Anterior Uveitis: Common Infectious and Non-Infectious Etiologies
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Disclosures
• Shire
• B+L (Valeant)
• Allergan
• Glaukos

Outline
• Classification
  – Anatomy
  – Clinical course
  – Histopathology
  – Etiology
• Specific Conditions
  – Non-infectious
  – Infectious
  – Other

Clinical Approach to Uveitis

Classification Based on:
• Anatomy
  • what part of the uveal tract is affected
• Clinical Course
  • Acute
  • Chronic
  • Recurrent
• Histopathology
  • Granulomatous
  • Nongranulomatous
• Etiology
  • Infectious
  • Noninfectious
  • Masquerades
Summary Anatomical Classification

- **anterior uveitis** (iritis, iridocyclitis, and anterior cyclitis)
- **intermediate uveitis** (para planitis, posterior cyclitis, and hyalitis)
- **posterior uveitis** (focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis)
- **panuveitis** (anterior chamber, vitreous, retina, and choroid)

Why Localize the Inflammatory Process?

- The anatomical location of the inflammatory process is one of the most important clues to **pathogenesis** and treatment
  - Anterior
  - Intermediate
  - Posterior
  - Panuveitis

2 Sub-classes of Anterior Uveitis: Differ in Histopathophysiology

**Granulomatous**
- May result from an autoimmune reaction or from the host's immune response to a systemic infectious process
  - Syphilis
  - Lyme disease
  - tuberculosis (TB)
  - local reactivation of herpetic viral infection.

**Non-granulomatous**
- Inflammation of the iris and the ciliary body causes a breakdown of the blood ocular barrier.
- This condition allows both protein and WBCs to extravagate into the aqueous, resulting in the typical iritis signs of cell and flare.
- Typically, but not always, non-infectious

Granulomatous Inflammation

- An inflammatory manifestation of infectious, toxic, allergic, autoimmune and neoplastic origin.
- Characterized by inflammatory cells of the mononuclear phagocyte system that take the form of:
  1. Macrophages
  2. Epithelial cells
  3. Multinucleated giant cells
- Can be an indicator of Chronic Inflammation too!

Clinical Course of the Uveitis

- **Acute** describes the course of specific uveitic syndromes characterized by sudden onset and limited duration
  - Lasts <3 months
- **Chronic** describes persistent duration with relapse <3 month after discontinuation of therapy.
  - Last >3months
- **Recurrent** describes repeated acute episodes separated by periods of inactivity without treatment > 3 months in duration.

Onset

- The **onset** described as sudden or insidious based on history.
  - Sudden
    - Symptoms and clinical signs "suddenly" appear
  - Insidious
    - Slow gradual development of symptoms, signs
    - Sometimes patients are only mildly symptomatic
Duration

- The *duration* of an attack of uveitis:
  - **Limited**
    - ≤ 3 months in duration
  - **Persistent**
    - > 3 months in duration.

International Uveitis Study Group (IUSG) in 2009

- Designed a simplified, *clinical* classification system for uveitis based on *etiological criteria*.

- 3 main categories:
  - **infectious** (eg, bacterial, viral, fungal, parasitic)
  - **noninfectious** (eg, known systemic associations, no known systemic associations)
  - **masquerade** (eg, neoplastic, non-neoplasmic).

What Causes Uveitis?

Based on the International Uveitis Study Group (IUSG) Clinical Classification of Uveitis

- Non-infectious
- Infectious
  - Bacterial
  - Viral
  - Fungal
  - Parasitic
  - Others
- Masquerade (Neoplasmic vs. Non-neoplasmic)
  - Intraocular cells not due to immune mediated uveitis

Assessment vs Impression

- Assessment:
  - anterior uveitis
- Impression:
  - Acute vs Chronic vs Recurrent
  - Unilateral vs bilateral
  - Granulomatous vs non-granulomatous
  - Infectious vs non-infectious vs masquerade

Clinical Approach to Uveitis
Underlying Causes of Anterior Uveitis

Non-Infectious Etiologies

<table>
<thead>
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Masquerades

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<td>Retinitis Pigmentosa (RP)</td>
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<td>Juvenile xanthogranuloma</td>
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HLA-B27

- Human cells and tissues contain surface markers that enable the body to differentiate its own cells from foreign material.
- Genotype located on the short arm of Chromosome 6.
- HLA-B27+ patients have a protein found on white blood cells that stimulate an immune reaction to self.
- Present in 1.4-8.0% of population
- 50-60% of acute or recurrent anterior uveitis, may be HLA-B27 positive.
- Non-granulomatous
- Several autoimmune diseases collectively called seronegative spondyloarthropathies(-RF)
- are strongly associated with both acute uveitis and +HLA-B27.

