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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint (TMJ) Arthritis and Systemic JIA

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ABSTRACT

Objective: To provide updated guidelines for pharmacologic management of juvenile idiopathic arthritis (JIA), focusing on treatment of oligoarthritis, temporomandibular (TMJ) arthritis and systemic JIA (sJIA), with and without macrophage activation syndrome (MAS). Recommendations regarding tapering and discontinuing treatment in inactive systemic JIA are also provided.

Methods: We developed clinically relevant **p**opulation, **i**ntervention, **c**omparator, and **o**utcomes (PICO) questions. After conducting a systematic literature review, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (high, moderate, low, very low). A voting panel including clinicians and patients/caregivers achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results: Similar to those published in 2019, recommendations are based on clinical phenotypes of people with JIA, rather than a specific classification schema. These guidelines provide recommendations for initial and subsequent treatment of JIA with oligoarthritis, TMJ arthritis and sJIA as well as for tapering and discontinuing treatment in inactive sJIA. Other aspects of disease management, including factors that influence treatment choice and medication tapering are discussed. Evidence for all recommendations was graded as low or very low in quality. For that reason, more than half of the recommendations are conditional.

Discussion: This clinical practice guideline complements the 2019 American College of Rheumatology (ACR) JIA and uveitis guidelines which covered polyarthritis, sacroiliitis,

enthesitis and uveitis. It serves as a tool to support clinicians, patients and caregivers in decision-making. These recommendations take into consideration the severity of both articular and non-articular manifestations as well as patient quality of life. Although evidence is generally low quality and many recommendations are conditional, the inclusion of caregivers and patients in the decision-making process strengthens the relevance and applicability of the guideline. It is important to remember that these are recommendations. Clinical decision-making, as always, remains in the hands of the treating clinician and patient/caregiver.

SIGNIFICANCE

These treatment recommendations emphasize:

- Decreased reliance on long-term nonsteroidal anti-inflammatory drugs and oral glucocorticoids.
- Early use of conventional synthetic and biologic disease-modifying antirheumatic drugs.
- Importance of shared decision-making with the patient/caregiver.

INTRODUCTION

Reflecting the changing medical landscape, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines and plans to review these annually and update, as needed. The process for updating the 2011 and 2013 JIA guidelines began in 2017[1, 2]. Important clinical topics for consideration were first identified at a meeting to define the scope of the guidelines. Advances in the treatment of JIA and better understanding of pathogenesis dictated separating this clinical practice guideline into several parts due to the breadth of topics. The first part, addressing polyarthritis, sacroiliitis, enthesitis and uveitis, was published in two manuscripts in 2019[3, 4]. The second part, presented here in 2 papers, covers a) oligoarthritis, temporomandibular joint (TMJ) arthritis, systemic arthritis (sJIA) and b) non-pharmacologic treatments, patient monitoring, immunizations and imaging. .[5]. The methods and literature review described below reflects the unified process used for the second part of these guidelines, including both manuscripts. Recommendations were intended to be complementary to the 2019 guidelines and are grouped based on disease phenotypes and severity, not by specific classification criteria, reflecting decision-making in clinical practice.

Following the selection of topics, we developed clinically relevant **p**opulation, **i**ntervention, **c**omparator and **o**utcomes (PICO) questions. Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, recommendations were then developed based on the best available evidence for commonly encountered clinical scenarios. Prior to final voting, input was sought from relevant stakeholders including a panel of young adults with JIA and caregivers of children with JIA to consider their values and perspectives in making recommendations. Both the patient/caregiver and guideline voting panels stressed the need for individualized treatment while being mindful of available evidence.

METHODS

This guideline follows the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which includes GRADE methodology [6, 7] and adheres to AGREE criteria[8]. Supplementary Appendix 1 includes a detailed description of the methods. Briefly, the core leadership team (KO, DH, DL, SS) drafted clinical PICO questions. PICO questions were revised and finalized based on feedback from the entire guideline development group and the public. The literature review team performed systematic literature reviews for each PICO, graded the quality of evidence (high, moderate, low, very low) and produced the evidence report (see Supplementary Appendix 2). Note that GRADE methodology does not distinguish between lack of evidence (i.e., none) and very low-quality evidence.

The core team defined multiple critical study outcome(s) for PICOs relevant to each JIA phenotype (see Supplementary Appendix 3).

A virtual panel of 15 members, including young adults with JIA and caregivers of children with JIA, moderated by the principal investigator (KO), reviewed the evidence report and provided input to the voting panel. Two members of this panel (JH, KM) were also members of the voting panel, to ensure that the patient voice was part of the entire process. The voting panel reviewed the evidence report and patient/caregiver perspectives and then discussed and voted on recommendation statements. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation as per ACR practice. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.

Rosters of the core leadership, literature review team and both panels are included in Supplementary Appendix 4.

Guiding Principles

1) Consistent with the ACR's 2019 JIA guidelines, these recommendations are for persons diagnosed with JIA.

2) Aside from poor prognostic features specified within the recommendations themselves (e.g., specific joints for oligoarthritis, MAS), extra-articular coexisting conditions that would influence disease management, such as uveitis, psoriasis or inflammatory bowel disease, are not addressed within these guidelines.

3) Recommendations are intended to be used by all clinicians caring for persons with JIA and assume that patients do not have contraindications to the recommended pharmacologic treatments

4) Longer-term glucocorticoid therapy in childhood is not appropriate because of its effects on bone health and growth. Thus, wherever glucocorticoids are suggested, recommended treatment should be limited to the lowest effective dose for the shortest duration possible.

