Pediatric Uveitis Committee Workshop:
Core Concepts for the Pediatric Ophthalmologist

COURSE PRESENTERS

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Course Overview:
- Introduction
- Diagnostic work-up for new-onset uveitis
- Management guidelines for non-infectious chronic anterior uveitis, focus on JIA-associated
- Case Presentations
- Questions and Answers

Presentation Resources
- Presentation slides available as a handout
- Bonus Material: Additional Resources and References
  - Link to abstract or article for key references
  - Hungry for more? Expanded content and resources available in handout

Objectives:
- Integrate clinical examination findings to arrive at a differential diagnosis including infectious and non-infectious causes
- Develop a diagnostic plan for laboratory and/or imaging studies
- Understand the American College of Rheumatology (ACR) updated guidelines for management of JIA-associated uveitis initial systemic treatment, treatment escalation, and monitoring of JIA-associated uveitis
- Apply guidelines to common clinical cases of increasing complexity
Introduction
Virginia Miraldi Utz, MD
Cincinnati Children’s Hospital Medical Center

Uveitis in Children: Introduction

• 75-88% of cases non-infectious (NIU)\textsuperscript{1-3}
• Juvenile idiopathic arthritis (JIA) is the most common systemic association (20-30%)\textsuperscript{1-3}

Location:
• Anterior (≈40-60%) > Intermediate (≈20%) > Pan-uveitis (≈16%) > Posterior (6%) \textsuperscript{1-3}

Infectious Causes of Uveitis in Children

\begin{tabular}{|c|c|c|}
\hline
Anterior & Intermediate & Posterior/Pan-uveitis \\
\hline
\end{tabular}

Always rule out Syphilis and Tuberculosis

- Herpes (HSV, VZV, CMV*)
- Lyme Disease
- Bartonella
- Toxocariasis
- Toxoplasmosis
- Herpes (HSV, VZV, CMV)
- Rubella, Rubella

Expanded list available

* CMV can cause an isolated anterior presentation in immunocompetent patients
Non-infectious Causes of Uveitis in Children

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Intermediate</th>
<th>Posterior/Pan-uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Presentation (usually)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• HLA-B27 related</td>
<td>• Pars planitis</td>
<td>• Sympathetic ophthalmia</td>
</tr>
<tr>
<td>• JIA / enthesitis</td>
<td>• Sarcoidosis</td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td>• Tubulo-interstitial nephritis and uveitis (TINU)</td>
<td>• Multiple Sclerosis</td>
<td>• Autosomal Dominant Systemic Granulomatous Disease (Blau Syndrome)</td>
</tr>
<tr>
<td>• Behcet Syndrome</td>
<td>• Tubulointerstitial nephritis and uveitis (TINU)</td>
<td>• Behcet Disease</td>
</tr>
<tr>
<td>Chronic Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Juvenile idiopathic Arthritis (JIA)</td>
<td>• TINU (rare)</td>
<td>• Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td></td>
<td>• Behcet Disease</td>
<td>• ANCA-associated</td>
</tr>
<tr>
<td></td>
<td>• Sarcoidosis</td>
<td>• Vogt-Koyanagi-Harada (VKH)</td>
</tr>
<tr>
<td></td>
<td>• Auotosomal Dominant Systemic Granulomatous Disease (Blau Syndrome)</td>
<td>• TINU</td>
</tr>
</tbody>
</table>

Diagnostic Approach

- History of Present Illness
  - GET ALL RECORDS
  - Clinical course
  - Current treatments
  - Response to prior treatments
    - ROS – Families may “brush” through the ROS form
      - Key ROS: Ask about rashes, joint pain or limping, GI issues, blood in urine

Comprehensive History is Key

Temporal progression – initial onset, disease course

If history of ocular hypertension, was IOP high on presentation or after steroids were initiated?
Comprehensive History

- Past Medical History (immune status, existing medical conditions)
- Medications (e.g. medication-induced uveitis)
- Family History of autoimmune diseases
- Social History: Pets/animals, travel history, sexual practices, history of drug use

Careful, Comprehensive Examination with Descriptive Naming

- Pathology (granulomatous/non-granulomatous)
- Anatomical location of disease (anterior, intermediate, posterior, pan-uveitis)
  - CME or papillitis can occur as complications of anterior disease
  - Anterior vitreous spill-over v. intermediate uveitis
    - Look for pars plana involvement for intermediate uveitis (snow balls, snow-banking, exudate)

Key Anterior Segment Findings

- Cornea:
  - Keratitis/endotheliitis
  - Keratic precipitates:
    - Size and appearance (stellate)
    - Granulomatous v. non-granulomatous
    - Distribution (diffuse, central, paracentral Arlt's triangle)
- Iris: nodules, synechiae, transillumination defects?

Pearl: Quantifying AC Cell

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells/HPF</th>
<th>Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 1</td>
<td>None</td>
</tr>
<tr>
<td>0.5+</td>
<td>1-5</td>
<td>Faint</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
<td>Moderate (iris and lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>26-50</td>
<td>Marked (iris and lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 50</td>
<td>Intense (fibrin or plastic aqueous)</td>
</tr>
</tbody>
</table>

Additionally:
- I document as Cells/HPF for grades 0.5+ and 1+.
- For grades 0.5+, pay close attention to the presence of new KPs.

