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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

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Objective. To provide recommendations for the management of juvenile idiopathic arthritis (JIA) with a focus on nonpharmacologic therapies, medication monitoring, immunizations, and imaging, irrespective of JIA phenotype.

Methods. We developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes questions. After conducting a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation approach was used to rate the quality of evidence (high, moderate, low, or 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. Recommendations in this guideline include the use of physical therapy and occupational therapy interventions; a healthy, well-balanced, age-appropriate diet; specific laboratory monitoring for medications; widespread use of immunizations; and shared decision-making with patients/caregivers. Disease management for all patients with JIA is addressed with respect to nonpharmacologic therapies, medication monitoring, immunizations, and imaging. Evidence for all recommendations was graded as low or very low in quality. For that reason, more than half of the recommendations are conditional.

Conclusion. This clinical practice guideline complements the 2019 American College of Rheumatology JIA and uveitis guidelines, which addressed polyarthritis, sacroiliitis, enthesitis, and uveitis, and a concurrent 2021 guideline on oligoarthritis, temporomandibular arthritis, and systemic JIA. It serves as a tool to support clinicians, patients, and caregivers in decision-making. The recommendations take into consideration the severity of both articular and nonarticular 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 decisions, as always, should be made by the treating clinician and 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 juvenile idiopathic arthritis (JIA) guidelines (1,2) began in 2017. 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 2 articles in 2019 (3,4). The second part, presented here in 2 articles, covers 1) oligoarthritis, temporomandibular joint (TMJ) arthritis, and systemic JIA, and 2) nonpharmacologic treatments, patient monitoring, immunizations, and imaging (5). The methods and literature review described below reflect the unified process used for the second part of these guidelines, including both articles.

We developed clinically relevant Patient/Population, Intervention, Comparison, and Outcomes (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 and the need to include recommendations on nonpharmacologic therapies.

METHODS

This guideline followed 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 include GRADE methodology (6,7), and adheres to Appraisal of Guidelines, Research and Evaluation criteria (8). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract) includes a detailed description of the methods. Briefly, the Core Leadership Team (KBO, DBH, DJL, 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 (for search terms, see Supplementary Appendix 2,

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https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract), graded the quality of evidence (high, moderate, low, or very low), and produced the evidence report (Supplementary Appendix 3, https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract). It should be noted 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 (Supplementary Appendix 4, https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract).

A panel of 15 members, including young adults with JIA and caregivers of children with JIA, met virtually (moderated by the principal investigator [KBO]), reviewed the evidence report, and provided input to the Voting Panel. Two members of this panel 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. Examples of each class of intervention addressed in the recommendations are shown in Table 1. Rosters of the Core Leadership Team, Literature Review Team, and both panels are included in Supplementary Appendix 5 (https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract).

Table 1. Classes of interventions

Nonsteroidal antiinflammatory drugs	Any at therapeutic dosing (ibuprofen, naproxen, tolmetin, indomethacin, meloxicam, nabumetone, diclofenac, piroxicam, etodolac, celecoxib)
Conventional synthetic disease-modifying antirheumatic drugs	Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors (cyclosporin A, tacrolimus)
Biologic disease-modifying antirheumatic drugs	Tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol); other biologic response modifiers (abatacept, tocilizumab, anakinra, canakinumab)
Targeted synthetic disease-modifying antirheumatic drugs	JAK inhibitor (tofacitinib)
Glucocorticoids	Oral (any); intravenous (any); intraarticular (triamcinolone acetonide, triamcinolone hexacetonide)
Immunizations	Live attenuated; inactivated
Nonpharmacologic therapies	Physical therapy; occupational therapy; dietary changes; herbal supplements

Guiding principles

The development of the recommendations presented herein was guided by the following principles:

1. Consistent with the ACR's 2019 JIA guidelines, these recommendations are for persons already diagnosed as having JIA.
2. Coexisting extraarticular conditions that would influence disease management and monitoring, such as uveitis, psoriasis, or inflammatory bowel disease, are not addressed within these guidelines.
3. Recommendations for immunizations were evaluated to be consistent with guidelines from the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) while taking into consideration the unique needs of persons with JIA.
4. Recommendations are intended to be used by all clinicians caring for persons with JIA.
5. Shared decision-making with families and patients is critical.