Most Common Non-Infectious Underlying Etiology for AU

- 50% of acute anterior uveitis (AAU) test +HLA-B27
- AND 50% of HLA-B27+ AAU will go on to develop one of the seronegative arthritides
  - Chronic/Inflammatory Bowel diseases
  - Reiter’s Syndrome (Reactive Arthritis)
  - Ankylosing Spondylitis
  - Psoriatic Arthritis
- 25% who have been dx with HLA-B27 arthritis will develop AAU
- Up to 70% of Caucasian pts with AAU are HLA-B27 positive.
- 1st attack 20-40 yrs of age
- 10% suffer severe visual impairment or blindness
  - Most commonly due to CME

Typical Penotype of HLA-B27-positive AAU

- Sudden onset (Acute)
- Unilateral
  - Often alternating
  - Rarely bilateral
  - Reiter’s the exception
- Non-granulomatous AAU
- More likely to have:
  - fibrin
  - hypopyon
  - Posterior Synechia
- High tendency for recurrences
- Significant association with other HLA-B27-related systemic diseases
- Males more than females

Seronegative Spondyloarthropathies

- Ankylosing Spondylitis
- Reiter’s Syndrome (Reactive Arthritis)
- Chron’s/Inflammatory Bowel diseases
- Psoriatic Arthritis

Seronegative Spondyloarthropathies

- Group of disorders that share many clinical, pathological and immunogenic features
  - Radiographic sacroiliitis with or without accompanying spondylitis
  - Inflammatory asymmetric peripheral arthritis predominantly of lower limbs
  - RF and ANA negative
  - HLA-B27 likely positive
Ankylosing Spondylitis (AS)

- Inflammatory arthropathy most frequently seen in males.
- Early symptoms include lower back pain and stiffness after inactivity (i.e., sleeping) that can progress to severe deformity of the lower back.

www.espine.com

SI x-rays may show sclerosis and narrowing of the joint space.

www.med.mun.ca

- SI x-rays may show sclerosis and narrowing of the joint space.

www.med.mun.ca

The AS Stereotype?

- Onset in young 20-30 yo
- 1% of population
- More in Caucasians
- Male (4:1)
- Acute non-granulomatous Anterior uveitis
- Lower back pain that improves with movement/exercise

Reiter’s Syndrome

Reactive Arthritis

- Classic diagnostic triad:
  1. Arthritis-98%
  2. Urethritis -74%
  3. Conjunctivitis-58%
- Anterior Uveitis in 3-12%
- Etiology is thought to result from infection from Chlamydia, Ureaplasma urealyticum, Shigella, Salmonella, and Yersinia.
  - Arthritis begins within 30 days of infections?
    - Knees, ankles, feet, wrists

What to do if You Suspect AS?

- Labs:
  - HLA-B27
  - ESR
    - But non-specific
- Imaging:
  - X-rays of the SI joints (poor imaging, but the standard)
  - CT or MRI of the SI joints (better, but more costly)
- Referral:
  - Rheumatologist

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### Infection and HLA-B27

- **Non-infectious immune-mediated inflammation**
  - Occurs after infections of the genitourinary or gastrointestinal tract.
  - Reiter’s/Reactive Arthritis
  - Chron’s

- **Bacteria thought to be responsible:**
  - *Salmonella*, *Shigella*, *Campylobacter*, *Klebsiella*, and *Yersinia*, or *Chlamydia trachomatis*.

### How Does Bacteria Cause a Non-Infectious AAU?

- “uveitogenic” peptides from certain bacteria are bound and presented by HLA-B27 to T cells.
- These microbe-derived antigens may trigger CD8+ T-cell immune responses that cross-react with self-tissue antigens (molecular mimicry)
- uniquely found in the uvea or joint tissue, resulting in autoimmune tissue inflammation.


