sJIA?** Average score 4.05, percentage of agreement 90%, level of agreement: high.

How to diagnose MAS:

- Sudden onset of non-remitting high fever with or without altered mental status, together with hepatosplenomegaly, lymphadenopathy, and hemorrhages.
- Hyperferritinemia and profound drop in all three blood cell lines, ESR decrease, and elevated serum liver enzymes, triglycerides and lactic dehydrogenase, and abnormal coagulation profile.
- Presence of macrophage hemophagocytosis in in the bone marrow aspirate may confirm MAS, but its absence does not exclude the diagnosis.

How to diagnose pulmonary involvement:

- Pulmonary involvement is suspected in patients presenting with dyspnea, shortness of breath, pleurisy, and radiographic evidence of interstitial lung disease (ILD). The features of chronic lung involvement, such as clubbing and pulmonary

artery hypertension (PAH) are often observed late in patients with ILD, usually one to two years after onset.

- Diagnostic tools include chest X-ray and HRCT showing pleural thickening, septal thickening, and ground-glass opacities, pulmonary function tests revealing restrictive lung disease, ultrasound disclosing pleural irregularities, granularity, thickening, and B-lines, and echocardiography detecting increased pulmonary artery pressure and signs of right ventricular dysfunction. Lung biopsy may be needed to confirm the diagnosis through the demonstration of pulmonary alveolar proteinosis or other typical histopathologic changes.

Recommendations for management

1. **In children with sJIA, what are the optimal treatment targets?** Average score 4, percentage of agreement 90%, level of agreement: high

The following treatment targets should be pursued in children with sJIA:

Early treatment goals:

- Achieving clinical and laboratory remission during the earlier stages of disease
- Prompt recognition and management of MAS and lung involvement
- Using the lowest effective dose of glucocorticoids

Late treatment goals

- Achieving a full social participation and age-appropriate school attendance.
- Complete remission off all therapies.

2. **In children with sJIA, which therapeutic strategy should be adopted as first-line management (taking into consideration the available medications)?** Average score 3.41, percentage of agreement 77.3%, level of agreement: moderate

1st line therapy

- In patient with prominent systemic features initial treatment should include high-dose glucocorticoids (IV MP pulse therapy or daily oral glucocorticoids at 1–2 mg/kg/day, with subsequent gradual dose reduction.

- Low-dose weekly methotrexate (oral or SC) in patients with polyarthritis
- NSAIDs may be given in first two weeks when the diagnostic workup is ongoing as adjunctive therapy.
- Anakinra can be administered as first-line therapy, especially in patients with prominent systemic features (see below).
- Tocilizumab can be used as first-line therapy, especially in patients with predominant arthritis features (see below).

3. **In children sJIA, what is the best second-line and third-line therapy (are there high-risk patients who should proceed to 2nd line or 3rd line immediately after diagnosis)?** Average score 3.59, Percentage of agreement 72.7%, level of agreement: moderate.

2nd line therapy:

- IL-1 blockade may be introduced in patients with predominant systemic features with persistent disease activity or experience a disease flare after 1st line therapy
- IL-6 blockade can be introduced in patients with predominant arthritis features who respond inadequately to MTX, with or without low-dose glucocorticoids
- In patients at high risk for poor outcome who show an inadequate response to IL-1 blockade as first-line, increase in the dose of anakinra should be considered
- Inadequate response to IL-6 blockade as first-line: addition of MTX, with or without low-dose glucocorticoids, should be considered.

3rd line therapy

- In case of inadequate efficacy of IL-1 blockade, switch to IL-6 blockade should be considered.
- In case of inadequate efficacy of IL-6 blockade, switch to IL-1 blockade should be considered.

For refractory disease:

- Abatacept, JAK inhibitors (tofacitinib) and rituximab can be used in patients with incomplete response to IL-1 and IL-6 inhibitors

Patients at high risk for poor outcome are those who possess the following features:

