Date: June 18, 2012

Title: Screening for Uveitis in Children with Juvenile Idiopathic Arthritis (JIA)

Clinical Question:

P	(population/problem):	In pediatric patients 0 to 18 years of age with JIA
I	(intervention)	what is the optimal ophthalmologic screening schedule
O	(outcome)	to prevent and minimize uveitis-associated morbidity?

Target Population:

Included: Children (0 to 18 years of age) diagnosed with JIA

Excluded: Children with JIA who have been previously diagnosed with uveitis

Definitions:

Juvenile idiopathic arthritis is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks; other known conditions are excluded *(Petty 2001 [5a])*. *[See table 1: International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis).*

Uveitis-associated morbidity includes cataracts, glaucoma, band keratopathy, phthisis bulbi and loss of vision *(Cassidy 2006 [5a])*.

Recommendations:

1. It is recommended that a referral for an initial screening examination for uveitis be made by the rheumatology provider upon diagnosis of JIA, and the exam be performed within one month after diagnosis of JIA *(Carvounis 2006 [1a], Grassi 2007 [4a]; Heiligenhaus 2007 [3a]; Cassidy 2006 [5a])*.
   Note: The onset of uveitis is often asymptomatic and/or occurs in children unable to recognize and verbalize symptoms *(Cassidy 2006 [5a]; Woreta 2006 [4b])*.

2. It is recommended that after the initial screening examination, regular follow-up screenings be maintained based on risk category and classification *(see Table 2: Suggested screening intervals in patients with JIA) (Heiligenhaus 2007 [3a])*.
   Note: Risk category and classification include the categories of the subtype of JIA, antinuclear antibody status, age of onset of JIA and duration of JIA *(Heiligenhaus 2007 [3a])*.

3. It is recommended that screening change from every six months to every twelve months in ANA positive patients with disease onset >6 years of age who have not had uveitis within the first two years of JIA diagnosis *(Heiligenhaus 2007 [3a]; Saurenmann 2010 [4a]; Woreta 2007 [4b])*.
   Note: The risk of developing additional complications between four years and six years of onset is minimal; this decreased risk supports a change in the screening recommendation in these patients *(Heiligenhaus 2007 [3a]; Saurenmann 2010 [4a]; Woreta 2007 [4b])*.

4. It is recommended that if the patient is < 6 years of age and the provider has a strong suspicion of JIA or the patient is known to test positive for antinuclear antibodies (ANA), the provider proactively refer the patient for a screening examination for uveitis *(Bolt 2008 [4a]; Woreta 2007 [4b]; Heiligenhaus 2007 [3a])*.
   Note: Given that the risk of uveitis is highest among ANA positive patients age < 2 years, it is beneficial to make every effort to schedule an ophthalmology assessment at the earliest possible time. This could be prior or on the day of the rheumatology assessment *(Local Consensus [5])*.

5. It is recommended that screenings for uveitis be performed by an optometrist or ophthalmologist experienced in pediatric care, using a slit lamp procedure *(Cassidy 2006 [5a]; Heiligenhaus 2007 [3a])*.

Table 1: International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis

Exclusions:

The principle of this classification is that all categories of JIA are mutually exclusive. This principle is reflected in the list of possible exclusions for each category:

a. Psoriasis or a history of psoriasis in the patient or first degree relative.

b. Arthritis in an HLA-B27 positive male beginning after the 6th birthday.

c. Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.

d. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.

e. The presence of systemic JIA in the patient.

The application of exclusions is indicated under each category, and may change as new data become available.

Category	Definition	Exclusions (above)
Systemic Arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis	a, b, c, d.
Oligoarthritis	Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized: 1. Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course 2. Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease	a, b, c, d, e
Polyarthritis (Rheumatoid Factor Negative)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.	a, b, c, d, e
Polyarthritis (Rheumatoid Factor Positive)	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.	a, b, c, e
Psoriatic Arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative	b, c, d, e
Enthesitis Related Arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute anterior uveitis 5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative	a, d, e
Undifferentiated Arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories.	

