ANTERIOR UVEITIS:
AN ORGANIZED APPROACH TO
DIAGNOSIS AND MANAGEMENT
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Disclosure Slide
- Dr. Tokumaru
  - Nothing to Disclose
- Dr. Than
  - Nothing to Disclose

Why Anterior Uveitis?
- Because it’s not uncommon
- Because these patients will show up as walk-ins or add-ons
- Anterior uveitis – because covering all of uveitis would take more than 2 hrs
  - Uveitis involving the posterior segment should be managed by a retinal specialist

Epidemiology
- Accounts for 10-15% of all legal blindness (30,000 new cases annually) in US
- 3rd leading cause of blindness in the world
- Disproportionately affects working adults; 70-90% of patients present between 20-60 yrs of age
- In the US, > $240 million spent annually on the treatment of uveitis and its complications
- Anterior uveitis most common form of uveitis: comprises 50-60% of all cases in tertiary care centers*
- Approximately 35%-40% are undifferentiated (Foster, 2016)
- Incidence varies greatly by geographic location

What causes vision loss in uveitis?
- Band keratopathy
- Cataract
- Macular Edema*
- Epiretinal membrane*
- CNVM*
- Retinal vasculitis
- Retinal detachment
- Glaucoma
- Optic neuropathy

Series from Moorfields Eye Hospital – at 10-yr f/u
- 80% had VA > 20/50
- 90% had VA > 20/200
- CME, Macular scarring*, ERM = 79% of vision loss <20/50
- Macular scarring, CME, RD, = 71% of vision loss <20/200

Tomkins-Netzer, Ophth, 2014

Principles of Uveitis Diagnosis
- Accurate diagnosis
- Accurate description/classification
- Understand the epidemiology and clinical characteristics of uveitic entities
- Targeted history and work up
Anterior Uveitis: Diagnosis And Description

Symptoms
- Deep seated pain/throbbing
- Blurred/distorted vision
- Photophobia
- Floaters
- Photopsia
- Halos
- Can be asymptomatic
  - Children with JIA (Juvenile Idiopathic Arthritis/JRA)
  - Sarcoid

Clinical exam
- Pupils
  - Usually miotic, less reactive
  - May be affected by posterior synechiae
- Conjunctiva
  - Ciliary flush around limbus
  - May not occur in JIA, Fuchs

Clinical exam - Cornea
- KP on endothelium, usually inf
  - Nongranulomatous: fine white deposits: collections of lymphocytes, plasma cells and pigment
  - Granulomatous: large, "greasy" appearance, "mutton-fat": collections of lymphocytes, plasma cells and giant cells

Clinical exam - Cornea
- IF epithelial involvement, edema, dendritic lesions, hypoesthesia, band keratopathy – think Herpes

Clinical exam – Anterior chamber
- Cells: WBCs/leukocytes
- Flare: protein - from vasodilation and permeability of inflamed blood vessels
  - Doesn’t = active inflammation
- Hypopyon: layering of WBCs
Clinical exam – Iris

- Posterior synechiae
- PAS: Peripheral anterior synechiae
- Nodules: associated with sarcoid, TB, syphilis

Posterior synechiae

- Sometimes this is all you get after dilation
- Complications
  - Poor view of posterior pole
  - Decreased vision
  - Secondary angle closure from iris bombe
  - Complicates cataract surgery
  - Can also get secluded pupil: “Seclusio pupillae”

Clinical findings – Vitreous

- Haze
- Cells (spillover from A/C)
- Snowballs
  - Collections of inflammatory cells
- Snowbanking
  - Inflammatory exudates over pars plana

Clinical findings – Retina/Choroid

- CME
- Retinal vasculitis
- Retinal ischemia/hemorrhage
- Retinal/choroidal lesions
- Retinal/choroidal NV
- Retinal detachment

If this is a lecture about anterior uveitis, why even mention posterior segment findings?

- Because uveitis ALWAYS involves the posterior pole until proven otherwise!
- So when should you dilate a patient who presents with a uveitis?
  - Always
  - At all times
  - 100% of the time
  - All of the above

Just Anterior Uveitis?