Key Posterior Segment Findings

- Vitreous Haze
- Snowbanks/Snowballs
- Exudative Detachment
- Vasculitis (Primary arteritis v. phlebitis)
- Infectious Lesions / CR scarring

Need to evaluate out to the ora serrata
Imaging Studies

- Macular OCT
- Optic nerve OCT
- Optos wide-field fundus photo
- Fluorescein angiography

Clinical Pearls: When to Suspect Viral Etiology

- Recurrent or chronic unilateral non-alternating anterior uveitis
- History of OHT with each episode of uveitis (trabeculitis)
- Small central/paracentral (occasionally diffuse) KPs; may appear larger if clumped
- Iris transillumination defects
- History of keratitis (dentritiform/pseudodentritiform, endothelitis)

Examples of HSV Keratouveitis

CLINICAL PEARL:
But my HSV serology was negative...

- Herpetic viral infection is always a clinical diagnosis.
- Consider empirical treatment with acyclovir (or valacyclovir) if suspected
- Aqueous tap for viral PCR or metagenomic deep sequencing for DNA/RNA can be helpful if not responding to treatment
- Even if negative testing, treat as herpetic disease if high suspicion.

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Clinical Pearls: Select Masquerade Syndromes in Children

<table>
<thead>
<tr>
<th>Entity</th>
<th>Anterior Segment Findings</th>
<th>Posterior Segment Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Hypopyon, pseudohypopyon</td>
<td>Cotton wool spots</td>
</tr>
<tr>
<td></td>
<td>(may be gray-yellow)</td>
<td>Peripheral NV</td>
</tr>
<tr>
<td></td>
<td>Huyopyon</td>
<td>Peripheral RD (if choroid involved)</td>
</tr>
<tr>
<td>Diffuse-infiltrating Retinoblastoma</td>
<td>Unilateral, Chemosis,</td>
<td>Dense vitreous, no calcification on B-scan, retina may be obscured by vitreous</td>
</tr>
<tr>
<td></td>
<td>Pseudohypopyon (white and</td>
<td>changing with head position)</td>
</tr>
<tr>
<td>Intraocular foreign body</td>
<td>Inflammation via mechanical, toxic, inflammatory or chemical irritation in any segment of the eye. High index of suspicion</td>
<td></td>
</tr>
<tr>
<td>Chronic Peripheral Retinal Detachment</td>
<td>Cell and flare</td>
<td>Peripheral retinal detachment May have CME</td>
</tr>
<tr>
<td></td>
<td>Open angle glaucoma (Schwartz Syndrome)</td>
<td></td>
</tr>
</tbody>
</table>

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Diagnostic Studies:

- No “one size fits all” panel of testing
- Guided by clinical phenotype, risk factors, and pre-test probability of disease
Infectious Causes: Consider in Any Child with Uveitis

- Treponemal specific testing (FTA-Ab, Syphilis IgG, MHA-TP)
- RPR/VDRL (correlates with disease activity)
- Consider HIV testing if positive
- TB (quant gold/PPD)
- Lyme (based clinical presentation and region)
- Consider Bartonella

Consider in Any Child with Uveitis

- ACE/Lysozyme
-CBC with diff
- ESR/CRP
- Complete metabolic panel
- UA + Urine beta-2 microglobulin
- ANA

Phenotype-Guided Testing

DDx: JIA, sarcoidosis, TINU, Fuch’s (if unilateral)
Labs: ANA, RF, Urine B2-microglobulin, ESR, ACE/Lysozyme

Asymptomatic, white quiet eye with anterior segment inflammation only, cataract and band keratopathy, mild IOP
Phenotype-Guided Testing

- DDX:
  - HLA-B27-associated Acute Anterior Uveitis
  - HLA-B27-associated seronegative spondylopathies (Enthesitis-related JIA, inflammatory bowel disease)
  - Behcet Disease
  - TINU
  - Bacterial endophthalmitis
  - Masquerade

Unilateral, acute onset uveitis with hypopyon, relative hypotony and eye pain in 10-year-old boy.


Studies to Consider:

- HLA-B27
- Rheum (ERA eval/MRI SI joints)
- GI eval (+/- EGD/Colonoscopy)
- TINU: Urine B2-microglobulin (UA, renal function tests)
- Behcet: Screen for organ involvement (clinical diagnosis)

Unilateral, acute onset uveitis with hypopyon, relative hypotony and eye pain in 10-year-old boy.


16 year old boy with new onset floaters with intermediate uveitis.

DDX: Infection (syphilis, toxoplasmosis, TB, Lyme, Toxocara), Sarcoidosis, MS, TINU (atypical), pars planitis.

Labs: Toxoplasmosis/Toxocara/Lyme serology, TB, FTA-Ab, RPR, ACE/Lysozyme, Urine B2-microglobulin

- Consider chest/abdominal CT if high index of suspicion for Sarcoidosis
- Consider MRI brain if high index of suspicion for MS (or consider if starting TNFi)
More examples of phenotype-driven testing?