- severe systemic manifestations (e.g. serositis)
 - severe polyarthritis with hip or cervical spine involvement
 - Patients with impending MAS
4. **In children with systemic JIA, what is the role of glucocorticoids (oral and intra-articular)?**
Average score 3.68, percentage of agreement 77.3%, level of agreement: moderate
- Systemic high-dose glucocorticoids are effective in the short term in treating sJIA symptoms, but long-term use can be associated with severe toxicity.
 - Intra-articular glucocorticoids may be used for treating residual arthritis.
5. **In children with systemic JIA, what is the role of glucocorticoids (oral and intra-articular)?**
Average score 3.68, percentage of agreement 77.3%, level of agreement: moderate
- Patients without MAS: cyclosporine at therapeutic dose of 3–5 mg/kg/day can be used (although with limited evidence) in frequently relapsing, glucocorticoid-dependent disease in resource-limited settings with no access to biologic DMARDs.
 - Patients with MAS: cyclosporine at 3–5 mg/kg/day can be effective. Measurement of blood level is required to monitor toxicity.
6. **In children with sJIA, which of the biologic DMARDs approved for JIA are available in African countries?**
- Average score 4.5, agreement percentage 95%, agreement level: high
- IL-1 inhibitors (anakinra and canakinumab), and the IL-6 inhibitor tocilizumab are approved, but not uniformly available
7. **In children with sJIA, what is the optimal management of MAS?**
- Average score 4.27, Percentage of agreement 90%, level of agreement: high
- High-dose glucocorticoids (IV or oral) are recommended as part of initial treatment of sJIA
- IL-1/IL-6 inhibitors are conditionally recommended over calcineurin inhibitors for resolution of MAS (IL-1 blockade is the preferred approach)
 - Cyclosporine at the dose of 3–5 mg/kg/day should be considered in resource-limited settings with no access to biologic DMARDs.
 - Emapalumab and MAS825 (bispecific anti-IL-1 β and IL-18 monoclonal antibody) can be used in refractory cases, whenever available
8. **In children with sJIA, how should pulmonary complications be managed?** Average score 3.64, percentage of agreement 81.8%, level of agreement: moderate.
- Tofacitinib (JAK inhibitor).
 - Ruxolitinib (JAK inhibitor).
 - MAS825
 - Mycophenolate mofetil (MMF)
- Despite some treatment options being available, the efficacy of these therapies remains uncertain and should be evaluated carefully based on each patient's response.
9. **In children with sJIA, how disease activity should be measured, and how often?** Average score 4.14, agreement percentage 95%, agreement level: high
- Disease activity should be assessed with a validated composite score at every visit, with the preferred tool being the systemic JADAS (sJADAS) (Figure 2 and 3)
 - Patients with active systemic features (e.g. serositis, fever) should be admitted to the hospital until resolution.
 - Monthly visits are advised if the patient has moderate–high disease activity
 - Evaluations every 3 to 6 months are recommended in patients in clinical remission
10. **In children with sJIA, when can medications be stopped?** Average score 4.05, percentage of agreement 86.4%, level of agreement: high
- Glucocorticoid therapy should be gradually tapered, starting two months after its initiation and over period of 6 to 12 months. Discontinuation of glucocorticoids is recommended once the disease is in remission.