- Chi et al
  - PLOS ONE 2015 Mar 27;10(3):e0122749
  - 65 eyes with anterior uveitis
  - Ultra-wide-field fluorescein angiography
Study Findings

- Peripheral Vessel Leakage
  - 42% (27/65) of eyes
    - 15 active
    - 12 inactive
    - 7 had CME
  - 44% had specific etiology

- Treatment altered based on results
- Clinical Implication?

Classification

Adapted from Seve 2015

SUN (Standardization of Uveitis Nomenclature) Working Group

- In 2005 diverse group of uveitis specialists met to develop standardized uveitis terminology for classification, to be able to better compare clinical outcomes
- Developed by consensus in small working groups
- Characterized uveitis by:
  - Anatomic type/location
  - Onset/duration and clinical course
  - Standardized evaluation

Onset, Duration, and Course

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inidious</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Limited</td>
<td>≤3 months duration</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
<td>&gt;3 months duration</td>
</tr>
<tr>
<td>Course</td>
<td>Acute</td>
<td>Episode characterized by sudden onset and limited duration</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration</td>
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<tr>
<td></td>
<td>Chronic</td>
<td>Persistent uveitis with relapse in &lt;3 months after discontinuing treatment</td>
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Anatomic Classification

SUN Grading of Anterior Chamber Cells and Flare
### Treatment of Anterior Uveitis

- **Goals**
  - Preserve vision
  - Relieve pain
  - Reduce ocular inflammation
  - Prevent sequelae

- **Success**
  - Induction of durable, corticosteroid-free remission

### Pathophysiology

- Exact pathophysiology is not known
- BAB and BRB normally do their job
- Inflammation → tissue changes → ↑ permeability

### Agents Utilized

- Topical corticosteroids
- Cycloplegics (and mydriatics)
- Oral corticosteroids
- Periocular steroids
- Immunomodulators

### Cycloplegics

- Immobilize inflamed iris
- Prevent posterior synechia
- Stabilize the blood-aqueous barrier

### Cycloplegics

- **Homatropine**
  - 5%
  - Solution only
  - Mild to moderate
  - If not available...

- **Atropine**
  - 1%
  - Solution and ointment
  - Use for severe inflammation
  - Bid to tid

- Not cyclopentolate or tropicamide
Mydriatics

- Phenylephrine
  - Direct acting $\alpha$-1 agonist
  - 2.5% and 10%
  - In-office to break posterior synechia
  - Can liberate pigment

Topical Corticosteroids

- Better to overtreat than undertreat early on in the disease process
- Stabilize cell membranes
- Inhibit release of lysozyme by granulocytes
- Suppress circulation of lymphocytes

Topical Corticosteroids

- Better to overtreat than undertreat early on in the disease process

Corneal Penetration and Antiinflammatory Efficacy

<table>
<thead>
<tr>
<th>Epithelium Intact</th>
<th>Epithelium Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred Acetate 1%:</td>
<td>51%</td>
</tr>
<tr>
<td>Pred Phosphate 1%:</td>
<td>28%</td>
</tr>
</tbody>
</table>

Objective

- To assess the efficacy and safety of Durezol® (difluprednate ophthalmic emulsion) 0.05% dosed QID, compared to Pred Forte® (prednisolone ophthalmic suspension) 1%, dosed eight times a day (8x/day) in subjects with anterior uveitis

Masking Scheme

- Patients were each given two bottles: Bottle A and Bottle B
- Each patient received 8 drops every day
- In the Durezol group Bottle A contained Durezol and Bottle B contained vehicle
- In the Pred Forte group, Bottle A contained Pred Forte and Bottle B contained Pred Forte
Conclusions

- Durezol dosed QID was not inferior to Pred Forte dosed eight times a day
- Durezol may offer increased patient compliance and satisfaction
  - QID dosing
  - Emulsion formulation
  - BAK free

Dosing of Steroids

- Mild
  - Every 4 hours
- Moderate
  - Every 2 hours
- Severe
  - Every ½ - 1 hour (or even more frequently)
  - Every 2-3 hours at night

