Introduction
- UC Berkeley School of Optometry 2008
- San Francisco VA Residency 2009
- VA Staff Optometrist – teaching
- Regular lecturer at AAO and other meetings
- No conflicts of interest

Epidemiology
- 30K cases of new blindness annually in US
  - 15-25% of blindness in US
- Incidence
  - 17, 52 per 100K person-years
  - 0.3% in general population (Wills)
  - Peak incidence 20-60 yrs, but >60 yrs Northern CA
- Prevalence
  - 38 - 270 per 100K persons, but 115.3 in Northern CA
- Females > Males


Ocular Immunity
- Immune privilege
  - Blood-eye barriers
  - Minimal lymphatic drainage
  - Little MHC expression
  - Proteins to inhibit immune response
- Anterior Chamber-Associated Immune Deviation (ACAID)
  - Different immune response than in body
  - Antigens can be tolerated

Presenting Symptoms
- Conjunctival hyperemia
- Blurry vision
- Photophobia
- Periorbital pain
- Floaters
- Headaches
- Watery eyes

How do you go through the differential diagnosis?
**Additional Signs**
- Corneal edema
- AC cells/flare
- KPs
- Miotic or mid-dilated pupils
- Posterior synechiae or PAS
- IOP changes
- Iris nodules
- Hypopyon

**Keratic Precipitates**
- White cells (leukocytes) on corneal endothelium
- Inferior, Arlt’s triangle, concentrated, or diffuse
- Usually resolve after treatment
- Older KPs can be pigmented

**Mutton Fat KPs**
- Larger, greasy-white
- Macrophages and epithelioid cells
- Granulomatous uveitis
Hypopyon

- Marker of severe inflammation; uncommon
- Layered WBCs in anterior chamber
- Risk factors: HLA-B27+, Behcet's, or spondyloarthropathy
- Resolves with treatment (specialist)
- Outcomes similar to those w/o hypopyon


Classification

- International Uveitis Study Group (IUSG)
  - 1987
- International Ocular Inflammation Society (IOIS)
  - 1998-2000
- Standardization of Uveitis Nomenclature (SUN)
  - 2004

Standardization of Uveitis Nomenclature (SUN)

- Started in 2004
- Worldwide experts
- Benefits include:
  - Type is determined by predominant site of inflammation
  - Helps narrow differential dx
  - Other complications don’t influence type CME doesn’t necessarily mean posterior

SUN Working Group.

Anterior Chamber Cells

<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>0.5+</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>

1mm x 1mm, high-intensity beam


Anterior Chamber Flare

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</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/lens clear)</td>
</tr>
<tr>
<td>3+</td>
<td>Marked (iris/lens hazy)</td>
</tr>
<tr>
<td>4+</td>
<td>Intense (fibrin/plastic aqueous)</td>
</tr>
</tbody>
</table>


SUN Classification

- Onset
  - Sudden or insidious
- Duration
  - Limited (<3m) or persistent (>3m)
- Course
  - Acute – sudden and limited
  - Chronic – persistent >3m
  - Recurrent – repeated after 3m w/o tx

SUN Working Group.

SUN Classification

- Anterior (60-90% of cases) = seen in AC
  - Iris and ciliary body (CB)
- Intermediate = seen in vitreous
  - CB and pars plana
- Posterior = seen in retina or choroid
- Panuveitis = all

**Significance of Flare?**
- Retrospective review
- 198 eyes of 114 children at Jules Stein
- Laser phorometry to quantify flare
- Flare related to: AC cells, KPs, band K, synechiae, and cataract
- Flare is not a function of disease duration
- High flare is associated with vision loss

**Interobserver Agreement in Grading Activity and Site of Inflammation in Eyes of Patients with Uveitis**

**Interobserver Grading**
- AC cells
  - Exact agreement: 51.4 – 57%
  - Within 1 grade: 93.1 – 100%
- AC flare
  - Exact agreement: 71.4 – 77.4%
  - Within 1 grade: 98.2 – 100%
- Vitreous cells
  - Exact agreement: 75.4 – 76.4%

**Considerations**
- Instrument variation
- Observer examination technique
- AC chamber depth
- Cell variations in different parts of AC
- Impact of NaFl on grading flare
- Media effects on vitreous haze
- Vitreous structure and cell location

**Uveitis Causes**
- Idiopathic
- Traumatic/Surgical
- Autoimmune
  - JIA, AS/Rheumat
  - Ulcerative colitis
  - Sjogren’s syndrome
  - Lyme induced
- Drug induced
- Masqueraders

**HLA-B27**
- HLA molecules present antigens on all nucleated cells in the body
- Mediate acquired immune response
- 15% relative risk of acute anterior uveitis
- Males
- Unilateral
- Non-granulomatous
- Frequent recurrences
- Order test?

