A Practical Approach to Uveitis Screening in Children with Juvenile Idiopathic Arthritis

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2. Drafting the work or revising it critically for important intellectual content; AND

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Synopsis

Screening for JIA-associated uveitis is important to enable timely treatment and reduce sight-loss. MIWGUC expert panel has developed a practical uveitis screening guidance to be safely used by eye care professionals in a local setting.

Abstract

Background: Juvenile idiopathic arthritis (JIA) associated uveitis typically presents as a silent chronic anterior uveitis and can lead to blindness. Adherence to current screening guidelines is hampered by complex protocols which rely on the knowledge of specific JIA characteristics. The Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) identified the need to simplify screening to enable local eye care professionals (ECP), who carry the main burden, to screen children with JIA appropriately and with confidence.

Methods: A consensus meeting took place in January 2023 in Barcelona, Spain, with an expert panel of 10 paediatric rheumatologists and 5 ophthalmologists with expertise in paediatric uveitis. A summary of the current evidence for JIA screening was presented. Nominal group technique was used to reach consensus.

Results: The need for a practical but safe approach that allows early uveitis detection was identified by the panel. Three screening recommendations were proposed and approved by the voting members. They represent a standardised approach to JIA screening taking into account the patient's age at onset of JIA to determine the screening interval until adulthood.

Conclusion: By removing the need for the knowledge of JIA categories, ANA positivity or treatment status, the recommendations can be more easily implemented by local ECP, where limited information is available. It would improve the standard of care on the local level significantly. The proposed protocol is less tailored to the individual than the 'gold standard' ones it references, and doesn't aim to substitute those where they are being used with confidence.

Key messages

- **What is already known on this topic:** Optimal JIA-associated uveitis screening is hampered by difficulties accessing uveitis screening appointments and interpretation of complex screening guidelines.
- **What this study adds:** The MIWGUC expert panel has developed a simplified and practical uveitis screening guide which is safe and easy to use and based on current evidence.
- **How this study might affect research, practice or policy:** This guidance will allow more reliable screening by local eye care professionals and it would improve the standard of care on the local level significantly.

A PRACTICAL APPROACH TO UVEITIS SCREENING IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

Introduction:

Juvenile idiopathic arthritis (JIA) associated uveitis is the commonest extra-articular manifestation of JIA, and the leading cause of uveitis in the paediatric population. [1–3] It is a sight-threatening condition that typically presents as silent chronic anterior uveitis, and may only lead to symptoms when ocular complications are present, or the vision is compromised. [4–7] Moreover, prolonged periods of untreated disease and severe uveitis at first diagnosis have been associated with poorer prognosis and non-reversible damage. [4,8] As a result, slit-lamp screening for uveitis has become an essential part of JIA management. [9,10]

Over the past two decades, numerous screening protocols have been developed and put into practice. [4,6,9,11–15] The introduction of uveitis screening, earlier diagnosis and timely treatment have led to a paradigm shift in the management of this disease and improved ocular outcomes. [16] Most screening protocols are designed to highlight high risk groups and take into account JIA categories, age at JIA diagnosis, duration of disease and laboratory markers status, such as positivity for antinuclear antibodies (ANA) and rheumatoid factor (RF). [9,11,12]

These protocols are complex and rely on the knowledge of JIA clinical characteristics and laboratory markers; information which may not be available to the local eye care professionals, who mostly carry the main burden of the uveitis screening.

Adherence to screening is suboptimal, with evidence showing that nearly a third of children are not seen in a timely manner.[17–19] Access to and availability of screening appointments is a significant barrier.[19]

The Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) identified the need to simplify JIA screening so local eye care professionals with no access to detailed information on JIA categories can carry out safe screening with confidence.

Methods:

The MIWGUC is an international collaboration of specialists aiming to tackle the challenges related to assessment and management of paediatric uveitis. The expert panel for this meeting consisted of 10 paediatric rheumatologists (SAH, JA, JCH, TC, IF, MG, EN, TS, GS, HI) and 5 ophthalmologists (RB, JB, JDC, EM, HP) with a special interest in JIA-associated uveitis. They were the 15 voting members on the committee. Additionally, there were two parents of children with uveitis acting as a patient representatives and participating in the discussions. The group met on January 26th and 27th 2023 for the Ninth MIWGUC meeting in Barcelona, Spain.

