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American College of Rheumatology (ACR)
Juvenile Idiopathic Arthritis Guideline

Project Plan – June 2017

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project of the American College of Rheumatology (ACR) has the broad objective of developing an evidence-based clinical practice guideline for the management of juvenile idiopathic arthritis (JIA).

BACKGROUND

Juvenile idiopathic arthritis (JIA) is a collection of chronic idiopathic autoimmune non-infectious arthritides. By definition, disease onset is prior to 16 years of age and includes joint inflammation that is present for 6 weeks or more. JIA affects approximately 1 in 1,000 children and approximately 50% of children have oligoarticular disease (involves 4 or fewer joints), 40% have polyarticular (involves 5 or more joints), and ~10% have systemic symptoms along with arthritis (i.e., systemic arthritis).

The cardinal clinical features are persistent swelling and pain of the joints. Morning stiffness may be present, and typically improves throughout the day with joint use. Linear growth delay can occur in children with JIA, and untreated arthritis can lead to severe joint deformities and disability. Uveitis is the most common extra-articular manifestation and can lead to ocular complications and permanent vision loss. Regular screening by ophthalmology for early detection and timely treatment is crucial.

Treatment depends on the severity of disease and associated manifestations, including presence of systemic features and/or extraarticular manifestations. Biologic therapies have significantly changed the approach to treatment for JIA and new data continue to accumulate regarding their effectiveness. Given these data, updated recommendations for the treatment of JIA patients are needed to help clinicians optimize the care of these patients.

OBJECTIVES

The objective of this project is to develop recommendations for the pharmacologic and non-pharmacologic treatments for treatment juvenile idiopathic arthritis (JIA).

Specifically, we aim to:

1. Develop recommendations for the use of glucocorticoids, and non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of children with JIA and a polyarthritis course taking into consideration both safety and efficacy issues.

2. Develop recommendations for the use of glucocorticoids, and non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of children with axial arthritis, taking into consideration both safety and efficacy issues.

3. Develop screening guidelines and recommendations for the use of non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) for the treatment for children with acute and chronic JIA-associated uveitis.

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) will be developed by the principal investigators, systematic literature review leader, and a research librarian, with input from the Core Team. The search strategies will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (1). Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960s +).

The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library.

Search Limits

Only English language articles will be retrieved.

Grey Literature

The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

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Inclusion/Exclusion Criteria

See PICO questions (*Appendix A*), which outline the defined patient population, interventions, comparators and outcomes.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (Reference Manager) (2), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (3). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.

Phases

1. A search for randomized controlled trials and observational studies about interventions aimed at treatment of JIA and JIA-associated uveitis, and prevention of JIA flares and complications, will be performed to determine existing studies covering outcomes of interest. Subsequently, identified studies will be assessed using the RevMan (4) and GRADE Pro tools (5).
2. Chosen studies will be quality-assessed using the Cochrane Risk of Bias Tool (6), the Cochrane Effective Practice and Organization of Care Risk of Bias Tool (7) or the Newcastle-Ottawa Scale (3).
3. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking.

GRADE Methodology

GRADE methodology will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as 'quality' of evidence) will be graded as high, moderate, low or very low. The strength of recommendations will be graded as strong or conditional. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patient preferences and values, and the weight between benefits and harms. A series of articles that describe the GRADE methodology can be found on the GRADE working group's website: www.gradeworkinggroup.org.

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Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. An evidence profile, including a GRADE Summary of Findings table, will be prepared for each PICO question using Review Manager (RevMan) (2) and GRADEprofiler (GRADEpro) software (5). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision and publication bias), or upgrading the certainty in a body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that would reduce a demonstrated effect).

Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of 10 pediatric rheumatologists, two ophthalmologists, and two patient representatives, will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be anonymous; this vote will only be used to determine where consensus might or might not already exist and develop the voting panel meeting agenda. At the face-to-face voting panel meeting, chaired by the principal investigators, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting discussions will be supported by the literature review leader, the GRADE expert, and selected members of the literature review team, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. GRADE evidence profiles and summary of findings tables for each PICO question

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AUTHORSHIP

Authorship of the guideline will include: co-principal investigators, Drs. Sheila Angeles-Han and Sarah Ringold, as the lead authors; Dr. James Reston, literature review leader; Drs. Timothy Beukelman and Daniel Lovell, content experts; and Dr. Carlos A. Cuello Garcia, GRADE expert. Members of the literature review team and voting panel will also be authors. The Co-PIs will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.