**HSV/VZV**
- Unilateral
- Diffuse, fine, stellate or dendriform KPs
- OHTN
- Iris atrophy (sectoral)
- Corneal scars (past episodes)
- Caution Pred Forte
- Antiviral use

**ORIGINAL ARTICLE**
*Visual Prognosis and Ocular Complications in Herpetic versus HLA-B27- or Ankylosing Spondylitics-associated Anterior Uveitis*
Lieve Heuckeroth, et al. and Leonor I. Lee, et al.²,³

- 45 pts with HSV
- 17 pts with VZV
- 115 pts with HLA-B27 or AS
- Retrospective, observational
Herpetic vs. HLA-B27

- Any complication
  - Herpetic 94%
  - HLA-B27 74%
- Glaucoma
  - Herpetic 23%
  - HLA-B27 4%
- Cataract
  - Herpetic 40%
  - HLA-B27 22%
- CME
  - Herpetic 1%
  - HLA-B27 9%
- Posterior synechiae
  - Herpetic 31%
  - HLA-B27 45%

Herpetic 94%
HLA-B27 74%

Herpetic 23%
HLA-B27 4%

Herpetic 40%
HLA-B27 22%

Herpetic 1%
HLA-B27 9%

Herpetic 31%
HLA-B27 45%

Herpetic 23%
HLA-B27 4%

Herpetic 40%
HLA-B27 22%

Herpetic 1%
HLA-B27 9%

Herpetic 31%
HLA-B27 45%

Hoeksema and Los, et al. Ocular Imm & Inflamm, Early Online, 1-11, 2015

Drug Induced

- Prostaglandin analogs
  - Cons:
    - Uveitis reportedly associated with travoprost, latanoprost, bimatoprost, etc
    - Granulomatous and non-granulomatous
    - CMV anterior uveitis has been reported in immunocompetent pts

Drug Induced

- Pros:
  - “There is little evidence that PGA disrupt the blood-aqueous barrier and only anecdotal evidence suggesting an increased risk of these rare findings”
  - “PGA may be used in uveitic glaucoma when other topical treatments have not lowered IOP to the patient's target range”

OA tends to be worse in herpetic uveitis
Corneal scarring and glaucoma

Uveitis Complications

- Band keratopathy
- Cataract
- Posterior synechiae
- Glaucoma
- Retinal detachment
- Phthisis
- ONH atrophy
- CME
- Blindness

Posterior synechiae

Adhesion of iris to lens
Acute anterior uveitis or chronic posterior uveitis
Can cause IOP issues, angle closure
Attempt to break with dilation
Acute anterior uveitis rarely results in macular or ONH edema
Retina and peripapillary RNFL were thicker in uveitis eyes vs. controls
Not correlated with type of uveitis
Only 28 eyes

Macular Abnormalities in Chinese Patients with Uveitis
- 58.6% of patients had macular involvement
- CME (25.4%) and ERM (12.6%) most common
- Tractional CME, macular hole, CNV, diffuse ME, and serous RD also occur

Risk of Relapse in Primary Acute Anterior Uveitis
- 102 pts with first time uveitis
- Seen within 90 days
- Female 60%, Caucasian 78%
- 40 pts had recurrence
- 24% relapse incidence per person-year
- At 1.5 years, 61% were in remission
- Main risk factor: 18–35 y/o group

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Topical cyclosporine A 0.05% for recurrent anterior uveitis
Patients on Restasis AND conventional tx:
- Fewer episodes of anterior uveitis
- Shorter duration of episodes
- Fewer total days of inflammation per year
- Small, retrospective study (only 8 pts)
Factors Predictive of Remission of New-Onset Anterior Uveitis