5) Shared decision-making with families and patients is important when considering treatment options.

RESULTS/RECOMMENDATIONS

The initial literature review included topics addressed in this manuscript and in the second paper (add ref to other JIA GL paper), identified 4308 manuscripts in searches for all PICO questions through August 7, 2019. A July 9, 2020 search update identified 367 more references, for a total of 4675 papers after duplicates and non-English publications were removed. After excluding 2291 titles and abstracts, 2384 full-text articles were screened. Of these, 1939 were excluded (see Supplemental Appendix 5, leaving 445 articles to be considered for the evidence report. In the end, 406 papers were matched to PICO questions and included in the final evidence report. Quality of evidence was uniformly low or very low; 17 PICO questions lacked any associated evidence (Tables 1 and 3-7). The following recommendations are based on 62 PICO questions. Several PICO questions were split into 24 sub-PICO questions to improve specificity. Nine questions initially posed were discarded by the voting panel because of redundancy or lack of relevance.

Final recommendations are described below and in Tables 3-7, which include reference(s) to which PICO question(s) in the evidence report correspond to the recommendation statement.

ACTIVE OLIGOARTHRITIS (Figure 1)

Oligoarthritis refers to children presenting with involvement of 4 or fewer joints without systemic manifestations. It may include patients categorized in different categories of JIA[9] but share in common limited numbers of joints involved; guidance for patients with active uveitis, sacroiliitis or enthesitis can be found in the 2019 guidelines[3, 4]. TMJ arthritis is discussed separately.

NSAIDs

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active oligoarthritis.

NSAIDs have long been the cornerstone of treatment for oligoarthritis and can ease discomfort[10-12]. However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as some panelists choose to avoid the use of NSAIDs altogether.

Glucocorticoids

Intra-articular glucocorticoids (IAGCs) are strongly recommended as part of initial therapy for active oligoarthritis.

Triamcinolone hexacetonide is strongly recommended as the preferred agent.

Despite low-quality evidence, IAGCs are strongly recommended due to low potential of adverse effects and high likelihood of sustained response[13-15]**.** Patients and caregivers agreed as to the utility of IAGC but voiced concerns over the need for sedation in younger children and associated risks.

Despite an overall grading of evidence as low, the panel was convinced by published randomized trials and large observational studies that triamcinolone hexacetonide leads to more durable clinical responses than triamcinolone acetonide, leading to the strong recommendation[16-18]. Triamcinolone hexacetonide has been unavailable in the US for several years. However, very recently, the FDA has allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA, to address this identified unmet medical need.

Oral glucocorticoids are conditionally recommended *against*, as part of initial therapy for active oligoarthritis.

Despite recommendations against, if oral glucocorticoids are given to quickly alleviate severe symptoms when IAGC is not available or feasible, or prior to the onset of action of DMARDs, treatment should be limited to the lowest effective dose for the shortest duration possible[19, 20].

Conventional synthetic DMARDs (csDMARDs)

csDMARDs are strongly recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs for active oligoarthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide, sulfasalazine or hydroxychloroquine (in that order).

Despite absence of comparator trials, methotrexate is the preferred agent given preponderance of evidence showing long-term safety and efficacy in childhood[21-23]. Because methotrexate tolerability is variable, additional treatment options are provided[24-27].

As for route of methotrexate, the 2019 JIA guidelines conditionally recommended subcutaneous methotrexate over oral methotrexate for polyarthritis[3]. This recommendation was conditional because the supporting evidence was of very low quality and patient preferences may guide choice of route of administration. There is little reason to suggest that methotrexate should be used differently in oligoarthritis than in polyarthritis.

Biologic DMARDs (bDMARDs)

bDMARDs are strongly recommended if there is inadequate response or intolerance to NSAIDs and/or IAGC and at least one csDMARD for active oligoarthritis.

There is no preferred bDMARD.

bDMARDs are preferred over combining csDMARDs or switching to a different csDMARD due to bDMARDs' having a greater likelihood of yielding rapid and sustained improvement in JIA[28, 29]. While combination csDMARDs have been used for adults with RA, in children the combination appears to be less effective and less tolerable. For these reasons, this recommendation is strong[30].

Although tumor necrosis factor inhibitors (TNFi) are the most commonly used bDMARDs in childhood[31-33], other bDMARDs of proven efficacy in the treatment of JIA may be used. In the absence of head-to-head trials for children with oligoarthritis[34], bDMARD selection may be driven by specific provider and patient/caregiver preferences and circumstances with the exception of IL-1 inhibitors, which are preferentially used for the treatment of sJIA[28, 35-37]

Risk factors for poor prognosis and disease activity measures

Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip, sacroiliac joint and/or TMJ, presence of erosive disease or enthesitis, delay in diagnosis, elevated inflammatory markers, symmetric disease) is conditionally recommended to guide treatment decisions.

Use of validated disease activity measures is conditionally recommended to guide treatment decisions, especially to facilitate treat-to-target (T2T) approaches.

Treatment for oligoarthritis can and should be modified based on the involvement of specific joints or disease features[38, 39]. This could include rapid escalation of treatment (e.g., if there is TMJ involvement or erosive disease at presentation) or alternative medication choice (e.g., sulfasalazine or bDMARD rather than methotrexate for sacroiliitis)[3].

