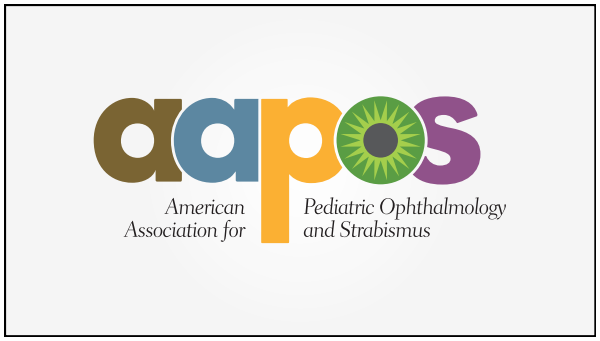
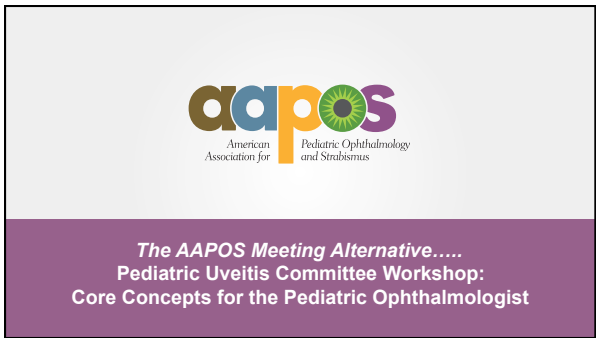




COURSE PRESENTERS

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

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

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

aapos
American Association for Pediatric Ophthalmology and Strabismus

Introduction

Virginia Miraldi Utz, MD
Cincinnati Children's Hospital Medical Center

Uveitis in Children: Introduction

- 75-88% of cases non-infectious (NIU)[1-3]
- Juvenile idiopathic arthritis (JIA) is the most common systemic association (20-30%)[1-3]
- Location:
  - Anterior (≈40-60%) > Intermediate (≈20%) > Pan-uveitis (≈16%) > Posterior (≈6%) [1-3]

10-15% are infectious

1. Kump et al. 2006, 2 Rosenberg et al. 2004, 3.Smith et al., 2009

Infectious Causes of Uveitis in Children

Anterior	Intermediate	Posterior/Pan-uveitis
*Always rule out **Syphilis** and **Tuberculosis***		
• Herpes (HSV/VZV/CMV*) • Lyme Disease • Bartonella	• Lyme Disease • Toxocariasis • Bartonella	• Bartonella • Toxoplasmosis • Toxocariasis • Herpes (HSV, VZV, CMV) • Rubella, Rubeola

Expanded list available

** CMV can cause an isolated anterior presentation in immunocompetent patients*

Non-infectious Causes of Uveitis in Children

Anterior	Intermediate	Posterior/Pan-uveitis
Acute Presentation (usually) • HLA-B27 related • JIA enthesitis • Tubulointerstitial nephritis and uveitis (TINU) • Behcet Syndrome **Chronic Presentation** • **Juvenile Idiopathic Arthritis (JIA)** • Sarcoidosis • Idiopathic orbital inflammation • Kawasaki Disease Other: Drug-induced, trauma	• Pars plantitis • Sarcoidosis • Multiple Sclerosis • TINU (rare)	• Sympathetic ophthalmia • Sarcoidosis • Autosomal Dominant Systemic Granulomatous Disease (Blau Syndrome) • Behcet Disease • Systemic Lupus Erythematosus • ANCA-associated • Vogt-Koyanagi-Harada (VKH) • TINU

aapos
American Association for Pediatric Ophthalmology and Strabismus

Diagnostic Approach

Comprehensive History is Key

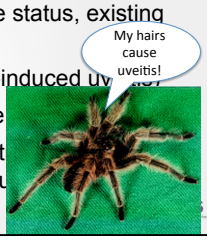
- History of Present Illness
  - GET ALL RECORDS
  - Clinical course
  - Current treatments
  - Response to prior treatments
  - ROS – Families may "brush" through the ROS form
    - Key ROS: Ask about rashes, joint pain or limping, GI issues, blood in urine

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 uv
- Family History of autoimmune
- Social History: Pets/animals, t
  sexual practices, history of dru



Careful, Comprehensive Examination with Descriptive Naming

- Pathology (granulomatous/non-granulomatous)[1]
- Anatomical location of disease (anterior, intermediate, posterior, pan-uveitis)[1]
  - 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)

1. Jabs DA, et al., Am J Ophthalmol. 2005;140(3):509-516. doi:10.1016/j.ajo.2005.03.057

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

The SUN Working Group Grading Scheme for Anterior Chamber Cell and Flare

Grade	Cells/HPF	Flare
0	< 1	None
0.5+	1-5	
1+	6-15	Faint
2+	16-25	Moderate (iris and lens details clear)
3+	26-50	Marked (iris and lens details hazy)
4+	> 50	Intense (fibrin or plastic aqueous)

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

1. Jabs DA, et al. Am J Ophthalmol. 2005;140(3):509-516. doi:10.1016/j.ajo.2005.03.057

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

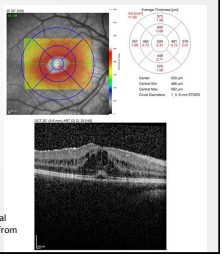
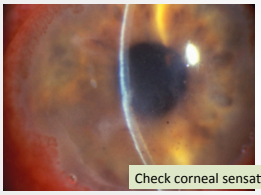


Image Source: Kemp PS, Longmuir SQ. Juvenile idiopathic arthritis with associated bilateral anterior uveitis in a four-year old girl. EyeRounds.org. Posted August 14, 2012. Available from http://www.EyeRounds.org/cases/154-JIA-associated-uveitis-macular-edema.htm

Clinical Pearls: When to Suspect Viral Etiology

- Recurrent or chronic <u>unilateral</u> 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, endotheliitis)

Examples of HSV Keratouveitis



Check corneal sensation prior to anesthesia

Image source: Welder JD, Kitzmann AS, Wagoner, MD. Herpes Simplex Keratitis. EyeRounds.org. December 31, 2012; Available from: http://EyeRounds.org/cases/160-HSV.htm

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.