- 999 eyes with first time uveitis
- Lower incidence of remission in:
  - Behcet’s
  - JIA
  - Bilateral uveitis
  - Pseudophakic eyes
  - 1+ vitreous cells or more
  - VA <20/200

CA Optometry Law

- Unilateral nonrecurrent nongranulomatous idiopathic iritis or episcleritis
- Consult with an opthalmologist if condition worsens 72 hours after the diagnosis or if it is not resolved in 3 weeks (or 1 week for traumatic iritis)
- If the patient is still receiving medication 6 weeks after diagnosis, the optometrist shall refer the patient to an ophthalmologist

Cycloplegia

- Benefits
  - Quick relief
  - Reduce pain and photophobia
  - Break/prevent posterior synechiae
  - Stabilize blood-aqueous barrier
- Atropine, homatropine, scopolamine, etc
- Dilate, but allow some constriction

Prednisolone Acetate

- Inhibits
  - Edema
  - Fibrous deposition
  - Capillary dilation
  - Phagocytic response of acute inflammation
  - Capillary proliferation
  - Collagen deposition
  - Scar formation
- Dosing

Loteprednol

- Loteprednol etabonate soln 0.5%
- Effective for GPC, seasonal allergic conjunctivitis and post-op inflammation
- Anterior uveitis
  - Effective but less than Pred Acetate
  - Less IOP elevation though

Prednisolone Acetate

- Mechanism of action
  - Glucocorticoid
  - There is no generally accepted explanation for the mechanism of action of ocular corticosteroids.
  - Induces phospholipase A2 inhibitory proteins → control biosynthesis of inflammatory mediators (prostaglandins and leukotrienes) by blocking release of arachidonic acid.
  - Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Table 2 Characteristics of uveitis episodes

<table>
<thead>
<tr>
<th></th>
<th>Control period (SD)</th>
<th>Cyclosporine period (SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average episode/eye</td>
<td>4.3 (3.5)</td>
<td>0.36 (0.32)</td>
<td>0.006</td>
</tr>
<tr>
<td>Average duration of episodes (days)</td>
<td>41.6 (20.5)</td>
<td>13.3 (14.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Average max AC cell grade per episode</td>
<td>1.2 (0.7)</td>
<td>0.53 (0.58)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Difluprednate
- Difluprednate ophthalmic soln 0.05%
- FDA approved in 2008
- Inflammation and pain due to surgery
  - QID x 14d, then BID x 1 wk, then taper
- Anterior uveitis
  - QID x 14d, then taper
- Effective at QID dosing compared to 8x/d for PF for uveitis

Follow Up
- No specific schedule
  - Tailored to severity, risk, experience, etc
- 1-3 days after initial presentation
  - Should be no worse
- Etiology?
  - Cataract surgery vs. HLA-B27 vs. herpetic?

Case 1
- 80 y/o Hispanic male
- CC minimal near blur
  - BCVA 20/25 due to mild cataracts
- IOPs 8/10 mmHg
- C/Ds 0.75

Exam Flow Sheet

<table>
<thead>
<tr>
<th>Date and Time</th>
<th>IOP</th>
<th>Meds/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/05/13 1027</td>
<td>8/10</td>
<td>none</td>
</tr>
<tr>
<td>12/13/13 1300</td>
<td>12/14</td>
<td>HVF, pachy</td>
</tr>
<tr>
<td>12/16/13 1300</td>
<td>12/14</td>
<td>HRF, start latanoprost 1/1</td>
</tr>
<tr>
<td>02/05/14 0940</td>
<td>12/12</td>
<td>none, HRF</td>
</tr>
<tr>
<td>02/15 115</td>
<td>9/12</td>
<td>Chemosis/redness, stopped latanoprost</td>
</tr>
<tr>
<td>02/21/13 1300</td>
<td>11/13</td>
<td>none, allergy</td>
</tr>
<tr>
<td>02/26/13 1000</td>
<td>9/10</td>
<td>HRF</td>
</tr>
<tr>
<td>03/03/14 1140</td>
<td>12/13</td>
<td>PF1% 4/0, Cyclop 2/0, 6 cells</td>
</tr>
<tr>
<td>03/05/14 1130</td>
<td>9/10</td>
<td>PF1% 4/0, Cyclop 2/0, 3 cells</td>
</tr>
<tr>
<td>03/07/14 1220</td>
<td>11/12</td>
<td>PF1% 4/0, Cyclop 2/0, 1 cell</td>
</tr>
<tr>
<td>03/10/14 1155</td>
<td>12/12</td>
<td>PF1% 4/0, Cyclop 2/0, 1 cell</td>
</tr>
<tr>
<td>03/12/14 1227</td>
<td>14/12</td>
<td>PF1% 4/0, Cyclop 2/0, clear (ophth)</td>
</tr>
<tr>
<td>04/03/14 1200</td>
<td>12/13</td>
<td>none, HRF</td>
</tr>
</tbody>
</table>