Voting panelists conditionally recommended formal assessment of disease activity using validated measures. Several validated disease activity measures for childhood arthritis exist[40]. The lack of demonstrated superiority of specific measures and the likelihood of future changes led voting panelists to defer stating formal preferences for particular measures. Measures that can be considered include Wallace preliminary criteria for Clinical Remission, ACR preliminary criteria for inactive disease, Juvenile Arthritis Disease Activity Score (JADAS) and clinical cJADAS, amongst others[41-43].

T2T approaches have been strongly endorsed for polyarticular JIA[41], and preliminary data has demonstrated feasibility as well as improved outcomes[44, 45]. Despite limited studies in oligoarticular disease, one would expect a similar response. Presence of risk factors for poor outcomes may justify rapid escalation of treatment.

ACTIVE TMJ ARTHRITIS (Figure 2)

TMJ disease may be isolated or part of generalized arthritis. Treatment of TMJ arthritis is critical, as patients/caregivers noted high impact on oral health related quality of life (QOL) and challenges with diagnosis and effective pharmacologic treatment[46, 47]. This guideline, therefore, suggests treating TMJ arthritis regardless of presence of clinical symptoms. While NSAIDs and/or IAGCs may be sufficient treatment for some patients, rapid escalation to bDMARDs (potentially in combination with csDMARDs) is often appropriate, given the impact and destructive nature of TMJ arthritis, despite limited evidence[48].

NSAIDs

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active TMJ arthritis.

NSAIDs have long been the cornerstone of treatment for JIA and can ease discomfort[10]. However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy as some panelists avoid the use of NSAIDs altogether.

Glucocorticoids

IAGCs are conditionally recommended as part of initial therapy for active TMJ arthritis.

There is no preferred agent.

IAGCs may alleviate joint symptoms and help restore function. This recommendation is conditional as there have been unique TMJ specific serious adverse events, including heterotopic ossification and impaired growth[48-51]. Therefore, IAGCs for TMJ arthritis should be

used sparingly for symptomatic children, preferably those who are skeletally mature[49, 52]. There is no comparative data between different IAGC formulations for TMJ injections.

Oral glucocorticoids are conditionally recommended *against* as part of initial therapy for active TMJ arthritis.

Despite recommendations against, if oral glucocorticoids are given to quickly alleviate severe symptoms prior to the onset of action of DMARDs, treatment should be limited to the lowest effective dose for the shortest duration possible[19].

csDMARDs

csDMARDs are strongly recommended for inadequate response or intolerance to NSAIDs and/or IAGCs for active TMJ arthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide.

TMJ is a high-risk joint due to major impact on activities of daily living, and, thus, early use of csDMARD therapy is encouraged. The limited evidence available supports the use of methotrexate[53]. However, because not all patients tolerate methotrexate well, leflunomide is recommended as an alternative, if needed.

bDMARDs

bDMARDs are conditionally recommended for inadequate response or intolerance to NSAIDs and/or IAGCs and/or at least one csDMARD for active TMJ arthritis.

There is no preferred bDMARD.

Voting panelists deferred recommending a specific bDMARD because current studies of TMJ arthritis have been small and observational[48, 54]. TNFi have been most commonly used. As noted earlier, the use of IL-1 inhibitors is restricted to the treatment of sJIA.

CF Note

SYSTEMIC JIA (sJIA) WITH AND WITHOUT MACROPHAGE ACTIVATION SYNDROME (MAS) (Figure 3)

sJIA is recognized as distinct from all other categories of JIA due to fever, rash and visceral involvement and is considered by some to be an autoinflammatory disorder[55]. Disease pathogenesis and cytokine involvement are different from other categories[56-58]. Up to 40% of cases of sJIA are associated with MAS, a secondary hemophagocytic syndrome that is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fevers, high ferritin, cytopenias, elevated liver function tests (LFTs), low fibrinogen and high triglycerides[59, 60]. As MAS may occur at any point during the disease course, careful monitoring is necessary for children with or without MAS at presentation.

Initial therapy: sJIA without MAS

bDMARDs

IL-1 and IL-6 inhibitors are conditionally recommended as initial monotherapy for sJIA without MAS.

There is no preferred agent.

IL-1 and IL-6 inhibitors are extremely effective and well-tolerated treatments for sJIA [56-58] and have been rapidly adopted in clinical practice[61, 62]. Use of IL-1 and IL-6 inhibitors to treat sJIA has allowed for marked reduction in glucocorticoid use[56, 57, 63]. Patients/caregivers agreed

with this recommendation, given historical delays and limits in clinical response and toxicities from other medications before the bDMARD era.

Some voting panelists preferred starting with a short-acting agent such as anakinra, but in the absence of controlled studies, no preferred agent was endorsed. Patients/caregivers noted preference for fewer injections, if possible. As response to individual agents is variable, switching amongst and between IL-1 and IL-6 inhibitors, when needed, for lack of efficacy or poor tolerability is appropriate.

Concerns were expressed about a highly fatal lung disease observed in some children with sJIA, most treated with bDMARDs. Observed risk factors include younger children with MAS, children with a history of reactions to tocilizumab and those with trisomy 21[64, 65]. The exact etiology for sJIA-associated lung disease and recommendations for screening remain under investigation. Affected children often present with acute digital clubbing, which should raise immediate concern[64, 65]. However, voting panelists noted the need to balance the effectiveness and relative safety of bDMARDs with the rarity of this serious outcome. Voting panelists were also motivated by the extent of morbidity from undertreated sJIA and glucocorticoid-associated toxicities before the bDMARD era[66, 67].

NSAIDs are conditionally recommended as initial monotherapy for sJIA without MAS.