Clinical Pearls: Select Masquerade Syndromes in Children

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

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

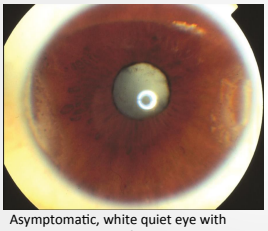
Rule out low-lying fruits → E.g. Infections that can be treated with abx, have significant phenotypic variability, and high morbidity if missed

Yes – kids can get syphilis ☹

Consider in Any Child with Uveitis

- ACE/Lysozyme ← Sarcoid – not that helpful in kids < 8 y; Biopsy of suspicious skin
  - ±CXR or CT/± serum/urine Ca^{2+}
- CBC with diff ← Blood dyscrasia/ systemic infection
- ESR/CRP ← Non-specific inflammation
- Complete metabolic panel ← Hepatic/renal dysfunction
- UA ± Urine beta-2 microgl
- ANA ← Non-specific, but JIA is the most common systemic diagnosis

Phenotype-Guided Testing

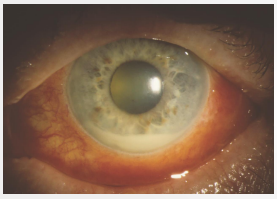


Asymptomatic, white quiet eye with anterior segment inflammation only, cataract and band keratopathy, nml IOP

DDx: JIA, sarcoidosis, TINU, Fuch's (if unilateral)

Labs: ANA, RF, Urine B2-microglobulin, ESR, ACE/ Lysozyme

Phenotype-Guided Testing

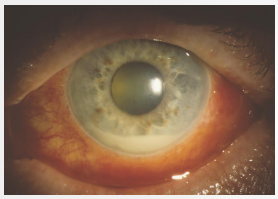


Unilateral, acute onset uveitis with hypopyon, relative hypotony and eye pain in 10-year-old boy.

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

Image source: © American Academy of Ophthalmology 2020 https://www.aao.org/image/hypon-in-acute-anterior-uveitis

Phenotype-Guided Testing

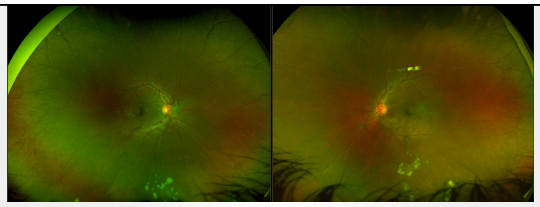


Unilateral, acute onset uveitis with hypopyon, relative hypotony and eye pain in 10-year-old boy.

Studies to Consider:

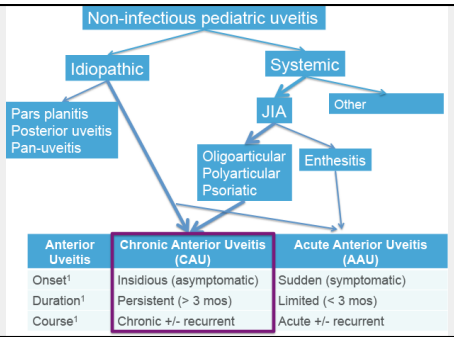
- HLA-B27
- Rheum (ERA eval/MRI SI joints)
- GI eval (+/-EGD/Colonoscopy)
- TINU: Urine B2-microglobulin (UA, renal function tests)
- Behcet: Screen for organ involvement (clinical diagnosis)

Image source: © American Academy of Ophthalmology 2020 https://www.aao.org/image/hypon-in-acute-anterior-uveitis



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?



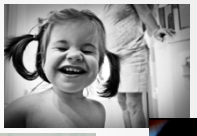
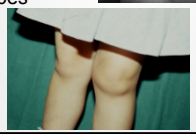
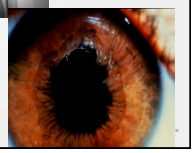
American Association for Pediatric Ophthalmology and Strabismus

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

Subtype		Phenotype	Uveitis Frequency
Oligoarticular	Persistent	Chronic, bilateral	**42%**
	Extended		15%
Polyarticular	RF (-) RF (+)	Chronic, bilateral	25% <1%
Psoriatic		Chronic, bilateral	7%
Undifferentiated			3%
Enthesitis related		**Acute (?), unilateral**	8%
Systemic			<1%

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]

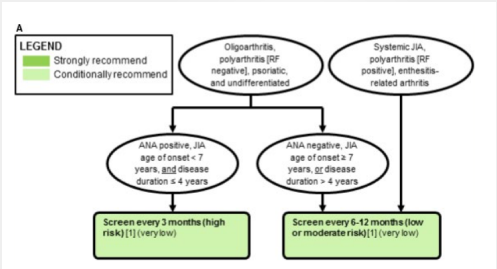
Woreta et al., 2007; Holland et al., 2009; Smith et al., 2009; Cann M et al., Pediatric Rheumatology, 2018: 16:51; Parker et al., AJO 2018 , Angeles-Han S, et al., Arthritis Care Res, 2015

