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RESEARCH

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Updated clinical practice treat-to-target guidelines for JIA management: the Egyptian College of Pediatric Rheumatology initiative

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Abstract

Background: These updated guidelines aimed to provide appropriate and convenient guidelines for the treatment of various types of juvenile idiopathic arthritis (JIA).

Using the Delphi technique, this study was conducted to reach expert consensus on a treat-to-target management strategy for JIA. According to the PICO (patient/population, intervention, comparison, and outcomes) approach, the preliminary scientific committee identified a total of 17 key clinical questions. To assemble evidence on the advantages and dangers associated with JIA treatments, an evidence-based, systematic literature review was conducted. Researchers and clinicians with experience in JIA management were identified by the core leadership team. To establish a consensus on the management suggestions for JIA patients, a Delphi approach (2 rounds) was used.

Results: An online survey was applied to the expert panel ($n = 27$), and 26 of them completed both rounds. At the conclusion of round 2, a total of eighteen (18) recommendation items were gathered, which were divided into four sections to address the four key JIA categories. The percentage of those who agreed with the recommendations (ranks 7–9) ranged from 83.2 to 100% (average 86.8%). The phrasing of all 18 clinical standards identified by the scientific committee was agreed upon (i.e. 75% of respondents strongly agreed or agreed). Algorithms have been proposed for the management of JIA polyarthritis, oligoarthritis, and systemic JIA.

Conclusion: A wide and representative panel of experts initiated a consensus about the management of JIA. The created guidelines give a complete approach to the management of JIA for all healthcare professionals involved in its management, as well as a means of monitoring and evaluating these guidelines on a regular basis.

Keywords: Guidelines, JIA, Arthritis, Methotrexate, Biologic therapy, Egypt, Egyptian guidelines JIA, Uveitis

Background

Juvenile idiopathic arthritis (JIA) is one of the most frequent chronic illnesses in children. JIA is predicted to affect one out of every 1000 children [1–3]. JIA is a heterogeneous set of arthritis types characterized by long-term joint inflammation that begins before the age of 16 and lasts longer than 6 weeks [4]. Its aetiology is unknown. The condition can affect one or more joints, and it can also cause additional systemic symptoms like fever or rash, as well as extra-articular inflammatory signs like uveitis.

With recent advancements in therapeutic approaches and the availability of a large number of treatment

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options for JIA, quick commencement of proper medical therapy has become critical in preventing lasting joint and organ damage. Furthermore, these advancements in JIA management have increased the chance of beneficial outcomes for children, such as better illness control. As a result, the treating healthcare practitioner is free to set even higher treatment goals, such as complete remission [5]. As a result, future therapy guidelines may contain an overarching aim of clinical remission or, at the very least, low disease activity [6].

At this time, there is a compelling argument about the impact of early diagnosis and expanded treatment options on standard paediatric rheumatology practice and whether it has made therapeutic medical decision-making more difficult for treating healthcare professionals, caregivers, and patients [7, 8]. Treatment recommendations are created to assist healthcare providers in a variety of ways, including encouraging the adoption of a consistent approach to care delivery, supporting the proper and effective use of available resources, and reducing the risk of inappropriate care [9].

Overall, the most significant potential advantage is an improvement in the patient's quality of treatment and improved health outcomes.

While controlling disease activity is certainly the primary goal, attention should also be paid to the patients' overall health, emotional well-being, and their functional, educational, social, and economic status. In 2018, the first recommendations for JIA in Egypt were released [10]. However, recommendations were made to update the methodology approach to ease the adoption of the treat-to-target (T2T) management strategy and make the decision-making process more transparent. Furthermore, considering that Egypt is a low- and middle-income country (LMIC), there is a significant difficulty in terms of limited resources and disparities in the management of this chronic condition. This was the main motive behind developing guidelines specific for Egyptian children living with JIA. By ensuring the optimum standards of care, all children with JIA would have the right to equitable access to the highest quality of clinical care, based on current evidence and delivered by appropriately resourced and experienced multidisciplinary teams. These standards of care are designed to help and support children and young people with JIA and their families, the treating healthcare professional teams, and the health authorities.

This work was carried out aiming at providing updated evidence-based management guidelines for children and adolescents with JIA in its various forms, adopting treat-to-target approach and incorporating recently published data. Recommendations for the treatment of chronic and acute JIA-associated uveitis were developed concomitantly and are included in these guidelines.

Method

Design

This was a multistep approach that followed the protocol for the "clinical, evidence-based, guidelines" (CEG) initiative (ethical approval code: 34842/8/21) to create an actionable clinical gold standard for treat-to-target management of inflammatory arthritic diseases. The process of developing the updated guidelines for treat-to-target JIA management had evolved through a pathway starting with the conduction of a scientific literature review and the involvement of experts' opinions using a Delphi technique until the development of consensus regarding treatment options and desired outcome throughout the journey of this chronic disease.

The study design and procedures were developed using a qualitative synthesis of scientific evidence and consensus based on clinical experience and current scientific information. The Egyptian College of Pediatric Rheumatology spearheaded the campaign.

Study teams

Core team

Four experts with experience in paediatric rheumatology and one expert in uveitis make up the group. The team was in charge of overseeing and coordinating the project, helping to define the project's scope and initial patient/population, intervention, comparison, and outcomes (PICO) questions and nominating the expert panel and authoring the book.

Literature review team

An experienced literature review consultant is in charge. The team finished the literature search, data abstraction, and evidence quality assessment.

Expert panel

The core leadership team nominated 27 participants. The criteria for their selection included professional knowledge and experience (at least 8 years of experience) in the field of paediatric rheumatology, its management and practice in the Egyptian health system, and active participation in scientific research on paediatric rheumatic diseases.

Scientific literature review

In concordance with the scientific team's previous guidelines [10], it was agreed to set the current guidelines on broad clinical phenotypes rather than ILAR categories. The patient populations addressed in this guideline included (1) polyarticular JIA; these are children with JIA and nonsystemic polyarthritis ($\geq$ 5 joints ever involved), whether rheumatoid factor positive or negative, psoriatic arthritis, and undifferentiated arthritis; (2) oligoarticular

and extended oligoarticular JIA; (3) systemic JIA; and (4) enthesitis/spondylitis-related JIA (Supplement 1).

Inclusion criteria

Systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, and observational studies such as cohort, case-control, and cross-sectional studies were among the articles included.

Exclusion criteria

Editorials, commentaries, conference abstracts, and narrative/personal reviews that were not based on evidence were excluded.

Formulation of PICOs

Using the PICO (population, intervention, comparator, outcome) structure [11], a preliminary scientific committee (5 members) has undertaken the task of identifying the key clinical topics, aiming at (1) defining the research questions and (2) developing criteria for selection of studies to be reviewed by the expert panel in the development of clinical and therapeutic recommendations for the children and adolescents living with JIA. The PICO framework aided in the identification of a precise definition of a group of participants (population), clear reporting of drug exposures (intervention) (Supplement 2) and control group interventions (comparator), and well-defined and clearly specified effect (outcomes) (Supplement 3) of the intervention under consideration. The scientific committee developed this guideline by formulating seventeen PICO research topics (Table 1).

A systematic search including a series of literature searches in the database MEDLINE/PubMed and the Cochrane Library for human studies published in English focusing on JIA management until the present was conducted on 1st January 2021. For each PICO question, the review was undertaken to accumulate evidence for the benefits and harms associated with treatments. All of the studies found were read in their entirety. Papers that were not related to the main theme (e.g. for a sickness or medicine) were not accepted.

Critical appraisal of identified studies

The degree of evidence in each of the included studies was determined using Oxford standards for evidence-based levels of evidence [12]. The levels of evidence that were employed in the analyses are indicated in the table below (Supplement 4). In terms of confidence and study design, evidence levels are a good indicator of quality. The experts' assessment of the clinical conclusions of the studies was combined with the definition of the evidence levels in defining the recommendations.

Consensus process

Two Delphi rounds were carried out to establish consensus regarding the T2T strategy in JIA. Once the main aspects of this strategy were identified, a discussion group has defined the aspects to be included in the questionnaire

Table 1 PICO research questions declared by the core team for development of the guidelines

Number	PICO formulation
RQ 1	Considering T2T, what would be the best initial therapy, most likely to achieve the treatment target, for the 4 clinical phenotypes of JIA?
RQ 2	What is the efficacy and safety of DMARDs?
RQ 3	Which DMARDs would be the first treatment option and what is its dose and route of administration?
RQ 4	What is the efficacy and safety of NSAID?
RQ 5	When NSAIDs should be considered in the management plan?
RQ 6	What would be the subsequent step of treatment in case the disease activity remains moderate/high in spite of DMARDs therapy?
RQ 7	What is the best choice DMARDs standalone or combination of biologic and DMARDs
RQ 8	When steroids therapy should be considered in the management plan and what its dose and route of administration?
RQ 9	What is the best approach for switching between biologic therapies?
RQ 10	What is the best schedule for monitoring disease activity and how frequent?
RQ 11	How treatment tapering or withdrawal can be undertaken?
RQ 12	What should be the treatment targets?
RQ 13	When physical therapy should be considered in the management pathway?
RQ 14	What are the treatment options for refractory polyarticular/oligoarticular JIA?
RQ 15	What are the treatment options for refractory systemic JIA?
RQ 16	What are the treatment options for refractory enthesitis/spondyloarthritis?
RQ 17	What are the treatment options for refractory uveitis?