Studies suggest that a small proportion of patients with sJIA will respond to NSAIDs alone[68]. Patients/caregivers agreed with a short trial of NSAIDs for those children. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as many panelists avoid the use of NSAIDs altogether for sJIA.

Glucocorticoids

Oral glucocorticoids are conditionally recommended *against* as initial monotherapy for sJIA without MAS.

In most cases, oral glucocorticoids should not be used as initial monotherapy and, if used, should be limited to the lowest effective dose for the shortest duration possible. This recommendation is conditional as bDMARDs may not always be immediately available, and glucocorticoids may help control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started.

csDMARDs

csDMARDs are strongly recommended *against* as initial monotherapy for sJIA without MAS.

This recommendation is strong despite limited evidence as authors took note of multiple small studies of sJIA that documented lack of efficacy at controlling systemic features that are typically present at onset of disease, leading to a continued need for glucocorticoids[62, 69]. csDMARDs can be considered in combination with bDMARDs for children with prominent arthritis[70]. In areas where biologic therapy is not rapidly attainable, thalidomide has been used to treat sJIA[71]. However, given ready bDMARD availability in North America and risks of thalidomide toxicity, use of thalidomide was not considered as part of these guidelines.

Subsequent therapy: sJIA without MAS

IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of csDMARDs for inadequate response or intolerance to NSAIDs and/or glucocorticoids for sJIA without MAS.

Most physicians and patients/caregivers preferred quickly starting IL-1 or IL-6 inhibitors for insufficient response to NSAIDs or glucocorticoids[62]. Panel members were persuaded by trials that documented resolution of systemic signs and ability to discontinue glucocorticoids [56, 72-74]

For sJIA without MAS with an inadequate response to IL-1 or IL-6 inhibitors and residual arthritis, the addition of a csDMARD or a switch to different bDMARD is strongly recommended over use of chronic glucocorticoids.

There is no preferred agent.

Given the potential toxicities from chronic glucocorticoids[19], patients should receive steroid-sparing treatments for residual arthritis. Many options exist (e.g., adding methotrexate, switching to abatacept or TNFi) and ample evidence supports the use of DMARDs for sJIA-associated synovitis[22, 75].

Initial therapy: sJIA with MAS

bDMARDs

Infections can trigger MAS; therefore, all persons with MAS should be evaluated for infection concurrently with or prior to therapy[76, 77].

IL-1 or IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS for sJIA and MAS.

There is no preferred agent.

IL-1 and IL-6 inhibitors have proven to be very helpful in the treatment of sJIA and MAS[78-80]. Some voting panelists noted that monotherapy may not be sufficient for severely ill

individuals[79]. Some may require bDMARDs combined with glucocorticoids and calcineurin inhibitors to control MAS[81].

Glucocorticoids

Glucocorticoids are conditionally recommended as part of initial treatment of sJIA with MAS.

The benefits of glucocorticoids for MAS often outweigh their risks, even in patients whose MAS is triggered by infection. Systemic glucocorticoids may be necessary for severely ill individuals because they can have a rapid onset of action. However, although treatment with high dose glucocorticoids may be required for disease control, subsequent glucocorticoid therapy should be limited to the lowest effective dose for the shortest duration possible. Longer-term glucocorticoid therapy in childhood is not appropriate because of its effects on bone health and growth[19].

Inactive sJIA with or without history of MAS

Tapering and discontinuing glucocorticoids is strongly recommended after inactive disease has been attained for sJIA.

The risk of flare from sJIA that is well controlled is considerably outweighed by possible harms from chronic glucocorticoid use, even at low doses, accounting for this strong recommendation[82]. If a patient is on both DMARDs and glucocorticoids, systemic glucocorticoids should be tapered and discontinued first before attempting to taper bDMARDs or csDMARDs. It is unclear how soon or rapidly these can be safely discontinued in inactive disease for sJIA.

Tapering and discontinuing bDMARDs is conditionally recommended after inactive disease has been attained for sJIA.

Children with sJIA and inactive disease states may be able to maintain these states on lower doses of bDMARDS or after stopping them[70,83]. It is unclear how soon after achievement of inactive disease these can be tapered. No method of tapering is specified (e.g., decreasing dosage vs. spacing out intervals between doses) given lack of evidence, but patients/caregivers tended to prefer spacing out intervals[82].

DISCUSSION

The recommendations presented in this work are a companion to those published in 2019[3, 4] and cover areas not previously addressed: oligoarthritis, TMJ arthritis and sJIA with and without MAS. In many ways, one must view this guideline as a map for future study. Most of the available evidence was very low quality for the relevant PICO questions, contributing to 22/33 of the recommendations being conditional. None of the recommendations was supported by moderate or high-quality evidence. Similar to the 2019 guidelines, recommendations are grouped based on disease phenotype and not by specific classification criteria, reflecting clinical practice where disease characteristics, severity and risk of damage generally drive treatment decisions. These recommendations differ quite substantially from those published in 2011 and 2013[1, 2], reflecting increased experience with and availability of bDMARDs as well as a deeper understanding of JIA pathogenesis and long-term risks of undertreatment.