A summary of the current evidence for JIA-associated uveitis risk-factors, risk of complications, and screening was presented to the expert panel. This evidence comprised international and national screening guidelines published within peer-reviewed journals enabling rigorous assessment of the underpinning evidence base, as well as details of the supporting consensus processes. The results were discussed by the panel and a new recommendation was formulated when the need for change was identified.

Nominal group technique was used to reach consensus,[15] and the recommendations were approved if >90% agreement was reached amongst the voting members of the committee.

Table 1 contains a summary of peer-reviewed JIA-associated uveitis screening guidelines considered by the committee. The 2019 American College of Rheumatology guideline is based on a combination of the 2007 German Uveitis in Childhood Study Group guidance by

Heiligenhaus et al. (12), which follows the International League of Associations for Rheumatology (ILAR) classification; and the American Academy of Pediatrics (AAP) recommendations from 2006, which didn't include all JIA categories; whilst proposing additional monitoring and treatment recommendations.[9,11,12,20,21] More recently, Leinonen suggested an alternative guideline that takes into account treatment status for planning the screening intervals, as well as an age limit of 16 years. [6]

Table 1 Comparison of JIA-associated uveitis screening guidelines

	JIA subtype	ANA	JIA age onset (yrs.)	JIA duration (yrs.)	Screening intervals (months)	Screening duration
Heiligenhaus at al. 2007 [12]	Oligoarthritis RF- polyarthritis psoriatic arthritis other arthritis	+	≤ 6	≤ 4 > 4 ≥ 7	3 6 12	No end date
			> 6	≤ 2 > 2	6 12	
		-	≤ 6	≤ 4 > 4	6 12	
			> 6	NA	12	
	ERA Systemic JIA RF+ polyarthritis	NA	NA	NA	12	

ACR 2019 [9]	Oligoarthritis RF- polyarthritis psoriatic arthritis undifferentiated arthritis	+	< 7	≤ 4 > 4	3 6-12	No end date
			≥ 7	≤ 4 > 4	6-12	
		-	< 7	≤ 4 > 4	6-12	
			≥ 7	≤ 4 > 4		
	ERA Systemic JIA RF+ polyarthritis	NA	NA	NA	6-12	
Leinonen 2022 [6]	Oligoarthritis RF- polyarthritis psoriatic arthritis undifferentiated arthritis	+	≤ 6	≤ 4 4-7 >7	3 or 6* 6 or 12* 12	Until age 16
			> 6	≤ 2 > 2	6 or 12* 12	For 2-4 yrs. (or until age 16)
		-	≤ 6	≤ 4 >4	6 or 12* 12	Until age 16

			> 6	NA	12	For 2-4 yrs. (or until age 16)
	ERA	NA	≤ 6	NA	12	4-7 yrs. (or until age 16)
			> 6			For 2-4 yrs. (or until age 16)
	Systemic JIA RF+ polyarthritis	NA	NA	NA	Only at diagnosis	NA

*JIA: Juvenile idiopathic arthritis; ANA: Antinuclear antibodies; yrs.: years; ACR: American College of Rheumatology; NA: Not applicable; RF-: Rheumatoid factor negative (seronegative); ERA: enthesitis-related arthritis; RF+ PA: Rheumatoid factor positive (seropositive). *if on treatment with methotrexate or TNF-inhibitors (excluding etanercept) the screening interval is increased; if treatment is interrupted, screening should be resumed in <6 months.*

Results:

The group raised the concern that local eye care professionals who may screen most patients with JIA could not have the information and the knowledge required to make a judgment on screening frequency based on guidelines currently published. The need for a practical but knowledge-based approach for local ophthalmologists and other local allied eye care professionals was identified by the panel.

Compelling evidence reviewed at the consensus meeting suggests that the majority (>70%) of JIA patients will develop uveitis within the first year of diagnosis.[4,7,12,22] This underpins the intensive screening recommended by all protocols within the first 12 months; however, it was the panel's conclusion that a review every 2 months (rather than every 3 months as per most protocols) would be more appropriate during that timeframe for younger children diagnosed with JIA. As the risk decreases after the first 12 months of disease duration, the proposed screening interval was stretched after that to 3-4 months up to 4 years. This was thought to compensate for the increased burden in the first 12 months of the disease course. At the end of the discussion, three screening recommendations were proposed (table 2).