T2T Treat to target, *DMARDs* Disease-modifying antirheumatic drugs, *JIA* Juvenile idiopathic arthritis, *NSAIDs* Nonsteroidal anti-inflammatory drugs

with the scientific committee. The structured Delphi approach ensures that the opinions of participants are equally considered, and it is particularly conforming to geographically diverse centres as in Egypt. The Delphi process was conducted through online questionnaires.

Delphi process

The Delphi method is an organized way for gathering vital information about a certain issue that is extensively used. It is based on the main assumption that group projections are often more accurate than individual forecasts. The Delphi method's goal is to build consensus forecasts from a group of experts in a structured iterative manner. Its methodology is based on the completion of a series of questionnaires or "rounds" directed at experts.

The Delphi approach is usually divided into the following stages:

(1) A panel of specialists is assembled.
(2) Forecasting jobs and problems are distributed among professionals.
(3) Preliminary projections and arguments are provided by experts. In order to provide input, the core team compiles and summarises them.
(4) Experts receive feedback and utilize it to alter their projections in light of it. This approach can be repeated until an acceptable level of consensus is reached.
(5) The expert forecasts are combined to form the final forecasts. This technique has two significant advantages: participant anonymity and regulated feedback [13–15].

Chronogram of Delphi rounds

The first round took place between 5th and 8th March 2021 (3 days). Aspects on which there was no agreement in the first round were amended in light of the feedback and incorporated in the second round. The second round took place 1 week after the first and lasted 3 days, from March 11 to March 13, 2021.

Voting process

Live online voting was conducted in two rounds, each with a strict time limit. All members of the expert panel were invited to take part and were given advance notice of the start and end times of each round of voting. Anonymous votes were gathered and evaluated, and unique access links were sent out. At the same time as the voting procedure, comments on rephrasing, potential ambiguity, and unidentified overlaps were received for each statement. The statements could only be voted on by members of the expert panel.

Rating

Each statement was scored on a scale of 1 to 9, with 1 representing "total disagreement" and 9 representing "complete agreement". Disagreement, uncertainty, and agreement are represented by the numbers 1–3, 4–6, and 7–9.

If a comment is outside of a member's area of expertise, they should refrain from speaking. As a result, a vote of "uncertainty" shows "dissatisfaction with the recommendation's truthfulness". All statements allow for comments, which are reviewed by the core team after each round of voting. In the second round of voting, members were also urged to submit plausibility comments wherever they voted a disagreement. This will allow the panel to notice a misinterpretation of a statement and invalidate the vote on that remark.

Definition of consensus

Prior to data analysis, a definition of consensus was defined. It was determined that if at least 75% of participants attained agreement (scoring 7–9) or disagreement (score 1–3), consensus would be achieved [16–19]. If a statement received a mean vote of less than 4 or a "poor" degree of agreement, it was retired. In view of the feedback, statements with an uncertainty score of (4–6) were changed. The levels of agreement on each statement of suggestion were considered as "high" if all votes on a statement fell into the agreement bracket following the second round of voting [15, 20, 21].

Ethical aspects

This study was performed in accordance with the Helsinki Declaration. According to national regulations, ethics approval was not required. All participants in the study were required to give verbal informed consent in accordance with Egyptian national ethical committee requirements. In accordance with data protection standards, all participants were separated from the results and kept anonymous.

Results

Literature research and evidence selection

The study selection process revealed that 6843 potentially relevant studies were identified by the search strategy. By reviewing the titles and abstracts, 6597 were ruled out (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). As a result, the comprehensive article review included 246 relevant articles. One-hundred fifty-seven studies were eliminated because the citations did not fit the PICO. In a re-evaluation of the literature, two more studies were discovered. As a result, this research contained 91 studies.

Expert panel characteristics

The Delphi form was sent to expert panel ($n = 27$), of whom 26 (96.3%) participated in the two rounds. Respondents were drawn from different governorates and health centres across Egypt: Cairo University (25.9%), Ain Shams University (15.4%), Tanta University (7.4%), Benha University (3.7%), Alexandria University (7.4%), Suez Canal University (7.4%), Zagazig University (7.4%), Minia University (3.7%), Mansoura University (3.7%), Fayoum University (3.7%), Assiut University (3.7%), Menoufia University (3.7%), and Sohag University (3.7%).

Delphi round 1

The response rate for round 1 was 100% (27/27). The consensus was reached on the inclusion of clinical standards on 82.6% of the items (i.e. $\geq$ 75% of respondents strongly agreed or agreed). There were comments raised regarding the wording of some of the recommendations. Comments (excluding minor editing suggestions) were more frequent for general principles, polyarthritis section especially usage of corticosteroids, cDMARDs, and biologics. Diversity of opinion was greatest for the item "using sulfasalazine in some cases of polyarticular JIA". Three statements were retired, one on the use of anti-TNFs as initial therapy in polyarticular JIA and 2 statements for similarities to other statements. Following round 1, the following statements were added: 7, 3, 4, 1, and 7 statements in polyarticular, oligoarticular, enthesitis/spondylitis-related JIA, systemic JIA, and uveitis sections, respectively. Several statements were revised after round 1, most edited statements were in polyarticular JIA section (7 statements), only one statement was edited in uveitis section, and 4 statements were edited in each other sections (oligoarticular, enthesitis/spondylitis-related JIA and systemic JIA).

Delphi round 2

The response rate for round 2 was 96.3% (26/27). The percentage of high-rank recommendations (ranks 7–9) ranged from 83.2 to 100%. One statement was removed because it was too similar to another. On all of the clinical standards, there was agreement (i.e. 75% of respondents strongly agreed or agreed). Table 2 also shows the level of evidence assigned to each statement, in accordance with the Oxford Centre for Evidence-Based Medicine (CEBM) criteria as well as mean ± standard deviation and level of agreement. Agreement was unanimous (> 80% agreement) for the wording of the statements.

Recommendations for the initial and subsequent treatment of children and adolescents with JIA

At the end of round 2, a total of eighteen (18) recommendation items were gathered, which were divided into four sections to address the four key JIA categories. A breakdown is presented in Table 2.

Application of the primary recommendations to clinical practice guidelines

Figure 1 shows a summary of primary recommendations for the initial and follow-up therapy of children with juvenile idiopathic arthritis (JIA) and active polyarthritis (1), whereas Fig. 2 shows the management pathway (algorithm) for oligoarthritis JIA, and Fig. 3 shows a suggested treat-to-target approach for systemic JIA. Figure 4 is the treat-to-target management algorithm for systemic JIA, whereas Fig. 5 is the treatment algorithm for chronic anterior uveitis associated with juvenile idiopathic arthritis.

Discussion

Juvenile idiopathic arthritis (JIA for short) is an umbrella term for arthritis of an unknown cause in children under the age of 16. JIA not only causes joint pain, swelling, and stiffness in one or more joints but also decreased health-related quality of life and risk of permanent joint damage. Furthermore, the condition can last well into adulthood, resulting in severe morbidity and poor quality of life [16, 17, 22]. For most individuals with JIA, recent therapy advancements have made remission a realistic goal. JIA has also been the subject of a lot of recent research, with a greater understanding of the underlying biology and more treatments available [5, 18]; hence, it was important to update the treatment guidelines to implement treat-to-target approach into standard practice and accommodate new lines of management.

This guideline defined patient populations based on their clinical phenotypes rather than ILAR categories. This decision was taken in view of the data reporting that the current JIA categories may not accurately reflect the underlying biology and anticipated treatment responses in patients with juvenile arthritis. Similar approach was adopted in the 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis [19]. This also aligns with the ongoing effort to standardise as many criteria as feasible for disorders that affect both children and adults, whether for use in clinical trials, research, or in regular clinical practice [23–27].

This guideline was developed based on a structured PICO process. This is in agreement with recent publications that provide recommendations for JIA treatment [4, 19]. The PICO framework is intended to assist researchers in formulating relevant and precise questions that can be answered in a systematic review structure, as well as to improve the specificity and conceptual clarity of

