The Diagnosis & Treatment of Uveitis in Optometric Practice

Megan A. Hunter, OD, FAAO
Michelle M. Marciniak, OD, FAAO
Definition

- Inflammation of the uveal tract
  - Iris
  - Ciliary body
  - Choroid
- Uvea - derives from Latin word for grape
Uveitis Epidemiology

- 3rd-5th leading cause of visual impairment in U.S.
- Prevalence varies by study & population
  - 58-121/100,000
- Anterior is most common location

JAMA Ophthalmol 2016;134:1237-45
Location

- **Anterior**
  - iritis & iridocyclitis

- **Intermediate**
  - pars planitis, posterior cyclitis

- **Posterior**
  - choroiditis, chroioiretinitis, retinochoroiditis, retinitis, neuroretinitis

- **Panuveitis**
Duration

- **Acute**
  - Sudden onset, definite start date
  - Limited duration
  - More symptomatic
    - Pain, redness, photophobia

- **Chronic**
  - Insidious onset
  - Long duration
  - Relapse in <3 months after d/c treatment
  - Less symptomatic
    - Floaters, decreased VA

- **Recurrent**
  - Repeated episodes occurring after 3m of inactivity without treatment
Type

- Granulomatous
  - Mutton fat KP
  - Synechiae
  - Iris nodules
    - Koeppe & Bussaca

- Non-Granulomatous
Symptoms

- Pain
- Redness
  - Circumlimbal
- Photophobia
- Tearing
- Blurred vision
- Floaters
Clinical Signs: Anterior Segment

- Ciliary Flush/Circumlimbal Injection
- Corneal
  - Edema
  - Keratic Precipitates
  - Fibrin
- Anterior Chamber
  - Cell
  - Flare
  - Hypopyon
- Iris
  - Nodules
  - Posterior synechiae
  - Peripheral anterior synechia
- Anterior vitreal cell &/or flare
Keratic Precipitates

- Granulomatous
  - Mutton fat
- Non-Granulomatous
  - Pinpoint or stellar
- Epithelioid cells, lymphocytes & PMNs
Anterior Chamber Cells
SUN Working Group Scheme

- 1mm by 1mm slit beam

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>½+</td>
<td>1-5</td>
</tr>
<tr>
<td>1+</td>
<td>6-15</td>
</tr>
<tr>
<td>2+</td>
<td>16-25</td>
</tr>
<tr>
<td>3+</td>
<td>26-50</td>
</tr>
<tr>
<td>4+</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>
## Anterior Chamber Flare

### SUN Working Group Scheme

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Faint</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate (iris &amp; lens details clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris &amp; lens details hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin or plastic aqueous)</td>
</tr>
</tbody>
</table>
Clinical Signs: Posterior Segment

- Vitreal Inflammation/Vitritis
  - Cell
  - puff balls
  - Snow-banking
- Cystoid macular edema
- Phlebitis or arteritis
- Disc edema
Clinical Signs: IOP

- **Decreased**
  - CB ischemia leads to decreased aqueous production

- **Elevated**
  - Debris/cells clogging TM
  - PAS/Angle Closure
    - Gonioscopy!
  - System “Reboot”
    - CB “turning back on” & drainage system “starting back up”
  - Steroid response
  - Herpes!
    - Especially if present at time of diagnosis
    - Trabeculitis & outflow obstruction
    - IOP will normalize when tx is initiated
Steroid Response

- *Not an immediate reaction*
  - 2-4 weeks after initiating treatment
  - Can be delayed months to years

- Occurs to some degree in up to 1/3 of patients
  - Marked (>15mm increase) in ~5%

- More likely in glaucoma patients

- Don’t be fooled by the system rebooting

- More potent steroid delivered closer to CB produces the most pronounced effect
  - Greater likelihood with Durezol & Dexamethasone

- Manage with topical agents

- May still need to use steroids to control inflammation

- IOP will likely normalize after stopping steroids
Common Systemic Associations

- 30-45% have systemic association
- Sarcoid
- HLA-B27
  - Reactive Arthritis
  - Ankylosing Spondylitis
  - Psoriatic Arthritis & Inflammatory Bowel Disease
    - More common in females, bilateral, posterior to lens & chronic
    - Do not need a systemic manifestation
- Rheumatic Conditions
  - ????? Rheumatoid Arthritis without other associations
- Bechet’s Disease
Common Systemic Associations

- Infectious
  - Syphilis
    - On the rise AGAIN!
    - Treatable & curable
  - TB
  - Herpes Simplex & Varicella Zoster
  - Toxoplasmosis