DISCLOSURES/CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. *See Appendix B for participant disclosures.*

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APPENDIX A – PICO Questions

POLYARTHRITIS QUESTIONS

POPULATION:

This group includes children with JIA and polyarthritis (≥ 5 joints involved). This includes children from different ILAR JIA categories, but excludes children with systemic arthritis or axial arthritis. These guidelines are not intended to be applicable to children with JIA and other active extra-articular manifestations (e.g., psoriasis, uveitis, IBD) that may influence treatment decisions. Treatment groups currently considered are 1) low disease activity (LDA) versus moderate/high disease activity and 2) presence or absence of risk factors (presence of risk factors defined as one or more of the following: + RF, + anti-CCP, radiographic evidence of joint damage). Initial therapy is disease activity irrespective. The questions are intended to address typical patients.

INTERVENTIONS:

Nonsteroidal anti-inflammatory drugs (NSAIDs)	Any
Non-biologic disease modifying anti-rheumatic drugs (DMARDs)	Leflunomide, Methotrexate, Sulfasalazine Triple non-biologic DMARD: Methotrexate, Sulfasalazine, Hydroxychloroquine

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Biologic DMARDs	Tumor necrosis factor alpha inhibitors (TNFi): Adalimumab, Etanercept, Infliximab, Golimumab, [Certolizumab pegol] Other Biologic Response Modifiers (OBRM): Abatacept, Tocilizumab, Rituximab
Glucocorticoids	Oral: Any Intraarticular: Triamcinolone Acetonide, Triamcinolone Hexacetonide, Methylprednisolone Acetate
Medications *not* addressed	Tofacitinib (do not anticipate data available at the time of voting)
Non-medical interventions	Physical Therapy (PT) Occupational Therapy (OT)

OUTCOMES:

Critical Outcomes:

- QOL (e.g., PedsQL, CHQ, PROMIS, Quality Of My Life score)
- Disease activity (including active joint count, patient/parent global, MD global, ESR/CRP) as measured by the individual variables and/or composite disease activity measure (e.g., Pediatric ACR response, JADAS)
- ACR provisional criteria for clinical inactive disease

- Functional ability (e.g., CHAQ/PROMIS)
- Joint damage *requiring surgical intervention*
- Significant or life threatening adverse events (e.g., hospitalization, infection, malignancy)

Important Outcomes:

- Arthritis-related pain
- Preservation of normal growth and development
- Fatigue
- Joint damage
- Significant medication side effects leading to medication discontinuation

GENERAL MEDICATION

Non-biologic DMARDs

For the purposes of these recommendations, we will consider adequate trial of methotrexate to be 3 months. If no or minimal response after that time, recommend changing or adding therapy. If improvement has occurred, may consider an additional 3 months of treatment to assess full effectiveness.

1. In patients with polyarticular JIA, should methotrexate subcutaneous (SQ) versus methotrexate oral (PO) be recommended?
2. In patients with polyarticular JIA, should methotrexate versus leflunomide be recommended?
3. In patients with polyarticular JIA, should methotrexate versus sulfasalazine be recommended?

<u>*Glucocorticoids*</u>

For the purposes of these recommendations, bridging therapy is considered to be a short course of prednisone intended to control disease activity during DMARD or biologic initiation.

4. In patients with polyarticular JIA and LDA (risk factor irrespective), should adding a limited course of prednisone (e.g. bridging/dosing TBD) to initial therapy versus not adding prednisone be recommended?
5. In patients with polyarticular JIA and moderate/ HDA (risk factor irrespective), should adding a limited course of prednisone (e.g., bridging/dosing TBD) to initial therapy versus not adding prednisone be recommended?
6. In patients with polyarticular JIA and LDA (risk factor irrespective) with initial non-biologic DMARD therapy, should treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus adding a biologic be recommended?
7. In patients with polyarticular JIA and LDA (risk factor irrespective) with biologic therapy (+/- non-biologic DMARD), should adding treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus switching biologic be recommended?
8. In patients with polyarticular JIA and moderate/HDA (risk factor irrespective) with biologic therapy (+/- non biologic DMARD), should adding treatment with chronic low dose prednisone (e.g., 0.2 mg/kg/day or max 10 mg day) versus switching biologic be recommended?
9. In patients with polyarticular JIA and active disease (risk factor and current/prior treatment irrespective), should treatment with intraarticular glucocorticoids versus no treatment with intraarticular glucocorticoids be recommended?
10. In patients with polyarticular JIA, should treatment with intraarticular triamcinolone acetonide versus triamcinolone hexacetonide be recommended?

