

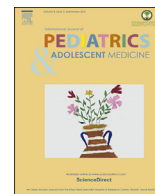
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Clinical practice guidelines

## Consensus clinical approach for a newly diagnosed systemic juvenile idiopathic arthritis among members of the pediatric rheumatology Arab group

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## ABSTRACT

**Background:** Systemic juvenile idiopathic arthritis (sJIA) is a diagnosis of exclusion. The complex nature and clinical variety of the disease, as well as the vast clinical variation of disease presentation, may lead to difficulties in disease detection and subsequent delays in treatment.**Aim:** To provide a consensus guidance on the management of newly diagnosed sJIA patients among pediatric rheumatologists in Arab countries.**Methods:** This work was conducted in two phases. The first phase utilized an electronic survey sent through an email invitation to all pediatric rheumatologists in Arab countries. In the second phase, a Task Force of ten expert pediatric rheumatologists from Arab countries met through a series of virtual meetings. Results obtained in phase one were prioritized using a nominal group and Delphi-like techniques in phase two.**Results:** Seven overarching principles and a set of recommendations were approved by the Task Force to form the final consensus.**Conclusion:** This is the first consensus on a clinical approach for pediatric rheumatic diseases among Arab pediatric rheumatologists. It is presented as a guidance on the clinical approach to sJIA that requires further evidence, and future updates are anticipated.© 2021 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood chronic arthritis of unknown etiology. It encompasses a phenotypically heterogeneous group of several disease subtypes that share

similar inflammatory articular changes. About 10%–20% of patients with JIA have systemic JIA (sJIA) subtype. It is a rare and serious distinctive category characterized by arthritis and non-specific systemic inflammation manifested by a quotidian fever, rash, diffuse lymphadenopathy, hepatosplenomegaly, and serositis [1–3]. sJIA is

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a diagnosis of exclusion; thus, adequate investigations are often necessary to exclude serious mimics such as infections, autoinflammatory diseases, or even malignancies [4]. The spectrum of the clinical presentation of sJIA is quite broad. Typically, patients have arthritis and systemic manifestations; however, occasionally, patients may present with recurrent episodes of fever and rash and arthritis appears later on [2]. The most serious association of sJIA is the macrophage activation syndrome (MAS) [4,5]. Patients with sJIA might experience a variable disease course. Prognostic markers have been suggested; accordingly, patients may have monocyclic disease course with good outcome, recurrent attacks of relapse and remission, or persistent active disease with a high risk of disability and severe complications [6–9]. The complex nature and clinical variety of the disease as well as the vast clinical variation of disease presentation may lead to difficulties in disease detection and subsequent delays in treatment. This is aggravated by the lack of standardized clinical guidelines and the variation in the management of such cases worldwide. Our study aims to provide a consensus clinical approach and guidance on the management of newly diagnosed patients with sJIA among members of the Arab Pediatric Rheumatology Group (PRAG), which is a newly formed group of pediatric rheumatologists in Arab countries under the umbrella of Arab League Against Rheumatism. The general methods of the research in the PRAG have been previously described [10].

## 2. Methods

### 2.1. Evidence review

A Task Force was organized on June 1, 2020, to provide consensus guidance on the management of newly diagnosed patients with sJIA among PRAG members. The Task Force leadership group (HMK and SMM) gathered evidence through systematic literature review to address questions within the assigned clinical domains (diagnostic/classification criteria, differential diagnosis and investigations, and treatment and monitoring/assessment). A systematic literature search was conducted, comprising all English articles from 1980 onward in the Cochrane, EMBASE, and MEDLINE databases. MEDLINE was searched through Pubmed by applying the following medical subject heading terms (MeSH terms): (sJIA OR (juvenile AND systemic AND arthritis) OR (juvenile AND rheumatoid AND arthritis)) AND (treatment OR management OR approach). Articles that describe only different arthritis subtypes were excluded. Relevant evidence was collated and utilized to generate questions categorized into two parts: 1) explored diagnostic evaluation for a patient with new onset sJIA, and 2) explored management options for patients with sJIA. Additionally, we gathered demographic features such as gender, age, and country of practice of all participants. Other information such as practice settings and age limit of patients observed were requested as well. This work was conducted in two phases:

### 2.2. Phase I

Following the evidence review, an invitation through email was sent to all pediatric rheumatologists in Arab countries, members of the Saudi Society for Rheumatology, and PRAG encompassing pediatric rheumatologists from Saudi Arabia, Jordan, Oman, Kuwait, United Arab Emirates, Egypt, Libya, Bahrain, Qatar, and Morocco. A total of 77 pediatric rheumatologists were identified and asked for their participation by completing an online survey (through [SurveyMonkey.com](https://www.surveymonkey.com)) on June 6, 2020, and a reminder e-mail was sent on June 30, 2020. Anonymity was ensured as no identifying information was collected. Consent was obtained from all participants.