Uncommon Systemic Associations

- **Infectious**
  - Lyme Disease (*Borrelia burgdorferi*)
  - Cat Scratch Disease (*Bartonella henselae*)
  - Whipple’s disease (*Tropheryma whippelli*)
  - Brucellosis (*Brucella species*)
- Tubulointerstitial Nephritis & Uveitis Syndrome (TINU)
Laboratory Work-Up

- Indications:
  - Bilateral
  - Granulomatous
  - Recurrent
  - Non-resolving
  - Severe
Laboratory Work-Up

- Tailor based on a general review of systems
  - Joint pain
  - Rash
  - Dyspnea
  - Fever, malaise
  - Dysuria, pain on urination
  - Apthous ulcers
- Systemic medications
Laboratory Evaluation

- CBC with Differential
- ESR
- ANA including titer
- Syphilis Panel
  - Treponemal (FTA-Abs, MHATP, CIA)
  - Non-Treponemal specific (RPR & VDRL)
- Quantiferon TB gold
- HLA-B27, HLA-B51, HLA-B5
- HIV Testing
- Lyme Titer/Western Blot
- ACE/lysozyme
Laboratory Evaluation
Uncommon Diagnoses

- Bartonella Titers
- pANCA & cANCA
- Toxoplasmosis IFA
- Blood cultures
- PCR testing
  - Requires AC or vitreal tap
  - Herpes
Treatment

- Treat associated infection
- Topical steroids & cycloplegia
- Systemic medications
  - Immunomodulation
- Control IOP
  - ? Use of latanoprost
Treatment:
Topical Corticosteroids

- Prednisolone vs. Pred Forte
  - Better penetration with Pred Forte
    - Finer milled particles in suspension
  - SHAKE!!!!
- Durezol
  - IOP spikes
  - Dosing and taper?
- Dexamethasone
- Vexol
  - Less steroid response
  - Use for maintenance dose or taper

Arch Oph 1998:116;703
J Ocul Pharmacol Ther 2007;23;182-7
Treatment: Pred Forte Dosing

- Hit hard and taper upon resolution
- Longer duration & greater recurrences require longer tapers
- Maintenance dose
Treatment:
Periocular & Intraocular Corticosteroids

- Subtenon’s or orbital floor injection
  - Triamcinolone (2-4m)
- Intravitreal Triamcinolone (3-6m)
- Intraocular implants
Treatment:
Periocular & Intraocular Corticosteroids

- Cautions:
  - Watch IOP
  - Unable to be reversed
  - Risks: cataract progression, infection

- Benefits
  - Helps with compliance
  - Higher dose to posterior segment
Treatment: Systemic Corticosteroids

- Typical Dose: 1mg/kg/day
- If required >3m, consider immunomodulatory therapy
- Systemic Side Effects
  - Weight gain/increased appetite
  - Hyperglycemia
  - Hypertension
  - Susceptibility to infection
  - Osteoporosis
    - Calcium and Vitamin D supplements, weight bearing exercise
  - Cushing’s syndrome
  - Mental status changes/Psychosis
- Long term treatment vs. short pulse
- H2 blockers or proton pump inhibitors: reduce risk of GI ulcers
Treatment: Cycloplegia

- Relaxes CB & Iris
  - Decreased pain
  - Reduces inflammation
- Homatropine or Scopolamine
  - Want some pupil movement to avoid synechiae
  - More frequent dosing with cyclogel
- If stop too early may see rebound inflammation
  - Discontinue when chamber is quiet
- Counsel patient on blur and need for sun protection
Treatment: Immunomodulatory Drugs

- In conjunction with Rheumatologist
- Therapeutic response may not occur for several weeks
- Treat until steroid free remission for at least 1 yr
  - Slow taper
- SITE study: no increased risk of mortality or malignancy
  - except TNF alpha

Expert Opin Biol ther 2012;12:995-1008
Treatment: Immunomodulatory Drugs
Antimetabolites

- Inhibits proper nucleotide synthesis or processing
- **Methotrexate** (oral, IV or IM)
  - Supplement with folic acid
  - Side Effects: Bone marrow suppression, infection, liver toxicity, pulmonary fibrosis
  - Abstain from sun exposure, heavy alcohol use, acetaminophen, eating grapefruit & star fruit
- **Azathioprine** (oral)
  - Side Effects: bone marrow suppression & infection
- **Mycophenylate mofetil**
Treatment: Immunomodulatory Drugs
Calcineurin Inhibitors