Ophthalmic Steroid Ointment

- FML 0.1%
- Lotemax

Topical Steroids

- Tapering
- Chronic cases

Ocular Side Effects of Treatment

- Iatrogenic (Steroid) OHT
  - Interference with phagocytosis in Schlemm’s canal
  - Increased accumulation of glycosaminoglycans (GAGS) in TM
- Steroid Uveitis
  - Cause is steroid rather than vehicle
- Management

Periocular Steroids

- Recalcitrant anterior uveitis
- r/o steroid responder
- Triamcinolone or methylprednisolone
- Subconjunctival or sub-Tenon’s
- Do not administer if etiology is infectious
Oral Steroids
- Prednisone
  - Start high and taper quickly
  - 1-2 mg/kg/day (~60-120 mg/day)
- Medrol Dosepak
- Add H2 receptor antagonist

Immunomodulators
- Antimetabolites
  - Methotrexate, Azathioprine
- Inhibitors of T-lymphocytes Signaling
  - Cyclosporine, Tacrolimus
- Alkylating Agents
  - Cyclophosphamide, Chlorambucil
- Biologic Response Modifiers

What's New?

Tumor Necrosis Alpha (TNF-α) Inhibitors
Vitamin D Levels in AU

- Role in regulatory effects on immune system

Vitamin D Levels in AAU

- Lower Vit D in AAU compared to controls
- No recurrence after supplementation
- Clinical Implication?

Simvastatin


Results: Fifty patients were enrolled in the study. Twenty-five patients were randomly assigned to receive simvastatin with conventional treatment and 25 to conventional treatment alone. Simvastatin was associated with significantly higher rates of steroid-sparing uveal inflammation control, decrease in anterior chamber inflammation, and improvement in visual acuity. The treatment was well tolerated, no serious adverse effects were observed.

Conclusions: Our findings suggest that statins may have therapeutic potential in uveitis. These results need to be confirmed in double-blind, randomized, controlled trials.
### Overall Management

- Re-evaluate 1-7 days
- Cycloplegic usually stopped before steroid
  - No need to taper
- Continue topical steroid until cells are gone
  - Taper
- Evaluate patient during taper and post-taper

### Overall Management

- Check IOP
  - Baseline IOP before treatment
  - Monitor IOP every 1-2 weeks
  - Treat with topical ocular hypotensive agents
    - Avoidé
- What is the etiology?
- Patient Education

### Surgical

- Cataract surgery
  - 3 months of quiescence
  - Pre-treat with topical steroids
    - 48 hours before
    - Every 1-2 hours while awake

### Targeted history and diagnostic work up

### Why work up a uveitis patient?

- To determine if they have an infectious etiology that can be treated
- To diagnose an underlying systemic disorder that could be managed and therefore improve their quality of life
- Finding an associated disorder is not curative!

### Categories of Etiology

- Infectious (HSV, Syphilis, TB, “bugs”)
- Systemic immune-mediated
  - Systemic inflammatory diseases
- Drugs and hypersensitivity reactions
- Ocular conditions
## Infectious disorders

### Bacterial diseases
- Syphilis
- Tuberculosis
- Lyme disease
- Cat-scratch disease
- Rickettsiosis
- Leptospirosis
- Brucellosis
- Whipple's disease

### Parasitic diseases
- Toxoplasmosis
- Toxocariasis
- Onchocerciasis

### Viral diseases
- Herpes virus
- CMV
- HTLV-1

### Fungal diseases
- Candidiasis
- Histoplasmosis

## Inflammatory diseases

### HLA-B27-associated uveitis
- Sarcoidosis
- Behcet's disease
- Vogt-Koyanagi-Harada disease
- juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Multiple sclerosis
- Chronic inflammatory bowel disease

### Drug-induced
- Rifabutin
- Bisphosphonates
- Fluoroquinolones

### Masqueraders
- Trauma
- Intraocular FB
- Tumors
- Oculocerebral lymphoma
- Melanoma
- Retinoblastoma
- Metastases

## Anatomic Location

<table>
<thead>
<tr>
<th>Infectious Systemic Disease</th>
<th>No Systemic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior uveitis</td>
<td>CMV</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>Toxoplasmic retinitis</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>Syphilis</td>
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</tbody>
</table>