<u>*Biologics*</u>

This set of questions is intended to identify optimal administration (monotherapy versus combination with non-biologic DMARD) for the biologics addressed in these recommendations. The subsequent questions will assume optimal use of each biologic with the understanding that there may be situations in which biologic monotherapy is acceptable due to adequate patient response, side effects or other considerations. For patients

receiving a biologic in a "non-optimal" manner, would consider trial of optimal administration, as well as options below if response is inadequate and if not otherwise contraindicated.

11. In patients with polyarticular JIA, should etanercept monotherapy versus etanercept + non-biologic DMARD be recommended?
12. In patients with polyarticular JIA, should adalimumab monotherapy versus adalimumab + non-biologic DMARD be recommended?
13. In patients with polyarticular JIA, should infliximab monotherapy versus infliximab + non-biologic DMARD be recommended?
14. In patients with polyarticular JIA, should golimumab monotherapy versus golimumab + non-biologic DMARD be recommended?
15. In patients with polyarticular JIA, should abatacept monotherapy versus abatacept + non-biologic DMARD be recommended?
16. In patients with polyarticular JIA, should tocilizumab monotherapy versus tocilizumab + non-biologic DMARD be recommended?
17. In patients with polyarticular JIA, should abatacept monotherapy versus abatacept + non-biologic DMARD be recommended?

INITIAL THERAPY

No risk factors

18. In patients with polyarthritis on NSAID therapy and no risk factors, should continued NSAID monotherapy versus addition of non-biologic DMARD as initial therapy be recommended?
19. In patients with polyarthritis and no risk factors, should initial therapy with *triple* non-biologic DMARD versus methotrexate monotherapy as initial therapy be recommended?
20. In patients with polyarthritis and no risk factors, should initial therapy with *triple* non-biologic DMARD versus TNFi as initial therapy be recommended?
21. In patients with polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus TNFi as initial therapy be recommended?
22. In patients with polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus abatacept as initial therapy be recommended?

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23. In patients with polyarthritis and no risk factors, should initial therapy with non-biologic DMARD versus tocilizumab as initial therapy be recommended?
24. In patients with polyarthritis and no risk factors, should initial therapy with TNFi versus tocilizumab as initial therapy be recommended?
25. In patients with polyarthritis and no risk factors, should initial therapy with TNFi versus abatacept as initial therapy be recommended?
26. In patients with polyarthritis and no risk factors, should initial therapy with abatacept versus tocilizimab as initial therapy be recommended?

Risk factors present

27. In patients with polyarthritis plus risk factors receiving NSAIDs, should continued NSAID monotherapy versus the addition of non-biologic DMARD as initial therapy be recommended?
28. In patients with polyarthritis plus risk factors, should *triple* non-biologic DMARD versus methotrexate monotherapy as initial therapy be recommended?
29. In patients with polyarthritis plus risk factors, should *triple* non-biologic DMARD versus TNFi as initial therapy be recommended?
30. In patients with polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus TNFi as initial therapy be recommended?
31. In patients with polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus abatacept as initial therapy be recommended?
32. In patients with polyarthritis plus risk factors, should initial therapy with non-biologic DMARD versus tocilizumab as initial therapy be recommended?
33. In patients with polyarthritis plus risk factors, should initial therapy with TNFi versus tocilizumab as initial therapy be recommended?
34. In patients with polyarthritis plus risk factors, should initial therapy with TNFi versus abatacept as initial therapy be recommended?
35. In patients with polyarthritis plus risk factors, should initial therapy with abatacept versus tocilizumab as initial therapy be recommended?

SUBSEQUENT THERAPY – LOW DISEASE ACTIVITY

No risk factors

36. In patients with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?
37. In patients with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to triple non-biologic DMARD therapy versus adding TNFi to original non-biologic DMARD be recommended?
38. In patients with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?
39. In patients with low disease activity (cJADAS < 2.5) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?
40. In patients with low disease activity (cJADAS < 2.5) and no risk factors, receiving TNFi, should changing to second drug within same class (TNFi) versus changing to OBRM be recommended?

Risk factors present

41. In patients with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?
42. In patients with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to triple non-biologic DMARD therapy versus adding TNFi to original non-biologic DMARD be recommended?
43. In patients with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?

44. In patients with low disease activity (cJADAS < 2.5) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?
45. In patients with low disease activity (cJADAS < 2.5) plus risk factors, receiving TNFi, should changing to second drug within same class (TNFi) versus changing to OBRM be recommended?