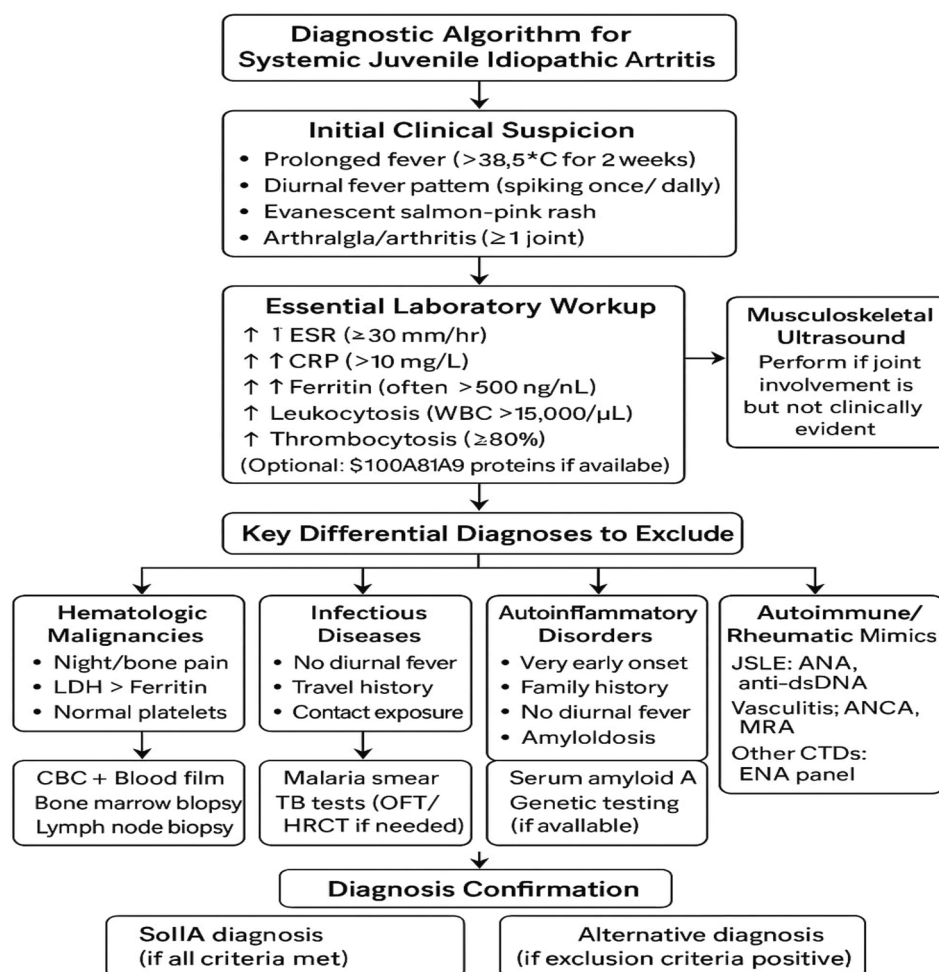


Fig. 2 Suggested scheme for evaluating suspected sJIA

- In patient treated with biologic DMARD monotherapy the medication should be conditionally tapered 1 to 2 years after achievement of inactive disease.)

11. In children with sJIA, what non-pharmacological treatment is recommended? Average score 4.14, percentage of agreement 86.4%, level of agreement: high

1. Physical and occupational therapy (PT/OT). PT and OT are conditionally recommended, regardless of concomitant pharmacologic therapy, to maintain or improve joint range of motion (particularly in case of contractures), increase muscle strength, reverse functional deficits, improve endurance, prevent injury, and promote improved participation in activities of daily living (ADL), family routines and occupations.
2. Nutrition

- Healthy, age-appropriate diet is strongly recommended, with consideration for specific nutritional requirements (e.g., fat, calcium)
 - Use of a specific diet to treat sJIA is strongly recommended against.
 - Some overly restrictive diets (e.g., gluten-free, dairy-free) may result in nutritional deficits and cause the risk of other harms (e.g., delay in treatment, cost, inconvenience).
 - Monitoring medication toxicity: The lab tests to be done to monitor drug toxicity and treatment effectiveness are CBC, liver and kidney function tests, ESR, CRP and ferritin.
3. Immunization:
- Annual inactivated influenza immunization is strongly recommended for all children with sJIA.
 - Inoculation of live-attenuated and inactivated vaccines are recommended for children who are not receiving immunosuppressive drugs.