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### Other findings

- Keratoderma blennorrhagicum
- Circinate balanitis
- Plantar fasciitis
- Achilles tendonitis
- Sacroiliitis
- Nailbed pitting
- Palate ulcers
- Tongue ulcers

### Reiter’s/Reactive Uveitis

- Acute, chronic, or recurrent, non-granulomatous AU
- Often bilateral
- Male > females
- 20-40 yo
- Joint deformities
- Urethral discharge

### Inflammatory Bowel Disease

- Includes:
  - Ileo-Colitis (Crohn’s disease)
    - 2.4% will have anterior uveitis
  - Ulcerative Colitis
    - 5-12% will have anterior uveitis
- Symptoms include abdominal pain, diarrhea, weight loss, fever, fatigue, joint pain
- 20% will have sacroiliitis
- 60% will be HLA-B27 positive

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### What to Do if You Suspect Reiter’s?

- **Labs:**
  - HLA-B27 (+ 70-90%)
  - ESR is often elevated
- **ROS:**
  - Classic clinical signs
    1. Urethritis
    2. Arthritis
    3. Conjunctivitis (or Ant Uveitis)
- **Referrals:**
  - Urologist for urethral cultures, urine analysis
  - Rheumatologist for arthritis evaluation and possible imaging of the spine/joints
What to Do if You Suspect Inflammatory Bowel Disease?

- Labs:
  - HLA-B27

- Referrals:
  - Internal Medicine
  - Gastroenterologist

Psoriatic Arthritis

- 7-25%
- acute, chronic, recurrent non-granulomatous anterior uveitis
- Psoriasis with arthritis
- Erythematous hyperkeratotic rash
- Tissue swelling, distal joint inflammation
- Nail bed pitting (ungual changes), discoloration, thickening, cracking, ridging

Psoriatic Arthritis

- Diagnosis made by cutaneous changes, terminal joint inflammation, ungual involvement
- Pts suffer with Conjunctivitis and anterior uveitis
- Psoriasis may precede arthritis by several yrs
- M = F
- 40-50 yo

What to do if You Suspect Psoriatic Arthritis?

- Labs:
  - HLA-B27

- Referrals:
  - Dermatologist
  - Rheumatologist

Ocular Treatment of the Uveitis of +HLA-B27

- Aggressive Topical Steroids
  - Dosing every hour (12-14x/day with pred acetate 1% vs Durezol 4-6x/day)
- Cycloplegics
- HLA-B27 AU recur and can be chronic
  - Recommended a 4 week treatment to lessen relapse
  - Occasionally need oral immunosuppressive agents
    - Salsalazine and methotrexate reduce recurrence?
  - Properly educate patient
- Get systemic work-up
  - Appropriate referral to subspecialty
- We can make the diagnosis of an HLA-B27 related uveitis, but must rely on sub-speciality to confirm condition (ie: CRAP)
  - 50% of HLA-B27+ AAU will go on to develop one of the seronegative arthritis

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Sarcoidosis

- Multisystem granulomatous disease of unknown etiology
- Non-caseating granulomas form in multiple systems
  - composed of epitheloid and giant cells
  - Granulomas secrete ACE

Most commonly characterized by:
- bilateral hilar lymphadenopathy,
- pulmonary infiltration
- dermatological manifestations
- Ocular involvement in 15-50%:
  - Uveitis; Orbital, lid, conjunctival granulomas; dry eye

Sarcoid Presentation

- Inflammation:
  - Chronic iritis in 3-10% of all uveitis cases
    - Uveitis may be acute, recurrent or chronic
  - Posterior uveitis (choroiditis, retinitis), perivasculitis, optic neuritis
  - May be bilateral or unilateral
- Females slightly more than males
- 20-50 years of age, but may occur in children as well
- African American 10-20x more than Caucasians

Lacrimal gland involvement occurs in 15-28% of patients.
- Lacrimal gland involvement
  - painless, bilateral, palpable swelling of the gland.
  - Moderate-to-severe keratitis sicca may result.
- Posterior findings occur in 25-30% of patients with sarcoidosis

You Suspect Sarcoid?