Non-infectious pediatric uveitis
- Idiopathic
- Systemic
  - JIA
  - Other
- Other
  - Oligoarticular
    - Polyarticular
    - Pediarticular
  - Enthesitis

Anterior Uveitis
- Chronic Anterior Uveitis (CAU)
- Acute Anterior Uveitis (AAU)

Onset
- Ocular
- Duration
- Course

Chronic (asymptomatic)
- Persistent (>3 mos)
- Acute (≥ recurant)
- Sudden (symptomatic)
- Limited (<3 mos)
- Acute (≥ recurant)

American Association for Pediatric Ophthalmology and Strabismus

Treatment Approach for JIA-associated Uveitis and other forms of Non-infectious Chronic Anterior Uveitis

Melissa Lerman, MD, PhD, MSCE
Division of Rheumatology, Children’s Hospital of Philadelphia
Juvenile Idiopathic Arthritis (JIA)
- JRA, JCA → JIA
- Chronic arthritis
- Onset <16 yo
- Multiple subtypes

Uveitis in JIA Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Phenotype</th>
<th>Uveitis Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarticular</td>
<td>Persistent</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>Extended</td>
<td>15%</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>RF (-)</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>RF (+)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>Chronic, bilateral</td>
<td>7%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>Acute (?), unilateral</td>
<td>8%</td>
</tr>
<tr>
<td>Systemic</td>
<td>&lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

JIA-Associated Uveitis Morbidity Children
- Rates visual impairment:
  - VA < 20/50: 18-36%\(^1-4\)
  - VA < 20/200: 4-24%\(^1-4\)
- Ocular complications in up to 67%\(^1-4\)
- Impacts psychosocial well-being child and family\(^5\)

References:
Wear et al., 2021; Holland et al., 2020; Smith et al., 2009; Cash PC et al., Pediatric Rheumatology, 2018; Parker et al., AJO, 2018; Angeles-Han S et al., Arthritis Care Res, 2015
Risk Factors for JIA-U

- Female, young age JIA onset, ANA+, oligo
- Can develop at any time
  - Highest risk 2-4 years after diagnosis
  - Genetic: HLA-DR5; DRB1*11, 1*13

ACR 2019 Guidelines: JIA-U Screening

Risk Factors for Severe Disease Course / Poor visual outcomes

- Short duration between arthritis and uveitis diagnoses
- Uveitis diagnosed prior to arthritis
- Presence of complications at first examination
- Male gender
- Race (non-Hispanic African American)
Monitoring *Arthritis* on treatment

- Uveitis most often painless
- Arthritis flares can be painless
- Do joints and eye activity correlate?
- Eyes often driver of systemic treatment

**Goals of Uveitis Treatment**

- Decrease inflammation (<0.5+)
- Shortest possible time to control
- Maintain control
- Spare steroid exposure

**Treatment Algorithm**
Treatment Guidelines

- ACR/AF Guidelines for Screening, Monitoring and Treatment of JIA-U (2019)
- Update on evidence based, interdisciplinary guidelines for treatment of JIA-U (2019)


ACR/RF

ACR/RF: Patients with JIA and active CAU

- Initial treatment:
  - Prednisolone acetate 1% (PA)
  - Preferred over difluprednate
Indications for Systemic Treatment

- Cannot taper PA < 2 drops for ≥ 3 mos
- Uveitis flare with each taper

PA = prednisolone acetate 1%

Disease Modifying Anti-rheumatic Drugs

- Methotrexate
  - Mycophenolate mofetil (CellCept)
  - Azathioprine (Imuran)
  - Cyclosporine/tacrolimus
  - Leflunomide (Arava)

Methotrexate

- **Benefit:** ~75% of patients with JIA-U respond
- Route
- Frequency
- Lab monitoring q3-4 mo
- Minimal adverse effects
- Precautions: no live virus vaccines

Persistent Activity on Methotrexate

- Persistent activity and/or inability to taper PA. ≥ 3 mo
- Complications related to steroid-treatment
- ADD ON

Biologics

Initial Biologics in JIA-U
Tumor Necrosis Factor α inhibitors

- Monoclonal Antibodies
  - Infliximab (Remicade™) – chimeric, IV
  - Adalimumab* (Humira™) – fully human, SQ
  - Golimumab, Certolizumab

- Soluble receptor – Etanercept (Enbrel™)

* FDA Approved for JIA-U
**TNFi**

- **Benefit:**
  - ~75% of those who fail methotrexate respond
  - ADA vs. IFX
  - Rule out TB
  - Lab q6 mo, abnormalities rare


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**Safety of Adalimumab**

- Meta-analysis 577 children (1440.7 PY)*
  - Minor AE:
    - URI (24.3), Nasopharyngitis (17.3), HA (19.9)
  - Serious infections (4) - pneumonia (0.6)
  - By disease: 2.7 JIA, 0.8 Psoriasis, 6.6 Crohn’s Disease.
  - No malignancies

*AE/100 PY

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**Poor Response to TNFi/Strategies to Improve**

- Dose insufficient
  - Increase dose
  - Increase frequency
- Neutralizing antibodies to biologic drug (next slide)
  - Check drug levels and antibodies
- Non-adherence
  - ADA drug levels as above
  - IFX infusions easy to track
- Increase DMARD (MTX) or change to SQ if oral
Anti-drug Antibodies

- Adverse reactions, decreased effect of drug
- Immunogenicity to drug:
  - Inversely related to dose (IFX)
  - Reduced by Methotrexate
- Meta-analysis in JIA (ADA): RR 0.33 (95% CI 0.21, 0.52)

References:
Tapering

- When?
  - ACR/AF: ≥ 2 years controlled
  - Biomarkers?
- How?
  - Biologic or DMARD first?
  - Biologic: Dose or interval?
- Risks

Case 1

- 21 month-old F
- R knee swelling
- Started on naproxen
- Undergoing work-up
Slit lamp exam by any means necessary!

- 1+ cell OU
- No complications

What next?

- Presumed JIA
- Start prednisolone acetate 1% QID OU
- Coordinate with rheum re: IMT
  - Methotrexate
  - 1 mg/kg in uveitis
  - Max dose 25 mg/week SQ

What if it’s not a “slam dunk”? 