### Herpes Simplex
- HSV-1 or 2 enters through mucous membranes or compromised epithelium
- Initial infection: acute oropharyngitis
- Virus enters latent period, usually within trigeminal ganglion

### HSV: Epithelial involvement
- Epithelial disease: SPK and dendrites; +/- blepharoconjunctivitis,
- Dendrites: heaped up edges, can +/- ulcers
- Lasts 2-4 weeks
- Treatment (with topical or oral antivirals) decreases duration of symptoms and helps maintain virus latency

### HSV: Stromal involvement
- Most likely an immune response, so rarely presents initially, but seen in 20-60% of recurrent disease
- Stromal NV, thinning, leads to vision loss
- Necrotizing stromal keratitis (IK) - Viral infection of stroma; may lead to perforation
HSV Keratouveitis
– how to stay out of trouble

- ALWAYS look at the cornea – in most non-herpetic uveitis, the anterior part of the cornea is NOT involved and there is NO corneal edema.
- Check corneal sensitivity – which could be reduced in HSV.
- Use rose Bengal stain – this will stain the devitalized epithelial cells at the edges of the dendrites.
- Consider dendrite masqueraders: e.g. epithelial regeneration line after a corneal abrasion.
- If cornea is compromised, do NOT use a steroid.
- When in doubt do NOT use a steroid.
- All other times, use a steroid!

Herpes Zoster

- Most common > age 50 OR immunosuppressed.
- In one population based study, 2.5% of all pts with HZ had ocular involvement.
- ~1/3 of cases involving the ocular dermatome had ocular involvement.
- HZ vaccine reduces the rate of HZ ~ 50% in pts > age 60.

HZ uveitis

- Occurs in ~ 40% of pts with HZ.
- Usually starts 1-3 weeks after rash.
- Unilateral; usually mild and transient.
- Increased IOP.
- Diffuse small KP.
- Iris atrophy (sectoral or diffuse) and irregular pupil.
- Chronic or recurrent.

Herpetic Eye Disease and Atopy

- Pacific Ocular Inflammation Project
  - Retrospective, population-based case control study.
  - N = 251 pts with HSV or HZO.
  - Atopy = atopic dermatitis, asthma, or allergic rhinitis.
  - Pts with atopy had:
    - 2.6x greater odds of having HSV; 1.6x for HZO.
  - For those with 2+ atopic conditions:
    - 8.9x greater odds of having HSV; 2.9x for HZO.
  - Due to underlying autoimmune dysregulation?
  - Other studies suggest longer course, more recurrences.

Syphilis

- “The great imitator” – can affect any organ, and has protracted natural history that can last years.
- A chronic, multistage sexually transmitted disease caused by the spirochete Treponema pallidum.
- Primary: sores at original site of infection.
- Secondary: skin rash, swollen lymph nodes, fever.
- Latent: no symptoms.
- Tertiary: neurologic, sometimes cardiovascular involvement.


Herpes Zoster


Herpetic Eye Disease and Atopy

Borkar et al, JAMA Ophth 2014

Syphilis

Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 2015

Syphilis

www.cdc.gov/std/syphilis
**Ocular Syphilis**

- March 2016, the CDC issued a Clinical Advisory on Ocular Syphilis in the United States
- May occur as part of a neurosyphilis syndrome or as an isolated manifestation
- In addition to ant/post/panuveitis, can also have episcleritis, vitritis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment
- Recommended HIV testing in all pts with syphilis, and examine all syphilis patients with ocular complaints
- Report to Health Dept

**Tuberculosis - epidemiology**

- Worldwide In 2015, 10.4 million people developed TB and 1.8 million died
- Six countries account for 60% of the total: India, Indonesia, China, Nigeria, Pakistan and South Africa
- In 2015, ~66% of TB cases in the US occurred in foreign-born individuals
- The majority of these cases are in people from 7 countries: Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala
- African Americans, prison, and homeless populations disproportionately affected

**Latent TB Infection**

- TB bacteria live in the body without making the person sick
- No symptoms; patients don’t feel sick
- Can’t spread TB
- May develop active TB disease if untreated
- Usually have a positive PPD