RESULTS/RECOMMENDATIONS

The initial literature review (through August 7, 2019) identified 4,308 articles in searches for all PICO questions pertaining to oligoarthritis, TMJ arthritis, systemic JIA, and the topics addressed in this report, including nonpharmacologic therapies, nutrition, supplements, medication monitoring, immunizations, and imaging. A July 9, 2020 search update identified 367 more references, for a total of 4,675 articles after duplicates and non-English publications were removed. After exclusion of 2,291 titles and abstracts, 2,384 full-text articles were screened. Of these, 1,939 were excluded (Supplementary Appendix 6, on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract), leaving 445 articles to be considered for the evidence report. Ultimately, 336 articles 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 and, as per GRADE methodology, were categorized as very low (Tables 2–6). The recommendations that follow are based on 62 PICO questions. Several PICO questions were split into 24 sub-PICO questions to

Table 2. Strength of recommendations and quality of supporting evidence

Topic	Strength of recommendation			Quality of supporting evidence			
	No. of recommendations	Conditional	Strong	Very low	Low	Moderate	High
Nonpharmacologic therapies	4	2	2	4	0	0	0
Medication monitoring*	20	17	3	17	0	0	0
Infection surveillance/immunizations	7	3	4	5	2	0	0
Imaging	2	1	1	2	0	0	0
Total	33	23	10	28	2	0	0

* Lack of evidence for tofacitinib given the US Food and Drug Administration approval date.

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 3–6, which include reference(s) to which PICO question(s) in the evidence report correspond to the recommendation statement.

Nonpharmacologic therapies (Table 3)

Patient/caregiver panelists specifically asked that recommendations for nonpharmacologic treatment be included in this guideline, although they understood that evidence to support specific statements is generally lacking.

Physical and occupational therapy (PT/OT)

PT and OT are conditionally recommended regardless of concomitant pharmacologic therapy.

Reasons for using PT or OT include maintaining or improving joint range of motion (particularly for contractures), improving strength, reversing functional deficits, improving endurance, preventing injury, and promoting improved participation in activities of daily living, family routines, and occupations (9,10).

Nutrition

A discussion of healthy, age-appropriate diet is strongly recommended.

Use of a specific diet to treat JIA is strongly recommended *against*.

Ample evidence supports the value of a healthy, balanced, nutrient-dense diet for all children, with consideration of specific age-appropriate nutritional requirements (e.g., fat, calcium)

Table 3. Nonpharmacologic therapies*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
A discussion of healthy, age-appropriate diet is **strongly** recommended.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	48–49
Use of a specific diet to treat JIA is **strongly** recommended *against*.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	48–49
Use of supplemental or herbal interventions specifically to treat JIA is **conditionally** recommended *against*.	Very low	PICO 17. In children with JIA with active TMJ arthritis, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	60
Physical and occupational therapy are **conditionally** recommended regardless of concomitant pharmacologic therapy.	Very low	PICO 8. In children with oligoarticular JIA, regardless of disease activity and poor prognostic features, should PT/OT versus no PT/OT (regardless of concomitant medical therapy) be recommended?	49–51
		PICO 18. In children with JIA with active TMJ arthritis, regardless of disease activity and poor prognostic features, should PT versus no PT (regardless of concomitant medical therapy) be recommended?	60

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis; TMJ = temporomandibular joint; PT = physical therapy; OT = occupational therapy.
† In Supplementary Appendix 3, on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract.

Table 4. Medication monitoring*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
NSAIDs: Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months is **conditionally** recommended.	Very low	PICO 30. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children receiving long-term daily NSAID treatment?	144–145
MTX: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **strongly** recommended.	Very low	PICO 31. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children being treated with MTX (oral or subcutaneous)?	145–150
Decreasing the MTX dosage or withholding MTX is **conditionally** recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.	Very low	PICO 32. After MTX (oral or subcutaneous) is initiated, is there a recommended medication change in response to elevated LFT results and decreased neutrophil or platelet count?	150–153
Use of folic/folinic acid in conjunction with MTX is **strongly** recommended.	Very low	PICO 7. In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are used, versus not recommending them?	60
SSZ: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 33. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children with JIA being treated with SSZ?	153–155
Decreasing the SSZ dosage or withholding SSZ is **conditionally** recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.	Very low	PICO 34. After SSZ is initiated, is there a recommended medication change in response to elevated LFT results and decreased neutrophil or platelet count?	155–157
LEF: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3-4 months thereafter is **conditionally** recommended.	Very low	PICO 35. Should children with JIA receiving LEF have serum creatinine testing, urinalysis, CBC count, and LFTs before and during treatment, per manufacturer's recommendations?	157–158
Altering LEF administration is **conditionally** recommended if a clinically relevant elevation in LFT results occurs (temporary withholding of LEF if the ALT level is >3 times the upper limit of normal [ULN]), as per the package insert.	Very low	PICO 36. After LEF is initiated, should medication dosage be altered according to the package insert in response to elevated LFT results?	158–159
Baseline and annual retinal screening after starting HCQ are **conditionally** recommended.	Very low	PICO 37. Should children with JIA receiving treatment with HCQ have annual screening tests with automated visual fields, if age appropriate, plus spectral-domain optical coherence tomography, versus starting annual screening 5 years after treatment initiation?	159
HCQ: Monitoring via CBC counts and LFTs annually is **conditionally** recommended.	Very low	PICO 38. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel) for children with JIA being treated with HCQ?	159
TNFi: Monitoring via CBC counts and LFTs annually is **conditionally** recommended.	Very low	PICO 39. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving TNFi treatment?	160–161
Abatacept: Doing no routine laboratory monitoring is **conditionally** recommended.	Very low	PICO 40. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving abatacept treatment?	161–162
Tocilizumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels every 6 months is **conditionally** recommended, as per the package insert.	Very low	PICO 41. Should children with JIA receiving tocilizumab have serum creatinine testing, urinalysis, CBC count, and LFTs before and during treatment, per manufacturer's recommendations?	162