The voting and patient/caregiver panels both engaged in vigorous discussions over the use of NSAIDs and oral glucocorticoids[84] in the treatment of JIA, regardless of phenotype. Given the availability of safer, effective alternatives, both panels agreed that these medications should be

used sparingly and largely as a bridge until more definitive treatment is available. This is a marked change from previous clinical practice where both were mainstays of treatment and subsequent risk of chronic disability was high.[85, 86]

Another major change in recommendation for the treatment of sJIA is the use of bDMARDs as initial treatment or upon inadequate response to a short course of NSAIDs. The addition of csDMARDs is only recommended for persistent synovitis despite treatment with bDMARDs. This recommendation reflects growing understanding about the roles of specific cytokines in this disease and the ability to induce remission with targeted therapy against IL-6 and IL-1[58, 70, 87]. Reports of a highly fatal lung disease in some bDMARD-treated young children with sJIA temper this enthusiasm, and additional investigation is required to determine what role, if any, bDMARDs play in the pathogenesis of this complication[64, 65].

This guideline's focus on oligoarthritis complements previously published recommendations for polyarthritis[3]. However, it was clear in voting panel discussions that the number of involved joints alone was insufficient to tailor treatment decisions. Specific involvement of key joints (e.g., TMJ, wrist, sacroiliac, hip and ankle) and other features (e.g., erosions) were considered reasonable justification for early escalation of therapy[88]. This approach is reflected in a distinct set of recommendations specifically addressing TMJ arthritis.

The use of IAGCs was extensively discussed. Recommendations from 2011 and 2019 to preferentially use triamcinolone hexacetonide for oligoarthritis were reaffirmed, [1, 3] while no specific formulation for TMJ IAGC injection was noted. Triamcinolone hexacetonide has been

shown to be superior to alternative injectable glucocorticoids in achieving and maintaining remission in children with JIA[16-18]. Triamcinolone hexacetonide has been commercially unavailable in the U.S. for many years, forcing physicians to consider less effective, more toxic or more costly alternatives. However, very recently the FDA allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA, to address an identified unmet medical need[89].

There is much that remains to be learned. Studies that lead to high quality data to fill in the evidentiary gaps must be done (see Supplemental Appendix 6). Important areas remain with little or no evidence to guide management, setting a road map for future investigation. Head-to-head trials are needed to understand the optimal order and roles of csDMARDs and bDMARDs for children with JIA. We need improved understanding of which class of medication is best for a particular child allowing for more precise treatment and less time before remission is attained. Biosimilars were not addressed in these guidelines, as these medications were not included in the literature review, and there was no available evidence assessing their use in JIA. More widespread use of biosimilars will add more questions about their relative safety and effectiveness in children who start or switch to them for JIA.

Patient/caregiver input was instrumental in creating these recommendations. Several major themes emerged from their participation. Patients/caregivers stressed the need for individualizing treatments because what works for one does not work for all[90]. To facilitate individualization, no rigid time frames were required for an advancement of treatment. Moving quickly may be needed for a patient who is rapidly worsening, while moving slower may be appropriate for somebody who has improved substantially but not fully. Panel participants emphasized the critical importance of shared decision-making that considers patients' and caregivers' values, goals, and preferences[91]. The depth and breadth of impact that JIA has on

the lives and well-being of affected children and their families cannot be overstated[92, 93]. Hopefully in the future, more effective, reliable treatments will be available for JIA[94].

This guideline breaks new ground in recommending treatment withdrawal for children with sJIA, who may have lower risks of flare than other forms of JIA[95, 96]. As we look toward the future, we can only hope that similar recommendations around tapering medications can be made for every JIA category. Biomarkers are needed that can help distinguish between disease that is treated from that which has completely resolved as currently the risk of relapse remains high upon medication tapering.

The low quality of evidence supporting these recommendations underscores the importance of clinical judgment and shared decision-making in everyday care of individuals with JIA. Similarly, these guidelines and the many uncertainties therein represent a powerful reminder of the need for more high-quality evidence to support (or refute) current practices and improve the management and well-being of all individuals living with JIA.

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Table 1: Strength of recommendations/quality of supporting evidence							
Arthritis Phenotype	Strength of Recommendation			Quality of Supporting Evidence			
	Number of Recommendations	Conditional	Strong	Very Low	Low	Moderate	High
Oligoarthritis	9	4	4	6	2	0	0
TMJ Arthritis	6	4	1	5	0	0	0
Systemic JIA	10	5	4	9	0	0	0
Total	22	13	9	20	2	0	0

Table 2: Classes of interventions	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Any at therapeutic dosing [Ibuprofen, Naproxen, Tolmetin, Indomethacin, Meloxicam, Nabumetone, Diclofenac, Piroxicam, Etodolac, Celecoxib]
Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)	Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide, Calcineurin inhibitors [cyclosporin A, tacrolimus]
Biologic DMARDs (bDMARDs)	Tumor necrosis factor alpha inhibitors (TNFi): Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab pegol Other Biologic Response Modifiers (OBRM): Abatacept, Tocilizumab, Anakinra, Canakinumab
Targeted synthetic DMARD (tsDMARD)	JAK inhibitor: Tofacitinib
Glucocorticoids	Oral: Any Intravenous: Any Intraarticular: Triamcinolone Acetonide, Triamcinolone Hexacetonide

Table 3: Oligoarthritis			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
A trial of consistent NSAIDs is **conditionally** recommended as part of initial therapy.	Very Low	PICO 1: In children with oligoarticular JIA, should a trial of consistent NSAIDs be recommended?	6-9
Intra-articular glucocorticoids (IAGCs) are **strongly** recommended as part of initial therapy.	Very Low	PICO 2: In children with oligoarticular JIA, should adding intraarticular glucocorticoids to initial therapy be recommended?	10-19
Triamcinolone hexacetonide (THA) is **strongly** recommended as the preferred agent.	Low	PICO 4: In children with oligoarticular JIA, should a specific steroid type be recommended for intraarticular injection?	21-27
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy	Very low	PICO 3: In children with oligoarticular JIA, should adding oral steroids to initial therapy be recommended?	19-20
csDMARDs are **strongly** recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs.	Low (MTX) Very Low (Lef, Sulfa, Hydroxy)	PICO 5. In children with oligoarticular JIA, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexate (subcutaneous or oral),	28-41