The survey was in English (the common language of medical practice in most Arab countries). The survey comprised five main

sections: demographics, sJIA initial diagnosis and diagnostic evaluation, treatment approach, and medications used. Questions were both open- and close-ended. Response to the survey was received from 49 pediatric rheumatologists distributed over eight Arab countries (64% response rate). This phase aimed to explore the clinical approach of Arab pediatric rheumatologists in managing newly diagnosed patients with sJIA. Results obtained were used to formulate the clinical scenarios for phase II of the study.

### 2.3. Phase II

An iterative process that utilizes a Delphi-like and nominal group technique were used in this phase of study [11,12]. Based on the initial survey from phase I, the Task Force leader (SMM) generated eight clinical scenarios surrounding sJIA. These scenarios included pertinent history, relevant physical examination findings, and essential laboratory data. Subsequent questions were both open- and close-ended and were used to determine the various diagnostic and treatment approaches. Through webinar, the Task Force included ten pediatric rheumatologists from six Arab countries with experience to manage children with sJIA carried out two rounds of a consensus process. The Task Force agreed that votes of a minimum of eight out of the ten group members ( $\geq 80\%$ ) were required to reach a consensus. Statements that did not reach consensus agreement from round one was presented and discussed at round two. All panelists were available for the first round; one panelist was unavailable for the second round, and an observer from the first round replace her.

## 3. Results

The literature review revealed lack of standardized clinical guidelines for diagnosing and managing newly diagnosed sJIA. Results from phase I were reviewed and discussed. Individual guidance statements were also discussed and voted anonymously. Statements with a low consensus ( $<80\%$ ) were reviewed. The Task Force members were encouraged to comment on all the items presented in the initial voting process. The process resulted in a favorable vote by the majority in seven overarching principles and a set of recommendations. [Table 1](#) shows the overarching principles together with the percentage of agreement. One statement “systemic glucocorticoids should not be used before the diagnosis is confirmed” received a less favorable voting rate (78%). A detailed discussion follows:

### 3.1. Overarching principles

1. All children with suspected sJIA should be referred to a pediatric rheumatologist.

sJIA is a distinctive subset of JIA, characterized by an autoinflammatory phenotype. Its nonspecific onset and resemblance to some infectious, malignant, and autoinflammatory diseases can be discomfiting. Given the nature of sJIA presentation and current recommended treatments, the Task Force members highly recommend that all patients with a suspected diagnosis of sJIA be referred to a pediatric rheumatologist for assessment and management. It was also underlined that the management of sJIA requires the involvement of a multidisciplinary team that should include, besides pediatric rheumatologists, hematologists, and physiotherapists.

2. The classification of sJIA should be based on validated classification criteria.

JIA, and subsequently its sJIA subset, is currently a diagnosis of exclusion as no specific clinical diagnostic tests are available thus far. The Task Force members recommend that patients be classified

**Table 1**  
Overarching principles to manage systemic juvenile idiopathic arthritis.

Overarching principle	Agreement (%)
1 All children with suspected sJIA should be referred to a pediatric rheumatologist.	100%
2 The classification of sJIA should be based on validated classification criteria.	89%
3 The goals of treating sJIA is to control disease activity and prevent disease-related damage while keeping treatment-related side-effects at a minimum.	100%
4 Treatment should be adjusted until the target is achieved.	100%
5 Long-term use of systemic glucocorticoids to maintain treatment target should be avoided.	100%
6 Disease activity should be assessed using a validated composite disease activity score.	100%
7 The classification of sJIA-associated MAS should be based on validated criteria.	100%

sJIA = systemic juvenile idiopathic arthritis and MAS = Macrophage Activation Syndrome.

based on the 1995 consensus driven ILAR criteria [1]. Alternatively, patients can be classified based on the more recent classification suggested by the PRINTO international consensus [2]. These are, however, preliminary criteria that require further validation.