Risk Factors for JIA-U

- Female, young age JIA onset, ANA+, oligo
- Can develop at any time
  - Highest risk 2-4 years after diagnosis [2,4]
- Genetic: HLA-DR5; DRB1*11, 1*13 [5,6]

1. Saurenmann, RK et al. Arthritis Rheum. 2007; 56(2):647.
2. Heiligenhaus A, et al. Rheumatology. 2007;46:1015.
3. Saurenmann, RK et al. Arthritis Rheum. 2010; 62(6):1824.
4. Calandra, S et al. J Rheumatol. 2014; 41(7): 1416.
5. Angeles-Han ST, et al. IOVS. 2015;56(10):6043.
6. Haasnoot, AM et al, Arthritis Rheum, 2018, Vol.70(7): 1155.
7. Angeles-Han, S et al. J Rheumatol 2013;40:2088.

ACR 2019 Guidelines: JIA-U Screening



Angeles Han, S et al. ACR 2019;April 25

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)

Woreta et al., 2007; Holland et al., 2009; Smith et al., 2009, *Angeles-Han ST, et al., Int J Clin Rheumatol 2013, Angeles-Han, et al., Am J Ophthalmol, 2015*

Monitoring *Arthritis* on treatment

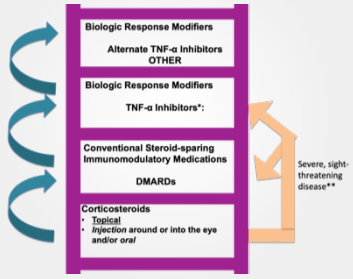
- Uveitis most often painless
- Arthritis flares can be painless

- 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

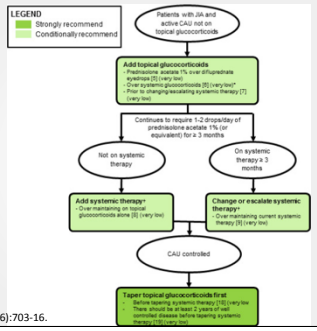


Treatment Guidelines

- ACR/AF Guidelines for Screening, Monitoring and Treatment of JIA-U (2019)
- Consensus-based Recommendations for management of JIA-U: the SHARE Initiative (2018)
- Update on evidence based, interdisciplinary guidelines for treatment of JIA-U (2019)

Angeles-Han ST et al. Arthritis Care Res. 2019;71(6):703.
Constantin T et al. Ann Rheum Dis. 2018;77(8):1107.
Heiligenhaus A, et al. Semin Arthritis Rheum. 2019;49(1):43-55.

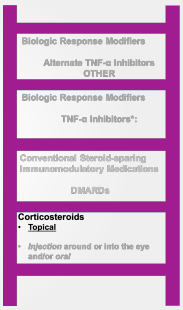
ACR/RF



Angeles-Han ST, et al. AC&R. 2019;71(6):703-16.

ACR/RF: *Patients with JIA and active CAU*

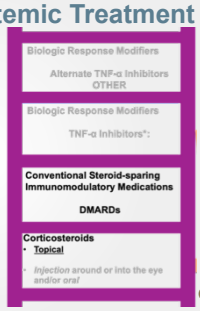
- Initial treatment:
  - Prednisolone acetate 1% (PA)
  - Preferred over difluprednate



Angeles-Han ST, et al. AC&R. 2019;71(6):703-16.

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)

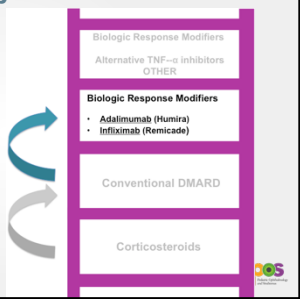
Methotrexate

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

Simonini G, et al. Rheumatology 2013, May;52(5):825.
McCracken C, et al. Eye. 2019;33(4):629.

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

Simonini G, et al. Arthritis Care Res 2014, Jul;66(7):1073.

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

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 on oral*

Anti-drug Antibodies

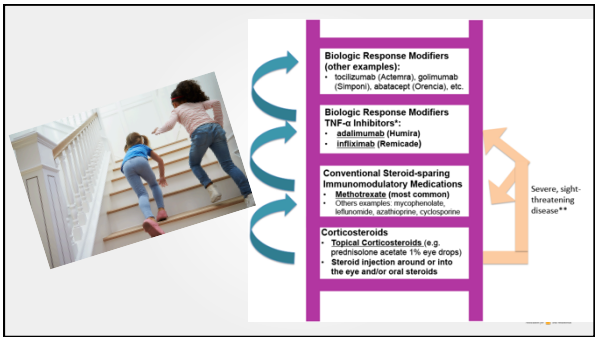
- Adverse reactions, decreased effect of drug
- Immunogenicity to drug:
  - Inversely related to dose (IFX)
  - Reduced by Methotrexate

Meta-analysis in JIA (ADA): RR 0.33 (95% CI 0.21, 0.52)

Krieckaert CL, et al. Ann Rheum Dis. 2012;71(11):1914. Jani M, et al. Rheumatology. 2014;53(2):213.
Doeleman MJH, et al. Rheumatology. 2019;58(10):1839. Jani M, et al. Rheumatology. 2018;57(11):1896.