Methotrexate is *conditionally* recommended as a preferred agent over leflunomide, sulfasalazine and hydroxychloroquine (in that order).		leflunomide, sulfasalazine, and/or hydroxychloroquine?	
bDMARDs are **strongly** recommended if there is an inadequate response or intolerance to NSAIDs and/or IAGC and at least one csDMARD. --- There is no preferred bDMARD.	Very Low	PICO 6. In children with oligoarticular JIA, should biologic therapies be recommended, and should there be any preferred order of treatment: anti-TNF treatment, biologic treatments with other mechanisms of action?	42-47
Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip and/or TMJ, presence of erosive disease, delay in diagnosis, elevated inflammatory markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 9. In children with oligoarticular JIA, should poor prognostic features alter the treatment paradigm? --- PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	51-52, 60
Use of validated disease activity measures is **conditionally** recommended to guide treatment decisions, especially to facilitate treat-to-target approaches.	Very low	PICO 10. In children with oligoarticular JIA, should disease activity measures alter the treatment paradigm?	52

Table 4: TMJ arthritis			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
A trial of consistent NSAIDs is **conditionally** recommended as part of initial therapy.	Very Low	PICO 11. In children with JIA with active TMJ arthritis, should a trial of consistent NSAIDs be recommended and should there be any preferred NSAID treatment?	53
IAGCs are **conditionally** recommended as part of initial therapy. --- There is no preferred agent.	Very low Very low	PICO 12. In children with JIA with active TMJ arthritis, should adding intraarticular glucocorticoids to initial therapy be recommended? --- PICO 14. In children with JIA with active TMJ arthritis, should a specific steroid type be recommended for intraarticular injection?	53-57 58
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy.	Very low	PICO 13. In children with JIA with active TMJ arthritis, should adding oral glucocorticoids to initial therapy be recommended?	58
csDMARDs are **strongly** recommended for inadequate response or intolerance to NSAIDs and/or IAGCs. ---	Very low	PICO 15. In children with JIA with active TMJ arthritis, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexate	58-59

Methotrexate is **conditionally** recommended as a preferred agent over leflunomide.		(subcutaneous and oral), leflunomide, sulfasalazine, and/or hydroxychloroquine?	
bDMARDs are **conditionally** recommended for inadequate response or intolerance to NSAIDs and/or IAGCs and at least one csDMARD. --- There is no preferred biologic agent.	Very low	PICO 16. In children with JIA with active TMJ arthritis, should systemic biologic therapies be recommended, and should there be any preferred order of treatment: anti TNF, biologic treatments with other mechanisms of action?	59
Consideration of poor prognostic features (e.g., involvement of ankle, wrist, hip and/or TMJ, presence of erosive disease, delay in diagnosis, elevated inflammatory markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	60

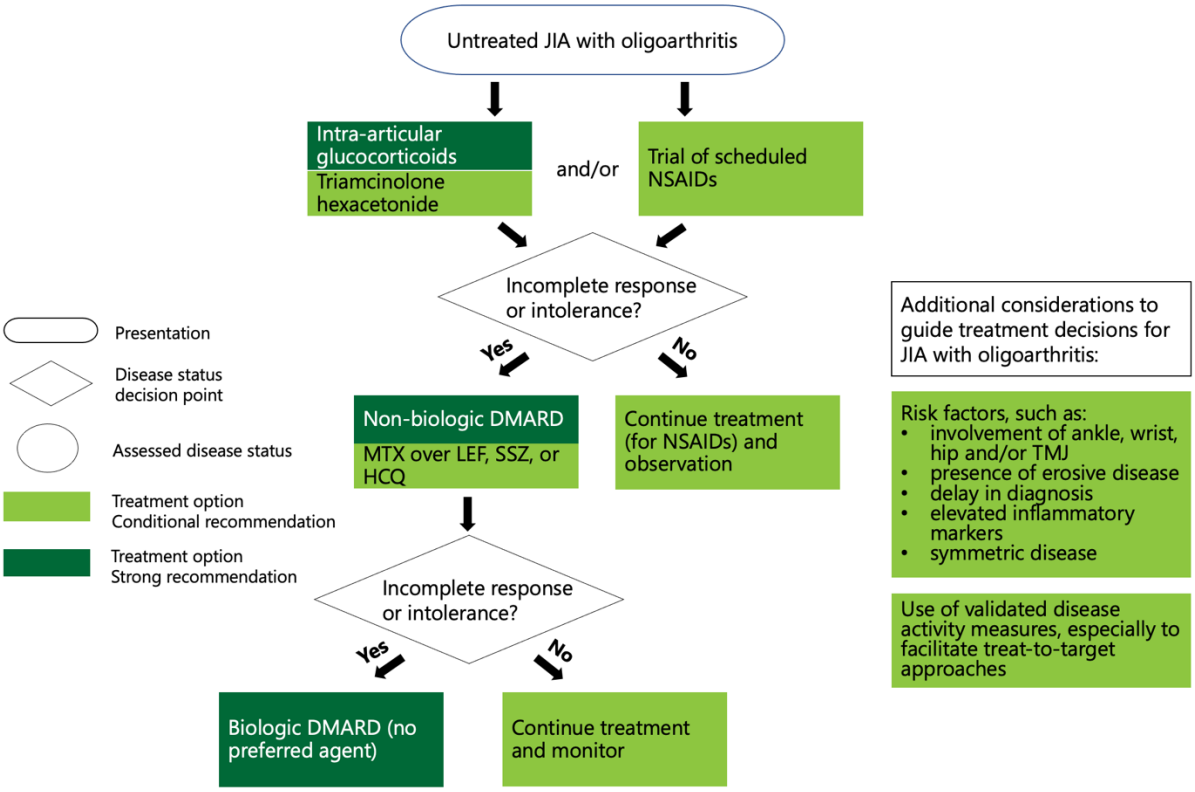
Table 5: sJIA without MAS			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
NSAIDs are **conditionally** recommended as initial monotherapy. Oral glucocorticoids are **conditionally** recommended *against* as initial monotherapy.	Very low	PICO 20: In patients with treatment naïve, newly diagnosed sJIA without MAS, should non-DMARD treatment (NSAIDs, glucocorticoids) be used as initial therapy?	61-67
csDMARDs are **strongly** recommended against as initial monotherapy.	Very low	PICO 21. In patients with treatment naïve, newly diagnosed sJIA without MAS, should DMARD treatment (methotrexate, calcineurin inhibitor) be used as initial therapy and is there a preferred order?	67-68
Biologic DMARDs (IL-1 and IL-6 inhibitors) are **conditionally** recommended as initial monotherapy. --- There is no preferred agent	Very low	PICO 22. In patients with treatment naïve, newly diagnosed sJIA without MAS, should biologic treatment (Anakinra, Canakinumab, Tocilizumab or others) be used as initial therapy and is there a preferred order?	69-71
IL-1 and IL-6 inhibitors are **strongly** recommended over a single or combination of csDMARDs for inadequate response or intolerance to	Very low	PICO 23. In patients with sJIA without MAS who do not respond to initial therapy with non-biologic treatments (NSAIDs, glucocorticoids, DMARDs), should	72-130