(Petty 2001 [5a])

Table 2: Suggested screening intervals for uveitis in patients with JIA as classified by International League of Associations for Rheumatology (ILAR) criteria

JIA subgroup	ANA	Age at JIA onset (yrs)	JIA duration (yrs)	Recommended screening intervals (months)
OA, RF−PA, PsA, AA	+	≤6	≤4	3
OA, RF−PA, PsA, AA	+	≤6	>4	6
OA, RF−PA, PsA, AA	+	≤6	≥7	12
OA, RF−PA, PsA, AA	+	>6	≤2	6
OA, RF−PA, PsA, AA	+	>6	>2	12
OA, RF−PA, PsA, AA	−	≤6	≤4	6
OA, RF−PA, PsA, AA	−	≤6	>4	12
OA, RF−PA, PsA, AA	−	>6	n.a.	12
ERA	n.a.	n.a.	n.a.	12
RF+PA, Sys A	n.a.	n.a.	n.a.	12
Patients with uveitis	n.a.	n.a.	n.a.	According to uveitis course

Sys A = systemic arthritis; OA = oligoarthritis; RF−PA = seronegative polyarthritis; RF + PA = seropositive polyarthritis; ERA = enthesitis-related arthritis; PsA = psoriatic arthritis; AA = other arthritis; n.a. = not applicable.

(Heiligenhaus 2007)[3a])- adapted

Discussion/Summary of Evidence related to the recommendations:

A recent meta-analysis of cohort studies published 1980 through 2004 concluded that the guidelines from the American Academy of Pediatrics are supported by the evidence, with these exceptions; younger ANA-positive, oligoarticular-onset and polyarticular-onset patients are at the highest risk for uveitis, ANA-negative JIA patients with disease onset by age 4 years have moderate risk categories, irrespective of JIA subtype *(Carvounis 2006 [1a])*.

Uveitis is quite often detected at the first ophthalmologic consultation early during the course of JIA *(Kotaniemi 2003 [5b])*. At presentation with JIA, ocular complications were seen in 67% of eyes affected by JIA associated uveitis *(Woreta 2006 [4b])*. A 2007 study found that 73% of patients exhibited uveitis before or within the first 12 months after onset of arthritis and 77% and 90% within the first 2 and 4 years respectively *(Heiligenhaus 2007 [3a])*.

Given the level of scientific evidence available, it is recognized that some children may be over screened and others under screened by 1 to 2 months *(Local Consensus [5])*.

Reference List

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2. **Carvounis, P. E.; Herman, D. C.; Cha, S.; and Burke, J. P.:** Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefes Archive for Clinical & Experimental Ophthalmology,* 244(3): 281-90, 2006, *[1a]* _____ http://groups/p2/EBC_Files/Articles_Cited_in_EPIC_Ophth/OphthCarvounis2006.pdf.

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7. **Kotaniemi, K.; Savolainen, A.; Karma, A.; and Aho, K.:** Recent advances in uveitis of juvenile idiopathic arthritis. *Surv Ophthalmol,* 48(5): 489-502, 2003, *[5b]* _____ http://groups/p2/EBC_Files/Articles_Cited_in_EPIC_Ophth/OphthKotaniemi2003.pdf.

8. **Local Consensus:** During recommendation development timeframe. *[5]* .

9. **Petty, R. E. et al.:** International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol,* 31(2): 390-2, 2004, *[5a]* _____ http://groups/p2/EBC_Files/Articles_Cited_in_EPIC_Ophth/OphthPetty2004JIA.Criteria.pdf.

10. **Saurenmann, R.K.; Levin, A.V.; Feldman, B.M.; Laxer, R.M., Schneider, R.; and Silverman, E.D.:** Risk factors of development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Athritis & Rheumatism*, 62(6): 1824-1828, 2010, *[4a]*.

11. **Sim, K. T.; Venning, H. E.; Barrett, S.; Gregson, R. M.; and Amoaku, W. M.:** Extended oligoarthritis and other risk factors for developing JIA-associated uveitis under ILAR classification and its implication for current screening guideline. *Ocular Immunology & Inflammation,* 14(6): 353-7, 2006, *[4a]* _____ http://groups/p2/EBC_Files/Articles_Cited_in_EPIC_Ophth/OphthSim2006.pdf.

12. **Woreta, F.; Thorne, J.E.; Jabs, D.A.; Kedhar, S.R.; and Dunn, J.P.:** Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J. Ophthamol*, 143: 647-655, 2007, *[4b]*.