SUBSEQUENT THERAPY – MODERATE/HIGH DISEASE ACTIVITY

No risk factors

46. In patients with moderate/high disease activity (cJADAS> 2.51) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?
47. In patients with moderate/high disease activity (cJADAS > 2.51) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?
48. In patients with moderate/high disease activity (cJADAS > 2.51) and no risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?
49. In patients with moderate/high disease activity (cJADAS> 2.51) and no risk factors, receiving TNFi (+/-non-biologic DMARD), should changing to second drug within same class (TNFi) versus changing to different drug in different OBRM class be recommended?
50. In patients with moderate/high disease activity (cJADAS> 2.51) and no risk factors, should rituximab versus 3rd class OBRM approved for JIA be recommended?

Risk factors present

51. In patients with moderate/high disease activity (cJADAS> 2.51) plus risk factors, receiving non-biologic DMARD monotherapy, should changing to second non-biologic DMARD versus adding TNFi to original non-biologic DMARD be recommended?

52. In patients with moderate/high disease activity (cJADAS > 2.51) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding abatacept to original non-biologic DMARD be recommended?
53. In patients with moderate/high disease activity (cJADAS > 2.51) plus risk factors, receiving non-biologic DMARD, should changing to second non-biologic DMARD versus adding tocilizumab to original non-biologic DMARD be recommended?
54. In patients with moderate/high disease activity (cJADAS> 2.51) plus risk factors, receiving TNFi (+/-non-biologic DMARD), should changing to second drug within same class (TNFi) versus changing to different drug in different OBRM class be recommended?
55. In patients with moderate/high disease activity (cJADAS> 2.51) plus risk factors, should rituximab versus 3rd class OBRM approved for JIA be recommended?

PT/OT (REGARDLESS OF CONCURRENT MEDICATION USE)

56. In patients with polyarthritis regardless of disease activity and risk factors, should PT versus no PT (regardless of concomitant medical therapy) be recommended?
57. In patients with polyarthritis regardless of disease activity and risk factors, should OT versus no OT (regardless of concomitant medical therapy) be recommended?

SACROILIITIS & ENTHESITIS QUESTIONS

POPULATION:

This group is intended to include patients with sacroiliitis who will most likely be from the ILAR categories of enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, but may include patients from any of the ILAR JIA categories. Patients may or may not have active peripheral joint disease in addition to active sacroiliitis to be included in these recommendations, but it is anticipated that patients with peripheral spondyloarthropathy would be treated using the polyarthritis recommendations included in this update and oligoarthritis recommendations when available.

DEFINITIONS:

Active sacroiliitis is disease considered active by the examining clinician based upon clinical exam findings, patient-reported symptoms of inflammatory back pain, and prior or current MRI findings consistent with active axial disease.

Active enthesitis is tenderness and/or swelling of the entheses determined to require medical treatment per the treating provider.

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INTERVENTIONS:

Nonsteroidal anti-inflammatory drugs (NSAIDs)	Any
Glucocorticoids	Oral: Any Intraarticular: Triamcinolone Acetonide, Triamcinolone Hexacetonide Methylprednisolone acetate
Biologic DMARDs	Tumor necrosis factor-alpha inhibitors (TNFi): Adalimumab, Etanercept, Infliximab, Golimumab, [Certolizumab pegol]
Non-biological disease modifying anti-rheumatic drugs (DMARDs)	Methotrexate, Sulfasalazine
Medications *not* currently addressed	Apremilast, Tofacitinib, Secukinumab, Ustekinumab (not included due to lack of pediatric data; anticipated these will be included in future efforts)
Non-medical interventions	Physical therapy (PT)

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OUTCOMES:

Critical Outcomes:

- Quality of life (e.g., PedsQL, CHQ, PROMIS, Quality Of My Life Score)
- Disease activity components (e.g., active enthesis count, active joint count, patient/parent global, MD global, ESR/CRP) as measured by the individual variables and/or composite disease activity measure (e.g., Pediatric ACR response, JADAS)
- ACR provisional criteria for clinical inactive disease
- Functional ability (e.g., CHAQ/PROMIS)
- Joint damage *requiring surgical intervention*
- Significant or life threatening adverse events (e.g., hospitalization, infection, malignancy)
- Resolution of MRI findings consistent with active sacroiliitis

Important Outcomes:

- Arthritis-related pain
- Preservation of normal growth and development
- Fatigue
- Joint damage
- Significant medication side effects leading to medication discontinuation

ACTIVE SACROILIITIS

1. In children and adolescents with active sacroiliitis, should treatment with NSAID monotherapy versus no treatment with an NSAID in improving outcomes be recommended?