NSAIDs and/or glucocorticoids.		non-biologic treatments be combined or biologic treatment started?	
For sJIA without MAS with an inadequate response to IL-1 or IL-6 inhibitors and residual arthritis, the addition of a csDMARD or a switch to a different bDMARD is **strongly** recommended over use of chronic glucocorticoids. --- There is no preferred agent.	Very low	PICO 27. In sJIA patients who cannot achieve inactive disease despite treatment with both IL-1 and IL-6 agents and/or are chronically steroid dependent, is chronic stable steroid treatment superior to non-steroid treatments (cytoxan or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) at achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimize side effects/medication toxicity?	138

Table 6: sJIA with MAS			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
*Formal recommendation deferred	Very low	PICO 24. In patients with sJIA, does the presence of subclinical MAS alter the treatment paradigm?	130
IL-1 and IL-6 inhibitors are **conditionally** recommended over calcineurin inhibitors alone, in order to achieve inactive disease and resolution of MAS. --- There is no preferred agent. Glucocorticoids are **conditionally** recommended as part of initial treatment of sJIA with MAS	Very low	PICO 25. In patients with sJIA and overt MAS, Is biologic therapy superior to calcineurin inhibitors in achievement of inactive disease and resolution of MAS?	131-136
*Formal recommendation deferred	Very low	PICO 26. For non-response or partial response to biologic therapy, is addition of calcineurin inhibitor superior to etoposide or IVIG or plasmapheresis at achievement of inactive disease, resolution of MAS?	137-138
bDMARDs or csDMARDs are **strongly** recommended over chronic glucocorticoids	Very low	PICO 27. In sJIA patients who cannot achieve inactive disease despite treatment with both IL-1 and	138

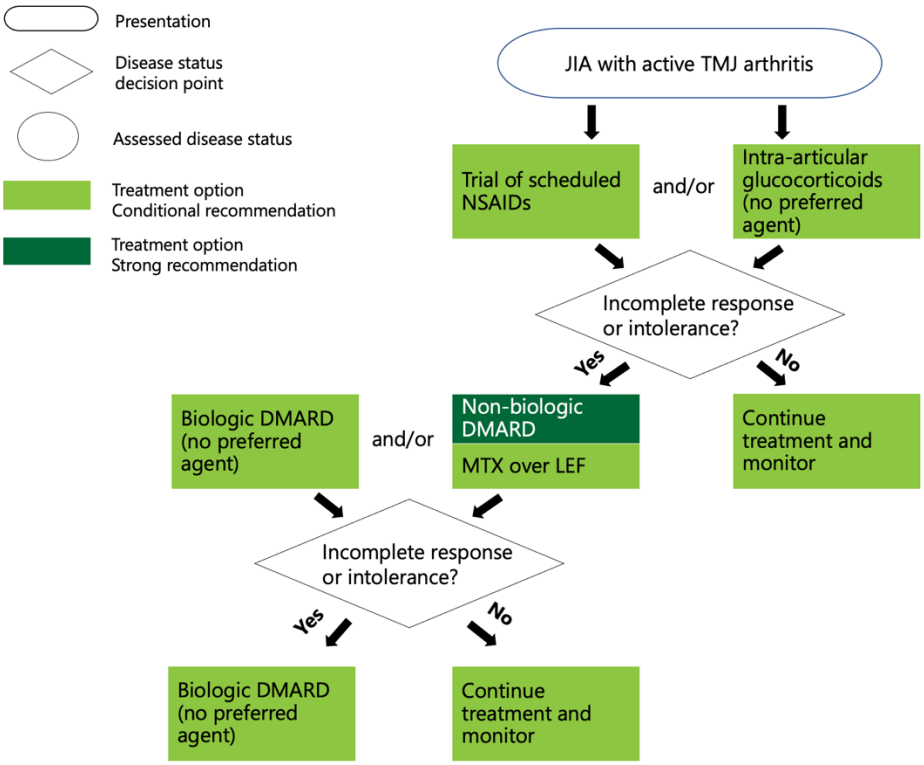
for residual arthritis and an incomplete response to IL-1 and/or IL-6 inhibitors. ---------- There is no preferred agent.		IL-6 agents and/or are chronically steroid dependent, is chronic stable steroid treatment superior to non-steroid treatments (cytoxan or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) at achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimize side effects/medication toxicity?	