**TB Disease**

- Feel sick: cough, weakness or fatigue weight loss, chills, fever, sweating at night
- Can spread to others
- Diagnosed by CXR or (+) culture

**Ocular Tuberculosis**

- Most common: posterior uveitis, anterior uveitis, panuveitis, and intermediate uveitis
- Other signs (most significant in endemic areas)
  - Broad posterior synechiae
  - Retinal perivasculitis
  - Multifocal serpiginoid choroiditis
  - Choroidal or optic disc granuloma

**Controversies in Ocular TB**

- No definite diagnostic criteria, so prevalence rates range from 1-18%
- Diagnostic difficulty
  - 70% with OTB have normal CXR
  - TST low specificity and doesn’t distinguish active from latent
  - Definitive diagnosis requires isolation of Mycobacterium tuberculosis through invasive procedures
  - Vitreous aspiration
  - Aqueous paracentesis
  - Or Retinal biopsy
  - Culture or histopathologically proven TB from eye is uncommon
  - Are ocular findings are from actual infection, or immune-mediated inflammatory response?

**Tick-Borne Diseases and anterior uveitis**

- Lyme Disease (Borrelia burgdorferi): ~95% of cases from NE and upper Midwest; < 1% have ocular involvement
- Q fever (Coxiella burnetii): main host: livestock; most central/Wn states
- Rocky Mountain spotted fever (Rickettsia rickettsia): ~60% of cases from NC, OK, AK, TN MO; main host: dogs, can be fatal
- Tick-borne relapsing fever (Borrelia): Western and SW USA, linked to sleeping in rustic, rodent-infested cabins in mountainous areas; host are chipmunks and squirrels
- Kyasanur forest disease (Kyasanur forest disease virus): limited to India
- Zika-Case of bilateral anterior uveitis in Brazil – confirmed by PCR

**Tuberculosis - latent TB infection**

- In 2015, ~66% of TB cases in the US occurred in foreign-born individuals
- The majority of these cases are in people from 7 countries: Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala
- African Americans, prison, and homeless populations disproportionately affected
Autoimmune/inflammatory disorders

Seronegative spondyloarthropathies (SAs)

- Group of inflammatory rheumatic diseases that cause arthritis of the spine (Seronegative = negative RF)
- Starts in teens and 20s (< age 40), males 2-3x > females
- Hereditary; major gene that causes it is HLA-B27
- Can affect the joints of the arms and legs (e.g., hips and shoulders) as well as involve the skin, intestines and eyes
- Eventually, bone destruction can cause deformities of the spine and poor function of the shoulders and hips
- Frequently undiagnosed; mean time to dx after onset of symptoms is 6 years

Types of spondyloarthropathies

- Ankylosing spondylitis: affects mainly the spine (most common)
- Axial spondyloarthritis: affects mainly the spine and pelvic joints, causing lower back pain and stiffness
- Peripheral spondyloarthritis: causing pain and swelling in the arms and legs
- Reactive arthritis (Reiter’s syndrome)- non-Gc urethritis
- Psoriatic arthritis
- Enteropathic arthritis/spondylitis associated with inflammatory bowel diseases (ulcerative colitis and Crohn’s disease)

SA/HLA-B27 associated uveitis

- Accounts for 20% of all uveitis
- Posterior synechiae common
- Non-granulomatous
- Of recurrent, acute, unilateral alternating anterior uveitis: 80% will have a SA or be HLA-B27 positive

SA/HLA-B27 associated uveitis

- Of patients with uveitis and (+) HLA-B27, 60-76% will have an associated SA
- And about half of these SAs will have been undiagnosed or misdiagnosed
- Can also present with a hypopyon; in the US, a patient with a hypopyon is more likely to have SA than Bechet

DUET (Dublin Uveitis Evaluation Tool)

- Sens: 96%
- Specif: 97%
- PPV: 96%
- NPV: 97%

Haroon, 2015; https://www.rheumatology.org

Zamecki Ophth 2010; Chang Surv 2005
Sarcoid
- A systemic inflammatory disorder of unknown etiology characterized histologically by non-caseating epithelioid cell granulomas that primarily affect the lungs and lymphatics, and clinically, by its variable manifestations and disease course.