Table 2 Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
1	**I — General principles**	A- Paediatric rheumatologists and rheumatologists with experience in paediatric rheumatology are the specialists who should primarily care for patients with JIA	I	8.32 ± 1.78	96	H
		B- There should be a good cooperation between rheumatologists and paediatric rheumatologists during transition of JIA cases. Adolescence transition clinic, implementing the appropriate transition care programme based on the available facilities, should be established with at least one adult rheumatologist and one paediatric rheumatologist at each centre	I	8.32 ± 1.78	96	H
		C- Baseline assessment of disease activity using JADAS 27 is recommended	I	8.32 ± 1.78	96	H
		D- When feasible, ultrasound can be used by healthcare professionals for more accurate evaluation of inflamed joints, monitoring disease activity, and guiding treatment decisions in JIA patients	II	8.32 ± 1.78	96	H
		E- Assessment of limited joint mobility and functional ability/health-related quality of life (HRQoL) is recommended	I	8.32 ± 1.78	96	H
		F- All patients should be screened for pre-DMARDs and pre-biologics laboratory, vaccination status, and radiological screening	I	8.32 ± 1.78	96	H
		G- In children and adolescents with JIA, particularly those with active polyarthritis, poor prognostic factors are defined as the presence of one or more of the following: positive rheumatoid factor, positive anticyclic citrullinated peptide antibodies, anti-nuclear antibody (ANA), involvement of high-risk joints (e.g. cervical spine, hip, and wrist), high disease activity, and/or for those judged by their physician to be at high risk of disabling joint damage (limited mobility, loss of cartilage thickness, erosion, loss of joint space)	I	8.32 ± 1.78	96	H
		H- The major therapeutic target, which should be determined on a shared decision with parents/patients, with the overriding goal to achieve clinical and/or imaging (MRI) and/or ultrasound remission, was defined as remission, with the alternative target of low disease activity should be incorporated in all JIA patients' treatment protocols	I	8.32 ± 1.78	96	H
		I- Consider early aggressive therapy particularly in polyarticular JIA with one or more poor prognostic factors or in moderate to severe disease activity status or in the presence of associated uveitis	I	8.32 ± 1.78	96	H
		J- Consider JDAS27 in measuring JIA disease activity; the cutoffs of disease activity states are as follows: - A joint with inactive disease: JDAS-27, ≤ 1 - Low disease activity: JDAS-27, ≤ 3.8 (polyarthritis) and ≤ 2 (oligoarthritis) - Moderate disease activity: JDAS-27, 3.9–8.5 (polyarthritis) and 2.1-4.2 (oligoarthritis) - High disease activity: > 8.5 (polyarthritis) and > 4.2 (oligoarthritis) - Changes in the JADAS-27 corresponding to clinically important difference were −5.5 for improvement and +1.7 for worsening	I	8.32 ± 1.78	96	H
		K- For patients with systemic JIA, JDAS can be used to assess disease activity, whereas juvenile spondyloarthritis disease activity (JSpADA) index can be used for patients with juvenile spondylarthritis	I	8.32 ± 1.78	96	H
		L- Personalize non-pharmacologic interventions to optimize supportive care in JIA patients who at risk of functional limitations, (by using physical therapy and/or occupational therapy and/or surgical intervention)	I	8.32 ± 1.78	96	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement considering children and adolescents with polyarticular JIA						
	1- Nonsteroidal anti-inflammatory drugs (NSAIDs)	• NSAIDs are the adjunctive therapy in all JIA categories. Naproxen and ibuprofen are effective and can be used safely in JIA patients. Considering safe choices in children and age of approval, diclofenac can be used as an alternative rational NSAIDs (evidence I). Meloxicam (evidence level II). Selective COX inhibitors, such as celecoxib (evidence I) for children and adolescents with JIA, and etoricoxib (evidence I) for children over 12 years old, might be used as alternatives if the former drugs are contraindicated or intolerable • When using a nonselective COX form, a gastroprotective is better to be used • NSAIDS can be used in the early state of the disease, particularly in cases with severe pain, until results of the investigations are available and cDMARDs therapy is commenced	I/II	8.08 ± 2.24	92	H
	2- Corticosteroids	**a. Intra-articular corticosteroids** • Intra-articular glucocorticoids are used as the first line of therapy for oligoarticular JIA and as adjuvant therapy in other JIA categories (evidence II) • Triamcinolone hexacetonide is the drug of choice in large joints injections, and methylprednisolone acetate is an alternative (evidence I) **b. Systemic corticosteroids** • Systemic corticosteroids may be used as bridging therapy with short course (< 3 months) of oral glucocorticoids (initial: 0.5–1 mg/kg/day once daily [maximum daily dose: 60 mg/day) with rapid tapering) during initiation or escalation of therapy in patients with high or moderate disease activity to control severe active polyarthritis refractory to other therapies. It also can be used as bridging therapy in the setting of limited mobility and/or significant symptoms (evidence III) • Bridging therapy with a very short course (mini pulse steroid, adjusted to the child's body weight) such as 100-mg daily dose of methylprednisolone for a maximum of 3 days can be used for resistant active polyarticular JIA • Bridging therapy with a limited course of oral glucocorticoids (< 3 months) is not advised in patients with low disease activity • In all JIA categories, the lowest possible dose of corticosteroids (0.1–0.2 mg prednisone/kg/day or equivalent) should be used and for the shortest possible period to avoid the adverse events particularly on growth and bone • Chronic low-dose glucocorticoids are not recommended for JIA patients, irrespective of risk factors or disease activity • Intra-articular glucocorticoid injection is considered preferable in patients whose arthritis is hindering their ambulation or interfering with important daily activities and more when prompt disease control is required • Supplementation with calcium and vitamin D is advised to avoid long-lasting side effects of systemic glucocorticoids • It is advisable to continue physical activity and limit carbohydrate and fat intake in children and adolescents on systemic corticosteroid therapy	I/II III III I	8.32 ± 1.34	92	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
			I	8.32 + 1.34		H
			I			
			II			
			II			
	3- Conventional disease-modifying antirheumatic drugs (cDMARDs)	a. Initial DMARD therapy is strongly recommended over NSAID monotherapy b. In patients without risk factors, initial DMARD therapy is recommended over biological therapy c. In some patients with multiple risk factors and involvement of high-risk joints as cervical spine, hip, and wrist, high disease activity, and/or for those judged by their physician to be at high risk of disabling joint damage, biological therapy may be considered as appropriate initial therapy d. Triple cDMARDs is not advised e. Assessment of csDMARDs therapy should be considered at 3 and 6 months from starting csDMARDs therapy	II	8.32 ± 1.22	92	H
		Methotrexate (MTX) a. MTX is recommended as initial DMARD therapy over leflunomide or sulfasalazine b. Initial MTX monotherapy is advised over combined cDMARDs therapy c. The usual dose of MTX is 10–15 mg/m2/week or 0.3–0.6 mg/kg/week (max 20 mg/week) parenterally (subcutaneously or intramuscularly) or orally d. Intramuscular or subcutaneous MTX injection may be considered is a preferable option than oral MTX e. Patient preferences may guide the choice of route of administration f. In order to prevent adverse events, folic acid for all children in the dose of 1 mg tablets of folic acid daily, for 6 days except on methotrexate day, or 2.5–5 mg of folic acid once a week on the day after MTX administration g. Patients should be reviewed at 1 and 3 months after starting methotrexate therapy. If the patient achieved the treatment target (remission or low disease activity), reassessment should be carried out at 6 months from starting methotrexate therapy h. MTX intolerance is one of common causes of stopping MTX treatment and use alternatives, so discussion and shared decision with patient or parents are very important	I	8.32 ± 1.22	92	H
			I			
		Leflunomide (LEF) Leflunomide could be an alternative option for polyarticular JIA patients unresponsive or intolerant to MTX. The usual dose in children < 40 kg is 10 mg/day, and in those > 40 kg, the dose is 20 mg/day) LEF might be used in combination with MTX in patients with polyarticular JIA refractory to standard doses of MTX, in the absence of poor prognostic factor or when biological therapy is unavailable	II	8.32 ± 1.22	92	H
		Sulfasalazine (SSZ) a. Sulfasalazine may be used in some cases of polyarticular JIA where MTX as well as leflunomide are not effective, intolerable, or contraindicated and, also, if biologic therapy is not available b. Assessment of G6PD and risks of Stevens-Jonson syndrome should be considered before starting SSZ	II	8.32 ± 1.22	92	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
	4- Biologic agents	a. In children and adolescents with JIA and active polyarthritis, biological therapy recommended in these guidelines refers to anti-TNFs, tocilizumab, and abatacept b. TNF inhibitors (etanercept, adalimumab, and golimumab) c. In view of the limited data available regarding infliximab, it can be used as an alternative to other TNF inhibitors if they are not available or contraindicated "in children aged 4 years or above in dose 3 mg/kg" d. Tocilizumab can be used as initial biologic therapy for children and adolescents with JIA in patients with poor prognostic factors and severe active disease e. Assessment of risk of patients and family history, e.g. of demyelinating diseases, is recommended before treatment initiation	I III I	8.76 ± 0.65	96	H
		• Mono biologic versus combined biologic and cDMARD therapy a. In children and adolescents with JIA and polyarthritis (whose disease continues to run moderate/severe activity course) in spite of 6 months cDMARDs with appropriate adherence to therapy, initiating treatment with biologics in combination with cDMARDs is recommended over biologics monotherapy (particularly with adalimumab and infliximab) b. It is advisable that biological therapy is combined with MTX	II	8.76 ± 0.65	96	H
		• In children and adolescents with JIA and active polyarthritis, initiation of treatment with TNF-α inhibitors (etanercept, adalimumab, golimumab, and infliximab) is indicated in polyarticular JIA patients who failed cDMARDs for 6 months, one of which must be MTX in recommended doses for at least 3 months, unless contraindicated, or toxicity/intolerance occurs • Before 2 years of age, safety and efficacy of TNFi are not established • The paediatric dose of etanercept is 0.8 mg/kg s weekly not exceed 50 mg/week • The paediatric dose of adalimumab is 20 mg s/2 weeks if less than 30 kg weight and 40 mg s/2 weeks if exceed 30 kg body weight • The paediatric dose of golimumab is 30 mg/m^2 s every 4 weeks not exceed 50 mg/4 weeks • Tocilizumab is considered as an alternative initial therapy or switch therapy in patients intolerable or contraindicated to anti-TNFs • Abatacept may be indicated in polyarticular JIA patients, older than 6 years old refractory to treatment with MTX and anti-TNF agents	I	8.76 ± 0.65	96	H
		• Switching between treatments is as follows: a. In children and adolescents with JIA and active polyarthritis with moderate/high disease activity after receiving first anti-TNF therapy (with or without cDMARDs) for at least 6 months, switching to a non-TNFi biologic (tocilizumab or abatacept) is recommended over switching to a second anti-TNF b. A second TNFi may be appropriate for patients with good initial response to their first TNFi (i.e. secondary failure) c. Using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is conditionally recommended over rituximab	II	8.76 ± 0.65	96	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
	5- Treatment withdrawal or tapering	The decision regarding which medication to stop first is individualized depending upon response to the medication, tolerance of the administration regimen, and other patient factors Starting treatment tapering may be considered in patients with the following: - Persistent inactive disease (for > 6 months) - Inactive disease is defined by the criterion of Wallace - No joints with active arthritis - No active uveitis (defined as "grade 0 cells", indicating < 1 cell in field sizes of 1 mm by a 1-mm slit beam) - Erythrocyte sedimentation rate (ESR) ≤ 20 mm or C-reactive protein (CRP) level ≤ 10 mg/L (or ≤ 1 mg/dl or ≤ 100 µg/dl) or, if elevated, not attributable to JIA (if both ESR and CRP are available, both of them should be in the normal range) - Physician's global assessment of disease activity score (< 10/100 visual analogue scale) - Duration of morning stiffness ≤ 15 min (within 7 days before the visit) In disease remission, tapering of biologic therapy is by decreasing dosage superior to tapering dosing interval	II	8.81 ± 0.55	96	H
Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement considering children and adolescents with oligoarticular juvenile idiopathic arthritis						
	General principles	1- Oligoarticular juvenile idiopathic arthritis (JIA) is classified as JIA that affects fewer than five joints 2- It is the most frequent subgroup, representing for around half of all JIA cases 3- This subgroup of JIA is further differentiated into persistent oligoarthritis, which has no new joint involvement after the first 6 months of illness, and extended oligoarthritis, which has additional joint involvement after the first 6 months and eventually affects more than four joints 4- About half of all children with oligoarticular disease develop extended oligoarticular disease	I	8.68 ± 0.68	100	H
	Baseline assessment	- Disease activity assessment - Joint limited mobility - Functional ability/quality of life (PROMs) - Poor prognostic markers: if at least one of the following features is present, the patient is considered to have a poor prognosis: ° Hip or cervical spine arthritis ° Ankle or wrist arthritis ° Marked or prolonged elevation of ESR or CRP ° Radiographic evidence of joint damage ° ANA (for association with uveitis) - Blood check for ESR, CRP, ANA, rheumatoid factor, anti-CCP - Baseline pre-DMARDs blood tests	II	8.32 ± 1.46	96	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
	Patients with low disease activity + no risk factors	- NSAID: start to relieve symptoms within 2 weeks - A different NSAID can be tried if no response is seen within the first 2 weeks of therapy - Intra-articular steroid injection(s) - If the patient has responded well to the NSAID therapy, the patient should be reassessed every 3 months and reinject joints if required - The patient should be monitored until a minimum of 6 months of disease inactivity - Inactive disease: JADAS-27, 1 - Low disease activity: JADAS-27, 2 If arthritis persisted in spite of the NSAID therapy/local injection, arthritis extended > 4 joints or > 2 injections/one joint in 12 months, or severe/erosive arthritis in any joint, or persistent inflammatory arthritis recorded on joint ultrasonography, the patient should be treated as moderate/high disease activity category	I	8.32 ± 1.46	96	H
	Moderate/high disease activity (JADAS-27 > 4.2) and/or present > 1 of the poor prognostic features	Initial therapy: methotrexate + intra-articular steroids The usual dose of MTX is 10–15 mg/m2/week (max 20 mg/week) orally or parenterally (subcutaneously or intramuscularly) (evidence level I, recommendation grade A) Adjunct NSAID can be used if required Reassess after 3 months of therapy If low disease activity: adjust methotrexate dose If after 3 months of methotrexate therapy, disease activity remained in the moderate-high status (JADAS-27 > 4.2) Leflunomide might be used in combination with MTX (or instead of MTX when MTX intolerance occurred) in patients with oligoarticular JIA refractory to standard doses of MTX, in the absence of poor prognostic factor, or when biological therapy is unavailable + intra-articular steroids Adjunct NSAID can be used if required Reassess disease activity after 3 months If after 3 months the disease activity remained in the moderate/high status (JADAS-27 > 4.2) or persisted inflammatory arthritis documented by joint ultrasonography - Add biologic as follows: • TNFi • Tocilizumab • Abatacept (older than 6 years old) • The presence of uveitis is an important aspect while choosing the treatment. including type of biologic - Assess disease activity at 3 and 6 months 6 months after biologic therapy, assess disease activity, if as follows: Disease activity: in remission 1. Continue current medication 2. Monitoring DMARDs/biologic therapy Disease activity: low; escalate therapy -1. Intra-articular steroid injection(s) -2. Increase DMARD or biologic dose or change biologic Disease activity: moderate/high -Primary TNF failure: tocilizumab, or abatacept -Secondary TNFi failure: another TNFi, followed by tocilizumab or abatacept In children and adolescents with oligoarticular JIA who have or are at risk of functional limitations, it is recommended to use physical therapy	I	8.32 + 1.46	100	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
			III			
			I			
			II			
			I			
			III			
	Treatment withdrawal or tapering	The decision regarding which medication to stop first is individualized depending upon response to the medication, tolerance of the administration regimen, sustained remission, comorbidities, and other patient factors ° Starting treatment tapering may be considered in patients with the following: - Persistence of inactive disease (for a period > 12 months) - MSUS should confirm remission before tapering treatment - Inactive disease is defined by the criterion of Wallace No joints with active arthritis, No active uveitis (defined as "grade 0 cells", indicating < 1 cell in field sizes of 1 mm by a 1-mm slit beam) Erythrocyte sedimentation rate (ESR) ≤ 20 mm or C-reactive protein (CRP) level ≤ 10 mg/L (or ≤ 1 mg/dl or ≤ 100 µg/dl) or, if elevated, not attributable to JIA (if both ESR and CRP are available, both of them should be in the normal range) Physician's global assessment of disease activity score (< 10/100 visual analogue scale) Duration of morning stiffness ≤ 15 min (within 7 days before the visit) - Strategy of tapering that starts to tapper corticosteroids then biological DMARDs and finally with sustained remission conventional DMARDs In disease remission, tapering of biologic therapy is by decreasing dosage superior to tapering dosing interval	III	8.56 ± 0.98	100	H
Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement considering enthesitis/spondylitis-related JIA						