Table 7: sJIA inactive disease			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
Tapering and discontinuing glucocorticoids is **strongly** recommended after inactive disease has been attained	Very low	PICO 28. In sJIA patients with inactive disease treated with oral steroids, is taper to discontinuation of steroids superior to continuing long-term stable dose steroids for preventing disease flare and minimizing side effects/medication toxicity?	139
Tapering and discontinuing bDMARDs is **conditionally** recommended after inactive disease has been attained.	Very low	PICO 29: In sJIA patients in clinical remission on biologic monotherapy, is tapering by decreasing dose superior to tapering dosing interval at preventing disease exacerbation, preventing development of anti-drug antibodies and minimizing medication toxicity?	140-143



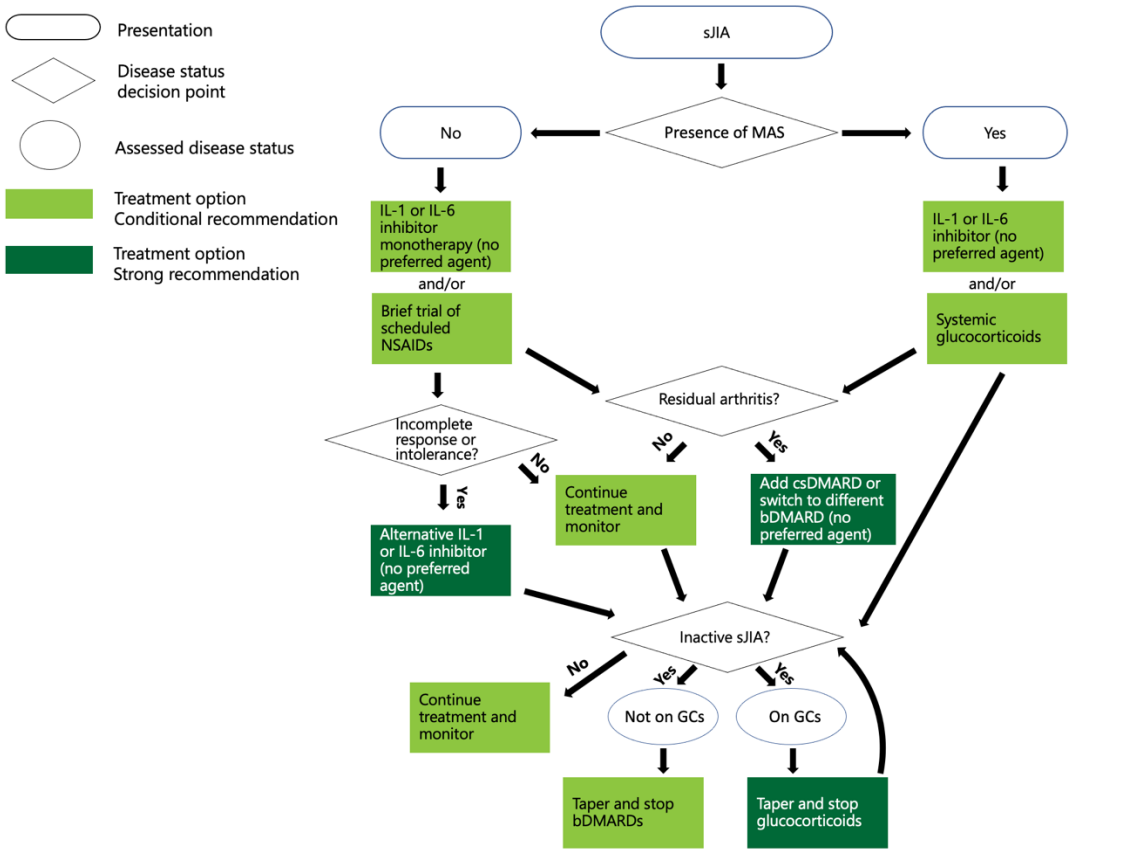
DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, LEF = leflunomide, MTX = methotrexate, NSAIDs = non-steroid anti-inflammatories, SSZ = sulfasalazine, TMJ = temporomandibular joint

Figure 2. Treatment algorithm for TMJ arthritis



DMARD = disease-modifying antirheumatic drug, LEF = leflunomide, MTX = methotrexate, NSAIDs = non-steroid anti-inflammatories, TMJ = temporomandibular joint

Figure 3. Treatment algorithm for systemic JIA



bDMARD = biologic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug, GCs = glucocorticoids, IL = interleukin, NSAIDs = non-steroid anti-inflammatories

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