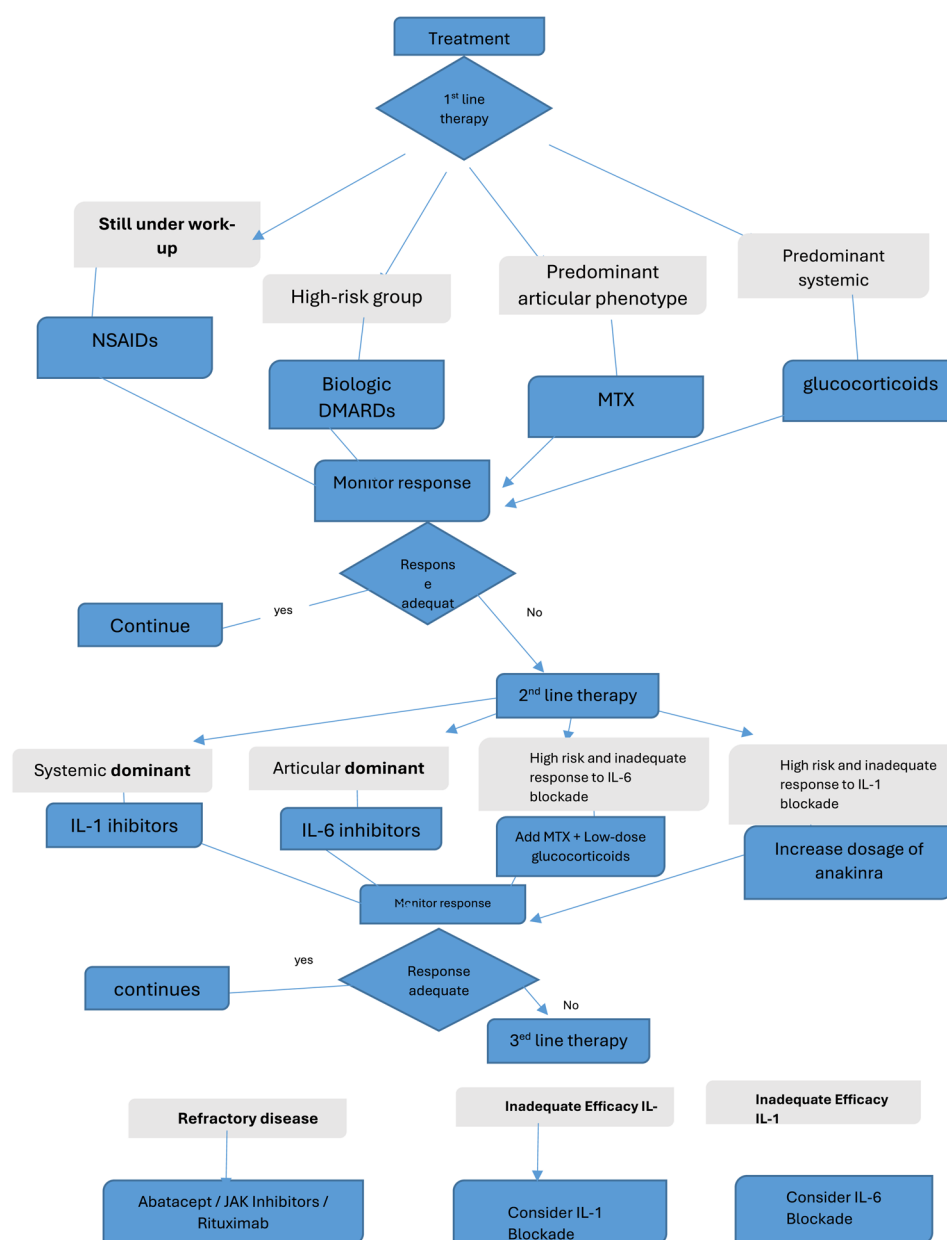


Fig. 3 Proposed scheme for treating sJIA

- Inactivated vaccines are strongly recommended for children with sJIA who are receiving immunosuppressive drugs.
- Children who are taking immunosuppressive drugs should receive the 23-valent pneumococcal polysaccharide vaccine in addition to the 13-valent pneumococcal conjugate vaccine.
- Vaccines are strongly recommended for household contacts of children with JIA who are taking immunosuppressive drugs.

4. Imaging

- X-ray imaging should be restricted to the assessment of JIA-associated damage or to rule out alternative diagnoses.

Magnetic resonance imaging (MRI) and musculoskeletal ultrasound are superior X-rays to monitor joint disease activity.

Discussion

The development of the first African recommendations for the diagnosis and management of sJIA, under the umbrella of PAFLAR, marks a pivotal advancement in pediatric rheumatology across the continent. These

recommendations were established through a rigorous, evidence-based methodology and by incorporating expert consensus, while accounting for the specific socioeconomic and healthcare challenges that exist in many African countries. The recommendations achieved over 70% agreement among pediatric rheumatologists in the Delphi survey, which ensures that they were thought to be clinically relevant and feasible.

A key strength of these recommendations lies in their emphasis on early diagnosis and timely referral, which represent critical steps in preventing severe complications, such as MAS and irreversible joint damage, especially in regions where access to specialist care is limited. The recommendations also stress the importance of differentiating sJIA from common mimics, like infections (e.g., malaria, tuberculosis) and hematologic malignancies, which are quite prevalent in Africa. In light of limited access to advanced diagnostics, the recommendations favor cost-effective and practical tools, such as MSK US, when available, alongside essential laboratory tests, like CBC, ESR, CRP, and ferritin.

Treatment recommendations reflect the realities of resource-constrained environments through a tiered, pragmatic approach. High-dose glucocorticoids are endorsed as first-line therapy due to their widespread availability, with a strong emphasis on early tapering to minimize adverse effects. Methotrexate is advised for patients with predominantly articular disease, while biologic DMARDs, especially IL-1 and IL-6 inhibitors, are conditionally recommended for high-risk patients, acknowledging the challenges in their accessibility. The inclusion of cyclosporine as a therapeutic option for MAS and refractory disease further highlights the practical considerations taken into account.