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
	Enthesitis	• Ultrasonography is recommended as a method of choice in diagnosis and activity assessment of enthesitis • NSAIDs are the first-line drugs in all enthesitis. Diclofenac, naproxen, ibuprofen, and indomethacin are effective and can be used safely in JIA patients (evidence I). Meloxicam (evidence II) and celecoxib (evidence I) and etoricoxib (evidence I) for children over 12 years old might be used as alternatives if the former drugs are contraindicated • In case of a limited number of the affected entheses along with low-moderate disease activity, local glucocorticoid injection for management of enthesitis can be used as a first-line treatment • In children and adolescents with JIA and active enthesitis despite treatment with NSAIDs, local glucocorticoid injections and using a TNFi are conditionally recommended over methotrexate or sulfasalazine • In children and adolescents with JIA and chronic active enthesitis despite treatment with NSAIDs, and local glucocorticoids injections particularly those with high disease activity, limited mobility, and/or significant symptoms, bridging therapy with a limited course of oral glucocorticoids (< 3 months) during initiation or escalation of therapy is advised • Sulfasalazine is recommended in enthesitis-related arthritis • In children and adolescents with JIA and enthesitis who have or are at risk for functional limitations, using physiotherapy is recommended	I/II II	8.68 ± 0.73	100	H
	Sacroiliitis	• X-ray/MRI sacroiliac joints can be used to assess sacroiliitis, with MRI sacroiliac joints is recommended as the method of choice in the diagnosis and assessment of early as well as established sacroiliitis • In children and adolescents with JIA and active sacroiliitis, treatment with an NSAID is strongly recommended over no treatment with an NSAID • If the decision of using NSAIDs is made, they should be given at a full dose and continuously (not on demand). No combinations should be made. In case of using nonselective COX inhibitor, gastroprotective should be used. If contraindicated or intolerable, switching to selective COX-II inhibitors is recommended. Assessment of the treatment response should be done after 4 weeks of NSAIDs initiation. If no response, another NSAID from another family may be used with application of the previously mentioned roles. If no response after 4 weeks, switching to anti-TNF therapy is recommended • In children and adolescents with active sacroiliitis despite NSAIDs, adding a TNFi is strongly recommended over continued NSAID monotherapy • In children and adolescents with active sacroiliitis despite NSAIDs, using sulfasalazine for patients who have contraindications to TNFi or have failed more than one TNFi can be an option • Non-TNFi biologics (e.g. interleukin-17 [IL-17] inhibitors) have not been included in these guidelines as there are no published paediatric studies • In children and adolescents with active sacroiliitis despite NSAIDs, it is not recommended to use methotrexate monotherapy Steroids: • In children and adolescents with active sacroiliitis despite treatment with NSAIDs, intra-articular glucocorticoid injection of the sacroiliac joints as adjunct therapy may be useful • In children and adolescents with sacroiliitis who have or are at risk for functional limitations, using physiotherapy is advised	II	8.6 ± 0.98	96	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement considering systemic onset JIA						
	General considerations	• The manifestations of systemic inflammation (i.e. elevated C-reactive protein, erythrocyte sedimentation rate, leukocytes, and/or ferritin) are essential for diagnosing SJIA at disease onset • Many conditions should be ruled out before diagnosis of SJIA as malignancies, infections, and other autoinflammatory disorders • When malignancy is suspected, bone marrow aspiration should be done before initiating a glucocorticoid therapy • When there is insufficient response to corticosteroids, interleukin-1, or interleukin-6 blockade, the diagnosis of SJIA should be revised • Macrophage activation syndrome (MAS) should be considered in patients with clinical or laboratory deterioration especially if associated with dropped ESR • Assessment of disease activity should be carried out using sJADAS • Treat to target should be considered achieving a clinically inactive disease (resolution of fever and improvement of sJADAS score and CRP by at least 50%) • The only approved DMARD for treating SJIA is methotrexate		8.84 ± 0.61	100	H
	Statements	**Mild-to-moderate acute disease** • Mild-to-moderate acute disease means non-disabling symptoms (fever, rash, mild-moderate arthritis) without evidence of MAS • Initial therapy with nonsteroidal anti-inflammatory drug (NSAID) as monotherapy should last no more than 1 or 2 weeks. (evidence level I, recommendation grade B) • In patients who resist NSAIDs or develop significant symptoms despite use of NSAIDs (such as continued high fevers, rash, arthritis, serositis organomegaly, and lymphadenopathy) should be managed as with moderate-to-severe disease	I	8.88 + 0.32	100	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
		Moderate-to-severe disease • Moderate-to-severe disease: patients with initial symptoms include serious systemic manifestations as serositis, moderate-to-severe polyarthritis, high fevers with a poor response to NSAIDs, or early MAS • High dose of systemic corticosteroids (either i.v pulse and/or as daily corticosteroids with subsequent dose reduction) is an effective and proven treatment for SJIA • Using the minimum dose and duration of systemic corticosteroids therapy whenever possible is recommended to minimize their side effects (as possible as you can keep the dose below 0.5 mg/kg per day of prednisone (or its equivalent), with the duration of therapy should not exceed 6 months) • Intravenous pulse corticosteroids (30 mg/kg/d for 1–3 days) could be used to reduce the toxicity associated with daily oral glucocorticoids or to treat pericarditis severe anaemia or MAS • Intraarticular corticosteroids may be used in treatment of arthritis in patients with SJIA • Using biologics may be more effective if used early in the disease course, rather than as "rescue" therapy when other therapies have failed • Starting one of the biologic drugs as interleukin (IL)-1 inhibitor or IL-6 inhibitor, such as anakinra, canakinumab, or tocilizumab, is recommended for patients with predominant systemic features. Methotrexate can be added as a first-line option besides steroids in patients with predominant arthritis • Anakinra is the first biologic of choice in SJIA due to its rapid action and short duration that allows dose modification or switching to other biologics in nonresponders or when side effects occurred • If biologics are unavailable; start with corticosteroids, and methotrexate may be an option • Methotrexate can be used as a steroid-sparing agent and adjunct to a treatment regimen containing a biologic therapy if the arthritis is not adequately controlled (with dose 0.5 to 1 mg/kg) per week, with a maximum dose of 25 mg per week. Above 15 to 20 mg/m2 (roughly 0.5 mg/kg), oral absorption is unreliable, and parenteral administration may be advantageous) • Starting biologics gives more effect than nonbiologic disease-modifying antirheumatic drugs • In case of inadequate response, i.v pulse corticosteroids therapy may be repeated, or biologics dose increases, or a change of the biologic can be considered • Biological therapy may be applied in combination with corticosteroids and/or methotrexate • IL-1 or IL-6 inhibitors are the most effective biologics in managing both systemic manifestations (e.g. fever, rash, and serositis) and may be effective for chronic arthritis as well • TNF inhibitors and T-cell costimulation blockers (abatacept) are not recommended for initial therapy or systemic disease; these agents, particularly in combination with methotrexate, can be helpful for chronic arthritis management • Other nonbiologic DMARDs, such as cyclosporine and tacrolimus, and cytotoxic drugs, such as cyclophosphamide, are also options in patients who fail standard therapy, including biologic agents	I	8.8 ± 0.49	100	H