(Continued)

Table 4. (*Cont'd*)

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Altering tocilizumab administration is **conditionally** recommended if monitoring reveals elevated LFT results (if 1–3 times the ULN, decrease the dosage or increase the interval between doses, if >3 times the ULN, withhold administration, if >5 times the ULN, discontinue treatment), neutropenia (500–1,000/mm^3), or thrombocytopenia (50,000–100,000/mm^3), as per the package insert.	Very low	PICO 42. After tocilizumab is initiated, should medication dosage be altered according to the package insert in response to elevated LFT results, neutropenia, and/or thrombocytopenia?	163
Anakinra: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 43. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving anakinra treatment?	163–164
Canakinumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended.	Very low	PICO 44. Is there a recommended laboratory screening schedule (CBC count, comprehensive metabolic panel, and urinalysis) for children with JIA receiving canakinumab treatment?	164
Tofacitinib: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels 1–2 months after starting treatment is **conditionally** recommended, as per the package insert. Altering tofacitinib administration is **strongly** recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is <8 gm/dl or decreases by >2 gm/dl, or for severe neutropenia (<500/mm^3) or lymphopenia (<500/mm^3), as per the package insert.	‡	‡	‡

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; CBC = complete blood cell; LFTs = liver function tests; MTX = methotrexate; JIA = juvenile idiopathic arthritis; SSZ = sulfasalazine; LEF = leflunomide; ALT = alanine aminotransferase; ULN = upper limit of normal; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor.
† In Supplementary Appendix 3, on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract.
‡ Given recent approval for JIA and limited experience, recommendations are based on clinical trial, US Food and Drug Administration guidance, and evidence in adults.

(11,12). Therefore, it is worthwhile to address the importance of an age-appropriate diet (13). However, there is no evidence to date that supports the use of a specific diet alone to treat JIA (14,15). Furthermore, some overly restrictive diets (e.g., gluten-free, dairy-free) may result in nutritional deficits and risk of other harms (e.g., delay in treatment, cost, inconvenience).

Supplements

Use of supplemental or herbal interventions specifically to treat JIA is conditionally recommended *against*.

Voting panelists had concerns about the safety of unregulated supplements and herbal formulations and stressed the importance of discussion and transparency regarding their use. Some evidence of efficacy supports the use of supplements (e.g., fish oils) to treat joint inflammation in adults, but there are only very limited efficacy and safety data for JIA (16).

Monitoring

Medications (Tables 4 and 5)

When making decisions regarding laboratory monitoring to detect medication toxicity, the risk of adverse events and patients'/caregivers' desire for safety should be balanced with the pain, inconvenience, and cost of phlebotomy and laboratory tests. The following recommendations pertain to specific medications or medication classes. If a child is receiving >1 medication, the more frequent schedule for laboratory testing is recommended. In formulating the recommendations below, the Voting Panel considered the US Food and Drug Administration (FDA) prescription drug labels (package inserts) in addition to the studies included in the systematic review.

For medications that are known teratogens (e.g., methotrexate, leflunomide), when applicable, pregnancy testing should be considered before usage, and counseling on effective methods of contraception is recommended (17). When required by the

Table 5. Medication monitoring*

	MTX†‡	SSZ†	LEF‡	Tocilizumab	Anakinra	Tofacitinib	Canakinumab	NSAIDs†	HCQ	TNFi	Abatacept
CBC/diff. count and LFTs											
Baseline 1–2 months after starting Every 3–4 months thereafter§	X	X	X	X	X	X	X	–	–	–	–
CBC/diff. count and LFTs Baseline Every 6–12 months	–	–	–	–	–	–	–	X	–	–	–
CBC/diff. count and LFTs Baseline Once yearly	–	–	–	–	–	–	–	–	X	X	–
Lipid panel Baseline Every 6 months	–	–	–	X	–	–	–	–	–	–	–
Lipid panel Baseline 4–8 weeks after starting	–	–	–	–	–	X	–	–	–	–	–
Eye examination Baseline Once yearly	–	–	–	–	–	–	–	–	X	–	–
None required	–	–	–	–	–	–	–	–	–	–	X