Beyond Adalimumab and Infliximab

- Indications:
  - Persistent activity ≥ 3 mo
  - Unable to taper steroids
  - Complications
- Move to:
  - Other mechanisms
  - Newer TNFi



Tapering

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

aapos

aapos
American Association for Pediatric Ophthalmology and Strabismus

KC LaMattina, MD
Boston University School of Medicine
Boston Medical Center

BOSTON MEDICAL

BOSTON UNIVERSITY

Case 1

- 21 month-old F
- R knee swelling
- Started on naproxen
- Undergoing work-up

aapos

Slit lamp exam by any means necessary!

- 1+ cell OU
- No complications

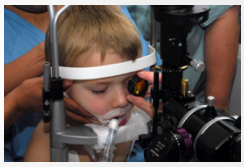


Photo courtesy of Debra Goldstein

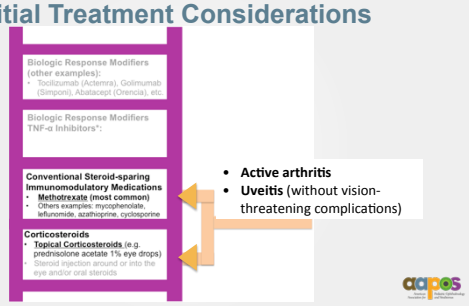
What next?

- 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



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

aapos
American Association for Pediatric Ophthalmology and Strabismus

Bharti Nihalani-Gangwani, MD
Boston Children's Hospital
Harvard Medical School

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

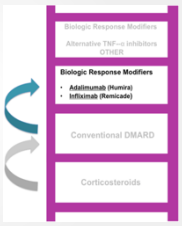
	Right eye	Left eye
Vision	20/20	20/30 -1
Refraction	-0.50, +1.25 @ 90	-1.00, +1.50 @ 90
IOP	11	12
Cornea	Clear	Fine KPs inferiorly in Arlt's triangle
Pupil	Round	1 synechia at 7'o clock
AC	Clear	2+ cells, 1+ Flare
Lens	Clear	Few pigments over anterior lens capsule
Fundus	0.1 cd	0.1 cd

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

ADA (Humira™)	IFX (Remicade™)
SC	IV infusion
Fully humanized Less immunogenic	Chimeric monoclonal Ab More immunogenic
No malignancy	Malignancy

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-Associated Uveitis with Severe Disease Presentation and Complications

Alex V. Levin, MD, MHSc, FRCSC

Wills Eye Hospital
Thomas Jefferson University

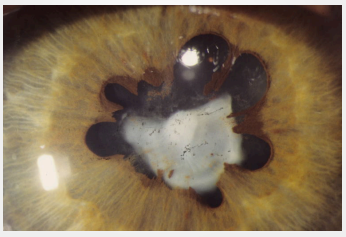
JIA can be bad!

- 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

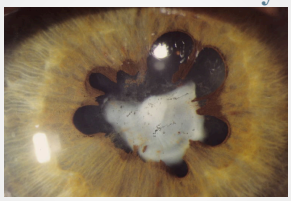
(Wolf, 1987)

Fast Forward 2020: Poor Prognostic Factors at Baseline Presentation :

- **Synechiae on presentation[1-3,4,6]**
- Any ocular complications on presentation (BK, synechiae, cataract, CME, IOP abnormalities)[1,2,4]
- Flare, intermediate uveitis, papillitis[2]
- Hypotony[3]
- Panuveitis[4]
- Nuclear cataract at baseline presentation[5]

1.Woreta et al., Am J Ophthal, 2007; 2.Holland GN, Denove CS, Yu F. Am J Ophthalmol. 2009;147(4):667-78; 3. Oray et al., Graefes Arch Clin Exp Ophthalmol. 2016;254(9):1841-9. 4. Moradi et al., Am J Ophthalmol 2016;169: 113–124 5. Suelves et al, J AAPOS 2016;20:232-238;

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?

ight-
ing

Treat the whole family!

Emotional impact
Family impact

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

What's Next: After Traditional TNFi?

Stefanie L. Davidson, MD
Division of Ophthalmology
Children's Hospital of Philadelphia

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.
Monoclonal antibody TNF inhibitor is recommended over etanercept.
In severe uveitis with sight-threatening complications*, combination methotrexate and TNFi 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 dose or frequency, abatacept, tocilizumab, mycophenolate, leflunomide, and cyclosporine are recommended alternative options.

Adapted from: Angeles-Han S, et al. Arthritis Care Res (Hoboken) 2019;71(6):703-16.

Case Management

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

1. Correll et al., Clin Rheumatol 2018, 37:549-553; 2. Lee et al., Ophthalmology 2020, in press]

Recommendations 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.

Adapted from: Angeles-Han S, et al. Arthritis Care Res (Hoboken) 2019;71(6):703-16.

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. . .

Case Management: Now What?