The recommendations also address pulmonary complications—an emerging and serious manifestation of sJIA. While the evidence is still evolving, the conditional recommendation about JAK inhibitors and other immunomodulatory agents provides a starting point for managing this complex organ involvement.

Access to biologic therapies remains highly variable across African countries. Published cost data are limited and often not comparable across healthcare systems. Nevertheless, treatment cost, lack of reimbursement, and inconsistent drug availability remain major barriers to optimal care and may delay achievement of treatment targets in children with sJIA.

Beyond documenting these access-related challenges, there is an urgent need for future prospective, multi-center studies designed to evaluate the quantifiable impact of limited treatment availability on long-term disease outcomes in African children with sJIA. Specifically, research should focus on how restricted access to biologic and targeted synthetic DMARDs influences key

endpoints such as rates of sustained clinical remission, time to flare, cumulative glucocorticoid exposure, and the development of chronic joint damage. Furthermore, prospective data are critically needed to assess the association between delayed or suboptimal treatment and the incidence, severity, and mortality of MAS and sJIA-associated lung disease. Such studies should also incorporate health economic analyses to identify the most cost-effective strategies for improving outcomes within resource-limited settings. Generating this evidence will not only inform future updates of these PAFLAR recommendations but also provide a compelling rationale for advocacy efforts aimed at improving medication access, reimbursement policies, and supply chain reliability across the continent.

Thalidomide has been reported as a potential option in selected refractory cases of sJIA in limited observational studies. However, due to the very low level of evidence and concerns regarding toxicity, the expert panel did not consider it a routine therapeutic recommendation. The recommendations underscore the role of non-pharmacological interventions, such as physical therapy, adequate nutrition, and routine immunizations, thereby promoting a comprehensive, holistic model of care aimed to improve long-term outcomes. While the African recommendations are aligned with international standards regarding core diagnostic criteria and treatment goals (such as achieving remission and preventing long-term damage), they distinguish themselves by addressing the specific limitations faced in African healthcare settings. These include limited drug availability and socioeconomic disparities, for which alternative treatment pathways are thoughtfully proposed. Furthermore, the recommendations highlight the importance of cultural sensitivity in delivering pediatric care in diverse African communities.

By integrating up-to-date, evidence-based practices with regional expertise, these recommendations represent a significant contribution to the global understanding and management of sJIA. They offer practical, relevant, and scalable recommendations tailored to the African context. Continued updates and revisions will be essential to ensure their ongoing relevance and their adaptation to the evolving landscape of sJIA care.

Conclusion

This PAFLAR initiative presents the first African recommendations for the diagnosis and management of sJIA. Although aligned with international standards, it addresses Africa-specific challenges, emphasizing early diagnosis, timely referral, and individualized treatment to improve outcomes. These guidelines aim to support consistent, effective care across the continent and serve as a foundation for future updates, incorporating local

experience and emerging evidence to advance sJIA management in Africa.

Abbreviations

PAFLAR	Pediatric Society of African League Against Rheumatism
sJIA	Systemic onset juvenile idiopathic arthritis
PICO	Patient/Population, Intervention, Comparison, Outcome
JIA	Juvenile Idiopathic Arthritis
ILAR	International League of Rheumatology Associations
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
RCTs	Randomized controlled trials
MAS	Macrophage activation syndrome
NSAIDs	Nonsteroidal anti-inflammatory drugs
cDMARDS	Conventional disease modifying agents
bDMARDS	Biologic disease modifying agents
ESR	Erythrocyte sedimentation rate
CRP	C reactive protein
WBC	White blood cell count
PLT	Platelet count

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Author Contribution

S H : sJIA Subcommittee Coordinator Manuscript Coordination drafting and editing. Reco drafting and Parts writing Intro Method results Corresponding author. A M : Reco drafting and Parts writing Intro Method. A R, P P Q, W H, M H A, W H, D M, A F, T T L, E P, H L F, A S, H L, C M D, Y M, Y T, Y H F, W M, A S, S I N, Q G M N, C S, D H : Expert Panel. H E, E A A Reco drafting. S S Steering committee methodologist. Da H : Project coordinator Steering committee coordinator.

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Data availability

All data supporting the findings of this study are included within the article and its supplementary materials. Additional information can be made available upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this guideline development as it did not involve primary data collection from human participants. Where applicable, the guideline development process adhered to established standards for ethical conduct in research and consensus development.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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