* If the patient is receiving >1 medication, a more restrictive schedule should be used. MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; NSAIDs = nonsteroidal antiinflammatory drugs; HCQ = hydroxychloroquine; TNFi = tumor necrosis factor inhibitor; CBC/diff. = complete blood cell with differential; LFTs = liver function tests.
† Include renal function testing with laboratory studies.
‡ Pregnancy testing should be considered before use, and counseling on use of effective methods of contraception is recommended.
§ Should be rechecked sooner if dosage is increased.

FDA, a Risk Evaluation and Mitigation Strategy should be applied (18).

Baseline laboratory testing is conditionally recommended prior to treatment initiation, for all medications.

Baseline laboratory evaluation is recommended to identify potential contraindications to a specific treatment. This should include complete blood cell count (CBC) with differential cell count and liver function tests (LFTs) (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase), plus renal function tests (e.g., blood urea nitrogen, creatinine, and urinalysis) for patients being treated with methotrexate, sulfasalazine, or nonsteroidal anti-inflammatory drugs (NSAIDs) and lipid profiles for patients being treated with tocilizumab and tofacitinib. Additional laboratory testing may be performed at the discretion of the treating clinician.

NSAIDs (all)

Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months is conditionally recommended.

NSAIDs are known to be associated with gastrointestinal (GI) bleed risk and liver and kidney toxicity in adults with rheumatic diseases. Although these may be rare in children, the Voting Panel deemed it important to monitor for laboratory abnormalities periodically in children receiving long-term NSAIDs. Because GI distress when consistently taking NSAIDs is common, patients/caregivers strongly suggested that clinicians should inquire about and potentially treat GI symptoms, which may not always be spontaneously reported (19,20).

Methotrexate

Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is strongly recommended.

Voting panelists debated whether frequent methotrexate toxicity monitoring (as per the package instructions, i.e., CBC count monthly and renal/liver function every 1–2 months) should be recommended for children, given the low incidence of liver toxicity (21,22). However, rare potential for serious harm in children and consistency in monitoring schedule during pediatric-to-adult care transition influenced the panel's decision to provide a strong recommendation for frequent monitoring (23).

Decreasing the methotrexate dosage or withholding methotrexate is conditionally recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.

The panel did not reach consensus on specific values to define elevated LFT results or reduced cell counts. Clinically relevant laboratory abnormalities may include repetitive minor abnormalities or a single major abnormality. LFT results may be transiently elevated if testing is done within 2 days after administration of methotrexate; hence, testing within this window is discouraged.

Use of folic/folinic acid in conjunction with methotrexate is strongly recommended.

Use of folic/folinic acid with methotrexate may mitigate adverse events and improve tolerability (24,25).

Sulfasalazine

Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Recommended monitoring is less frequent than suggested in the package insert for sulfasalazine (which suggests CBC counts and LFTs every second week in the first 3 months, monthly during the next 3 months, and then every 3 months) because most children have fewer comorbidities and polypharmacy usage is rare, allowing for fewer drug interactions (26–28).

Decreasing the sulfasalazine dosage or withholding sulfasalazine is conditionally recommended if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found.

While adverse reactions can be serious, including Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) (29), the Voting Panel thought the data were too limited to make this recommendation strong.

Leflunomide

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Recommended LFT monitoring is less frequent than suggested in the leflunomide package insert (which recommends CBC counts and ALT testing monthly for 6 months and then every 6–8 weeks) (30) because most children have fewer comorbidities and polypharmacy usage is rare, allowing for fewer drug interactions (31).

Altering leflunomide administration is conditionally recommended if a clinically relevant elevation in LFT results occurs (temporary withholding of leflunomide if the ALT level is >3 times the upper limit of normal [ULN]), as per the package insert.

Elimination of leflunomide can be accelerated with the use of cholestyramine or activated charcoal (30), when required.

Hydroxychloroquine

Monitoring via CBC counts and LFTs annually is conditionally recommended.

As per the hydroxychloroquine package insert (32), periodic laboratory monitoring should be performed if patients are receiving prolonged therapy.

Baseline and annual retinal screening after starting hydroxychloroquine are conditionally recommended.

Yearly screening should be performed in pediatric patients, rather than waiting 5 years between baseline and subsequent annual screening as recommended for hydroxychloroquine-treated adults (33). The cumulative and developmental effects of hydroxychloroquine are a concern because children may be receiving treatment for prolonged periods and may not be able to articulate vision concerns. Baseline retinal screening should be completed as soon as possible and combined with screening for uveitis when feasible. Treatment does not need to be delayed for initial retinal screening.

