Pediatric Uveitis Task Force: A Multi-Disciplinary Approach to Management Challenges in Pediatric Uveitis

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Course Objectives:
• To provide a cutting-edge, systematic approach to the diagnosis, workup and management of pediatric patients
• To educate on the clinical evaluation and treatment of both common and challenging presentations using a multi-disciplinary, interactive, case-based approach

Introduction:
Virginia Miraldi Utz, MD – Task Force Chairperson
Abrahamson Pediatric Eye Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH

I. AAPOS PEDIATRIC UVEITIS TASK FORCE
1. AAPOS Pediatric Uveitis Task Force is a multi-disciplinary team of pediatric ophthalmologists, uveitis specialists, and rheumatologists with the following objectives:
   • To provide education to AAPOS members on the management of pediatric uveitis
   • To improve coordination of care between rheumatologists and ophthalmologists
   • To provide support resources for patients and families
2. Resources soon to be available to AAPOS Members on our website:
   • 504 plan template for patient with uveitis +/- systemic disease [Includes a background on uveitis for the educator, frequent appointment and treatment needs of the child, as well as request for low vision resources and emotional support based on child’s needs.
   • Coming soon: Example prior authorization templates to share with rheumatologist to aid in the acquisition of evidence-based treatment such as biologic response modifiers
   • Coming soon: Support resources for patients and families
Have additional recommendations? Needs? Questions? Referral? Please email aapos@aaoo.org
II. DIAGNOSTIC APPROACH TO UVEITIS:

A. Laboratory testing should be driven by uveitis phenotype based on the following:
1. Careful HPI, PMH, FHx, SocHx, ROS
2. Anatomic location of uveitis
3. Temporal (acute, sub-acute, chronic)
4. Collaborate with rheumatologist as systemic findings may increase pre-test probability of a specific systemic disease

B. Develop a Differential Diagnosis: (Figure 1)

C. Considerations for Laboratory Testing In Children with Uveitis:

<table>
<thead>
<tr>
<th>Uveitis Phenotype</th>
<th>Labs / Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subtypes</td>
<td>Infectious*</td>
</tr>
<tr>
<td></td>
<td>Test</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Specific treponemal antibody test (TTA-ABS or TP-PA or IA) + nonspecific (VDRL or RPR)</td>
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<tr>
<td></td>
<td>Tuberculosis (PPD/quant gold)*</td>
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<tr>
<td></td>
<td>Lyme*</td>
</tr>
<tr>
<td></td>
<td>HIV Ab*</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>ACE, lysozyme, CXR , Ca²⁺</td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>+/- ESR/CRP</td>
</tr>
<tr>
<td>Hematology</td>
<td>CBC</td>
</tr>
<tr>
<td>Metabolic + Urinalysis</td>
<td>Basic metabolic panel (or Complete metabolic panel)</td>
</tr>
</tbody>
</table>

* Context of age, region, risk factors

Figure 1. Diagnostic considerations to drive workup based on uveitis phenotype (history, location, temporal sequence, systemic considerations).

* Do not assume non-infectious
** Other: trauma, medication, toxic
C. Considerations for Laboratory Testing in Children with Uveitis continued:

<table>
<thead>
<tr>
<th>Uveitis Phenotype</th>
<th>Labs / Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, subacute, chronic iridocyclitis</td>
<td>Labs for all subtypes plus:</td>
</tr>
<tr>
<td></td>
<td>+/- ANA Non-specific, really most helpful in subcategorizing patients with JIA who are at a higher risk of developing uveitis</td>
</tr>
<tr>
<td></td>
<td>+/- RF Non-specific, really most helpful in subcategorizing patients with JIA who are at a higher risk of developing uveitis (RF negative, polyarticular)</td>
</tr>
<tr>
<td></td>
<td>HLA-B27 Acute presentation, occasionally chronic presentation.</td>
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<tr>
<td></td>
<td>Urine β2 microglobulin TINU (especially if acute, bilateral)</td>
</tr>
<tr>
<td></td>
<td>+/- Bartonella serology* Consider if exposure*</td>
</tr>
<tr>
<td></td>
<td>ASO titers Recent sore throat/URI*</td>
</tr>
</tbody>
</table>