In addition, the group deemed it important to highlight the need for **all** children who have or previously had chronic anterior uveitis (with or without known systemic involvement) to be investigated by a paediatric rheumatologist, and seen at regular intervals (table 3), to assess for the development of subclinical joint disease. This is due to the high association of chronic anterior uveitis and JIA in children; and the fact that uveitis can precede the onset of arthritis in a minority of patients.[7,23–25] Joint disease could go unnoticed without detailed joint count assessment, as it may not be painful, or not be reported or noticed, especially in younger children. Currently, there is no compelling evidence regarding the dynamic of the involvement of the arthritic component in children who present with idiopathic anterior uveitis, therefore this proposal was made based on clinical experience as a specialist recommendation (table 3.)

Table 2 JIA-associated uveitis screening recommendations by the MIWGUC specialist panel

Recommendation	**Voting**
1) All children should be screened within 4 weeks of diagnosis of JIA (excluding systemic JIA), regardless of age.	15/15

2) If under 7 years at time of JIA diagnosis:	15/15
a. Screen every 2 months for the first 12 months.	
b. Screen every 3-4 months for the 2nd, 3rd and 4th years.	15/15
c. Screen every 6 months for the 5th, 6th and 7th years.	15/15
d. Screen every year until adulthood (18years of age).	15/15
3) If 7 years or over at the time of JIA diagnosis:	
a. Screen every 3-4 months for the first 12 months.	15/15
b. Screen every 6 months for the 2nd, 3rd and 4th years.	15/15
c. Screen every year until adulthood (18 years of age).	15/15

JIA: Juvenile idiopathic arthritis

Table 3 MIWGUC recommendation for paediatric rheumatologist follow-up

Recommendation	Voting
All children and young people with previous anterior uveitis should be investigated by a paediatric rheumatologist, and followed-up at least yearly until the end of growth OR up to 7 years after the onset of the eye disease.	15/15

Discussion:

Multiple studies have looked at risk factors for the development of uveitis in different JIA populations. In addition to the JIA categories and ANA positivity, they consider important epidemiological features of JIA associated uveitis:

1. More than half the children who develop uveitis will either have it before (approximately 10%) or develop it within 6 months of a JIA diagnosis;[12] the majority will develop uveitis within the first year of diagnosis, justifying more intense screening soon after disease onset [4,7,12,22].

2. Children diagnosed with JIA at older age (≥7 years old) are less likely to develop uveitis, which justifies an increase in screening interval after that age, especially after the first year following JIA diagnosis.[6,26–29]

Additionally, current evidence suggests that JIA subtypes often considered as lower-risk for asymptomatic uveitis, such as enthesitis-related arthritis, could present with silent ocular inflammation in almost 40% of uveitis cases, differently than the classic adult presentation of acute anterior uveitis seen in HLA B27 patients. [30] The uveitis onset is more common in the

first 2 years after joint disease onset.[30] Therefore, the traditionally-proposed longer uveitis screening intervals for these patients may not represent the safest option, especially in the first years following disease onset.

Recently, van Straalen at al. published a validated model that predicts the risk of new-onset chronic uveitis in JIA, taking into account the age at JIA diagnosis, ILAR category and ANA status.[22] This tool is an elegant visual aid for clinicians wanting to educate patients and proxies of their uveitis risk, emphasizing the importance of screening. It also supports the development of evidence-based predictive modelling for screening. Based on their prediction model, they propose changes to currently used guidelines, such as reducing the screening intervals to 2 months in the first year in higher risk groups with JIA onset before or at 6 years of age. [22]

To our knowledge, no study so far has compared different screening intervals for JIA-associated uveitis. Most recommendations follow clinically convenient intervals of 3, 6 and 12 months, depending on the assumed risk of uveitis (from higher to lower). [6,9,12,15] However, uveitis screening intervals of 2 months have been recommended by the British Society for Paediatric and Adolescent Rheumatology (BSPAR) and Royal College of Ophthalmology (RCOphth) since 2006 [15,31]. Although this uveitis screening recommendations were not published in a peer-reviewed journal, and therefore not added to the summary table 1, they hold particular importance in light of more compelling evidence. [4,7,12,22] The group reached through consensus the agreement, that , as the evidence base suggested greatest risk of sight threatening early in JIA disease course a higher frequency of assessment were needed. Therefore, the MIWGUC recommendation proposes a more frequent screening interval of 2 months for the population at a higher risk of uveitis and poorer prognosis (children with JIA onset before the age of 7 years, during the first year of disease); as a trade-off, the frequency of screening is decreased to every 3-4 months when the risks of uveitis and permanent ocular damage are reduced [3–5,7,12].