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
			II			
			I			
			I			
			I			
			II			
			III			
		• **Patients presenting with severe symptoms or who have suspected early MAS:** should be treated with i.v. pulse corticosteroids in addition to an anti-IL-1 or anti IL-6 (if anti-IL-1 is not available). Concomitant use of a biologic agent may allow relatively rapid tapering of corticosteroids • **Refractory acute disease**: for patients started on a biologic DMARD as part of the initial therapy, add a corticosteroids within a week if there is continued polyarthritis, fever, and rash. A corticosteroids should be added sooner if there was evidence of MAS or severe serositis. IVIG may be used in refractory cases	I	8.8 ± 0.4	100	H
			II			
Breakdown of statements of recommendations, its individual rank by experts opinion, and level of agreement considering management of uveitis						
	General considerations	• Juvenile idiopathic arthritis-associated uveitis often occurs in oligoarticular JIA and enthesitis-related arthritis • Risk factors for the development of JIA-associated uveitis (younger age at the onset of JIA, oligoarticular JIA and enthesitis-related arthritis, ANA-positive, females gender, high ESR at the time of JIA diagnosis) • Early diagnosis is essential in uveitis to prevent serious vision-threatening complications • If uveitis is severe with sight-threatening complications, adalimumab or infliximab (monoclonal antibody TNF inhibitors) are preferred to etanercept as an added option with methotrexate • If active uveitis is refractory to methotrexate and two monoclonal antibody TNF inhibitors, alternative options for nonbiologic DMARDs include leflunomide, mycophenolate, and cyclosporine and for biologic DMARDs include tocilizumab or abatacept • Other biologics that have demonstrated efficacy for arthritis may also serve as rescue options for treatment-refractory uveitis, including IL-6 inhibitors, T-cell costimulation modulators, JAK inhibitors, and CD20 inhibitors • Due to the relatively short duration of acute anterior uveitis episodes in patients currently on systemic therapy for JIA spondyloarthritis, it is recommended that they continue their current regimen and add topical glucocorticoids as a first step • Treatment of uveitis should be carried out in collaboration of the managing paediatric rheumatologist and ophthalmologist, and decision to treat should be a shared rheumatology-ophthalmology decision in management of uveitis associated with JIA • Infection and parasitic infestation should be excluded first particularly before application of steroid therapy	I	8.8 ± 0.63	100	H
			II			
			II			

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
	Control of activity	Bottom line: uveitis associated with JIA is an aggressive vision-threatening disease. It is in the best interest of the affected child that the treating team should have zero tolerance to uveitis activity of any grade We use the following stepladder approach: If a certain step is inadequate, we add and not replace 1) Topical steroids - Prednisolone achieves a higher intraocular bioavailability than dexamethasone - An aggressive hourly application regimen is needed - If activity is controlled (no cells in anterior chamber), slow and cautious tapering is started, accompanied by frequent meticulous examinations for any recurrence of activity 2) Oral NSAID • A variety can be used, but the one with the longest track record is naproxen 3) Immunomodulatory therapy (IMT) • A variety can be used, but the one with the longest efficacy and safety track record is methotrexate • Methotrexate therapy is commenced in the dose of 10–15 mg/m2/week. Dose to be adjusted to, as required and as tolerated, to achieve the goal of treatment. In general, uveitis associated with JIA requires higher doses of methotrexate to attain and to maintain a remission than arthritis associated with JIA, so in many cases, the dose is titrated according to the ocular activity rather than the joint inflammation activity • Dose increments are made at 6–8 weekly intervals • Methotrexate is maintained for a minimum of 2 years after the above-mentioned goal is achieved: "Freedom of ALL recurrences of ALL forms of intraocular inflammation at ALL times of the day (due to the diurnal variation observed in the activity of uveitis) off ALL steroids (by any route including the topical route)" • As the bioavailability of methotrexate after oral administration is variable, subcutaneous administration is the preferable route of administration • Careful monitoring for the complications of methotrexate, both clinically and by lab tests, is mandatory • In particular, in view of the higher doses of methotrexate used to control uveitis, CBC and liver enzymes are requested monthly, and the symptoms of interstitial pneumonitis such as dry cough are periodically reviewed with the child and his parents • Folic acid supplement is administered 4) Adalimumab (currently, it is the only FDA-approved medication for use in noninfectious uveitis) • Adalimumab every 2 weeks dose in children: (< 30 kg is 20 mg and in children > 30 kg is 40 mg) • 40 mg every 2 weeks, in combination with methotrexate • When the aforementioned goal of therapy is achieved, we stop the adalimumab and maintain the methotrexate • Children, who develop complications during the use of methotrexate, are given mycophenolate mofetil or oral prednisolone. • If oral prednisolone is used, it should not be given for longer than 3 months. If the treatment goal is not achieved, we shift to mycophenolate mofetil or to adalimumab	I	8.88 ± 0.43	100	H
			II			
			I			