- Mainly used as adjunct to other medications
- Interrupts T-cell activity & growth

- **Cyclosporine**
  - Side Effects: bone marrow suppression, renal & nephrotoxicity, HTN, hyperlipidemia, gingival hyperplasia or hemorrhage, hyperkalemia, hirsutism

- **Tacrolimus**
  - Same effectivity with fewer side effects
Treatment: Immunomodulatory Drugs Biologics

- **TNF Alpha Inhibitors**
  - **Infliximab** - IV
  - **Adalimumab** (Humira) - subcutaneous injection
  - *Both extremely effective

- Risks: activation of latent infection, hepatotoxicity, anaphylaxis, demyelinating disease, drug-induced autoimmune disease & secondary malignancies

- **Rituximab** - anti-CD 20, IV
  - Shown effective in JIA
Treatment:  Immunomodulatory Drugs

Alkylating Agents

- Chlorambucil (oral)
- Cyclophosphamide (oral)

- Severe, stubborn or refractory uveitis
  - Wegner’s, PAN, PUK, necrotizing scleritis

- Interfere with DNA replication

- Weekly CBC with differential
  - Bone marrow suppression
Chronic Non-resolving uveitis

- Repeat labs
- Look for the needle in the haystack
- Refer
Guidelines for referral

- Uveitis specialist, rheumatologist, infectious disease

- Reasons for referral:
  - Posterior segment involvement
  - Systemic association
  - Non resolving with conventional treatment
  - Need for systemic treatment
Cases & Pearls
Traumatic Uveitis

- Inflammation is part of the healing
- Cycloplegia alone often adequate
- Steroids if severe
  - May see rebound when taper
- Don’t miss hyphema
Unique Situations not to Overlook!

- Drug Toxicity
  - Cidofovir
  - Biphosphonates
  - Rifambutin
Rifabutin Associated Uveitis

- Mechanism unknown
- Increased risk w/ concomitant use of azoles or macrolides
- Distinguishing features:
  - Lack of pain, photophobia & KPs
  - Quick response to treatment
Biphosphonates

- Used to treat osteolytic bone lesions
  - Prostate Ca, multiple myeloma, other solid tumors, etc.
  - Osteoporosis
- (Fosamax), risedronate (Actonel), zoledronic acid (Zometa), etidronate (Didronel), tiludronate (Skelid), pamidronate (Aredia), ibandorate (Boniva)
Biphosphonate Side Effects

- Transient Flu-like symptoms
- Ocular Adverse Effects:
  - Conjunctivitis
  - Uveitis (0.8%)
  - Episcleritis
  - Scleritis
  - Orbital inflammatory disease
Orbital Inflammation 2’ Biphosphononates

- Generally does not recur with re-challenge
- Immunologic or toxic reaction?
  - Activates antigenic receptor T-cells
    - Cytokine release
    - Less pronounced w/ each treatment
Masquerade Syndromes

- Cells are not due to immune-mediated uveitis
- Cancer
  - Intraocular B-cell Lymphoma - *most common*
  - Melanoma
  - Blood dyscrasias
- Immune recovery in HIV
- Ischemia in DM or OIS
Special Presentations

- **Glucomatocyclitic Crisis/Posner Schlossman**
- **Fuch’s Heterochromic Iridocyclitis**
  - Stellate KP
  - Heterochromia often subtle
- **Sympathetic Ophthalmia**
  - Penetrating injury/surgery to fellow eye
    - 90% within 1 year of trauma
  - Bilateral granulomatous panuveitis
  - No definitive test to confirm diagnosis
Posner-Schlossman Syndrome (Glaucomatocyclitic Crisis)

- Recurrent episodes
- Mild iritis
- Markedly elevated IOP
- Diffuse epithelial corneal edema
- Few fine keratin precipitates (KPs)
- Open angles on gonioscopy
- Normal IOP in between attacks
Fuchs Heterochromic Iridocyclitis (Fuchs Uveitis Syndrome)

- Unilateral
- Chronic, asymptomatic mild inflammation
- Diffuse characteristic KP
- No posterior synechiae
- Iris atrophy/heterochromia
Viral Uveitis

- Second most common causative agent (4.5-18.6%)
  - Herpes
    - Varicella, Simplex, CMV
    - Clinical features vary with immune status
  - Rubella
  - Chikungunya
- Clinical Features:
  - Diffuse, fine, stellate or dendritiform KPs
  - Elevated IOP
  - Iris atrophy (50-90%)
- PCR of aqueous or vitreous
  - Yield depends on timing in the disease course
Herpes Anterior Uveitis