- When do you see the patient?
- When do you think about oral steroids/IMT?
  - Severe inflammation
  - Presence of complications
Initial Treatment Considerations

- Active arthritis
- Uveitis (without vision-threatening complications)

Take-Home Points

1. Handheld slit lamps ≠ standard slit lamps
2. Instruct family to shake bottle well
3. Avoid difluprednate in kids
4. Early initiation of IMT
Case 2
6.5-year-old girl with JIA-associated CAU OS presents for follow-up
- Uveitis recently active and undergoing tapering regimen
- On Pred acetate (PA) 1% TID, cyclopentolate QHS, SC MTX
- Non-adherent to MTX prior to recent flare
- No active joint pain since age 3 years

History
- Medical history:
  - ANA -ve, Oligoarticular JIA diagnosed at age 2 - h/o steroid injections - PO MTX started at age 3
- Past Ocular History:
  - First episode of uveitis [OS] at age 4.6 years
  - Switched to SC MTX

Exam

<table>
<thead>
<tr>
<th></th>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
<td>20/20</td>
<td>20/30 -1</td>
</tr>
<tr>
<td>Refraction</td>
<td>-0.50, +1.25 @ 90</td>
<td>-1.00, +1.50 @ 90</td>
</tr>
<tr>
<td>IOP</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Cornea</td>
<td>Clear</td>
<td>Fine KPs inferiorly in A/P's triangle</td>
</tr>
<tr>
<td>Pupil</td>
<td>Round</td>
<td>Synechias at 7 o'clock</td>
</tr>
<tr>
<td>AC</td>
<td>Clear</td>
<td>2+ cells, 1+ Flare</td>
</tr>
<tr>
<td>Lens</td>
<td>Clear</td>
<td>Few pigments over anterior lens capsule</td>
</tr>
<tr>
<td>Fundus</td>
<td>0.1 cd</td>
<td>0.1 cd</td>
</tr>
</tbody>
</table>
Management

- Inflammation recurred to 2+ when PA 1% was tapered to TID
- Increased PA to QID, Increased SC MTX to 25 mg weekly
- Attempted taper, but could not taper to <3 times per day and inflammation persisted grade 1+ to 2 over the next 2 months

What next?

- Unable to taper PA < 3 drops after 4 months
- 25 mg MTX SC
- Time to take the next step!

Adalimumab vs. Infliximab

<table>
<thead>
<tr>
<th>ADA (Humira™)</th>
<th>IFX (Remicade™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>IV infusion</td>
</tr>
<tr>
<td>Fully humanized</td>
<td>Chimeric monoclonal Ab</td>
</tr>
<tr>
<td>Less immunogenic</td>
<td>More immunogenic</td>
</tr>
<tr>
<td>No malignancy</td>
<td>Malignancy</td>
</tr>
</tbody>
</table>
Infliximab

- Given the adherence issues, the consensus was to start Infliximab infusion - 6 mg/kg q 4 wk after loading
- Continued MTX to prevent anti-chimeric antibody formation
- Tolerated well

Followup

- After 6-8 weeks of combined therapy of MTX + Infliximab, inflammation was controlled, noted to have 2 cells/HPF (Gr 0.5+) OS
- Topical steroids were successfully tapered

Last Followup

- No recurrence of uveitis on MTX + Infliximab in 2 years
- Recently started tapering her systemic IMT - MTX 20 mg + Infliximab q6 weeks
Take home pearls

- Long and tough course
- Team approach – with Rheumatologist
- Regular follow-up
- Timely management - Step-ladder approach

JIA can be bad!

- Crippling joint disease
- Systemic symptoms
- Pain
- Drug side effects
- Depression/anxiety
JIA-associated uveitis can be bad!

- exudative RD
- panuveitis
- vitritis
- papillitis
- pars planitis
- cyclitic membrane, hypotony
- PERMANENT VISION LOSS

JIA until proven otherwise

JIA Iritis: Prognostic Factors

1st exam no synechia
- 28% cataract
- 17% glaucoma
- 5% band keratopathy
- 3% < 20/200

(Wolf, 1987)
**JIA Iritis: Prognostic Factors**

1st exam synechia
- 81% cataract
- 45% glaucoma
- 77% band keratopathy
- 58% < 20/200

(Wolf, 1987)

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**Fast Forward 2020: Poor Prognostic Factors at Baseline Presentation:**

- Synechia on presentation1,3,4,5
- Any ocular complications on presentation (BK, synechia, cataract, CME, IOP abnormalities)1,2,4
- Flare, intermediate uveitis, papillitis5
- Hypotony3
- Panuveitis4
- Nuclear cataract at baseline presentation5

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**Prevention is the key**

Too late? (prognosis awful)
No correlation

Bad uveitis can be found in a well child
Sick child can have great eyes

Treatment caveats

Drops don’t treat joints
Not all systemic meds treat the eyes
e.g. NSAIDs, Enbrel
Uveitis often requires more than steroids
Don’t undertreat or wean too fast

Want to kill an elephant?
Initial Treatment: Sick eyes need big guns

- For inflammation > 2+ cell, +/- posterior segment involvement:
  - Acute steroids
    - Q1 hr topical
    - PO
    - IV (Rarely)
    - Sub-Tenon
    - Intraocular implants

Sick eyes need big guns

Systemic meds
go early/strong or go home!
call your rheumatologist
Stay out of the eye if you can
Don’t flail at hypotony
no good treatment
is it hurting the eye?
Treat the whole family!