Table 2 (continued)

No.	Standard	Statement	LE	Mean rate ± SD	% of agreement	Level of agreement
			I			
	Management of complications	1) Glaucoma • Tension-lowering drops are administered. Prostaglandin analogues are not the first line due to their potential to promote inflammation • Iris bombe is an indication for peripheral iridotomy if it is associated with secondary glaucoma caused by the pupillary block • An elevated intraocular pressure that is not controlled by medical treatment is indicated for glaucoma surgery in order to save the optic nerve 2) Band-shaped keratopathy • If visually significant, it is indicated for chelation using EDTA (ethylenediamine-tetraacetic acid) 3) Cataract • If visually significant, it is indicated for cataract extraction • Before the surgery, a period of 6 months of clinical quiescence is needed • Primary intraocular lens implantation will usually do more harm than good	II	8.8 ± 0.62	100	H

LE Level of evidence according to the Oxford Centre for Evidence-Based Medicine (CEBM) criteria, *H* High level of agreement, *T2T* Treat to target, *NSAIDs* Nonsteroidal anti-inflammatory drugs, *DMARDs* Disease-modifying antirheumatic drugs, *JIA* Juvenile idiopathic arthritis, *EDTA* Ethylenediaminetetraacetic acid, *JADAS* Juvenile arthritis disease activity score, *HRQoL* Health-related quality of life, *ANA* Anti-nuclear antibodies, *JSpADA* Juvenile spondyloarthritis disease activity, *MTX* Methotrexate, *TNF* Tumour necrosis factor, *IL* Interleukin, *MAS* Macrophage activation syndrome, *EDTA* Ethylenediaminetetraacetic acid

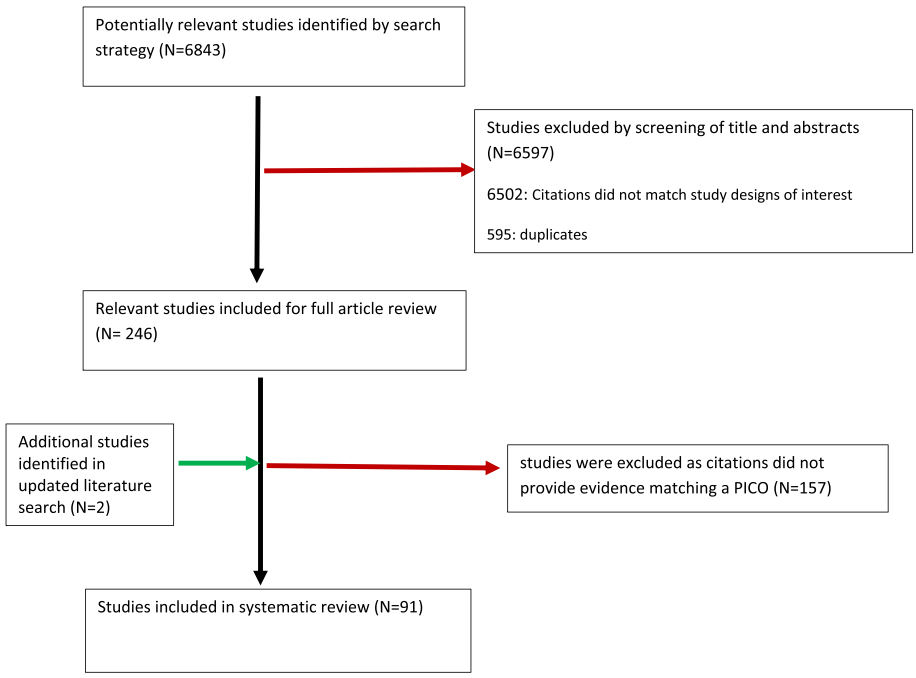


Fig. 1 Flow chart for the study selection process

clinical questions by breaking them down into smaller, more manageable components that are easier to identify during the literature search process [28].

The Delphi technique is a reliable tool for establishing new concepts and determining the direction of future-oriented research [29]. The technique enlists the help of a group of experts to assess the degree of agreement and settle disagreement on a topic [30]. There was broad agreement among the experts when asked about the feasibility of accomplishing a well-defined objective in osteoporosis. Almost everyone who contributed agreed that the treat-to-target technique may be used in JIA clinical practice. Consensus is reached in Delphi methodology when the percentage of people who agree or disagree is between 50 and 80% [31]. The agreement in our study varied from 83.4 to 100%, demonstrating a strong trend among Egyptian healthcare providers to use a T2T strategy for JIA management. The results of the American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis support these findings [19], the international task force [5], and the German consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis [32] which revealed similar agreement on the treat to target policy.

Although the literature analysis did not reveal trials that compared a treat-to-target method to another or no strategy, it did provide indirect evidence of a better approach to therapy, which aided in the formation of recommendations. In 2018, an international task force issued recommendations for treating JIA with the goal of achieving [5]. The task force discussed particular treatment goals and the T2T technique for achieving them. Their recommendations were meant to provide professional advice on broad treatment options in order to improve patient care in normal clinical practice. This study went above and beyond by presenting a T2T approach to the various JIA categories. According to the task force, there are several goals for treating patients with JIA to target. These include the following: "to control signs and symptoms; to prevent structural damage; to avoid comorbid conditions and drug toxicities; and to optimise function, growth and development, quality of life, and social participation" [5]. The essential premise of a T2T strategy is that a treatment that is aggressively directed at the target will have "domino effects" on all other objectives [33–35].

In the absence of joints with overt active illness, treating to target in JIA necessitates a multimodal treatment plan that may include physiotherapy and early pain/fatigue coping strategies administered by a multidisciplinary team for children with tiredness or chronic pain [8, 36, 37]. Furthermore, while these treatment guidelines are meant to improve the quality of clinical decision-making, each individual case is unique, and this should be taken into account in everyday practice. The guidelines given indicated T2T-based algorithms for the management of

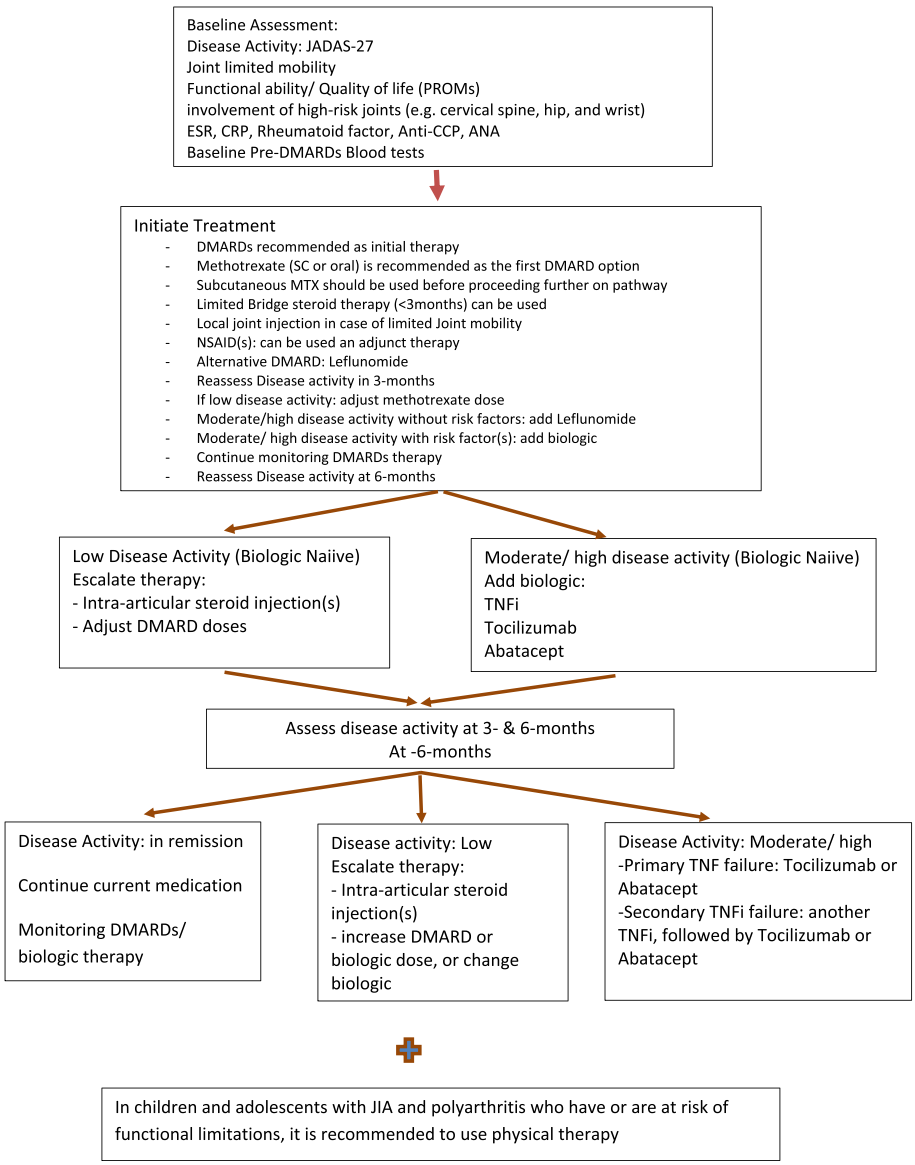


Fig. 2 A summary of primary recommendations for the treat-to-target management of children with juvenile idiopathic arthritis (JIA) and active polyarthritis

JIA patients. Clinicians require information that is simple to understand and use. The treatment suggestions should spell out the right lines of management, how to keep track of the patient, and how to deal with refractory instances. Nonsteroidal anti-inflammatory medicines, disease-modifying antirheumatic therapies, biologics, and intra-articular and oral glucocorticoids are among the medications recommended in this guideline. There are additional suggestions for using physical and occupational therapy. Treatment algorithms were created to outline the implementation of treatment methods targeted at establishing and maintaining tight disease control in routine paediatric rheumatology practice.