- 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

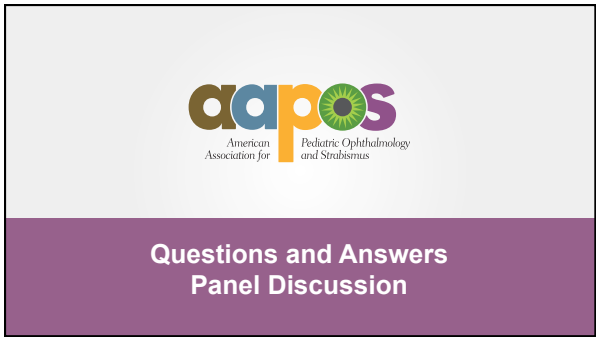
Recommendations for DMARDs/Biologics

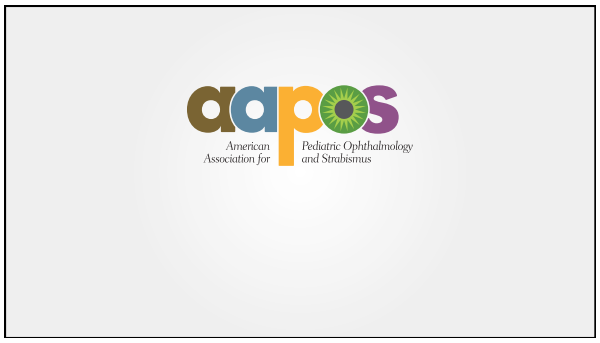
Subcutaneous methotrexate is recommended over oral methotrexate.
Monoclonal antibody TNF inhibitor is recommended over etanercept.
In severe uveitis with sight-threatening complications*, combination methotrexate and TNFi is recommended over methotrexate monotherapy.
In inadequate response to one TNFi, 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.
If inadequate response to 2 TNFi at above-standard dose or frequency, abatacept, tocilizumab, mycophenolate, leflunomide, and cyclosporine are recommended alternative options.

Adapted from: Angeles-Han S, et al. Arthritis Care Res (Hoboken) 2019;71(6):703-16.

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


aapos
American Association for Pediatric Ophthalmology and Strabismus
Questions and Answers
Panel Discussion


aapos
American Association for Pediatric Ophthalmology and Strabismus

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@aao.org

American Association for Pediatric Ophthalmology and Strabismus

Pediatric Uveitis Information

PRIOR AUTHORIZATION DOCUMENT FOR BIOLOGIC RESPONSE MODIFIERS

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.

Key References

Clinical Guidelines:

U.S./North America:

1. American College of Rheumatology (ACR)/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis.

   - 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.
   - Full text link: https://onlinelibrary.wiley.com/doi/full/10.1002/acr.23871

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.
   - Full text link: https://www.rheumatology.org/Portals/0/Files/JIA-Uveitis-Guideline-2019.pdf

Europe:

1. Consensus-based recommendations for the recommendations for the management of uveitis associated with juvenile idiopathic arthritis: The SHARE (The Single Hub and Access point for pediatric Rheumatology in Europe) Initiative.

   -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/

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
- Full text link:

https://www.sciencedirect.com/science/article/pii/S0049017218304621?via%3Dihub

Quality of Life/Psychosocial Implications of Pediatric Uveitis:

- Parker DM, et al., Chronic Anterior Uveitis in Children: Psychosocial Challenges for Patients and Their Families, American Journal of Ophthalmology 2018, 191, DOI:https://doi.org/10.1016/j.ajo.2018.03.028
https://www.ajo.com/article/S0002-9394(18)30133-8/fulltext (AAO members can log-in for access to full PDF)

- Angeles-Han ST, Measuring visual outcomes in children with uveitis using the "effects of Youngsters' Eyesight on Quality of Life" questionnaire. Arthritis Care Res (Hoboken). 2015 November ; 67(11): 1513–1520. doi:10.1002/acr.22627.
https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC4624475&blobtype=pdf

Standardization of Uveitis Nomenclature (SUN) Working Group:

- Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-516. doi:10.1016/j.ajo.2005.03.057

Free full text:
https://www.researchgate.net/publication/235422258_The_Standardization_of_Uveitis_Nomenclature_SUN_Project_Development_of_a_Clinical_Evidence_Base_Utilizing_Informatics_Tools_and_Techniques

Key References

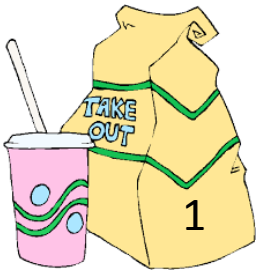
Nice Review Article:

Clarke SL, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol Online J. 2016;14(1):27. Published 2016 Apr 27. doi:10.1186/s12969-016-0088-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4848803/pdf/12969_2016_Article_88.pdf

Meta-analysis of TNFi:

Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor α treatment efficacy in childhood chronic uveitis: A systematic review and meta-analysis approach of individual drugs. Arthritis Care Res (Hoboken) 2014, Jul; 66(7):1073-84.