3. The goals of treating sJIA are to control disease activity and prevent disease-related damage while keeping treatment-related side-effects at a minimum.

The treatment option should be tailored in accordance with presented clinical manifestations. This principle emphasizes the importance of early suppression of inflammation, and optimization of function, growth and quality of life, and prevention of medication-related toxicity.

It was widely agreed upon that the advent of biological disease-modifying anti-rheumatic drugs (bDMARDs) in the past decades has made the goal of achieving minimal disease activity and even disease remission as achievable goals. Few randomized controlled trials were published with regard to sJIA treatment [13–17]. Recommendations from the American College of Rheumatology (ACR) were published in 2011 with an update in 2013 [18,19]. Updated recommendations from the ACR are expected to be published early this year.

4. Treatment should be adjusted until the target is achieved.

This principle highlights the need for frequent medication adjustment to have a firm control of the disease, which is more important than the particular medication used. Recently, a consensus on a set of endorsements to define a treat-to-target strategy for JIA was published [20,21]. The Task Force members were in full agreement to recommend following a treat-to-target approach.

5. Long-term use of systemic glucocorticoids to maintain treatment target should be avoided.

High doses of glucocorticoids are needed mostly early in the disease course, mainly to control disease-related life-threatening complications and subsequently, at a lower dose until the selected DMARD controls disease activity. Numerous side effects of long-term glucocorticoids use in children have been documented [22]. The Task Force members were in full agreement to avoid the long-term use of systemic glucocorticoids to maintain the long-term treatment target.

6. Disease activity should be assessed using a validated composite disease activity score.

Regular assessment and measurement of the disease activity level are essential in monitoring the disease course over time, assessing therapeutic measures, and employing treat to target strategies [20]. The systemic Juvenile Arthritis Disease Activity Score

(sJADAS) is a validated instrument that has shown good measurement properties [23]. There was a debate among Task Force members with regard to the frequency of assessments of newly diagnosed patients with sJIA. The Task Force members agreed that the patients need to be closely monitored and assessed particularly during the initial period of their illness. Further assessment decisions are left to the discretion of the treating physician considering the patient's condition and the response to treatment.

7. The classification of sJIA-associated macrophage activation syndrome (MAS) should be based on validated criteria.

MAS is a potentially lethal complication of sJIA. It occurs because of a devastating inflammatory response resulting from an overproduction of proinflammatory cytokines, with a mortality rate of around 8% [24,25]. sJIA-associated MAS encompasses heterogeneous clinical, laboratory, and histopathological features. The Task Force members emphasized the importance of keeping a high index of suspicion when suspecting MAS, particularly in the setting of devastating clinical features in the presence of inappropriate laboratory results. Members were in full agreement to recommend classifying patients with sJIA with MAS by applying the 2016 classification criteria proposed by the European League Against Rheumatism/American College of Rheumatology/Pediatric Rheumatology International Trials Organization collaborative initiative. More recent classification criteria have been proposed to better capture MAS in routine clinical settings [26,27].

### 3.2. Recommendations

#### 3.2.1. Investigations

To date, there are no pathognomonic laboratory investigations that aid to ascertain the diagnosis of sJIA. Nonspecific laboratory findings include leukemoid reaction with neutrophilic leukocytosis, anemia, thrombocytosis, and elevated inflammatory markers [28]. Serum ferritin levels can be significantly elevated [29]. Autoantibodies do not help diagnose sJIA: antinuclear autoantibodies are positive in only 4%–6% of diagnosed patients with sJIA [30,31]. More commonly than pleuritis, serositis with pericarditis can occur silently and can only be detected with a chest x-ray (CXR) and echocardiography. Thus, the Task Force members recommend that serum ferritin levels, CXR, and echocardiography are requested for all patients with suspected sJIA.

A set of investigations should be requested before the initiation of bDMARDs. The Task Force members recommend that hepatitis B and C serology, varicella zoster virus serology, and tuberculosis screening as per the local guidelines be requested.

#### 3.2.2. Bone marrow aspirate and biopsy

Because of the importance of the diagnostic yield of a bone marrow aspirate and biopsy, the Task Force agreed that it warrants a separate mention. Systemic symptoms and musculoskeletal complaint can occur in children with hematological malignancies

that mimicks sjJA [32,33]. The Task Force members recommend that bone marrow aspirate and biopsy should be performed for all patients, when sjJA is suspected prior to the initiation of immunosuppressive therapy specifically systemic glucocorticoids.