2. In children and adolescents with active sacroiliitis, is treatment with an NSAID in addition to ongoing therapy with a systemic DMARD or TNFi more effective than no treatment with an NSAID in improving outcomes?
3. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with sulfsalazine versus no treatment with sulfasalazine be recommended?
4. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with methotrexate versus no treatment with methotrexate be recommended?
5. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with TNFi versus no treatment with TNFi be recommended?
6. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with treatment with systemic corticosteroids versus no treatment with systemic corticosteroids be recommended?
7. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with treatment with systemic corticosteroids versus sulfasalazine be recommended?
8. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus no intraarticular glucocorticoids be recommended?
9. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus sulfasalazine be recommended?
10. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with intraarticular glucocorticoid injections of the sacroiliac joints versus TNFi be recommended?
11. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with treatment with TNFi versus sulfasalazine be recommended?
12. In children and adolescents with active sacroiliitis despite treatment with NSAIDs, should treatment with TNFi versus systemic corticosteroids be recommended?

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ACTIVE ENTHESITIS

13. In children and adolescents with active enthesitis, should NSAID monotherapy versus no NSAIDs be recommended?
14. In children and adolescents with active enthesitis, is treatment with an NSAID in addition to ongoing therapy with a systemic DMARD or biologic more effective than no treatment with an NSAID in improving outcomes?
15. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with methotrexate versus TNFi be recommended?
16. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with methotrexate versus sulfasalazine be recommended?
17. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with sulfasalazine versus TNFi be recommended?
18. In children and adolescents with active enthesitis despite treatment with NSAIDs, should treatment with systemic glucocorticoids versus TNFi be recommended?

PT (REGARDLESS OF CONCURRENT MEDICATION USE)

19. In children and adolescents with active sacroiliitis, should treatment with any form of PT versus no PT (regardless of concomitant medical therapy) be recommended?
20. In children and adolescents with active enthesitis, should any form of PT versus no PT (regardless of concomitant medical therapy) be recommended?

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UVEITIS QUESTIONS

POPULATION:
This group includes all children with JIA and non-infectious uveitis.

DEFINITIONS/ABBREVIATIONS:

CAU: chronic anterior uveitis
AAU: acute anterior uveitis
Controlled uveitis: inactive OR <1+ cell without new complications due to active inflammation

- *Complications due to active inflammation:* peripheral anterior synechiae, posterior synechiae, inflammatory membranes, or cystoid macular edema
- *Additional signs of active inflammation:* fresh keratic precipitates (KP), increased flare, and hypoyon
- *Complications representing cumulative damage:* cataract, glaucoma/elevated IOP, hypotony, sequelae of KP (hyalinized spots or ghost KP). These are not reversible changes and should not be indications to change treatment in the absence of active inflammation

Loss of control: increase of cells to 1+ or more or new signs of inflammation/complications of inflammation

INTERVENTIONS:

Glucocorticoids	Topical steroids Systemic steroids Intraocular steroid injections

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Non-biological disease modifying anti-rheumatic drugs (DMARDs)	Methotrexate, Leflunomide, Mycophenolate, Cyclosporine
Biologic DMARDs	Adalimumab, Etanercept, Infliximab, Abatacept, Tocilizumab, Rituximab
Medications *not* currently addressed	Tofacitinib

OUTCOMES: Vary depending on the question.

SCREENING questions	*Critical Outcomes:* - New diagnosis of uveitis - New diagnosis of uveitis with ANY ocular complications
MONITORING questions	- Loss of control of uveitis - New complications due to inflammation *Important Outcomes:* - Severity/level of inflammation
MEDICATION questions	*Critical Outcomes:* - Loss of control of uveitis - Incidence of loss of control of uveitis - Control of uveitis at 1 month and 3 months - New ocular steroid complications (cataracts,

	glaucoma/increased IOP, infection) - New ocular complications due to inflammation - Incidence of uveitis - Recurrence of uveitis *Important Outcomes:* - Side effects of systemic therapy - Time to control of uveitis - Time to loss of control of uveitis - General anesthesia risk

UVEITIS SCREENING IN JIA PATIENTS

1. In JIA children with high risk of developing uveitis (oligoarthritis or rheumatoid factor seronegative polyarticular JIA, psoriatic JIA, ANA+), does screening more frequently than current guidelines decrease risk of developing ocular complications of uveitis?