Anterior location (see comments) Labs for all subtypes plus:

<table>
<thead>
<tr>
<th>Labs for all subtypes</th>
<th>Fine, diffuse stellate KP (non-Arlt distribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- HSV1 &amp; 2 IgM/IgG</td>
<td>Corneal involvement</td>
</tr>
<tr>
<td>+/- CMV IgM/IgG</td>
<td>Unilateral &gt; Bilateral</td>
</tr>
<tr>
<td></td>
<td>Hypertensive presentation (trabeculitis)</td>
</tr>
<tr>
<td></td>
<td>Iris atrophy/ TIDs</td>
</tr>
<tr>
<td></td>
<td>Poor response to topical steroids</td>
</tr>
</tbody>
</table>

**Note:** HSV is always a clinical diagnosis. Negative serology makes the diagnosis less likely, does not rule the diagnosis out. Aqueous PCR may be helpful in some cases.

Intermediate Uveitis Labs for all subtypes plus:

| Toxocara IgM/IgG                          | Toxocara and Toxoplasmosis are both clinical diagnoses; Serology does not rule the diagnosis out. |
| Toxoplasmosis IgM/IgG                     |                                                  |
| Bartonella IgM/IgG                        |                                                  |

Posterior +/- Retinal Vasculitis Labs for all subtypes + intermediate labs

| ANCA panel (MPO/PR3)                     | Granulomatosis with polyangiitis (GPA) + Microscopic polyangiitis (MPA) |
| ANA/anti-dsDNA/anti-phospholipid panel   | Systemic lupus erythematosis (SLE) work-up / Anti-phospholipid Syndrome |
| ENA panel                                | Mixed connective tissue disorder/SLE/Sjogren’s |
| +/- HLA-B51                               | Behcet’s Disease (Behcet’s Disease is a clinical diagnosis) |
| HLA-B27                                   | Rarely causes posterior segment disease, usually in setting of inflammatory bowel disease |
| HSV IgM/IgG                               | CMV depends on if immunocompromised |
| CMV IgM/IgG*                              |                                                  |

* Context of age, region, risk factors
III. Treatment Paradigm for Non-infectious Uveitis

A. Goals of treatment:
   Short-term:
   - Disease quiescence (no inflammation)
   - Steroid-free remission [or at least < 3 drops prednisolone acetate 1%/day]
   Long-term: Disease remission (not always possible)

B. Step Ladder Approach to Treatment

- Disease severity, complications, and patient factors (comfort, adherence, access) are key in guiding treatment
- Occasionally will need to “jump” the ladder (aka MTX/Biologic started simultaneously)

References:
Corticosteroids in Pediatric Uveitis

Erin Stahl, MD
Associate Professor, Division Director, Children’s Mercy Hospital, Kansas City, MO

I. Role of Corticosteroids in Treatment:
- Corticosteroids are an essential element in the initial management of uveitis (and occasionally chronic management of disease)
- Judicious use of corticosteroids to maximize effect and minimize side effects

II. Corticosteroid Options:

<table>
<thead>
<tr>
<th>Route</th>
<th>Examples</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>methylprednisone</td>
<td>-Rapid control of systemic/ocular disease</td>
<td>-Major systemic side effects -Risk of cataract/glaucoma</td>
</tr>
<tr>
<td>Oral</td>
<td>prednisone</td>
<td>-Rapid control of systemic/ocular disease -Once daily dosing</td>
<td>-Major systemic side effects -Risk of cataract/glaucoma</td>
</tr>
<tr>
<td>Periocular</td>
<td>Triamcinolone methylprednisolone</td>
<td>-Effective for 3-6 mos -No adherence issues -Treats posterior segment</td>
<td>-Most kids require sedation -May expose eye to high dose longer than needed -Kids are more likely to have ocular hypertension -High risk of cataract</td>
</tr>
<tr>
<td>Intraocular</td>
<td>fluocinolone (implant, Retisert) Dexamethasone (implant, Ozurdex) Triamcinolone Dexamethasone</td>
<td>-Effective for 3-6 mos, (2 years for Retisert implant) -No adherence issues -Treats posterior segment</td>
<td>-Most kids require sedation -May expose eye to high dose longer than needed -Kids are more likely to have ocular hypertension -High risk of cataract -Infection risk</td>
</tr>
<tr>
<td>Topical</td>
<td>prednisolone acetate 1% (Omnipred, Pred Forte) difluprednate (Durezol) Dexamethasone loteprednol (Lotemax) fluoromethalone 0.25%, 0.1% (FML)</td>
<td>-Can adjust dose/frequency easily</td>
<td>-Adherence is difficult -Most forms only treat anterior disease</td>
</tr>
</tbody>
</table>