### 3.2.3. Treatment and follow-up

A treatment plan should be discussed with the patients and caregivers. The rationale to select a particular medication and treatment goals should be communicated clearly. The Task Force felt that patients and caregivers must be informed that prescribed medications might be changed over time based on the disease response. They should also be made aware that there is no fixed treatment course; however, treatment should be continued to achieve the treatment goals.

Therapeutic options, particularly bDMARDs, were discussed extensively, with slight variations in management noticed among the Task Force that reflects local medication unavailability or financial constrictions. Other factors such as patient preference and cost have a role to choose treatment recommendations. The Task Force members agreed that patients should be followed biweekly, at least in the initial period of their illness. The frequency of further assessment is left to the discretion of the physician who treats based on the response to treatment. A recent consensus has recommended weekly assessment for those with active systemic features [20]. The Task Force recommended that patients and caregivers be made aware that the course is highly variable and unpredictable. Approximately 50% of the patients with sjJA recover and achieve complete remission, often after a monophasic disease course, while other patients have a drug-dependent course with recurrent episodes of systemic features and progressive arthritis.

## 4. Discussion

sjJA is extremely variable in its severity and disease course, which makes it distinct from other JIA subtypes. It has a strong association with MAS, which accounts for significant morbidity and mortality in patients with sjJA. sjJA remains a clinical diagnosis; there are no specific laboratory tests for diagnosis. All these make early diagnosis and treatment a challenge and require expertise in this field. In the last decade, there have been advances in clinical and laboratory assessment and treatment of patients with sjJA [13,34–36]. Several plans of treatment recommendations have been developed for sjJA. The ACR established treatment plans that have been adopted by most centers worldwide and have served and united the pediatric rheumatology community well [18,19]. Also, a consensus treatment plan based on the providers' usual clinical practice within The North American Childhood Arthritis and Rheumatology Research Association (CARRA) was developed [37]. More recently, the German Society for Pediatric Rheumatology developed practice and consensus-based statements to manage new onset sjJA [38,39]. These guidance plans are important and probably more applicable to North America and European countries.

There are no available data from countries in the Middle East and North Africa about consensus-based treatment plans for pediatric rheumatic diseases to the best of our knowledge. Lack of data about pediatric rheumatologists' practice to manage newly diagnosed patients with sjJA in Arab countries was the motivation to define and develop consensus-based guidance focus on the management of newly diagnosed patients with sjJA. Unfortunately, the precise prevalence of JIA, which includes sjJA is unknown in Arab countries [40]. Currently, PRAG countries represent a large geographic area, which include Saudi Arabia, Jordan, Oman, Kuwait, United Arab Emirates, Egypt, Libya, Bahrain, Qatar, and Morocco. Most of the population depends on the government-funded health service. Nevertheless, the

health care systems vary among Arab countries due to financial, administrative, and organizational obstacles that may delay timely care access. It is worth mentioning that the number of pediatric rheumatologists is very limited in PRAG countries. Thus, because of the paucity of pediatric rheumatologists in Arab countries, other medical specialists such as general pediatricians and adult rheumatologists manage pediatric patients with sjJA.

In this work, the consensus-based guidance was conducted in two phases. The process was initiated by an online survey followed by the two-round consensus virtual meetings. The generated statements are aimed at pediatric rheumatologists and other health care providers involved in the care of newly diagnosed patients with sjJA; however, the Task Force raised the importance of easy accessibility to pediatric rheumatology clinics.

Ideally, treatment plans should be based on evidence. However, several aspects of the management of newly diagnosed patients with sjJA, such as the most appropriate DMARDs as the initial treatment, lack enough evidence. Despite that the Task Force members considered the best available standard of practice. Although there was a full agreement that other diseases should be ruled out prior to initiating treatment, two experts felt that systemic glucocorticoids can be started in special situations, particularly life-threatening conditions or typical clinical and laboratory features assessed by an expert pediatric rheumatologist, even without bone marrow aspirate and biopsy.

The Task Force felt that to recommend certain DMARD (conventional and biological) therapeutic options as the initial treatment is beyond the work's scope. However, all Task Force members emphasized the value of treat-to-target approach, they agreed to consider it and tailored treatment according to the patient's status, treatment modalities, and availability of resources. All Task Force members discouraged using extended courses of glucocorticoids and highlighted drug-related toxicity.