MONITORING AFTER UVEITIS DIAGNOSIS

2. In JIA children with inactive uveitis on stable therapy, should ophthalmologic monitoring no longer than every 3 months until tapering versus monitoring less frequently than every 3 months be recommended?
3. In JIA children with inactive uveitis who are tapering or discontinuing therapy, should ophthalmologic monitoring within 1 month after each change of topical steroid therapy versus monitoring less frequently be recommended?
4. In JIA children with inactive uveitis who are tapering or discontinuing therapy, should ophthalmologic monitoring 2 months after each change of systemic therapy versus monitoring less frequently be recommended?

5. In JIA children with active CAU in which therapy is being changed/escalated, should ophthalmologic monitoring visits no longer than every 2 weeks versus monitoring less frequently than every 2 weeks the appropriate frequency of ophthalmologic monitoring be recommended?

TOPICAL STEROIDS

6. In JIA children with chronic uveitis controlled who have achieved control of their uveitis on systemic therapy and 1-2 drops/day of prednisolone acetate 1% (or equivalent), should weaning topical steroids first versus weaning systemic therapy first be recommended?
7. In JIA children with chronic uveitis controlled on (but still requiring) 1-2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months, not on systemic therapy, should adding systemic therapy in order to taper topical steroids versus not adding systemic therapy and maintaining on topical steroids be recommended?
8. In JIA children with chronic uveitis controlled on (but still requiring) 1-2 drops/day of prednisolone acetate 1% (or equivalent), also on systemic therapy, should changing/escalating systemic therapy versus not changing systemic therapy and maintaining current therapy be recommended?
9. In JIA children with chronic active uveitis, irrespective of use of topical or systemic therapy, should giving intraocular steroid injections versus not giving intraocular steroid injections be recommended?
10. In JIA children with chronic active uveitis, should treatment with prednisolone acetate 1% topical drops versus difluprednate topical drops be recommended?

SYSTEMIC STEROIDS

11. In JIA children with active CAU, should adding systemic steroids to topical steroid therapy for short term control versus not adding systemic steroids, which may include increasing frequency of topical steroids, be recommended?

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INITIATING SYSTEMIC DMARD THERAPY

12. In JIA children with new uveitis activity (either no prior uveitis or uveitis that was previously controlled, no active arthritis, and no topicals currently) regardless of current systemic therapy, should topical steroid therapy only and changing/escalating systemic therapy if unable to taper versus topical steroid therapy and changing/escalating systemic therapy immediately be recommended?
13. In JIA children with active CAU regardless of joint disease (assume uveitis guides therapy), should methotrexate PO versus methotrexate SQ be recommended?

ETANERCEPT

14. In JIA children starting a systemic medication for their arthritis with no history of uveitis, should etanercept versus other TNFi in influencing the incidence of uveitis be recommended?
15. In JIA children with active arthritis and active CAU, should starting etanercept versus any other medication like methotrexate, other TNFi or other biologics be recommended?
16. In JIA children with inactive uveitis, off of topical steroids and needing a change in systemic therapy for active arthritis, should starting etanercept versus another TNFi be recommended?

OTHER TNF INHIBITORS

17. In JIA children with active CAU regardless of joint disease (assume uveitis guides therapy), should adalimumab versus infliximab as first choice TNFi be recommended?
18. In JIA children with active CAU regardless of joint activity, should above standard dosing of infliximab (>10 mg/kg/dose every 4 weeks) versus standard JIA dosing be recommended?
19. In JIA children with active CAU regardless of joint activity, should above standard dosing of adalimumab (double dosing every 2 weeks or weekly dosing) versus standard JIA dosing be recommended?

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20. In JIA children with active CAU on TNFi at standard JIA dose regardless of joint disease (assume uveitis guides therapy) who have failed one TNFi at standard dose, should escalating dose and/or frequency to above-standard dose versus switching to another TNFi be recommended?
21. In JIA children with active CAU who have failed first TNFi, regardless of arthritis activity (assume uveitis guides therapy), should switching to another TNFi versus switching to a biologic in another category be recommended?
22. In JIA with severe active uveitis (2+ cells or more, or 1+ cells AND complications), should starting on MTX and a TNFi immediately versus methotrexate being trialed alone first be recommended?

OTHER NON-TNFi BIOLOGICS

23. In JIA children with active CAU, who have failed TNFi (one or more), should abatacept versus any other medication be recommended?
24. In JIA children with active CAU, who have failed TNFi (one or more), should tocilizumab versus any other medication be recommended?
25. In JIA children with active CAU, who have failed TNFi (one or more), should rituximab versus any other medication be recommended?

OTHER DMARDs

26. In JIA children with active CAU but no active arthritis, should mycophenolate versus any other medication be recommended?
27. In JIA children with active CAU but no active arthritis, should leflunomide versus any other medication be recommended?
28. In JIA children with active CAU but no active arthritis, should cyclosporine versus any other medication be recommended?