Tumor necrosis factor inhibitors (TNFi) (all)

Monitoring via CBC counts and LFTs annually is conditionally recommended.

As per package inserts, cytopenias and abnormal LFTs have been reported in association with TNFi treatment. Therefore, evaluation yearly at minimum is recommended (34,35).

Abatacept

Doing no routine laboratory monitoring is conditionally recommended.

In placebo-controlled clinical trials of abatacept for JIA, children had similar CBC counts and LFT results irrespective of treatment arm (36), and no laboratory monitoring is suggested in the package insert (37). The decision to perform laboratory monitoring may be discussed with patients/caregivers who, like some of the voting panelists, may prefer routine monitoring to identify potential adverse events, even if rare.

Tocilizumab

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Monitoring of lipid levels every 6 months is conditionally recommended, as per the package insert.

Altering tocilizumab administration is conditionally recommended if monitoring reveals elevated LFT results (if 1–3 times the ULN, decrease the dosage or increase the interval between doses, if >3 times the ULN, withhold administration, if >5 times the ULN, discontinue treatment), neutropenia (500–1,000/mm^3), or thrombocytopenia (50,000–100,000/mm^3), as per the package insert.

As per the package insert, initiation of tocilizumab treatment is not recommended in patients with elevated LFT results (>1.5 times the ULN) (38). In patients in whom LFT results become highly elevated (>5 times the ULN), treatment should be discontinued. The package insert does state that the decision to discontinue tocilizumab due to a laboratory abnormality should be based on the medical assessment of the individual patient. For that reason, this recommendation is conditional.

Anakinra

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Abnormal LFTs and neutropenia may occur with the use of anakinra (39). For that reason, as well as the severity of the underlying disease, regular monitoring should be performed.

Canakinumab

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Abnormal LFT results and cytopenias were noted during a phase III clinical trial of canakinumab for systemic JIA (40). For that reason, as well as the severity of the underlying disease, regular monitoring should be performed.

Tofacitinib

Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is conditionally recommended.

Monitoring of lipid levels 1–2 months after starting treatment is conditionally recommended, as per the package insert.

Altering tofacitinib administration is strongly recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is <8 gm/dl or decreases by >2 gm/dl, or for severe neutropenia (<500/mm^3) or lymphopenia (<500/mm^3), as per the package insert.

Data on tofacitinib were not part of the initial literature review, but the panel considered it important to include this recommendation because in 2020 tofacitinib was approved by the FDA for treatment of JIA (41). An additional Voting Panel session was organized for this purpose.

Infection surveillance (Table 6)

Tuberculosis (TB)

TB screening is conditionally recommended prior to starting biologic disease-modifying antirheumatic drug (DMARD) therapy and when there is a concern for TB exposure thereafter.

Concern for TB exposure should be interpreted broadly and could include contact with someone with active TB, travel to locations where TB is endemic, contact with high-risk individuals (e.g., prisoners, visitors from TB-endemic areas), or living in communities with a higher frequency of TB (42,43). The conditional recommendation reflects 2 major concerns: In certain urgent clinical situations, the harms of waiting for results of TB screening may outweigh the benefits of treatment. For example, in a child with active systemic JIA and macrophage activation syndrome (MAS), treatment should not be delayed pending TB screening results. Annual screening for TB can pose problems for children and families. Insurers or institutions may require a specific method that is potentially problematic (44,45). For example, TB screening may be done by questionnaire; however, this depends on knowledge of exposure. The interferon-γ release assay is expensive, not valid in young children, and subject to frequent indeterminate results, particularly during anergy. Tuberculin skin testing is user dependent and inconvenient because 2 visits are required. In addition, false-positive results often lead to unnecessary chest radiography and isoniazid treatment. For children living in areas with a low prevalence of TB, mandatory annual laboratory-based TB screening represents a high burden of cost, inconvenience, and pain that is not supported by the literature reviewed.