“Hungry for More?” Additional Resources

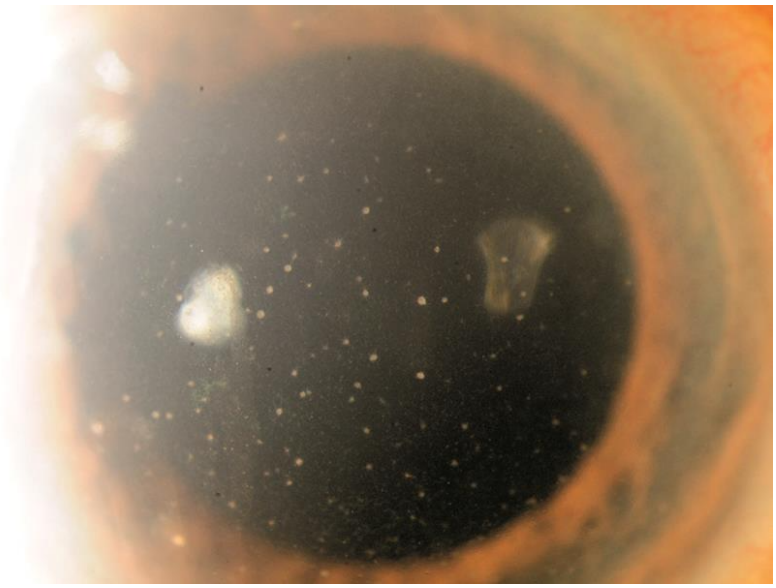


1. Etiologies of Pediatric Uveitis

Table 1. Infectious Causes: Extended List

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

*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

Anterior	Intermediate	Posterior/Pan-uveitis
Acute Presentation (usually) • HLA-B27 related • JIA enthesitis • Tubulointerstitial nephritis and uveitis (TINU) • Behcet Syndrome	• Pars plantitis • Sarcoidosis • Multiple Sclerosis • TINU (rare)	• Sympathetic ophthalmia • Sarcoidosis • Autosomal Dominant Systemic Granulomatous Disease (Blau Syndrome) • Behcet Disease • Systemic Lupus Erythematosus • ANCA-associated • Vogt-Koyanagi-Harada (VKH) • TINU
Chronic Presentation • **Juvenile Idiopathic Arthritis (JIA)** • Sarcoidosis • Idiopathic orbital inflammation • Kawasaki Disease • Fuch's heterochromic iridocyclitis (Rubella in some) Other: Drug-induced, trauma		

<u>Non-infectious Uveitis Clinical "Bites"</u>

- **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.)

- **Tubulointerestitial 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
- Nagashima T, et al, Three cases of tubulointerstitial nephritis and uveitis syndrome with different clinical manifestations. Int Ophthalmol. 2017;37(3):753-759 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440544/pdf/10792_2016_Article_321.pdf
- 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.
- Pakzad-Vaezi K, Pepple KL. Tubulointerstitial nephritis and uveitis. Curr Opin Ophthalmol. 2017;28(6):629-635 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5873972/pdf/nihms929621.pdf

What is metagenomic deep sequencing (MDS)?

A very small samsple 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 by infectious or if there is a poor or atypical treatment response.

https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0344-6

Doan, T., Wilson, M.R., Crawford, E.D. et al. Illuminating uveitis: metagenomic deep sequencing identifies common and rare pathogens. Genome Med 8, 90 (2016). https://doi.org/10.1186/s13073-016-0344-6

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

Masquerade Syndromes

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

Additional Examples of Phenotype-Driven Diagnostic Testing

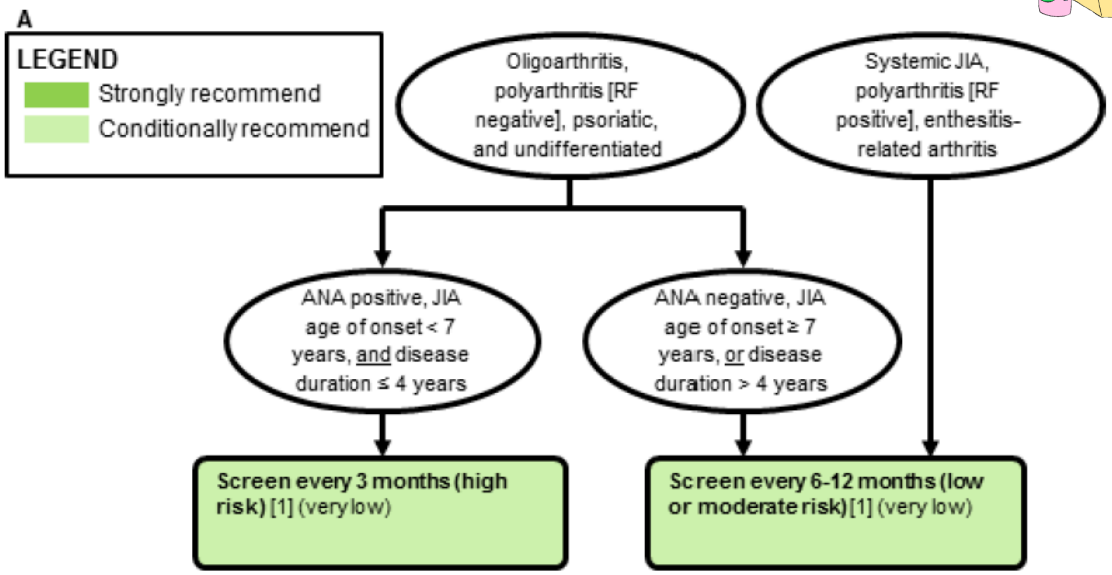
Table 5. (Not exhaustive list, consider clinical presentation, demographics, exposures, geographic region)

Scenario	Suspected Diagnosis	Diagnostic Testing Considerations
-Hypertensive unilateral uveitis on presentation -Iris atrophy -Reduced corneal sensation - KP above midline	-Viral (HSV, VZV, CMV) -Fuch's / Rubella	- Treat empirically with acyclovir or valacyclovir (in a kid) - Consider AC tap for PCR or MDS (often requires anesthesia) +/- Serology
Granulomatous KP Look for iris nodules	-Infectious, sarcoidosis, VKH	- Quantiferon gold - Treponemal testing - Toxoplasmosis serology (posterior involvement/CR scarring) - Toxocara serology - Bartonella serology - CXR (CT chest/abdomen if high suspicion for sarcoidosis) - Biopsy if skin/conj lesions - VKH (serous retinal disease) – clinical diagnosis, audiology eval, LP to document CSF pleocytosis
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