WEANING THERAPY

29. For children with uveitis that is well controlled on systemic therapy only, when should therapy be weaned?

ACUTE ANTERIOR UVEITIS

30. For children with spondyloarthropathy starting a TNFi for arthritis, does etanercept versus any other TNFi influence the risk of developing AAU or recurrent AAU?

31. For children with spondyloarthropathy starting a TNFi for arthritis, does the choice of TNFi influence the risk of developing AAU or recurrent AAU?
32. In children with spondyloarthropathy, is education regarding the warning signs of AAU more effective versus no education in decreasing delay in treatment, duration of symptoms, or complications of iritis?
33. In children with spondyloarthropathy, are TNFi monoclonal antibodies more effective in decreasing the occurrence or rate of recurrence of episodes of iritis versus etanercept?
34. In children with spondyloarthropathy who develop iritis while treated with a TNFi, is switching the TNFi more effective in decreasing recurrences of iritis versus continuing the same TNFi?

APPENDIX B – Participant Disclosures

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	Role	Primary Employer	Sources of Personal Income (salary information from primary employer is not required):	Intellectual Property	Research Grants/Contracts	Investments to Include Medical Industry and Nonmedical Industry	Organizational Benefit	Activities with Other Organizations	Family or Other Relations
Sarah Ringold	Co-PI/Core Team	Seattle Children's Hospital	Medpage Today; UptoDate; CARRA	N/A	PCORI; NIH; Crescendo Biosciences, Inc.	N/A	N/A	CARRA	N/A
Sheila T. Angeles-Han	Co-PI/Core Team	Cincinnati Children's Hospital Medical Center	N/A	N/A	National Institute of Health; Rheumatology Research Foundation; Emory Global Health Institute	N/A	N/A	N/A	N/A
Daniel Lovell	Core Team; Content Expert	Cincinnati Children's Hospital Medical Center	N/A	N/A	NIH; Bristol Meyers Squibb; AbbVie; Pfizer; Roche; Novartis; UBC; Jannsen; Takeda; GSK; Boehringer Ingelheim; Celegene	N/A	N/A	Genetech; Forest Research	N/A
Timothy Beukelman	Core Team; Content Expert	University of Alabama at Birmingham	Blue Cross Blue Shield of Alabama; UCB; Novartis; McKesson Health Solutions; Roche/Genentech	N/A	PCORI; AHRQ; NIH/NIAMS	N/A	N/A	CARRA; Journal of Rheumatology	N/A
James Reston	Core Team; Lit Review Lead	ECRI Institute	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Carlos A. Cuello Garcia	Core Team; GRADE Expert	McMaster University	PAHO/WHO	N/A	Cochrane	N/A	CONACYT	The Journal of Pediatrics; World Allergy Organization Journal	N/A
Marilynn Punaro	BOD Liaison	University of Texas Southwestern	N/A	N/A	NIAMS	N/A	N/A	N/A	N/A
Alexei Grom	Expert Panel	Cincinnati Children's Hospital Medical Center	Novartis; Baxalta, NoulmmuneN/A	N/A	NIH	N/A	N/A	N/A	N/A
Angela B. Robinson	Expert Panel	Rainbow Babies and Childrens Hospital	N/A	N/A	CARRA, Inc.	N/A	N/A	Arthritis Foundation; CARRA, Inc.	N/A
Grant Schulert	Expert Panel	Cincinnati Children's Hospital Medical Center	Novartis	N/A	N/A	N/A	N/A	N/A	N/A
Heather Tory	Expert Panel	Connecticut Children's Specialty Group	N/A	N/A	Pfizer	N/A	N/A	N/A	N/A
Matthew Stoll	Expert Panel	University of Alabama at Birmingham	MedAC Pharma; Novartis	N/A	NIH/NIEHS; NIH/NIAMS; CARRA; ACR	N/A	N/A	N/A	N/A
Meredith Profeta Riebschleger	Expert Panel	University of Michigan Hospitals	N/A	N/A	N/A	N/A	N/A	OMERACT; CARRA	N/A
Mindy Lo	Expert Panel	Boston Children's Hospital	N/A	N/A	Glaxo SmithKline	N/A	N/A	N/A	N/A
Richard K. Vehe	Expert Panel	University of Minnesota	American Board of Peds	N/A	Bristol-Myers Squibb; Pfizer; AF/CARRA	N/A	N/A	N/A	N/A