Whilst it is crucial our care is data-driven and evidence-based, the paediatric uveitis community has overlooked the reality that numerous local eye care professionals do not have the detail required to determine the appropriate screening interval. This lack of clarity often extends to patients and their proxies, leading to delays in screening and difficulties accessing specialised services.[18,19]

The MIWGUC recommendations represent a practical and evidence-based approach to screening children and young people with JIA. By removing the need for the knowledge of the JIA categories, ANA positivity or treatment status, they can be easily implemented in clinical practice by the local eye care professional. This also holds significance in areas with limited resources and lack of ophthalmology services, which is a global reality affecting not only developing countries but others with established public health systems, where allied eye care professionals could play a more intense role in uveitis screening [32,33] Moreover, the panel's recommendations take into account updated evidence and clinical experience providing a standardised, easy approach to uveitis screening (table 4).

Limitations exist. The proposed screening protocol is less tailored to the individual than those it references. Since some risk factors for uveitis are not considered, keeping shorter screening intervals for all JIA subtypes means that some children will be ‘over-screened’, which could result in extra burden for families and health systems. On the other hand, patient-specific circumstances that puts them at a greater risk of developing a recurrence or new onset uveitis are also not factored in, such as the interruption of immunosuppressant treatment potentially preventing the uveitis occurrence. This may result in longer screening intervals than the recommended consensus of the ACR and SHARE group.[9,10] Additionally, there are instances where a unanimous consensus is lacking, such as upper age limit for screening and screening throughout adulthood, which was not considered. We recognize that, by proposing uveitis screening until adulthood (till age of 18 years), this protocol results in an extended

duration of screening within certain settings, such as the United Kingdom, where surveillance within an ophthalmology-led service typically ends by age 12 for the majority of children.[15] There was also no health economist on the panel to analyse the impact of these proposed changes. Finally, although the MIWGUC is formed by a group of international specialists with prominent experience in the area, it is not able to properly represent the view of all paediatric rheumatologists and uveitis specialists in those countries, not to mention the views of those working in developing countries with fewer resources.

It is essential to strike a balance between acknowledging the limitations and considering the financial, psychological and physical burden associated with uveitis, its complications and the costs of delayed treatment.[34–36] We recommend this protocol to be used by eye care professionals who feel more comfortable having a simplified, easy-to-use ‘one size fits all’ approach that will allow them to practice safely and feel confident to perform uveitis screening on a local setting. This guideline does not aim to replace currently in place ‘gold standard’ screening protocols where those are being used with confidence. Therefore, for those who have the additional risk factor information and would like to offer their patients a more individualised approach, we would recommend using one of the previously published guidelines above.

Further work is needed to validate these recommendations and its application in a population setting . As more robust evidence emerges this recommendation will be amended. The structure of MIWGUC with annual consensus meetings and review of the evidence based, Is well placed to make the amendments.

In conclusion, the MIWGUC proposes a practical, simplified and yet evidence-based approach for the worldwide ophthalmic screening of JIA patients on a local setting, reducing the burden of specialised services and facilitating early diagnosis, referral and management of patients with JIA-associated uveitis.

Table 4 MIWGUC JIA uveitis screening recommendation

Eye screening interval		
< 4 weeks after JIA diagnosis*, then:		
	JIA age of diagnosis < 7	**JIA age of diagnosis ≥ 7**
Year 1	2 months	3-4 months
Year 2, 3, 4	3-4 months	6 months
Year 5, 6, 7	6 months	12 months
Year >7**	12 months	12 months

Except systemic JIA. Until adulthood. "Year": Timeframe since JIA diagnosis. "Eye screening": Slit-lamp exam by an eye care professional. JIA: Juvenile idiopathic arthritis.*

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