Viral infections

Voting panelists could not reach consensus on whether all children with JIA should have antibody titers for specific infections (e.g., measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication, although more panelists were against this practice than for it. Some panelists believed the information might be useful for risk management in case of an outbreak or exposure. Most believed that screening a fully immunized child was of low benefit and might delay treatment and incur unnecessary cost. Although

Table 6. Infection surveillance/immunizations*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
No consensus achieved.	Very low	PICO 45. Should all children with JIA have infection titers (measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication?	164–166
Immunization is **conditionally** recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting immunosuppressive medications.	Very low	PICO 46. Should children with JIA with no evidence of immunity to important infections have a booster immunization prior to starting immunosuppressive medication?	166
TB screening is **conditionally** recommended prior to starting biologic DMARD therapy and when there is a concern for TB exposure thereafter.	Very low	PICO 47. Should screening for TB be done prior to starting biologic DMARD therapy and then annually in children with JIA?	167–169
	Very low	PICO 48. In children with JIA receiving biologic DMARD therapy, is there a preferred method of TB screening?	169–171
Immunizations (live and inactivated) are **strongly** recommended for children with JIA who are not receiving immunosuppressive treatment.	Very low	PICO 49. In children with JIA not receiving immunosuppressive treatment, do inactivated or live attenuated vaccines result in flare of disease?	172–175
Annual inactivated influenza immunization is **strongly** recommended for all children with JIA.	Low	PICO 50. In children with JIA not receiving immunosuppressive treatment, are patients able to develop protective antibodies against infections targeted by the vaccine?	175–179
		PICO 52. In children with JIA receiving immunosuppressive treatment, are patients able to develop protective antibodies against infections targeted by the vaccine?	184–195
Inactivated vaccines are **strongly** recommended for children who are receiving immunosuppressive treatment.	Very low	PICO 51. In children with JIA receiving immunosuppressive treatment, do inactivated vaccines result in flare of disease?	180–184
Live attenuated vaccines are **conditionally** recommended *against* in children with JIA who are receiving immunosuppressive treatment.	Low	PICO 53. In children with JIA receiving immunosuppressive treatment, can treatment with live attenuated vaccines be given safely (initial dose, booster dose)?	195–198
Vaccines are **strongly** recommended for household contacts of children with JIA who are receiving immunosuppressive treatment.	Very low	PICO 54. Can live attenuated vaccines be used safely in the households of children with JIA receiving immunosuppressive treatment?	198

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis; TB = tuberculosis; DMARD = disease-modifying antirheumatic drug.
† In Supplementary Appendix 3, on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract.

screening for hepatitis B and C is done in adults prior to treatment with DMARDs, most children are effectively immunized against hepatitis B as infants (46), and the number of children below the age of 19 years with hepatitis C in the US remains exceedingly low (47).

Immunizations (Table 6)

Because some patients/caregivers have concerns about the safety of vaccines in JIA, clinicians must discuss with families the evidence that strongly supports their benefits and safety. Whenever possible, immunizations should be administered according to the schedule recommended by the ACIP and the AAP or corresponding national recommendations. As immunization schedules are frequently updated, clinicians should ensure that they are using the most recent versions (48). Multiple cohort studies have demonstrated that most children with JIA mount a protective response after immunizations and that immunizations do not cause disease flare (49–52).

Annual inactivated influenza immunization is strongly recommended for all children with JIA

All children with JIA, including children receiving immunosuppressive medication, should receive inactivated influenza immunizations annually (53). This recommendation is strong despite very low evidence in JIA, given the overwhelming preponderance of supporting literature in other inflammatory diseases and the risk of severe infection (54–57). Intranasal influenza immunization is contraindicated for children with JIA who are receiving immunosuppressive treatment, as it is a live attenuated immunization.

Table 7. Imaging*

Recommendation	Certainty of evidence	PICO evidence report(s) basis	Page no(s). of evidence tables†
Use of radiography as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is **strongly** recommended *against*.	Very low	PICO 55. In children with JIA, is any specific imaging technique recommended to best detect inflammation and damage, make a diagnosis, and predict structural damage, flare, or treatment response?	199–268
Imaging guidance is **conditionally** recommended for use with intraarticular glucocorticoid injections of joints that are difficult to access, or to specifically localize the distribution of inflammation.	Very low	PICO 56. In children with JIA who require intraarticular glucocorticoid injections, should injections be done with imaging guidance?	269–279

* PICO = Patient/Population, Intervention, Comparison, and Outcomes; JIA = juvenile idiopathic arthritis.
† In Supplementary Appendix 3, on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract.

Immunizations (live attenuated and inactivated) are strongly recommended for children with JIA who are not receiving immunosuppressive treatment

Children with JIA have a higher risk of severe infection compared to unaffected children, making adequate protections against infection essential (58). Considerations of the relative degree of immunosuppression from various immunosuppressive medications used for JIA is beyond the scope of this project. To err on the side of safety, these recommendations apply equally to any child receiving an immunosuppressive medication for JIA (e.g., DMARDs, long-term systemic glucocorticoids) (59).

Inactivated vaccines are strongly recommended for children with JIA who are receiving immunosuppressive treatment.