Sarcoidosis
- In the US, 3x more common in African Americans than white Americans.
- Highest incidence in northern European countries.
- Female preponderance.
- 70% of cases occur in those aged 25–40 years at presentation.

Symptoms:
- Persistent dry cough (~30%)
- Fatigue (27%)
- Weight loss (28%)
- Fever, night sweats, erythema nodosum

Female preponderance
- 70% of cases occur in those aged 25–40 years at presentation.

Symptoms:
- Persistent dry cough (~30%)
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Ocular Sarcoid
- 30–60% of patients have ocular involvement.
- 20-50% have uveitis.
- 80-90% bilateral.
- Accounts for 5-10% of all uveitis.
- Females> males.

Two peaks of incidence:
- age 20-30 yrs, then age 50-60.
- Can produce any type of uveitis; “silent uveitis.”
  - Ant uveitis: 41–75%.
  - Interm: 6–10%.
  - Post: 28%.
  - Panuveitis: 9–30%.

Ocular sarcoid- Anterior segment
- Bilateral.
- Granulomatous.
- Large mutton-fat and smaller granulom KPs.
- Anterior and posterior synechiae.
- Iris nodules (Koeppe and Busacca).

Ocular sarcoid- Posterior segment
- Retinal periphlebitis: segmental cuffing, extensive sheathing, and perivenous “candle-wax drippings.”
- NV.
- Patchy sheathing.
- Multifocal choroiditis.
- ~10% of patients with sarcoid uveitis develop blindness in at least one eye.
Behçet's disease

- Most prevalent along the ancient Silk Road that extends from the eastern Mediterranean to Japan
- Most common in Middle East, Turkey (42/10,000) and Japan (1/10,000)
- In Saudi Arabia, one of the most common causes of uveitis

Behçet's disease

- Chronic multisystem inflammatory disease of unknown etiology
- Characterized by recurrent episodes of:
  - Uveitis with hypopyon
  - Oral aphthous ulcers
  - Genital ulcers
  - Retinal vasculitis
  - Skin lesions

Diagnosis based on specific clinical findings, as there is no specific lab test
- Males > Females
  - Although reverse may be true in US and Western Europe

70-90% have eye involvement
- Usually bilateral (80%)
- In 20% of cases, ocular involvement may be the initial manifestation

Episodic and recurrent iridocyclitis, along with vitiritis, retinitis, occlusive vasculitis, and CME, with periods of inactivity
- Panuveitis most common (up to 89% - Arevalo 2015)
- Posterior seg involved in ~ 70% of patients:
  - Acute inflammation of retinal arteries and veins

Retinal vasculitis and occlusive vasculitis (CRVO, BRVO, NV)
- Retinal vasculitis initial presentation in ~ 50% of cases
- Potentially blinding; 20-50% have VA of < 20/200

Autoimmune inflammatory condition that targets melanocytes
- Most common in Asian, Latin American and Middle Eastern populations
- Age 30-50’s
- Females > males

Uncommon in US, comprising only 3-4% of cases in tertiary care centers
- Presents as severe bilateral granulomatous posterior or panuveitis with serous RDs, vitritis, and disc edema
VKH Phases
- Sudden bilateral granulomatous uveitis (70% of pts)
- Serous RDs
- Convalescent phase: weeks to months later, can get vitiligo, poliosis, and “sunset glow fundus”
- Chronic recurrent phase: Exacerbations of granulomatous anterior uveitis resistant to steroids; occurs 6-9 months later

Juvenile Idiopathic Arthritis (JIA)
- Group of clinically distinct arthritic disorders characterized by:
  - Asymmetric arthritis
  - Early age of onset
  - Female predilection
  - (+) ANA
- Multifactorial autoimmune disorder to which patients are genetically predisposed and may be influenced by environmental factors and infections

Juvenile Idiopathic Arthritis (JIA)
- Children < 16 yrs
- Most prevalent systemic disorder in children with uveitis
- Chronic bilateral anterior uveitis is usually ASYMPOTOMATIC
- Uveitis occurs in ~ 30% of JIA pts
- Fine or no KP with posterior synechiae