14 visits in 5 months

HVF – Taped Lids

Treatment started
- Latanoprost OU qhs
- Develops questionable allergy, d/c drops
- Allergy subsides
- Switched to Travatan OU qhs
- Develops mild anterior uveitis
Case 1 – Discussion points
- Prostaglandin induced uveitis
- Management
  - Discontinue PGA vs. using PF/cyclo
  - Follow-up schedule
- Overtreatment of glaucoma

Case 2
- 48 y/o Asian male
- Past Medical Hx:
  - HLA-B27+
  - Ankylosing spondylitis
  - Acromegaly
  - CAD/CHF
  - HTN
  - Hypercholesterolemia
  - Sleep apnea

Iritis Episodes
- Multiple recurrences of anterior uveitis
- VA 20:20 OU, IOP WNL
  - OD: 10/31/07 to 11/23/07
    - Tx w/ Pred Forte and Scopolamine
    - Pt did not return for last f/u
  - OS: 3/13/08 to 5/9/08
    - Tx w/ Pred Forte and Scopolamine less effective
    - Oral prednisone 60mg w/ taper

Latest Iritis
- OS: 12/18/08 to Feb 2008
- VA 20:20 OU, IOP WNL
  - Similar initial presentation, 3+ cells/2+ flare
  - Self medicated with PF q3-4 hrs and scopolamine
  - Increased PF to q1 hr, good response
  - After 1 week, 1+ AC cells remained

The Plan Changes
- 2 weeks into tx, significant flare-up
  - Stll on PF q 1 h, Scopolamine qd OS
  - Started oral prednisone
    - 60mg x 1 wk, 40mg x 1 wk, 20 mg x 1 wk
  - Consult about other tx options

Etanercept (Enbrel)
- Subcutaneous injection, 25 or 50 mg, 2x/wk
- Binds specifically to TNF, a naturally occurring cytokine involved in inflammatory and immune responses
- Blocks interaction with cell-surface tumor necrosis factor receptors (TNFRs)
- Elevated levels of TNF are found in involved tissues and fluids of patients with RA, JIA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis

TNF Inhibition
- Review of 69 papers in 2013
- Etanercept appears to be inadequate for ocular inflammation
- Infliximab and adalimumab show encouraging results
- More long-term studies are needed

Adalimumab (Humira)
- Subcutaneous injection, 40 mg, 2x/month
- Binds specifically to TNF-alpha, not TNF-B
- Blocks interaction with the p55 and p75 cell surface TNF receptors
- Also lyses surface TNF-expressing cells in vitro in the presence of complement
- Decreases levels of acute-phase reactants of inflammation (CRP, ESR, and cytokines (IL-6))
- RA, JIA, psoriatic arthritis, AS, psoriasis
TNF Blocker Warnings
- Tuberculosis, sepsis, and fungal infections
- CNS-demyelinating disorders
- Blood dyscrasias
- Lymphoma
- HBV reactivation
- Heart failure
- Injection site infection

Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study.

- 1250 pts with anterior uveitis and AS
- 51% reduction in recurrence overall
- 68% reduction in those with recent episode

Case 2 – Discussion points
- Recurrent uveitis
  - Treatment may not be the same each time
- Management
  - Consult with MD/uveitis specialist

Conclusions
- Anterior uveitis is highly variable
  - Full exam with DFE
- Determine etiology and properly classify
  - Helps guide treatment
- Be aggressive with treatment
  - Consult with PCP-ophthalmology

References

Thank you!

Questions?
davehicks.OD@gmail.com