This study has its limitations, and results should be interpreted carefully. In each step of the process, personal judgment is involved. A systemic literature review based on an undefined review that does not ensure objectivity. Results reflect what had been suspected, particularly the variability between centers and health care providers. Therefore, new findings are limited.

In conclusion, sjJA is a distinctive category characterized by arthritis and systemic manifestations, which mimic other disease entities. Because of disease complexity, there is a considerable variation in the management of newly diagnosed patients with sjJA. This study highlights the importance of updating and adopting practical guidance for managing complex pediatric rheumatic diseases such as sjJA across Arab countries. These findings provide a consensus that could be useful in clinical practice and in providing a guidance during decision-making when managing newly diagnosed sjJA. Hopefully, this consensus clinical approach will significantly improve the medical care of patients with sjJA.

### Compliance with ethical standards

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics committee of the Research Affairs Council at KFSH-RC approved the study protocol.

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## Author contributions

All authors were involved in drafting the manuscript or revising it critically for important intellectual content, and all authors approved the final version to be published.

## Declaration of competing interest

All authors declare that they have no competing interests.

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## References

- Petty R, Southwood T, Manners P, Baum J, Glass D, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
- Martini A, Ravelli A, Avcin T, Beresford M, Burgos-Vargas R, Cuttica R, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. *J Rheumatol* 2019;46:190–7.
- Palman J, Shoop-Worrall S, Hyrich K, McDonagh J. Update on the epidemiology, risk factors and disease outcomes of juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2018;32:206–22.
- Lee J, Schneider R. Systemic juvenile idiopathic arthritis. *Pediatr Clin North Am* 2018;65:691–709. <https://doi.org/10.1016/j.pcl.2018.04.005>. PMID: 30031494.
- Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of Macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter Study of 362 Patients. *Arthritis Rheumatol* 2014;66:3160–9.
- Spiegel L, Schneider R, Lang B, Birdi N, Silverman E, Laxer R, et al. Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. *Arthritis Rheum* 2000;43:2402–9.
- Modesto C, Woo P, García-Consuegra J, Merino R, García-Granero M, Aenal C, et al. Systemic onset juvenile chronic arthritis, polyarticular pattern and hip involvement as markers for a bad prognosis. *Clin Exp Rheumatol* 2001;19:211–7.
- Nalbanti P, Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsis P, Farmaki E, Bamidis P, et al. Juvenile idiopathic arthritis in the biologic era: predictors of the disease progression and need for early introduction of biologic treatment. *Rheumatol Int* 2018;38:1241–50. <https://doi.org/10.1007/s00296-018-4062-9>.
- Guzman J, Oen K, Loughin T. Predicting disease severity and remission in juvenile idiopathic arthritis: are we getting closer? *Curr Opin Rheumatol* 2019;31:436–49. <https://doi.org/10.1097/BOR.0000000000000620>. PMID: 31085941.
- Al-Mayouf SM, Almutairi A, Albrawi S, Fathalla B, Alzyoud R, AlEnazi A, et al. Pattern and diagnostic evaluation of systemic autoinflammatory diseases other than familial Mediterranean fever among Arab children: a multicenter study from the Pediatric Rheumatology Arab Group (PRAG). *Rheumatol Int* 2020;40:49–56.
- Sniderman A. Clinical trials, consensus conferences, and clinical practice. *Lancet* 1999;354(9154):327–30. [https://doi.org/10.1016/S0140-6736\(98\)11185-6](https://doi.org/10.1016/S0140-6736(98)11185-6). PMID: 10440326.
- Humphrey-Murto S, Varpio L, Gonsalves C, Wood T. Using consensus group methods such as Delphi and Nominal Group in medical education research. *Med Teach* 2017;39:14–9. <https://doi.org/10.1080/0142159X.2017.1245856>. Epub 2016 Nov 12. PMID: 27841062.
- Quartier P, Allantaz F, Cimaz R, Pillet P, Claude M, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis* 2011;70:747–54.
- Ruperto N, Brunner H, Quartier P, Constantin T, Wulfraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2396–406.