Persons with JIA should receive inactivated vaccines as per location-specific, published age-related schedule. Specifically, children undergoing immunosuppressive treatment should receive the 23-valent pneumococcal polysaccharide vaccine in addition to the 13-valent pneumococcal conjugate vaccine recommended for all children (60,61).

Live attenuated vaccines are conditionally recommended *against* in children with JIA who are receiving immunosuppressive treatment.

As reported by the US Centers for Disease Control and Prevention (CDC), severe complications have followed vaccination with certain live attenuated viral and bacterial vaccines among immunosuppressed persons (62). Therefore, guidelines recommend that persons with most forms of altered immunocompetence should not receive live attenuated vaccines. According to the CDC, live-virus vaccination should be deferred for 1–6 months after discontinuation of immunosuppressive treatment, depending on the specific agent (62). There is some evidence that booster immunization with live attenuated vaccines may be safe for children with JIA who are receiving certain specific immunosuppressants (52,63). More work is needed to support a formal recommendation in this setting, as studies thus far have been underpowered to detect rare, serious harms.

Immunization is conditionally recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting immunosuppressive medications.

This recommendation excludes active, untreated systemic JIA in which delaying treatment initiation for vaccinations may be prohibitive. As per the CDC, immunosuppressive therapy should not be initiated until 4 weeks after administration of a live vaccine and ideally 2 weeks after administration of an inactivated vaccine. If withholding/delaying medication is not feasible, live-attenuated vaccine immunization should be deferred and given at a later time when disease is in remission and the child is no longer being treated (64).

Vaccines are strongly recommended for household contacts of children with JIA who are receiving immunosuppressive treatment.

Immunization of household members of immunosuppressed children is critical to diminish exposure in the home. Household contacts and other close contacts of persons with altered immunocompetence should receive all age- and exposure-appropriate vaccines, whether inactivated or live, with the exception of smallpox vaccine (59,65). If a family member has received varicella vaccine and develops a rash, direct contact should be avoided until the rash resolves. Likewise, all members of the household should wash their hands after changing the diaper of an infant who recently received rotavirus vaccine, to minimize transmission. If concerns remain, CDC or local guidelines can be reviewed prior to immunization.

Imaging (Table 7)

Use of radiography as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is strongly recommended *against*.

Radiography is not sensitive enough to assess joint inflammation and enthesitis in children and may delay clinically appropriate imaging and treatment (66–68). Unnecessary radiation can result in significant harm to developing children (69). Conventional radiography should be restricted to the assessment of JIA-associated damage or to investigate alternative diagnoses.

Imaging guidance is conditionally recommended for use with intraarticular glucocorticoid injections of joints that are difficult to access, or to specifically localize the distribution of inflammation.

This recommendation includes ultrasound and/or fluoroscopy. Specific joints that may be difficult to access include sacroiliac joints, hips, TMJs, shoulder, midfoot, and subtalar joints. This recommendation is conditional because it is dependent on the skill of the practitioner, availability of imaging, costs, and risk of delay in treatment (70–72).

DISCUSSION

The recommendations presented in this guideline are a companion to those published in 2019 (3,4) and concurrently (73) and cover areas not previously addressed in JIA: nonpharmacologic treatments, medication monitoring, immunization, and imaging. Similar to recommendations made for oligoarthritis, TMJ arthritis, and systemic JIA with and without MAS, one must view this guideline as a road map for future study (Supplementary Appendix 7, available on the *Arthritis Care & Research* website at https://onlinelibrary.wiley.com/doi/10.1002/acr.24839/abstract). Most of the available evidence was very low quality for the relevant PICO questions, contributing to 23 of the 33 recommendations being conditional. None of the recommendations were supported by moderate- or high-quality evidence.

Nowhere is the discrepancy between patient/caregiver interest and available data more evident than in the consideration of nonpharmacologic therapies, for which recommendations were included at patient/parent request. Use of specific diets and supplements was discussed extensively by the patient/caregiver panel, including sharing of suggested regimens and reference materials. There was a general belief that disease manifestations could be ameliorated by changes in foods consumed and great interest in participating in formal research studies on nutritional interventions. Most panelists recognized the importance of PT/OT, and inclusion of PT and OT specialists on the Voting Panel would allow for more specific recommendations in future guidelines.

Likewise, patients and caregivers discussed the stress of dealing with chronic illness and the need for mental health interventions. As recently as 2017, when the scope of this project was established, mental health care for children and families affected by rheumatic diseases was not a major focus. For this reason, although mental health was recognized by the Voting Panel as important, it was not formally addressed in this guideline. Future guidelines should include recommendations addressing mental health screening and treatments, with input from mental health professionals on the Voting Panel. This is particularly important given the impact of the COVID-19 pandemic on the mental health of persons with chronic disease (74).