III. Difluprednate Considerations
- Resistant or severe disease
- Some penetration into posterior segment
- Improved adherence
- Not a benign drug:
  - IOP elevation occurs in up to 80% of children; mean 9 weeks, 2-30 weeks (Birnbaum et al.,)
- Creative tapering strategies

Steroid-free remission...should we taper?

Sheila Angeles-Han, MD  
Associate Professor  
Division of Rheumatology  
Cincinnati Children’s Hospital Medical Center,  
Cincinnati, OH

Ashley Cooper, MD  
Associate Professor, Interim Division Director  
Division of Rheumatology  
Children’s Mercy Hospital  
Kansas City, MO

1. Key Questions:
   • What is the optimal time to discontinue therapy if in steroid-free remission?
   • What is the optimal drug to withdraw if on multiple medications?

2. Challenges:
   • Studies differ by diagnosis, medication and follow-up duration
   • Relapse 1 year after treatment discontinuation between 43-73%

3. Factors Associated with Disease-free Remission (as defined by SUN)
   • Underlying uveitis diagnosis
   • Early age of uveitis diagnosis
   • Early treatment and early control of disease
   • Medication subtype

4. Guidelines:
   Angeles-Han ST, Ringold S, Beukelman R, et al., 2018 American College of Rheumatology/Arthritis Foundation Guidelines for the Screening Monitoring and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis, Arthritis Care and Research; Arthritis and Rheumatology. 2019. [Accepted]


   SHARE Recommendations:
   At least 2 years of steroid-free remission prior to reducing systemic immunosuppression

   ***Note: These guidelines only apply to JIA-associated uveitis.

   Adalimumab in JIA-associated Uveitis Stopping Trial (ADJUST)
1. Case Presentation:
5 year-old girl with alternating redness, treated as conjunctivitis.
Bilateral anterior uveitis with anterior vitreous spill-over
Referred for uveitis work-up and management

2. Non-Infectious Renal Disease and Ocular Inflammation Differential Diagnosis:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Ocular</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematous (SLE)</td>
<td>Glomerular disease</td>
<td>Uveitis, retinopathy, vasculitis</td>
</tr>
<tr>
<td>Granulomatous with polyangiitis (GPA)</td>
<td>Glomerular disease</td>
<td>Orbital/lacrimal, scleritis, peripheral ulcerative keratitis (PUK), uveitis, retinopathy, vasculitis</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis and uveitis (TINU)</td>
<td>Acute interstitial nephritis</td>
<td>Uveitis (acute, anterior bilateral most common)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Interstitial nephritis/glomerulonephritis</td>
<td>Orbital/lacrimal, scleritis, PUK, uveitis, retinopathy, vasculitis, optic neuropathy</td>
</tr>
<tr>
<td>Sjogren Syndrome</td>
<td>Tubular interstitial nephritis</td>
<td>Keratoconjunctivitis sicca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uveitis</td>
</tr>
</tbody>
</table>