- Lovell D, Giannini E, Reiff AO, Kimura Y, Li S, Hashkes P, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum* 2013;65:2486–96.
- Ilowite N, Prather K, Lohngyina Y, Schanberg L, Elder M, Milojevic D, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014;66:2570–9.
- De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, et al. Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: results from a phase III trial. *Arthritis Rheumatol* 2015;67:840–8.
- Beukelman T, Patkar N, Saag K, Tolleson-Rinehart S, Cron R, DeWitt E, 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;63:465–82.
- Ringold S, Weiss P, Beukelman T, DeWitt E, Ilowite N, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum* 2013;65:2499–512.
- Ravelli A, Consolaro A, Horneff G, Laxer R, Lovell D, Wulfraat N, et al. Treating juvenile idiopathic arthritis to target recommendations of an international Task Force. *Ann Rheum Dis* 2018;77:819–28.
- Klein A, Minden K, Hospach A, Foeldvari I, Weller-Heinemann, Trauzeddel R, et al. Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis. *Ann Rheum Dis* 2020;79:969–74.
- Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of long-course oral corticosteroids in children. *PLoS One* 2017;12(1):e0170259.
- Tibaldi J, Pistorio A, Aldera E, Puzone L, El Mieddany Y, Pal P, et al. Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2020;59:3505–14.
- Grom A, Passo M. Macrophage activation syndrome in systemic juvenile rheumatoid arthritis. *J Pediatr* 1996;129:630–2.
- Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol* 2014;66:3160–9.
- Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. A European League against rheumatism/American College of rheumatology/paediatric rheumatology international trials organization collaborative initiative. *Arthritis Rheumatol* 2016;75:481–9.
- Minoia F, Bovis F, Davi S, Horne A, Fischbach M, Frosch M, et al. Development and initial validation of the MS score for diagnosis of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Ann Rheum Dis* 2019;78:1357–62.
- Behrens E, Beukelman T, Gallo L, Gallo L, Spangler J, Rosenkranz M, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASO-JAR). *J Rheumatol* 2008;35:343–8.
- Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev* 2007;6:457–63.
- Ozdogan H, Kasapçopur O, Dede H, Arisoy N, Beceren T, Yurdakul S, et al. Juvenile chronic arthritis in a Turkish population. *Clin Exp Rheumatol* 1991;9:431–5.
- Karadağ Ş, Sönmez H, Tanatar A, Çakmak F, Çakan M, Ayaz N. Profile of new referrals to a single pediatric rheumatology center in Turkey. *Rheumatol Int* 2020;40:313–21. <https://doi.org/10.1007/s00296-019-04421-6>.
- Cabral D, Tucker L. Malignancies in children who initially present with rheumatic complaints. *J Pediatr* 1999;134:53–7.
- Tamashiro M, Aikawa N, Campos L, Cristofani L, Odone-Filho V, Silva C. Discrimination of acute lymphoblastic leukemia from systemic-onset juvenile idiopathic arthritis at disease onset. *Clinics (Sao Paulo)* 2011;66:1665–9.
- Nigrovic P, Mannion M, Prince F, Zeff A, Rabinovich C, van Rossum M, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis Rheum* 2011;63:545–55. <https://doi.org/10.1002/art.30128>.
- Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008;371:998–1006. [https://doi.org/10.1016/S0140-6736\(08\)60454-6](https://doi.org/10.1016/S0140-6736(08)60454-6).
- Nishimura K, Hara R, Umebayashi H, Takei S, Iwata N, Imagawa T, et al. Efficacy and safety of canakinumab in systemic juvenile idiopathic arthritis: 48-week results from an open-label phase III study in Japanese patients. *Mod Rheumatol* 2021;31:226–34. <https://doi.org/10.1080/14397595.2020.1783163>.
- DeWitt E, Kimura Y, Beukelman T, Nigrovic P, Onel K, Prahald S, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* 2012;64:1001–10.
- Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, et al. Evidence and consensus based GkJR guidelines for the treatment of juvenile idiopathic arthritis. *Clin Immunol* 2012;142:176–93.
- Hinze C, Holzinger D, Linka E, Hass J, Speth F, Kallinich T, et al. PRO-KIND SJIA project collaborators. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. *Pediatr Rheumatol Online J* 2018;16:7. <https://doi.org/10.1186/s12969-018-0224-2>. 2018 Jan 22.
- Al-Mayouf SM, Hashad S, Khawaja K, Alrasheedi A, Abdwani R, Abushhaiwia A, et al. Cumulative damage in juvenile idiopathic arthritis: a multi-center study from the Pediatric Rheumatology Arab Group (PRAG). *Arthritis Care Res (Hoboken)* 2020. <https://doi.org/10.1002/acr.24436>.