Medication monitoring remains especially challenging in JIA, and balancing safety, cost, pain, and inconvenience can be very difficult. Some panel members asserted that monitoring was perhaps less important in a generally healthy pediatric population relative to adults with comorbidities. Due to the low frequency of serious comorbidities and interacting medications, and limited-to-no exposure to alcohol and other toxins, laboratory abnormalities requiring medication discontinuation are rare in children with JIA. However, other panel members believed strongly that monitoring needs to be routinely performed to identify rare but serious adverse events. Recommendations as written attempted to balance these concerns. Future research and guidelines should consider altered, less frequent monitoring schedules for younger children, given the potentially lower risks of toxicity and greater risks of frequent testing at the youngest ages.

The list of available immunosuppressive medications for JIA for which monitoring is required has grown substantially and will continue to expand. Two new agents were recently approved for use in polyarticular-course JIA: golimumab (a TNFi) and tofacitinib (a JAK inhibitor) (41,75). With regard to laboratory testing to detect abnormalities in monitoring for toxicity, voting panelists could not agree on a single definition of "clinically relevant" abnormal results and left this to the discretion of treating clinicians. Caregivers and patients expressed the challenges of balancing the need to ensure medication safety with the cost and inconvenience associated with blood withdrawal. It is hoped that in the future, effective, reliable treatments that require less monitoring will be available for JIA.

Voting panelists did believe strongly that age must be taken into consideration in requirements for infection screening in the US prior to initiation of treatment with DMARDs. TB, hepatitis B, and hepatitis C are extremely rare in fully immunized nonimmigrant children in the US, and annual TB screening presents a large and unnecessary burden. There were engaged discussions about screening for viral infections prior to the use of DMARDs; however, most thought that lack of immunity in a child known to be immunized was likely to be rare. Even if antibody titers were low or absent after vaccination, cell-mediated immunity was considered likely to be present.

In light of the COVID-19 pandemic, discussion of immunizations in these guidelines proved to be extremely timely. Despite the potential severity of vaccine-preventable infections in immunosuppressed populations, vaccine hesitancy remains common. Nonetheless, preventing infectious illnesses in an immunosuppressed patient population is critical. Many families have concerns regarding vaccine safety, immunogenicity, risk of flare, and other potential long-term consequences. Studies in JIA have consistently demonstrated the safety and effectiveness of vaccines to induce protective immune responses. Regarding immunization for COVID-19, available immunizations vary by age, accessibility, and country. There are currently no preferences for a specific vaccine in a given population of children with rheumatic disease. Physicians should refer to local recommendations. At the time this manuscript was approved for publication, the Pfizer-BioNTech COVID-19 vaccine was approved in the US for adolescents age ≥16 years (76) and authorized for emergency use in children 5–15 years of age (77,78). No vaccines for COVID-19 were yet available for younger children, although studies are ongoing. As none of the currently available vaccines against COVID-19 are live vaccines, recommendations should be similar to those stated above for inactivated vaccines. While specific guidance on immunizing children with rheumatic diseases against COVID-19 is still lacking, the ACR has published guidance on COVID-19 vaccines for adults with rheumatic and musculoskeletal diseases (79). Patients and family members have articulated the importance of health care providers for reliable medical information. We must be mindful that clinicians are trusted sources of information about this important public health issue and should discuss immunizations with their patients.

With regard to imaging, it is clear that different modalities are appropriate for different indications. Radiographs are not useful for evaluation of soft tissue disease, and continued third-party payor requirements for radiographs prior to any and all magnetic resonance imaging (MRI) are a waste of resources and a potential hazard to persons with JIA. MRI itself may require sedation, and there is concern that repeated sedation in young children may carry risks (80). More research is needed to define and standardize the best approaches to imaging in children with JIA for different diagnostic and disease management decision-making purposes.

Addressing each area of the JIA guidelines at the same time proved to be a Herculean task. This update of the ACR JIA guidelines has taken 4 years to complete, leading to 4 manuscripts; certain areas are already ready for further updates. Health care around the world is quickly changing in unforeseen ways, and rheumatologists have been thrust into the forefront of recent pandemic developments in an unparalleled manner (81). The pace of change will likely only increase, and guidelines will need to be updated nimbly and more frequently over time.

The low quality of evidence supporting most of the recommendations underscores the importance of clinical judgment and shared decision-making in everyday care of patients 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 to improve disease management in—and well-being of—all individuals living with JIA.

In conclusion, this 2021 updated ACR guideline for JIA recommends the use of PT and OT interventions; a healthy, well-balanced, age-appropriate diet; specific laboratory monitoring for different antirheumatic medications; widespread use of immunizations; and need for shared decision-making with patients/caregivers. The JIA guidelines will continue to be updated as new evidence emerges.

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