Ronald Laxer	Expert Panel	The Hospital for Sick Children, Toronto	Novartis, Abbvie, Sobi, Canadian Rheumatology Association; Eli Lilly	N/A	N/A	N/A	N/A	Canadian Rheumatology Association; J-Rheumatology	N/A
Amit Shah	Lit Review Team	ACR	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ann Marie Szymanski	Lit Review Team	NIH	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kimberly Hays	Lit Review Team	MUSC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Marat Turgunbaev	Lit Review Team	ACR	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nancy Sullivan	Lit Review Team	ECRI Institute	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Olha Halyabar	Lit Review Team	Boston Children's Hospital	N/A	N/A	N/A	N/A	N/A	Ukrainian Medical Association of Northern America - member	N/A
Jennifer Horonjeff	Patient Rep/Voting Panel	Self-Employed; Columbia University Medical Center	ACR/ARHP; Hackensack Medical Center; FDA	N/A	N/A	N/A	N/A	Arthritis Foundation	N/A
Katherine Murphy	Patient Rep/Voting Panel	University of California, Berkeley	CARRA	N/A	N/A	N/A	N/A	Arthritis Foundation	N/A
Egla Rabinovich	Voting Panel	Duke University	Golberg Rosen PA	N/A	CARRA; AbbVie; UCB Pharma; Hoffman-LaRoche, Inc.; Janssen Research	N/A	N/A	N/A	N/A
Gary N. Holland	Voting Panel	University of California; U.S. Department of Veteran's Affairs	N/A	N/A	National Eye Institute; California Institute for Regenerative Medicine	N/A	N/A	American Uveitis Society	N/A
Harry L. Gewanter	Voting Panel	Self-Employed	Alliance for Safe Biologic Medicines; Children's Hospital of Richmond	N/A	N/A	N/A	N/A	Alliance for Safe Biologic Medicines	N/A
Jaime Guzman	Voting Panel	BC Children's Hospital	Province of British Columbia Medical Service Plan	N/A	Canadian Institutes of Health Research	N/A	Arthritis Society	Arthritis Society	N/A
Mara Becker	Voting Panel	Children's Mercy Kansas City	FDA	N/A	Rheumatology Research Foundation; CARRA; NIH; BMS	N/A	N/A	Society for Pediatric Research; CARRA; AAP SoRg	N/A
Michael J. Ombrello	Voting Panel	NIAMS, NIH	N/A	N/A	NIAMS Intramural Research Program	N/A	N/A	CARRA	N/A
Murray Passo	Voting Panel	Retired	N/A	N/A	N/A	N/A	N/A	External Scientific Advisory Committee Meeting; PR-CON	N/A
Peter Nigrovic	Voting Panel	Brigham & Women's Hospital; Boston Children's Hospital	CARRA; UpToDate; Sobi, Inc.; Novartis, Inc.; UCB, Inc.; Arthritis & Rheumatology; American Academy of Pediatrics	N/A	NIH; RRF; Novartis; Sobi	N/A	N/A	CARRA; Journal of Rheumatology; Arthritis & Rheumatology; RRF; ANRF	N/A
Polly Ferguson	Voting Panel	University of Iowa Carver College of Medicine	N/A	N/A	NIH; CARRA	N/A	N/A	American Board of Pediatrics	N/A
Rayfel Schneider	Voting Panel	The Hospital for Sick Children, Toronto	Novimmune; Sobi; Novartis; Innomar Strategies	N/A	Genentech; Novartis; UCB Pharma	N/A	N/A	Pediatric Rheumatology Collaborative Study Group	N/A
Robert Colbert	Voting Panel	NIAMS/NIH	N/A	N/A	Eli Lilly, Inc.	N/A	N/A	American Board of Pediatrics; March of Dimes; ACR/Arthritis & Rheumatology	N/A
Sampath Prahalad	Voting Panel	Emory Univ School of Medicine	Novartis; Medac Pharma; UCB Pharma	N/A	PFIZER (Site PI), NIH; Emory/Georgia Institute of Tech	N/A	N/A	N/A	N/A

Brian Feldman	Voting Panel	The Hospital for Sick Children, Toronto	BMS; Novarits; Pfizer, Amgen; Agility Clinical Inc.	N/A	International Prophylaxis Study Group; The Myositis Association; Canadian Institute of Health Research; The Arthritis Society; NIH/NIAMS	N/A	N/A	The Arthritis Society	N/A
Nida H. Sen	Voting Panel	NIH/NEI; GWU	N/A	N/A	NIH CC bench-to-bedside; NEI Intramural Research Program Support	N/A	N/A	N/A	N/A