TINU (tubulointerstitial nephritis and uveitis syndrome)
- Rare; first reported in 1975
- Often occurs in children; mean age 14-15, 3x F>M
- Often associated with an upper respiratory tract infection
- Usually presents with anterior uveitis, later followed by acute interstitial nephritis
- TIN acute renal failure is immune-mediated and initiated by medications, infection, and other causes
- The nephritis usually responds to corticosteroid therapy, as does the uveitis

Systemic Lupus Erythematosus-
- Chronic systemic autoimmune disease that can affect any organ system
- More common in women
- Main eye findings are: K sicca, episcleritis, retinal vasculitis (poor prognostic sign) with hemorrhages
- Uveitis is a very rare finding, probably < 0.5% of cases (Gallagher JAMA Ophth 2015)

Ocular Entities
Fuch's heterochromic iridocyclitis
Fuch's uveitis syndrome (FUS)
- Unilateral (90%), recurrent low grade uveitis, little injection or pain
- Iris heterochromia or atrophy
- NO posterior synechiae
- Stellate KP

Fuch's uveitis syndrome (FUS)
- Glaucoma, cataract
- Vitreous opacities, iris nodules, abnormal vessels in angle, chorioretinal scars
- Does not respond to steroids!
- Likely associated with rubella virus
- Quentin and Reiber (2004) found evidence of intraocular production of antibodies against rubella virus in all 52 of their FUS pts
- Since vaccination program against rubella started in US, sharp decline in FUS cases

Posner-Schlossman
Glaucomatocyclitic crisis
- Mild unilateral nongranulomatous anterior uveitis with markedly elevated IOP
- Minimal symptoms, open angles
- May also have diffuse iris atrophy
- Responds well to steroids (unlike Fuch's)
- Now believed to be due to infection with CMV
  26-52% of pts with PS were found to have CMV in the anterior chamber using PCR
- Could treat pts with PS unresponsive to steroids with topical or oral antivirals

Pars Planitis
- Subset of idiopathic intermediate uveitis, where vitreous is the primary site of inflammation
- Can also present with anterior uveitis and peripheral corneal edema
- Snow banking or snowball formation at the pars plana
- Typically children and adolescents
- M > F
- Usually bilateral
- Usually asymptomatic, may c/o: floaters
- Rarely associated with a systemic disease
- CME main cause of vision loss

Drug-Induced uveitis
- Rare – incidence < 1%
  - Rifabutin: oral anti-mycobacterial agent, used especially in immunocompromised pts
  - Oral bisphosphonates - management of osteoporosis – can cause ant uveitis or scleritis
  - Oral moxifloxacin (or ciprofloxacin) reportedly associated with bilateral anterior uveitis

Other Ocular Disorders
- Sympathetic Ophthalmia
  - Follows penetrating trauma or surgery
  - Insidious onset of (granulomatous) inflammation in noninvolved eye
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Masqueraders

- Trauma – intraocular FB
  - Traumatic uveitis
- Tumors
  - Oculocerebral lymphoma
  - Malignant Melanoma
  - Retinoblastoma, metastases
- Retinal Detachment

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Additional risk factors

- Pacific Ocular Inflammation Study, population-based case control study of Kaiser patients in Hawaii
- Smoking: 2x greater odds ratio of developing uveitis in smokers vs nonsmokers (Yuen 2015)
- Statin use: 33% less odds of a statin user developing uveitis compared to non-statin users (Borkar et al 2015)

Laboratory Testing

- Challenging
- Use history, ROS, knowledge of systemic diseases
- Practice evidence-based medicine
- Routine lab testing yield is not that high
- Know your lab tests
  - Sensitivity
  - Specificity
  - Likelihood ratios (LRs)

If You Order Tests...