Emotional impact
Family impact

Resources:
https://aapos.org/patients/patient-resources/pediatric-uveitis
www.pgftr.org
www.ccaa.org.uk
juvenilearthritisnews.com
www.arthritis.org/diseases/juvenile-idiopathic-arthritis

What’s Next: After Traditional TNFi?

Stefanie L. Davidson, MD
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Case 3 Presentation:
- 7-year-old girl presented to the Uveitis Coordinated Care clinic with a history of JIA-associated uveitis.
- Current medications:
  - Adalimumab every 2 weeks and MTX SQ weekly
  - Joints=controlled
  - Uveitis=ACTIVE, 1+ cell anteriorly OU
Additional History

- Diagnosed with JIA/chronic anterior uveitis (CAU) at age 2 years
- Enbrel started age 3 years
- Changed to infliximab and MTX at age 4 years
  - Developed allergic response to infliximab by age 5
- Changed to adalimumab biweekly and MTX

WHAT IS THE NEXT STEP IN MANAGEMENT?

Is this the time to say TNFi aren't working and switch to an alternative biologic?

Recommendations for DMARDs/Biologics

| Subcutaneous methotrexate is recommended over oral methotrexate. |
| Bispecific antibody TNF inhibitor is recommended over etanercept. |
| In severe uveitis with sight-threatening complications*, combination methotrexate and TNF is recommended over methotrexate monotherapy. |
| In inadequate response to one TNFi, dose or frequency escalation is recommended before switching to another TNFi.** |
| In inadequate response to above-standard dose or frequency of one TNFi, changing to another TNFi is recommended before switching to a different biologic target. |
| In inadequate response to 2 TNFi at above-standard dosing or frequency, abatacept, tocilizumab, mycophenolate, infliximab, and cyclosporine are recommended alternative options. |

Subcutaneous methotrexate is recommended over oral methotrexate.

Bispecific antibody TNF inhibitor is recommended over etanercept.

In severe uveitis with sight-threatening complications*, combination methotrexate and TNF is recommended over methotrexate monotherapy.

In inadequate response to one TNFi, dose or frequency escalation is recommended before switching to another TNFi.**

In inadequate response to above-standard dose or frequency of one TNFi, changing to another TNFi is recommended before switching to a different biologic target.

In inadequate response to 2 TNFi at above-standard dosing or frequency, abatacept, tocilizumab, mycophenolate, infliximab, and cyclosporine are recommended alternative options.
Case Management

- Failed infliximab & adalimumab at standard dose.
- Next step is to increase adalimumab to WEEKLY use
  - Joint=controlled
  - Uveitis=controlled
- Achieved steroid free remission for 2 years
- Now WHAT?


Recommenda9ons for Tapering Medications

In uveitis controlled on systemic therapy but requiring 1-2 drops of topical GC, tapering topical GC before systemic therapy strongly recommended.

In uveitis well-controlled on DMARD/biologic therapy, at least 2 years of well-controlled disease without steroid requirement recommended before tapering therapy.

Case Management

- Adalimumab was decreased to biweekly use
  - Joints=controlled
  - Uveitis=ACTIVE again!
- Uveitis recaptured on adalimumab weekly 40mg (coupled with continued MTX SC weekly 17.5mg)
- Remained controlled for 1.5 years UNTIL...
Uveitis and arthritis flared (ADA weekly & sc MTX)
SEND ANTIBODIES POSITIVE IN THIS CASE (SERUM LEVELS OF DRUG = 0)
She has now failed infliximab and weekly adalimumab
Time to change biologic agents? YES

Case Management: Now What?

Recommendations for DMARDs/Biologics
- Subcutaneous methotrexate is recommended over oral methotrexate.
- Monoclonal antibody TNF inhibitor is recommended over etanercept.
- In severe uveitis with sight-threatening complications*, combination methotrexate and TNF-inhibitor is recommended over methotrexate monotherapy.
- If inadequate response to one TNFi, dose or frequency escalation is recommended before switching to another TNFi.**
- If inadequate response to above-standard dose or frequency of one TNFi, changing to another TNFi is recommended before switching to a different biologic target.
- If inadequate response to 2 TNFis at above-standard dose or frequency, abatacept, tocilizumab, mycophenolate, leflunomide, and cyclosporine are recommended alternative options.

Other Biologic Options:
- Golimumab: newer anti-TNFα, less immunogenic
- Tocilizumab (Actemra™): IL-6 inhibition
  - Elevated IL-6 levels have been found in ocular fluids of patients and animals with uveitis.
  - IL-6 blockade suppresses Th1 and Th17 cell induction
- Abatacept (Orencia™): inhibits activation of T cells via CD 28 blockade
The AAPOS Meeting Alternative......
Pediatric Uveitis Committee Workshop:
Core Concepts for the Pediatric Ophthalmologist

Bonus Material: Additional Resources and References

Presenters:
Virginia Miraldi Utz, MD, FAAP
  Abrahamson Pediatric Eye Institute, Cincinnati Children's Hospital
Melissa Lerman, MD, PhD, MSCE
  Division of Rheumatology, Children's Hospital of Philadelphia
Bharti Gangwani, MD
  Dept of Ophthalmology, Boston Children's Hospital
Kara C. LaMattina, M,D
  Dept of Ophthalmology, Boston Medical Center
Alex L. Levin, MD, MHSc, FRCSC, FAAP
  Dept of Ophthalmology, Wills Eye Hospital
Stefanie L. Davidson, MD
  Division of Ophthalmology, Children's Hospital of Philadelphia