This work is the first to include imaging as one of the critical outcomes assessed. Whilst MRI is an approved tool for assessment of sacroiliitis, the role of musculoskeletal ultrasonography remains debatable. For JIA patients, musculoskeletal ultrasonography (MSUS) offers significant benefits, in comparison with other imaging modalities, including safety, non-invasiveness, repeatability, rapid performance, relatively low cost, and high acceptability even among very young patients. In

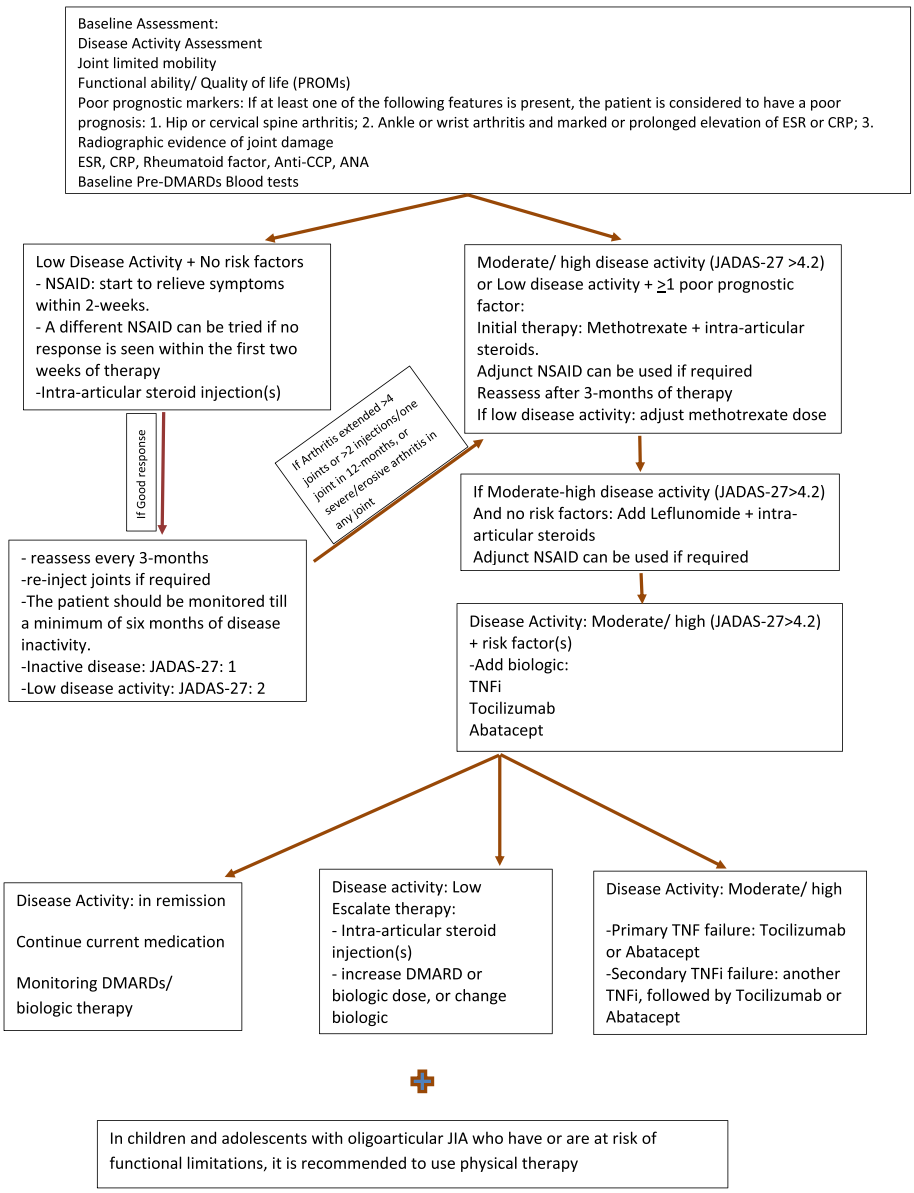
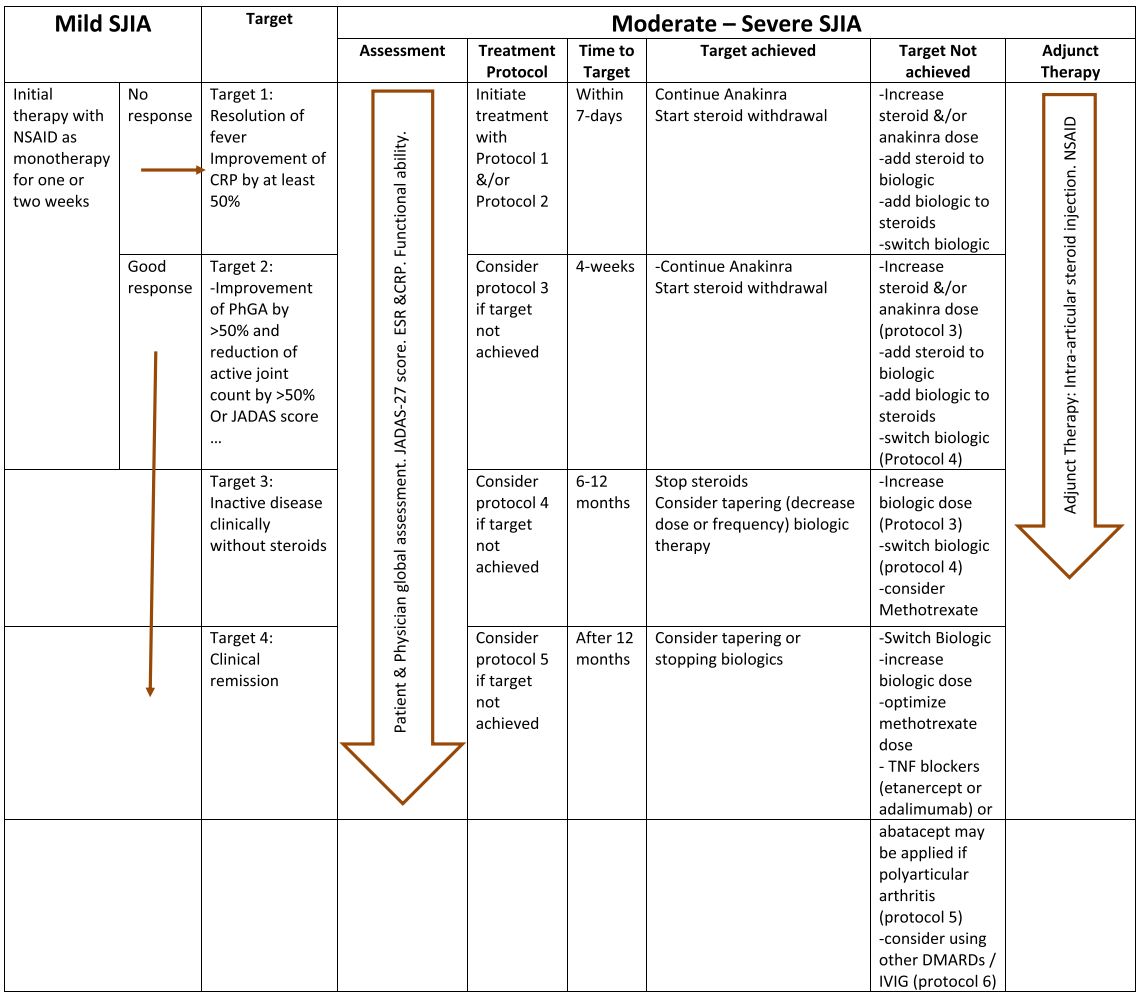


Fig. 3 Showing the treat-to-target management algorithm for oligoarthritis JIA

addition, MSUS can detect subclinical synovitis, improve the classification of subtypes, and capture early articular damage, as well as help clinicians monitor treatment response and guide intra-articular injections [38]. Moreover, across a majority of studies, many researchers have agreed that MSUS is superior to clinical examination in detecting synovial hypertrophy and synovial effusion [39]. In addition, ultrasonography has other useful applications, including educating young patients by showing them the appearance of both healthy and damaged joints. This exposure, as a pilot study [40] revealed, led to a 25% increase in young patients' adherence to prescriptions for both disease-modifying antirheumatic drugs and injectable antitumour necrosis factor drugs.

This guideline addressed some of the challenges that face JIA treatment in Egypt. The guidelines endorsed the use of combination therapy for patients with moderate disease activity without poor prognostic factors. In addition, the guidelines highlighted the important role of the biologic therapies: anakinra and canakinumab in the management of systemic JIA. This is in agreement with all the previously published guidelines including the 2013 American



Protocol 1: glucocorticoids: i.v. methylprednisolone pulse therapy (20–30 mg/kg/day [max. 500 mg/day) for 3 days or oral prednisolone 1–2 mg/kg/day (max. 60 mg/day). Can be repeated in 1-month if required

Protocol 2:

standard dose: anakinra 2-4mg /kg/day (max dose 100mg/day).