- Interpret
  - Laboratory Tests and Diagnostic Procedures
    - 6th edition - 2013
    - Chernecky and Berger
      - Includes Herbal interactions
- Communicate
- Treat
- Refer

ACE

- angiotensin converting enzyme
- best for patients > 20 YO
- helps confirm dx of sarcoidosis
  - ACE elevated in 60%
- 12 hour fast before test

Sarcoidosis: Other Lab Tests

- Laboratory Testing
  - Chest X-Ray
  - Serum Angiotensin Converting Enzyme (ACE)
  - Conjunctival or lacrimal gland biopsy
  - Serum lysozyme
  - Serum calcium
  - Gallium scan
    - Nuclear medicine test
    - Radioactive gallium citrate is injected
    - Hot spots at site of inflammation
ANA
- antinuclear antibody
- evaluates immune system
- screening test for SLE
  - 95% sensitive but not specific
- normal: nonreactive
- results in 4-5 days

ANA Sensitivity
- SLE- 95%
- Scleroderma- 60-90%
- Rheumatoid arthritis- 41%
- Sjogren’s syndrome- 48%
- JIA with uveitis ñ 80% positive
  - 2/3 with oligoarticular JIA

CBC with differential
- routine part of health care
- inexpensive
- Screening
- Reported
  - RBC count
  - Other indices
  - Hemoglobin
  - Hematocrit
  - Platelets

WBC (Part of CBC)
- Total
  - overall number
  - first line of defense
- Differential
  - 100 white blood cells
  - % of each
  - neutrophils
  - lymphocytes
  - monocytes
  - eosinophils & basophils

ESR
- erythrocyte sedimentation rate
- nonspecific test for inflammation
- mm/hr
- M: age/2
- F: (age+10)/2
- usually > 60 mm/hr in GCA
C-Reactive Protein (CRP)
- abnormal serum glycoprotein produced by liver during acute inflammation
- disappears rapidly once inflammation subsides
- 4 hour fast from food/fluids
- alternative to ESR
- more informative
  - ESR high in most elderly
  - no cross interference
- normal:
  - Qualitative ⨯ negative; Quantitative ⨯ 0-10 mg/L

HLA-B27
- HLA-B27
  - Up to 8% of general population
  - Seronegative spondyloarthropathies
    - AS
    - Reactive arthritis
    - IBD (ulcerative colitis; Crohn disease)
    - Psoriatic arthritis
  - Normal: negative
  - Most useful information

Rheumatoid Factor (RF)
- Positive titers in numerous collagen vascular diseases
- (+) in 70-80% of patients with Rheumatoid Arthritis
- Also (+) with:
  - SLE, Sjögren, TB, sarcoid, viral infection
- Negative finding most useful

p-ANCA
- Perinuclear-Antineutrophil cytoplasmic antibody
- ↑ in Crohn disease
- c-ANCA
  - Vasculitis
- Normal: titer <1:40

Anti-cyclic Citrullinated Peptide Antibody
- Auto-antibody frequently seen in RA
- Allows early diagnosis

Lyme Titer
PPD
- purified protein derivative
- TB skin test
- inject under skin
- check in 48-72 hours
- Normal < 5 mm
  - Redness
  - induration
- Positive for active and inactive

Syphilis Testing
- RPR (rapid plasma reagin)
- VDRL (venereal disease research laboratory)
  - more sensitive than RPR for primary syphilis
- FTA-ABS (fluorescent treponemal antibody absorption)
- MHA-TP (microhemagglutination treponemal pallidum)

Other Diagnostic Procedures
- Radiologic Studies
  - Chest X-Ray
  - Sacroiliac joint
  - Other affected joints
- Anterior chamber tap

Lab Testing in Anterior Uveitis
- Often Freebie if:
  - First occurrence
  - Acute
  - Mild
  - Unilateral
  - Nongranulomatous

No lab testing alsoé
- Evidence of HS, HZ
- Post-operative
- Trauma
- Known systemic disease
- Remember high % are idiopathic

Recommended Initial Lab Tests
Keep in Mind

- Acute, recurrent, unilateral (may be alternating eyes) anterior uveitis 50-80% are spondyloarthropathies
- Look closely for evidence of herpetic infection
- Think sarcoidosis if chronic granulomatous
- Have a suspicion about syphilis
- Refer as appropriate

Anterior Uveitis

- Treatment often straightforward
- Etiology not always so simple
- Look and listen for clues