Committee Members Assisting in Content: Jing Jin, MD, PhD; Erin Stahl, MD; Brenda Bohnsack, MD, PhD; Sheila Angeles-Han, MD, MS; Jennifer Jung, MD; Ashley Cooper, MD
OVERVIEW OF THE PEDIATRIC UVEITIS COMMITTEE & MEMBER AND PATIENT RESOURCES

The AAPOS Pediatric Uveitis Committee 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
- What else can we do for you? Please think about areas that AAPOS members would appreciate guidelines and please write down on notecard provided or email me (virginia.utz@cchmc.org)

2. Resources available to AAPOS Members on our website:

- Support resources for patients and families: Consider providing this resource to your patients with a new diagnosis of uveitis for reliable, web-based resources. https://aapos.org/patients/patient-resources/pediatric-uveitis
  “Resources for Patients and Families”

- Uveitis Assessment Form: Ophthalmology-Rheumatology Provider Communication: While communication may be easy if rheumatologist and ophthalmologist are in one system, some families may be managed by local rheumatologists (or ophthalmologists) and communication is key. While a telephone call is the best mode of communication for urgent concerns or changes, providers may incorporate the following template into their EMR system or print and document findings. The form can be faxed to the rheumatologist and a copy given directly to the patient/family. [Many thanks to the IU fellowship grads who provided additional feedback for this form]

- 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.

- Prior Authorization (or Letter of Medical Necessity) for Biologic Response Modifiers: Template letter to share with rheumatologist to aid in the acquisition of evidence-based treatment such as biologic response modifiers. [Must be logged in to AAPOS to access]

Have additional recommendations? Needs? Questions? Referral? Please email aapos@aaao.org
Pediatric Uveitis Information

RESOURCES FOR PATIENTS AND FAMILIES
- Iritis Information Sheet
- Juvenile Idiopathic Arthritis Information Sheet
- National Eye Institute
- The Ocular Immunology and Uveitis Foundation
  - Patient Guides
  - Kids Library
- The Pediatric Glaucoma and Cataract Family Association (PGCFA)
- Pediatric Low Vision Resources
- Prevent Blindness

RESOURCES FOR PHYSICIANS
- American Academy of Ophthalmology Knights of Templar Eye Foundation Pediatric Ophthalmology Education Center
  - Pediatric Anterior Uveitis
  - Pediatric Intermediate Uveitis
  - Pediatric Posterior and Panuveitis
- Uveitis Assessment Form: Ophthalmology-Rheumatology Communication

Children with uveitis miss school for frequent appointments, lab draws, and treatment. They may need regular administration of medications in school. In some cases, children have visual impairment and require special services and adaptations to address vision needs. Patients commonly feel "isolated" and "alone" since their friends and family are unfamiliar with "uveitis." To provide support to physicians, patients and families, the Pediatric Uveitis Task Force developed a template letter for a 504 plan. This template can be modified to fit the needs of the student.
**Clinical Guidelines:**

**U.S./North America:**

   - Applies to JIA-uveitis (or by extension idiopathic JIA-like, chronic anterior uveitis)
   - Reference: Angeles-Han ST, Arthritis Care & Research, 2019, 71 (6), 703-716.

2. Childhood Arthritis and Rheumatology Research Alliance (CARRA) Consensus Treatment Plans (CTPs) for Juvenile Idiopathic Arthritis-Associated and Idiopathic Chronic Anterior Uveitis
   - Applies to the design of prospective research to compare effectiveness of treatment
   - These are not treatment guidelines
   - References: Angeles-Han ST, Arthritis Care and Research 2019, 71 (4), 482-491.

**Europe:**

   - Overlapping features with ACR guidelines above, some differences
   - Reference: Constantin et al., Ann Rheum Dis 2018; 77 (8); 1107-1117.
   - Full text link: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6059050/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6059050/)

**Germany/Europe:**

   - Update of the evidence based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis.
   - References: Heiligenhaus et al., Seminars in Arthritis and Rheumatism, 2019, 49 (1), 43-55

**Quality of Life/Psychosocial Implications of Pediatric Uveitis:**


**Standardization of Uveitis Nomenclature (SUN) Working Group:**

**Nice Review Article:**

**Meta-analysis of TNFi:**
1. Etiologies of Pediatric Uveitis

Table 1. Infectious Causes: Extended List

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Intermediate</th>
<th>Posterior/Pan-uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always rule out Syphilis and Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Herpes (HSV/VZV/CMV*)</td>
<td>• Lyme Disease</td>
<td>• Bartonella</td>
</tr>
<tr>
<td>• Lyme Disease</td>
<td>• Toxocariasis</td>
<td>• Toxoplasmosis</td>
</tr>
<tr>
<td>• Bartonella</td>
<td>• Bartonella</td>
<td>• Bartonella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lyme Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Herpes (HSV, VZV, CMV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rubella, Rubeola (SSPE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HTLV-1 (Japanese patient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TORCH Others: Zika, Lymphocytic Choriomeningitis virus (LCMV)</td>
</tr>
</tbody>
</table>

*CMV anterior uveitis occurs in immunocompetent patients, can be acute-recurrent or chronic. Acute recurrent is usually unilateral and repeated episodes of OHT and mild reaction. Chronic form typically has nodular endothelial lesions with a surrounding translucent halo, coin-shaped keratic precipitates are characteristic. Usually unilateral, but may be bilateral in children. Look for iris atrophy. Poorly topical steroid responsive. Diagnosed via AC tap/PCR.