Implementation

Applicability Issues:

Issues to consider with implementation of these recommendations include parental understanding of the complications of uveitis and the need for prompt screening, rheumatology acceptance and follow-through with these recommendations, and use of and follow-through of the recommendations by ophthalmologists. The ability to collect the data may pose a challenge.

Relevant CCHMC Tools for Implementation:

Knowing Note: What you need to know about your eye exam

Outcome or Process Measures:
Outcome Measures:
Of active patients seen by Pediatric Ophthalmology for JIA-associated screenings:
- ▪ Percent who are within the recommended follow-up time period for uveitis screening
- ▪ Percent whose uveitis is inactive or in remission
- ▪ Percent with optimal visual acuity based on a non-verbal visual acuity exam
- ▪ Percent with best corrected visual acuity of 20/20 or better
- ▪ Percent whose uveitis is worsening

Process measure: Percentage of JIA patients screened for Uveitis (eye disease) at appropriate intervals
Complete operational definitions are on file.

SUPPORTING INFORMATION

Background/Purpose of BESt Development:
Juvenile idiopathic arthritis (JIA) is the most common systemic cause of pediatric uveitis in Europe and North America *(Cassidy 2006 [5a])*.

Uveitis frequently associated with JIA and JIA associated uveitis, is commonly considered to have a complicated course with frequent adverse visual outcomes *(Carvounis 2006 [1a] (see Table 3 below: Number of patients with ocular complications due to uveitis)*. Recent literature reports prevalence of uveitis among children with JIA in the range of 8.3% to 20.1% *(Carvounis 2006 [1a], Grassi 2007 [4a], Saurenmann 2010 [4a], Sim 2006 [4a])*. Although predictors for adverse visual outcome and severity in JIA-associated uveitis have been identified there exists no model that predicts which patients will develop JIA associated uveitis. It is reasonable and advisable to continue to subject children with JIA to frequent ophthalmological examinations for early diagnosis of uveitis, although only a small proportion develop it *(Carvounis 2006 [1a])*. Visual outcome has improved in the past 20 years; most children have a relatively good prognosis if the disorder is detected and treated early. However, uveitis in children with JIA remains a leading cause of loss of vision and blindness in the United States *(Cassidy 2006 [5a])*.

The purpose of this BESt is to provide clinicians that treat children with JIA reasonable and acceptable guidance for early and consistent screening for uveitis. Scheduled slit-lamp examinations by an ophthalmologist at specific intervals can detect ocular disease early, and prompt treatment can prevent vision loss *(Cassidy 2006 [5a])*.

Table 3: Number of patients with ocular complications due to uveitis

	Initial status (n=100) n (%)	Current status (n=106) n (%)
Posterior synechia	31 (31)	29 (27)
Cataract	22 (22)	27 (26)
Band-keratopathy	21 (21)	31 (29)
Vitreous opacities	10 (10)	7 (7)
Papille oedema	7 (7)	6 (6)
Secondary glaucoma	6 (6)	8 (8)
Macula oedema	4 (4)	6 (6)
Hypotony	3 (3)	4 (4)
Iris rubeosis	2 (2)	2 (2)
Other complications	9 (9)	22 (21)

Heiligenhaus 2007 [3a])

Search Strategy
1. Initial Search – performed 9-2011
   DATABASES
- - Scopus
- - Pubmed
- - OVID EBMR Review
- - CINAHL – OVID

SEARCH TERMS & MeSH TERMS
- Scopus: Juvenile Idiopathic Arthritis and Uveitis and diagnosis
- Pubmed: Uveitis/diagnosis and Arthritis, Juvenile Rheumatoid and English and last 5 years
- OVID EMBR Review: ("Uveitis/diagnosis"[Mesh]) AND "Arthritis, Juvenile Rheumatoid"[Mesh] AND (English[lang] AND "last 5 years"[PDat]) – No results
- CINAHL: Arthritis, Juvenile Rheumatoid and Uveitis+/DI
- Children; human; English, (2006 to present)

WEBSITE SEARCH of all known ophthalmology related websites – for guidelines related to JRA screening for uveitis
- National Guidelines Clearinghouse, American Academy of Pediatrics, American Academy of Ophthalmology, American Academy of Pediatric Ophthalmology and Strabismus, American Board of Ophthalmology, Association for Research in Vision and Ophthalmology, American Society of Retina Specialists, British Ophthalmic Anaesthesia Society, Ophthalmic Imaging Association, Canadian Ophthalmological Society, German Ophthalmology Society, Ophthalmic Anesthesia Society, Philippine Academy of Ophthalmology, Royal College of Ophthalmologists, Swedish Ophthalmological Society Guidelines, Systematic Reviews, and Meta-Analyses (2006 to present)