- Acute Unilateral
  - Redness & pain
- Often in older patient, female predominance
- Granulomatous or medium-sized KP in Arlt’s triangle
- Elevated IOP (50-90%)
- Patchy or sectoral iris atrophy - NOT seen early
  - Dilated/distorted pupil
- Posterior synechiae
Herpes Anterior Uveitis

- Zoster more likely to be chronic & older patients
- Simplex more likely to be acute recurrent
- Keratitis, K scarring and hypesthesia can be clues

- Treatment: acyclovir, valganciclovir
  - May require long term prophylaxis
CMV Uveitis

- Diffuse or patchy iris atrophy
- Synechiae uncommon
- Acute recurrent: typically middle aged patients
- Chronic: average 65yrs, 4:1 males
  - Nodular endothelial lesions, fine stellate KP evenly distributed
- Corneal edema
  - May develop endotheliitis
  - Owl’s eye sign on confocal microscopy
- Elevated IOP (>50mmHg)
- Fuchs or Possner Schlossman??
- Treatment: ganciclovir and valgancyclovir
Rubella Uveitis

- Chronic persistent iritis
- Diffuse, fine, stellate KP
- Diffuse iris atrophy &/or heterochromia
- Absence of posterior synechiae
- PSC
- Vitritis
- Sectoral peripheral retinal vascular leakage
- CME
- Disc edema
- No specific treatment
- Fuchs Heterochromic Iridocyclitis

AM J Ophthalmol 2004;138:46-54
AM J Ophthalmic 2007;144:424-28
Viral Uveitis

- Same virus has diverse presentations
  - May reflect viral load & immune status of the eye
Panuveitis

- Inflammation of all layers of the uvea: iris, ciliary body, choroid
- Bilateral
- Retina, optic nerve and vitreous involved
- Tuberculosis, Vogt-Koyanagi-Harada syndrome, sarcoidosis, idiopathic
- Poor visual outcome due to widespread inflammation
Vogt-Koyanagi-Harada

- Multisystem, autoimmune disease of pigmented tissue
- 20-50 years
- 2:1 Female
- Asians, Latinos, Middle Easterners, American Indians
- Bilateral granulomatous anterior uveitis, vitritis, papillitis, choroiditis, bullous serous retinal detachments
- Tissue depigmentation, vitiligo, poliosis, alopecia, diffuse fundus depigmentation
- HLA-DR4 and DRB1/DQA1
TB Uveitis

- Extrapulmonary manifestation
- Often precedes symptomatic evidence of systemic TB
- Many have no evidence of pulmonary TB
- May present in any location
- Lack of a gold standard for diagnostic testing
- PCR Testing
  - Negative result does not rule out TB

Collaborative Ocular TB Study (COTS)

- Retrospective cohort study
  - 25 centers worldwide (1 in US)
  - 801 Cases (75% from Asia, Australia or Middle East)
- 58.8% bilateral
- Uveitis anatomical distribution:
  - 36.3% posterior
  - 15.9% intermediate
  - 12.5% anterior
  - 35.3% panuveitis
- 42% retinal vasculitis
- 88% treated successfully with anti-TB treatment & corticosteroids
- 23% elevated ACE

Neurosyphilis: Criteria for Diagnosis

- + Serum FTA-Abs
- CSF showing one of the following:
  - elevated cell count
  - elevated protein levels
  - + CSF VDRL

- + CSF FTA-Abs is of uncertain significance
  - Unlikely if (-)
Syphilitic Uveitis

- Considered a manifestation of neurosyphilis
- Generally requires IV treatment
- ALL patients should receive HIV testing & +/- CSF analysis

“For most incident cases of uveitis, a strict rule of always placing syphilis in the differential diagnosis & including treponemal serological testing in any laboratory work-up is wise.” - Janet Davis
HLA-B27 Uveitis

- More commonly affects males ages 20-40yrs
- Recurrences are common
- Unilateral, flip-flop or bilateral
- Can have posterior segment involvement
- 49-84% have associated systemic disease
- Most common cause of hypopyon
  - Fibrin
- Posterior synechiae
Tattoo-Associated Uveitis

- Bilateral uveitis
  - Iridocyclitis to panuveitis
- Simultaneous cutaneous inflammation of tattoo sites
- Histologically: granulomatous inflammation
- Black tattoo ink may “contain toxic, mutagenic or carcinogenic compounds such as carbon black and polycyclic aromatic hydrocarbons or phenol”
- Prevalence of tattoos 24% in US ages 18-50