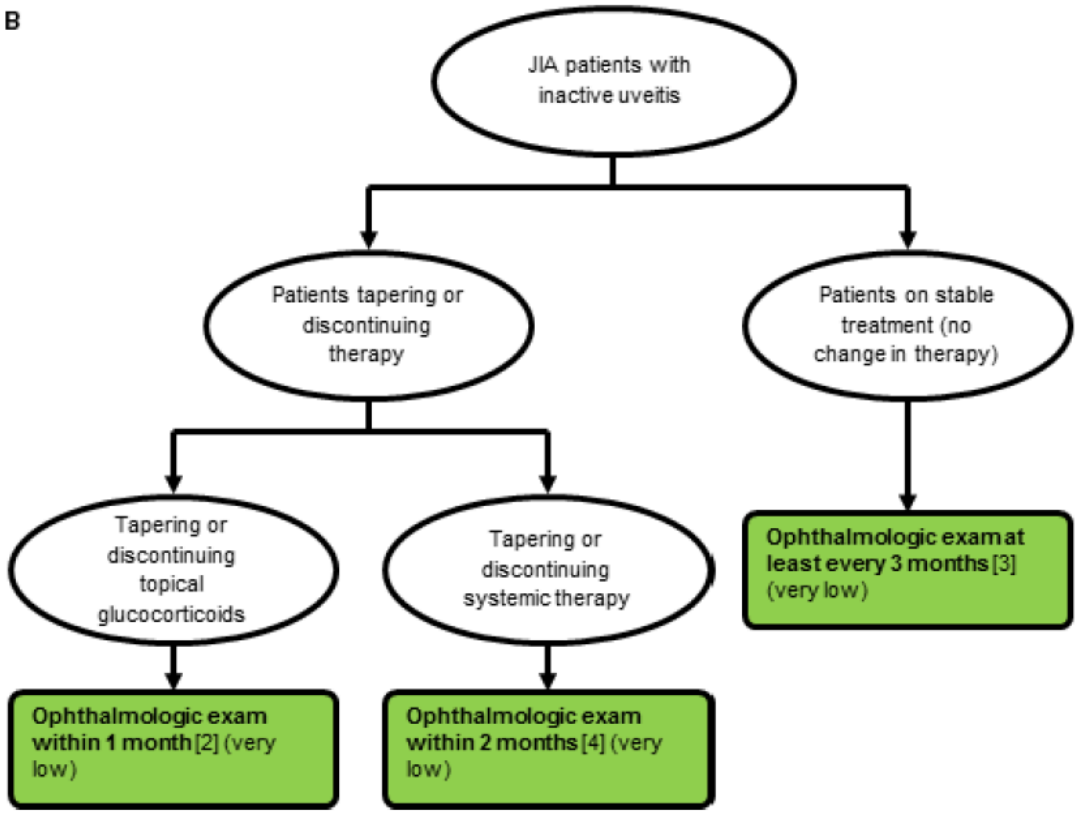
Poor consensus on standard laboratory testing even among the Executive Board of the American Uveitis Society: Lee CS, et al., Am J Ophthalmol. 2016; 170:161-167.

Screening, Management and Treatment Guidelines for JIA-associated Uveitis (or noninfectious CAU)