2. Additional articles identified by clinicians

3. Additional articles identified from a search based on the strategy from the Carvounis systematic review was conducted for publication dates subsequent to that review:

    2005 to present

    Ovid Medline, English, human

    Search terms:

        (Juvenile Arthritis OR JRA OR Juvenile Rheumatoid Arthritis OR Juvenile Chronic Arthritis OR JCA OR Juvenile Idiopathic Arthritis OR JIA Arthritis)

        AND

        (Eye OR Ocular OR Eye Diseases OR Ophthalmic OR Ophthalmological OR Iritis OR Iridocyclitis OR Uveitis OR cataract OR Glaucoma)

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Conflicts of Interest were declared for each team member:

☒ No financial conflicts of interest were found.

☒ No external funding was received for development of this BESt.

Note: Full tables of evidence grading system available in separate document:
- Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality *(abbreviated table below)*
- Grading a Body of Evidence to Answer a Clinical Question
- Judging the Strength of a Recommendation *(abbreviated table below, dimensions table above)*

Table of Evidence Levels *(see note above)*

Quality level	Definition
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

†a = good quality study; b = lesser quality study

Table of Language and Definitions for Recommendation Strength *(see note above)*:

Language for Strength	Definition
It is strongly recommended that… It is strongly recommended that… not…	When the dimensions for judging the strength of the evidence are applied, there is high support that benefits clearly outweigh risks and burdens. *(or visa-versa for negative recommendations)*
It is recommended that… It is recommended that… not…	When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.
There is insufficient evidence and a lack of consensus to make a recommendation…	

Given the dimensions below and that more answers to the left of the scales indicate support for a stronger recommendation, the recommendation statement above reflects the strength of the recommendation as judged by the development group.
(Note that for negative recommendations, the left/right logic may be reversed for one or more dimensions.)

Dimension			
1. Grade of the Body of Evidence	☐ High	☒ Moderate	☐ Low
Comments:			
2. Safety/Harm (Side Effects and Risks)	☒ Minimal	☐ Moderate	☐ Serious
Comments: Screening is of little harm as compared to the complications that can occur			
3. Health benefit to patient	☒ Significant	☐ Moderate	☐ Minimal
Comments: Minimizing complications that have life altering consequences would be of significance to patients and families			
4. Burden on patient to adhere to recommendation	☒ Low	☐ Unable to determine	☐ High
Comments: The frequency of ophthalmologic screening needs be weighed against risk of developing uveitis. Early identification of uveitis allows prompt initiation of treatment (Kotaniemi 2003 [5b]).			
5. Cost-effectiveness to healthcare system	☒ Cost-effective	☐ Inconclusive	☐ Not cost-effective
Comments: Preventing or minimizing complications is cost effective compared to treatment of uveitis and complications			
6. Directness of the evidence for this target population	☒ Directly relates	☐ Some concern of directness	☐ Indirectly relates
Comments:			
7. Impact on morbidity/mortality or quality of life	☒ High	☐ Medium	☐ Low
Comments: Living without complications or prolonging the development of complications has high impact on these patients' quality of life			

Copies of this Best Evidence Statement (BESt) and related tools (if applicable, e.g., screening tools, algorithms, etc.) are available online and may be distributed by any organization for the global purpose of improving child health outcomes.

Website address: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/best.htm
Examples of approved uses of the BESt include the following:
- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the BESt may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at EBDMinfo@cchmc.org for any BESt adopted, adapted, implemented, or hyperlinked by the organization is appreciated.

Please cite as: Cincinnati Children's Hospital Medical Center: Best Evidence Statement: Screening for Uveitis in Children with Juvenile Idiopathic Arthritis (JIA), http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/best.htm, BESt 011, pages 1-6, June 18, 2012.

This Best Evidence Statement has been reviewed against quality criteria by 2 independent reviewers from the CCHMC Evidence Collaboration.

For more information about CCHMC Best Evidence Statements and the development process, contact the Evidence Collaboration at EBDMinfo@cchmc.org.

Note
This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.