Chronic CMV Anterior Uveitis:
Slit-lamp photograph of a pseudophakic eye with cytomegalovirus-positive chronic anterior uveitis, showing diffuse, fine keratic precipitates and the absence of posterior synechiae.

Image source: © 2020 American Academy of Ophthalmology
https://www.aao.org/image/chronic-cmv-anterior-uveitis
Cited as per “Image License and Citation Guidelines”
Table 2. Non-infectious Etiologies

<table>
<thead>
<tr>
<th>Anterior</th>
<th>Intermediate</th>
<th>Posterior/Pan-uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Presentation (usually)</strong></td>
<td>• Pars planitis</td>
<td>• Sympathetic ophthalmia</td>
</tr>
<tr>
<td>• HLA-B27 related</td>
<td>• Sarcoïdosis</td>
<td>• Sarcoïdosis</td>
</tr>
<tr>
<td>• JIA enthesis</td>
<td>• Multiple Sclerosis</td>
<td>• Autosomal Dominant Systemic Granulomatous Disease (Blau Syndrome)</td>
</tr>
<tr>
<td>• Tubulointerstitial nephritis and uveitis (TINU)</td>
<td>• TINU (rare)</td>
<td>• Behçet Disease</td>
</tr>
<tr>
<td>• Behçet Syndrome</td>
<td></td>
<td>• Systemic Lupus Erythematous</td>
</tr>
<tr>
<td><strong>Chronic Presentation</strong></td>
<td></td>
<td>• ANCA-associated</td>
</tr>
<tr>
<td>• Juvenile Idiopathic Arthritis (JIA)</td>
<td></td>
<td>• Vogt-Koyanagi-Harada (VKH)</td>
</tr>
<tr>
<td>• Sarcoidosis</td>
<td></td>
<td>• TINU</td>
</tr>
<tr>
<td>• Idiopathic orbital inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kawasaki Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fuch’s heterochromic iridocyclitis (Rubella in some)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other: Drug-induced, trauma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-infectious Uveitis Clinical “Bites”

- **Uveitis in Setting of Idiopathic Orbital Inflammation**
  In a child with suspected IOI, check the AC. Children are more likely to have a chronic anterior uveitis (Bloom JN, Graviss ER, Byrne BJ. Orbital pseudotumor in the differential diagnosis of pediatric uveitis. J Pediatr Ophthalmol Strabismus. 1992;29(1):59-63.)

- **Tubulointerstitial Nephritis and Uveitis (TINU)**
  - May be more common than previously recognized in children
  - Usually acute onset and bilateral at initial presentation with fine KP (although occasionally a chronic, asymptomatic presentation)
  - Significant phenotypic variability: Pan-uveitis, choroidal infiltrates (sarcoid-like), intermediate uveitis, chronic and recurrent in 30% of patients
  - Evaluation: Renal function studies (Creatinine, Urine beta-2 microglobulin increased, Urinalysis (for protein, RBCs, WBCs) HLADR1/DQ5
  - Often requires nephrologist, rheumatologist and ophthalmologist for long-term management
  - Early systemic corticosteroids in all, IMT for chronic uveitis.
**What is metagenomic deep sequencing (MDS)?**

A very small sample of intraocular fluid (or corneal scraping) is obtained. Sample DNA or RNA is massively sequenced in parallel and analyzed. Human genetic material in intraocular fluid is filtered out leaving non-human DNA or RNA (fungi, eukaryotes, DNA or RNA viruses, bacteria) for further analysis and identification. This can be very helpful in uveitic disease suspected to be infectious or if there is a poor or atypical treatment response.


https://www.the-rheumatologist.org/article/metagenomic-deep-sequencing-uveitis-enhances-traditional-diagnostic-testing/?singlepage=1

### Masquerade Syndromes

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Anterior Segment Findings</th>
<th>Intermediate/Posterior Segment Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Hypopyon, pseudohypopyon (may be gray-yellow)</td>
<td>Vitritis (rare) Retinal hemorrhages Cotton wool spots</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral NV Exudative RD (if choroid involved)</td>
</tr>
<tr>
<td>Diffuse-infiltrating RB</td>
<td>Chemosis Pseudohypopyon (white and changing with head position)</td>
<td>Dense vitritis No calcification on B-scan, may be obscured by vitritis</td>
</tr>
<tr>
<td>Juvenile Xanthogranuloma</td>
<td>Spontaneous hyphema Iris nodules</td>
<td>Vitreous hemorrhage/peripheral neovascularization</td>
</tr>
<tr>
<td>Intraocular foreign body</td>
<td>Inflammation via mechanical, toxic, inflammatory or chemical irritation in any segment of the eye. High index of suspicion</td>
<td></td>
</tr>
<tr>
<td>Chronic Retinal detachment</td>
<td>Cell and flare Open angle glaucoma</td>
<td>Peripheral retinal detachment May have CME</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td></td>
<td>Vitritis CME poorly responsive to steroids (responds to CAIs) → FAF is very helpful</td>
</tr>
</tbody>
</table>
### Additional Examples of Phenotype-Driven Diagnostic Testing