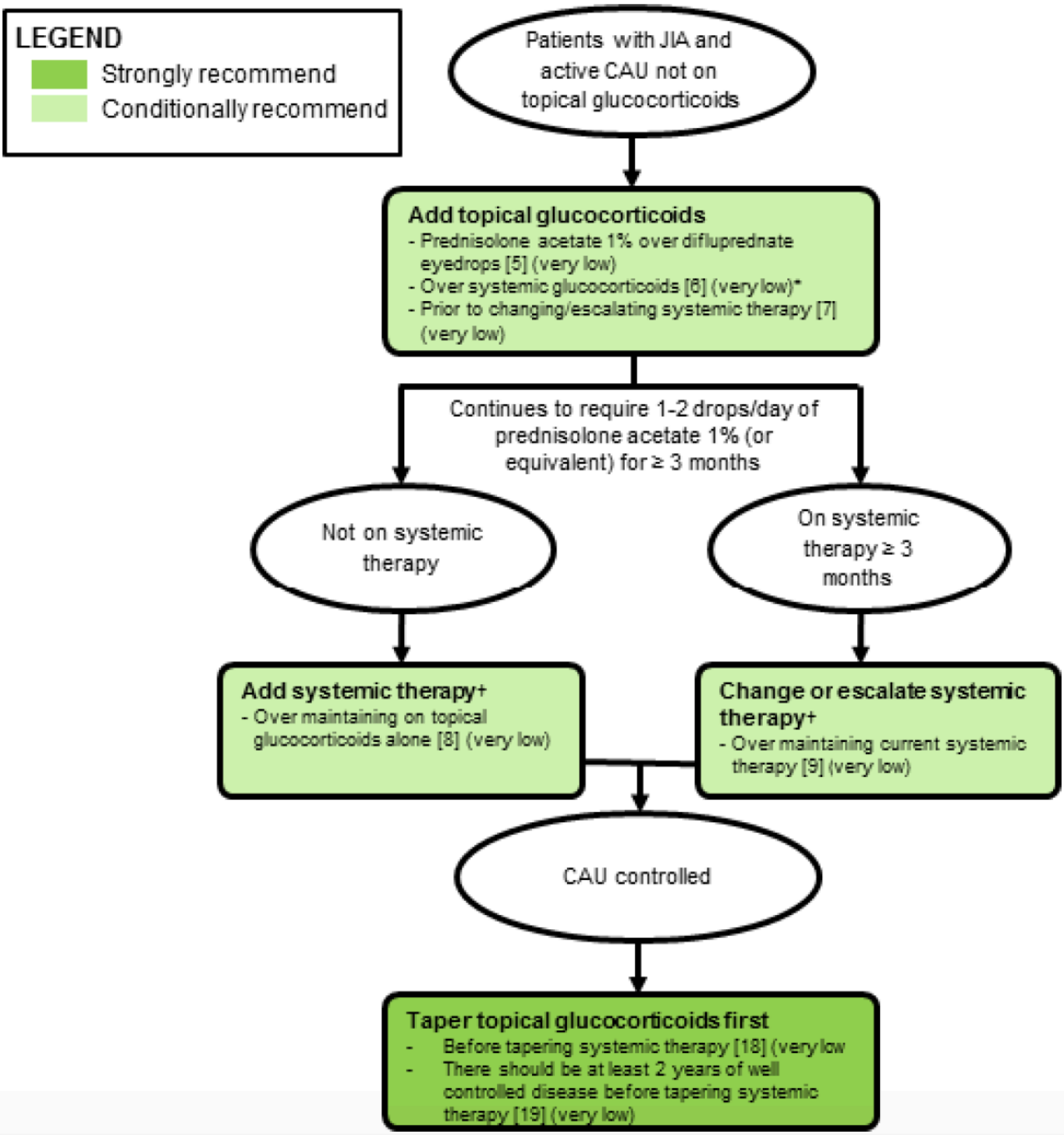
1. Screening in JIA

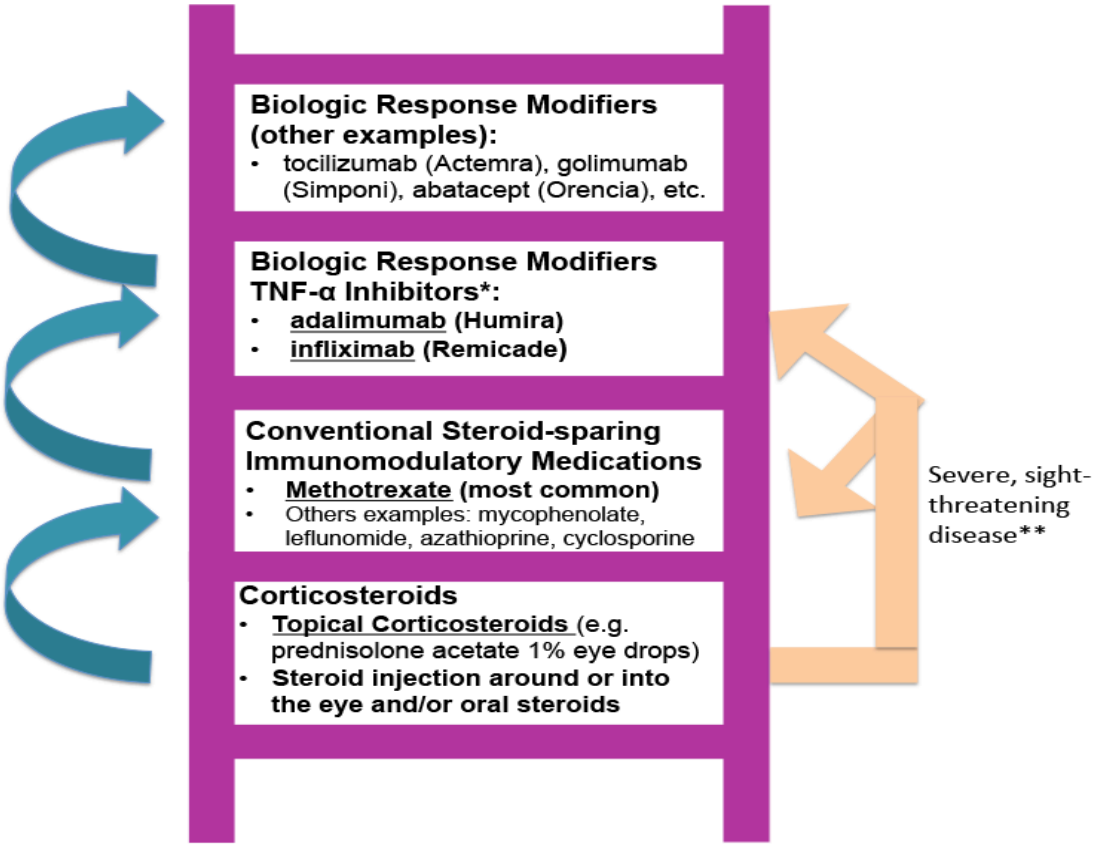


2. Follow-up schedule for ophthalmic monitoring with inactive uveitis (not discussed) (Figure 1B., Angeles-Han ST, Arthritis Care & Research, 2019, 71 (6), 703-716.)



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

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

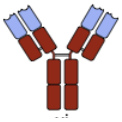
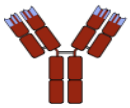
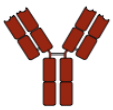
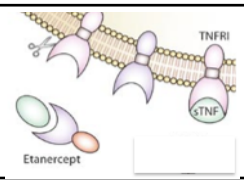
* Bioavailability for oral administration is less predictable than SC form

**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

Suffix	Definition	Structure	Examples
-ximab	Chimeric antibody [x-mouse]		**Infliximab (Remicade) [TNF-α]** Rituximab (Rituxan) [CD-20]
-zumab	Humanized antibody [some zoo [“zu”]]		Tocilizumab (Actemra) [IL-6]
-umab	Human antibody [“human” = “umab”]		**Adalimumab (Humira) [TNF-α]** Golimumab (Simponi) [TNF-α]
-cept	Fusion Protein		Etanercept (Enbrel) [TNF-α] Not for uveitis Abatacept (Orencia) [CTLA-4 agonist]

Bold = traditional “TNF-alpha inhibitors”

Want more? Clarke SL, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol Online J. 2016;14(1):27.