Protocol 3: higher doses

glucocorticoids: repeat i.v. methylprednisolone pulse therapy (20–30 mg/kg/day [max. 500 mg/day)
Anakinra High dose: Dose can be increased up to 8 mg/kg/day (max. 200 mg/day)

Protocol 4: Switch biologics:

Canakinumab max. 150 mg every 4 weeks

Tocilizumab (for body weight > 30 kg) 8 mg/kg (max. 800 mg) i.v. every 2 weeks and (for body weight <30 kg) 12 mg/kg every 2 weeks.

Protocol 5:
In case of a predominant polyarticular arthritis and in case of lack of treatment response despite the utilization of the approved biological agents, second-line agents, e.g. TNF blockers (etanercept or adalimumab) or abatacept may be applied. In addition, the use of methotrexate is reasonable and intraarticular glucocorticoids may be applied.

Protocol 6:
-cyclosporine and tacrolimus, and cytotoxic drugs, such as cyclophosphamide, are also options in patients who fail standard therapy, including biologic agents.
-Consider IVIG

Fig. 4 Showing a suggested treat-to-target management algorithm for systemic JIA

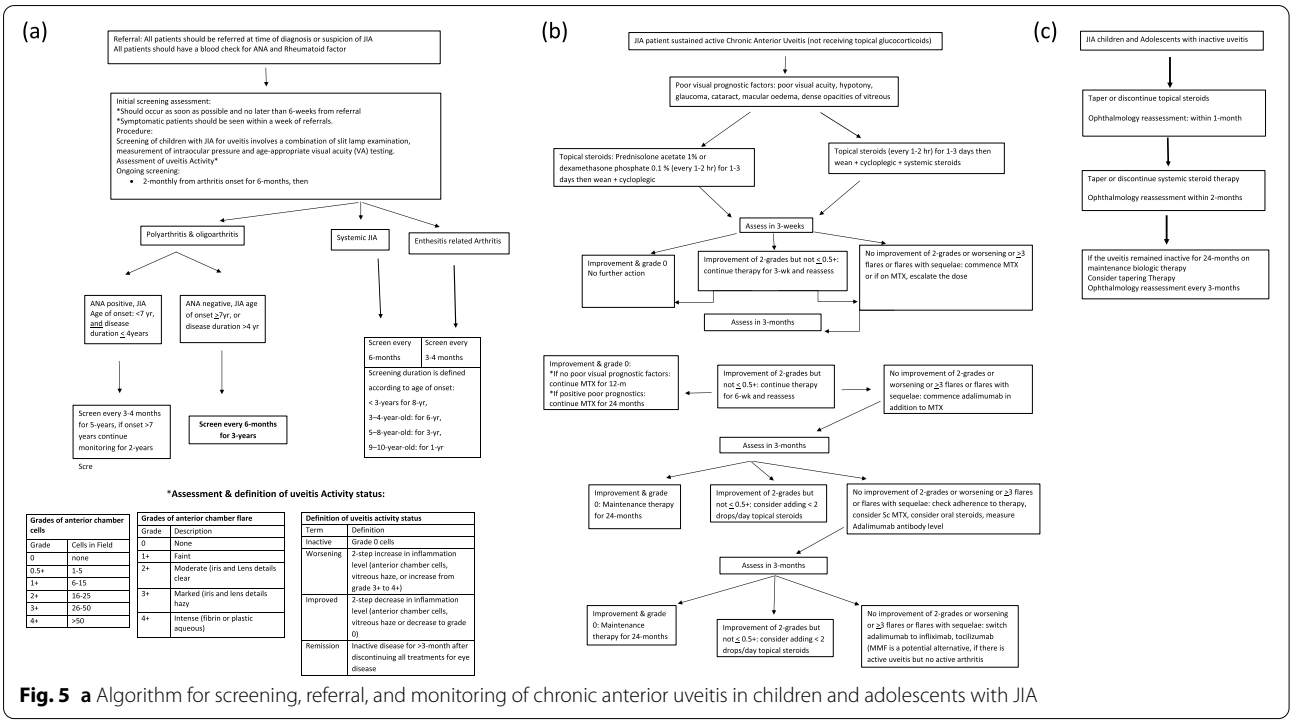


Fig. 5 **a** Algorithm for screening, referral, and monitoring of chronic anterior uveitis in children and adolescents with JIA

College of Rheumatology treatment recommendations for systemic JIA [41], the British recommendations regarding therapies for the treatment of juvenile idiopathic arthritis [42], and the German consensus-based strategies in diagnosing and managing systemic JIA [43]. Unfortunately, both biologic therapy agents are not available in Egypt. Therefore, a copy of this guidelines should be forwarded to the decision-makers in the biologic therapy section in the Ministry of Health to facilitate the presence of these 2 medications. High-dose glucocorticoids are commonly used to treat systemic JIA, but they have serious adverse effects including growth failure and osteoporosis [44]. TNF inhibitors and disease-modifying antirheumatic medications (DMARDs) show poor efficacy in sJIA [45, 46]. The discovery of the critical function of the proinflammatory cytokines interleukin 1 (IL-1) and interleukin 6 (IL-6) led to the creation of specific therapy techniques [47–50] that are very effective in the near term and may lead to a considerable shift in the disease's natural history.

We are in agreement with 2021 ACR Guideline for the Treatment of Juvenile Idiopathic Arthritis [51] in almost all lines of treatment in all categories of JIA, but we consider T2T strategy, and ACR 2021 consider temporomandibular joint in separate section and separate algorithm. And we in these recommendations added a separate section for uveitis management in JIA.

In our study, we depend on PICO manoeuvre and also consensus-based recommendations. We consider the treat-to-target strategy which differs than other previous recommendations; also, we had two steps recommendations: the first step was drug-dependent and then the second step was JIA subgroup-dependent; although these steps had more details, but it gives more clarifications.

The study's key strengths include the participants' variety as well as their experience, the high levels of consensus reached, and agreement with the most recently published JIA treatment recommendations. Though the treatment recommendations included in this guideline are in agreement with all the recently published guidelines [4, 5, 19, 41–43, 52], the study's main limitation remains the study's scope, which was conducted in Egypt, and the results may not be applicable to other nations.

In conclusion, Clinicians' treatment techniques can differ, and these advice notes offer a way to establish best practice based on current evidence or expert consensus. They will also help to improve practice consistency and promote the highest levels of care. The necessity of early and successful treatment for children and adolescents with JIA in its various manifestations is highlighted in this guideline and treatment recommendations. They also endorse a strict disease control strategy based on the treat-to-target method, with the goal of inactive illness. Because children with JIA are typically asymptomatic, it is critical that they be checked for poor prognostic markers and have routine ophthalmology screenings to detect uveitis early.

Abbreviations
ANA: Antinuclear antibodies; CEBM: Centre for Evidence-Based Medicine; DMARDs: Disease-modifying antirheumatic drugs; EDTA: Ethylenediaminetetraacetic acid; H: High level of agreement; HRQoL: Health-related quality of life; IL: Interleukin; JADAS: Juvenile arthritis disease activity score; JIA: Juvenile idiopathic arthritis; JSpADA: Juvenile spondyloarthritis disease activity; LE: Level of evidence according to the Oxford Centre for Evidence-Based Medicine (CEBM) criteria; LMIC: Low- and middle-income countries; MAS: Macrophage activation syndrome; MSUS: Musculoskeletal ultrasonography; MTX: Methotrexate; NSAIDs: Nonsteroidal anti-inflammatory drugs; PICO: Population, intervention, comparator, and outcome; RCTs: Randomized controlled trials; sJIA: Systemic juvenile idiopathic arthritis; T2T: Treat to target; TNF: Tumour necrosis factor.

Supplementary Information

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Additional file 1: Supplement 1. Population included. **Supplement 2.** Interventions included in the literature review. **Supplement 3.** The critical outcomes, as chosen by the Core Team. They varied among the different subgroups of pediatric patients with JIA (polyarthritis, oligoarthritis, systemic juvenile arthritis, sacroiilitis/enthesitis) and/or uveitis. **Supplement 4.** Levels of evidence [12].

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Authors' contributions
Conceptualization and design, YEM and MHAZ; acquisition of data, YEM, MHAZ, and SN; formal analysis, MEG; investigation, SS and HL; methodology, all authors; writing — original draft, YEM, MHAZ, and ST; final approval of the version to be submitted, all authors.

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Availability of data and materials
The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Helsinki Declaration. This was a multistep process which followed the "clinical, evidence-based, guidelines" (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold standard for treat-to-target management of rheumatic and bone diseases. As per the Egyptian national ethical committee regulations, verbal informed consent was required from all the participants included in the study. All the participants included in the study gave their verbal informed consent. All the participants were kept anonymous, in compliance with data protection regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that the corresponding author Dr. Mohammed Hassan Abu-Zaid is Associate Editor in the Egyptian Rheumatology and Rehabilitation. Co-authors Dr. Mohammed Mortada and Yasser El Miedany are among the Editorial Board of the journal.

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