**Table 5.** (Not exhaustive list, consider clinical presentation, demographics, exposures, geographic region)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Suspected Diagnosis</th>
<th>Diagnostic Testing Considerations</th>
</tr>
</thead>
</table>
| -Hypertensive unilateral uveitis  | -Viral (HSV, VZV, CMV)                                   | - Treat empirically with acyclovir or valacyclovir (in a kid)  
- Iris atrophy                      |  
- Reduced corneal sensation       | - Consider AC tap for PCR or MDS (often requires anesthesia)  
- KP above midline                  | +/- Serology  
- Fuch’s / Rubella                  |                                                                                                                                                                                                                                                                                                                                 |
| Granulomatous KP                  | -Infectious, sarcoidosis, VKH                            | - Quantiferon gold  
Look for iris nodules                | - Treponemal testing  
- Toxoplasmosis serology (posterior involvement/CR scarring)  
- Toxocara serology                 | - Toxocara serology  
- Bartonella serology                | - Biopsy if skin/conj lesions  
- CXR (CT chest/abdomen if high suspicion for sarcoidosis) | - VKH (serous retinal disease) – clinical diagnosis, audiology eval, LP to document CSF pleocytosis  
- CMV – ocular PCR                   |                                                                                                                                                                                                                                                                                                                                 |
| Focal chorioretinitis with vitritis| Toxoplasmosis (endemic area raw meat, unwashed vegetables)  
Toxocariasis (child, history of geophagia)  
CMV retinitis (? immunosuppressed, variable vitritis) | - Toxoplasmosis: serology (PCR of ocular fluid optional)  
- Toxocariasis (clinical diagnosis, Serology, CBC to evaluate for eosinophilia, PCR of ocular fluid (can have seronegative ocular disease)  
- CMV – ocular PCR                   |                                                                                                                                                                                                                                                                                                                                 |
| Retinal vasculitis                | Behcet (aphthous ulcers, hypopyon)  
SLE (malar rash, arthralgias, cytopenias)  
Granulomatosis with polyangiitis   | - Clinical diagnosis, screen for other organ involvement, rheumatology referral  
- ANA, anti-dsDNA (+/- ENA panel), C3, C4, anti-phospholipid panel, rheum referral  
- c-ANCA (rheum referral) / Renal/ Pulmonary work-up |                                                                                                                                                                                                                                                                                                                                 |
Screening, Management and Treatment Guidelines for JIA-associated Uveitis (or noninfectious CAU)

1. Screening in JIA

2. Follow-up schedule for ophthalmic monitoring with inactive uveitis (not discussed) (Figure 1B., Angeles-Han ST, Arthritis Care & Research, 2019, 71 (6), 703-716.)
3. Algorithm for Treatment Escalation in JIA-Associated Chronic Anterior Uveitis (Figure 2., Angeles-Han ST, Arthritis Care & Research, 2019, 71 (6), 703-716.)
**Select Traditional Disease-Modifying Anti-rheumatic Drugs (DMARDs)**

*Tables are for reference only, these will not be discussed in depth for fear of curing insomnia*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Route of administration</th>
<th>Side Effects (not exhaustive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (MTX)</td>
<td>Folic acid analog, interferes with DNA synthesis and ADP cell migration</td>
<td>FIRST LINE for anterior NIU (JIA-like)</td>
<td>Oral*</td>
<td>GI upset (most common) Hepatotoxicity Cytopenias Teratogen**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subcutaneous (SC) -preferred</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Interferes with purine synthesis, DNA synthesis</td>
<td>Alternative non-biologic options after failure of MTX or traditional TNFi -May be more effective in pars planitis or posterior segment disease</td>
<td>Oral</td>
<td>GI upset Headache Cytopenias Teratogenic</td>
</tr>
<tr>
<td>mofetil (Cellcept)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leflunomide (Arava)</td>
<td>Inhibitor of pyrimidine synthesis</td>
<td>Alternative non-biologic options after failure of MTX or traditional TNFi</td>
<td>Oral</td>
<td>GI upset Headache Teratogen</td>
</tr>
<tr>
<td>Cyclosporine/</td>
<td>T-cell activation via inhibition of IL-2</td>
<td>Alternative non-biologic options after failure of MTX or traditional TNFi</td>
<td>IV Oral</td>
<td>Hypertension Nephrotoxicity Headache/tremors</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bioavailability for oral administration is less predictable than SC form
** May lead to malformations in children of fathers on treatment
*** Traditional TNFi = adalimumab or infliximab

Key: NIU = non-infectious uveitis, JIA = juvenile idiopathic arthritis, SC = Subcutaneous, MTX = methotrexate, TNFi = TNF-alpha inhibitor
### Selected Biologic Response Modifiers

<table>
<thead>
<tr>
<th>Suffix</th>
<th>Definition</th>
<th>Structure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>-ximab</td>
<td>Chimeric antibody [x-mouse]</td>
<td><img src="image1.png" alt="Structure" /></td>
<td><strong>Infliximab (Remicade) [TNF-α]</strong>&lt;br&gt;Rituximab (Rituxan) [CD-20]</td>
</tr>
<tr>
<td>-zumab</td>
<td>Humanized antibody [some zoo [“zu”]]</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Tocilizumab (Actemra) [IL-6]</td>
</tr>
<tr>
<td>-umab</td>
<td>Human antibody [“human” = “umab”]</td>
<td><img src="image3.png" alt="Structure" /></td>
<td><strong>Adalimumab (Humira) [TNF-α]</strong>&lt;br&gt;Golimumab (Simponi) [TNF-α]</td>
</tr>
<tr>
<td>-cept</td>
<td>Fusion Protein</td>
<td><img src="image4.png" alt="Structure" /></td>
<td><strong>Etanercept (Enbrel) [TNF-α]</strong>&lt;br&gt;Abatacept (Orencia) [CTLA-4 agonist] Not for uveitis</td>
</tr>
</tbody>
</table>

**Bold = traditional “TNF-alpha inhibitors”**