Need to rule out infection (fungal, TB) based on exposure

3. Tubulointerstitial Nephritis and Uveitis:
   - Acute interstitial nephritis (AIN) and uveitis [Note: AIN without a clear medication or systemic cause should be screened for uveitis]
   - Uveitis Presentation is Heterogeneous:
     - Median onset = 15 years, Females: Males 3:1
     - Always in the ddx of patients with bilateral simultaneous acute uveitis
     - Symptomatic or asymptomatic
     - Acute, subacute or chronic
     - ANY location: anterior, intermediate, posterior, panuveitis
   - Workup:
     - Complete metabolic profile should be included
     - UA: proteinuria, pyuria, eosinophils, hematuria
     - TINU-specific lab = URINE beta-2 microglobulin
     - Renal Biopsy is Gold Standard
   - Treatment:
     - AIN (managed usually by nephrologist)
       - Mainstay of AIN treatment is systemic steroids → mycophenolate is next step
     - Uveitis:
       - If not controlled with mycophenolate, then biologics can be considered (usually in coordination with rheumatologist)
1. Pars Planitis is common in children 8.4-31.4% 
2. Associated with significant morbidity (cataract, CME, ERM, NV, VH, RD)

Case 1: 
13 yo WM with history of myopia with 20/20 OD/ 20/25 OS vision and exam significant for 2+ cell, no haze OD and 2-3+ cell, 1+ haze OS. No CME OU. Inferior peripheral vasculitis OS. Inferior snowbank and snowballs OU.

Case 2: 11 yo F with intermittent redness/blurry vision OD x 18 mos. History of remote neck trauma. Negative neuro ROS. VA 20/40 OD, 20/30 OS, IOP 26 OD, 15 OS. Anterior segment exam significant for BK, inferior synechiae OD. Posterior segment significant for optic nerve/macular edema, snowballs OU.

Considerations for Clinical Exam and Follow-up in Patients with Pars planitis

- Initial Exam:
  - SD-OCT macula (detect subtle edema or thickening) / OCT color map
  - Scleral depression if able
  - FA (IV/oral) with wide-field imaging (detect leakage, NV)
  - +/- UBM to be considered (especially if wide-field imaging not available/unable to do scleral depression)

- If history of CME, consider OCT at each visit (especially when changing/tapering therapy) to detect early recurrence

- If history of peripheral and/or posterior leakage, monitor with FA (frequency based on initial severity, changes in treatment, response to treatment). OCT color maps may be helpful

- MRI prior to TNFα-inhibitor in pars planitis patients? If neuro symptoms/signs present (strongly recommend) v. all patients (consider).

- If controlled, follow-up at least every 3 months

Considerations for workup in intermediate uveitis: ACE/lysozyme, Quant gold, Syphilis IgM/IgG, +/- CXR, +/- MRI [Lyme, Bartonella based on exposures/risk]

What are the indications for systemic treatment?

What are the indications for peripheral laser?
Glaucoma due to Pediatric Uveitis: “Hot Time in the Old Eyes Tonight”

Brenda Bohnsakc, MD, PhD
[Title]
Kellogg Eye Center, University of Michigan

Alex V. Levin, MD, MHSc
[Title]
Wills Eye Hospital

Case: 8 year old male with idiopathic uveitis OU, diagnosed 2 years ago, s/p cataract extraction/IOL OU 1 year ago, referred for uncontrolled IOP OS, unable to taper off of topical prednisolone acetate OU

VA: 20/25 OD, 20/30 OS
IOP: 15 mm Hg OD; 32 mm Hg OS
Gonio: Open, few scattered PAS OU
OCT RNFL - superior thinning over 18 months OS
Systemic treatment: MTX qweekly;
Local treatment: pred acetate BID, dorzolamide-timolol BID, brimonidine BID, lantanoprost QHS

Key Points:
1. Inflammatory control is inadequate → Advance systemic therapy
2. Taper topical steroids
3. Continue glaucoma medications

Discussion: What medications are okay in children? Uveitis?

Uncontrolled IOP on maximal glaucoma medical therapy

Able to taper/discontinue prednisolone acetate?

Yes

NO

IOP controlled?

Yes

NO

Advance systemic therapy

Steroid Response Mechanism (mainly)
Mixed mechanism;
Consider surgical intervention once inflammation controlled