Tubulointerstitial Nephritis & Uveitis (TINU)

- Bilateral sudden-onset acute interstitial nephritis
- Uveitis
  - 80% anterior
  - Generally follows nephritis
    - Course of renal disease is usually independent from ocular disease
  - Recurrence common
- Fever, arthralgia, mild anemia
- Markedly elevated ESR
- Definitive diagnosis requires renal biopsy
Tubulointerstitial Nephritis & Uveitis (TINU)

- Urinalysis: elevated β2-macroglobulin, sterile pyuria, proteinuria, hematuria
- Elevated BUN & creatinine
- HLA-DRB1
- Females predominance 3:1, no racial/ethnic association
- Mean age of onset 15yrs (9-74yrs)
- ?triggered by medications or infection
- Renal & ocular manifestations may not be concurrent
- Good prognosis: steroid treatment beneficial
Juvenile Idiopathic Arthritis (JIA)

- Girls>boys, 3:2
- 7 subtypes
  - Varying prevalence of uveitis - oligoarticular most common
- Diagnosis of exclusion
- Risk of Uveitis:
  - ANA positivity / RF seronegativity
  - Early age at onset of arthritis (<6yrs)
  - Female gender
- Uveitis course may not parallel arthritis course
- Bilateral, non-granulomatous & asymptomatic!
Juvenile Idiopathic Arthritis (JIA)

- Risks for poor visual outcome:
  - Severe uveitis at onset
  - Onset prior to or at time of arthritis diagnosis
  - Short duration between arthritis & ocular involvement
  - Male gender
- If initially unilateral for 12 or more months, unusual to develop in fellow eye
- Complications: CME, Cataract, Band K, Glaucoma, hypotony, maculopathy, amblyopia
  - Posterior synechia is a risk factor
# Ophthalmic Examinations for JIA Without Known Iridocyclitis

## Table 1. Screening Recommendations: Frequency of Ophthalmic Examinations for Children With JRA Without Known Iridocyclitis

<table>
<thead>
<tr>
<th>JRA Subtype at Onset</th>
<th>Risk of Developing Uveitis Based Upon age at Onset</th>
<th>Frequency of Screening</th>
<th>Frequency of Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;7 y old*</td>
<td>7 y old†</td>
<td></td>
</tr>
<tr>
<td>Pauciarticular</td>
<td>High‡</td>
<td>Every 3-4 mo</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>Every 6 mo</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Every 6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyarticular</td>
<td>High‡</td>
<td>Every 3-4 mo</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>Every 6 mo</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Every 6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Low</td>
<td>Every 12 mo</td>
<td>Low</td>
</tr>
</tbody>
</table>

High risk mandates ophthalmologic examinations every 3 to 4 mo. Medium risk mandates ophthalmologic examinations every 6 mo. Low risk requires ophthalmic examinations every 12 mo. If adequate slit lamp examination cannot be performed in the clinic, an examination under general anesthesia is necessary.

*All patients with arthritis onset <7 y old are considered at low risk 7 y after the onset of their arthritis and should have annual ophthalmic examinations indefinitely.

†All patients with arthritis onset after 7 y are considered at low risk 4 y after the onset of their arthritis and should have annual ophthalmologic examinations indefinitely.

‡All high-risk patients are considered at medium risk 4 y after the onset of their arthritis. ANA indicates antinuclear antibody; JRA, juvenile rheumatoid arthritis.
Intermediate Uveitis

- Associated with HLA-DR15
- Work-up: neurologic history & MRI
  - 17% develop MS
  - ~27% with MS develop uveitis
Special Considerations
Complications of Cataract Surgery

- Retained Cortex
  - May occur beyond post-op course
- UGH Syndrome
- Pseudophakodonesis
- Cycloplegia can be very helpful
Cataract Surgery in Uveitis Patients

- Should be well-controlled before surgery
- Quiet for at least 2-3 months
- Pre-op treatment with oral &/or topical steroids 1 day prior
Missing the forest through the trees?

- Inflammation may be related to another ocular condition
  - Episcleritis
  - Scleritis
  - Corneal abrasion
What’s New on the Horizon

- **Hypovitaminosis D may increase risk of Uveitis**
  - Receptor on immune cells
  - May upregulate anti-inflammatory type 2 T helper cells & suppress cytokine activity

- **Intestinal microbiota may play a role**
  - Large proportion of microbiome in GI tract - also location of large portion of the immune system
  - Promote & inhibit inflammation
  - Target for new therapies