- Exam:
  - Careful evaluation of the conjunctiva and lacrimal glands looking for granulomas/nodules
  - Skin nodules of eyelid, adnexa and systemic
- Labs:
  - Elevated serum lysozyme, ACE levels
- Other:
  - Chest x-ray or CT
  - Gallium scan
  - Tissue biopsy (lungs, lymph nodes, skin nodules, liver, conjunctiva, lacrimal gland)
  - Pulmonary function tests
- Referrals:
  - Internal medicine
  - Pulmonologist
  - Ophthalmology for ocular nodule biopsy
• Cells that make up granulomas secrete large amounts of angiotensin converting enzyme (ACE),
• ACE levels are often high in patients with sarcoidosis.
• ACE levels, however, are not always high in sarcoidosis patients,
  – increased ACE levels can also occur in other illnesses
  • DM, COPD, hyperthyroidism, cancers

Serum ACE Levels

• Combined use of ACE levels with gallium scans increased the diagnostic specificity in cases of clinically active systemic sarcoidosis from 83% to 99% when compared to ACE levels alone.

• CSF ACE levels may be elevated in up to 50% of patients with neuro-sarcoid.

Serum Lysosome

• The sensitivity of lysozyme for predicting sarcoidosis was 79.1% vs 59% with ACE
• Even in the cases without an elevated serum ACE level, a value of 72.1% was obtained.
• The serum lysozyme level demonstrated a significant tendency to increase with the number of organs involved (p < 0.01).

Treatment of Sarcoid

• **Systemic treatment:**
  – steroids are the mainstay
  – NSAIDs may offer some benefit
  – Immunosuppressant agents
    • methotrexate, cyclosporine, and azathioprine

• **Ocular treatment of uveitis:**
  – Topical steroids, cycloplegics
  – Due to chronic and recurrent nature, high risk of steroid complication
    • Cataract, GLC

Infectious Uveitis

• In patients you suspect have an infectious etiology, caution with steroid treatment, especially systemic steroid treatment.

  **WHAT IS ONE OF THE SIDE EFFECTS OF STEROIDS?**
  – Should treat the underlying infection either first or in conjunction with steroids.
  – Rely on lab studies, history, ROS, and the presence of granulomatous uveitis, posterior seg involvement

INFECTIOUS ETIOLOGIES
### Infectious Uveitis

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#### Syphilis

- **Syphilis** is a multisystem, chronic bacterial infection caused by the spirochete *Treponema pallidum*.

- It is associated with multiple ocular manifestations that occur in both the acquired and congenital forms.
- Transmission occurs via sexual contact or transplacental.

### CDC Primary and Secondary Syphilis 2016

- **In US**
  - 2000: 2.1 cases per 100,000
  - 2011: 4.5 per 100,000
  - 2013: 5.3 per 100,000
  - 2016: 7.2 per 100,000
- **Louisiana (1st)**
  - 16.1 per 100,000
- **Alaska (50th)**
  - 1.1 per 100,000
- **Illinois (ranked 9th of 50 States)**
  - 9.8 per 100,000
- **Wisconsin**
  - 2.3 per 100,000
- **Minnesota**
  - 5.6 per 100,000
- **District of Columbia**
  - 24.0 per 100,000

**Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2016**

- **Primary and Secondary Syphilis**
- **Early Latent**
- **Total Syphilis**

**Note:** Data reference: syphilis began in 1941; however, syphilis became nationally notifiable in 1944. Data on the National Notifiable Disease Surveillance System (NNDSS) website: https://wwwn.cdc.gov/nndss/conditions/syphilis/.
Primary and Secondary Syphilis — Rates of Reported Cases by State, United States and Outlying Areas, 2016

*NOTE:* The total rate of reported cases of primary and secondary syphilis for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 8.7 per 100,000 population.

Primary and Secondary Syphilis — Rates of Reported Cases by County, United States, 2016

In 2016, 1,699 (54.1%) of 3,140 counties in the United States reported no cases of primary and secondary syphilis. Refer to the NCHHSTP Atlas for further county-level rate information: [https://www.cdc.gov/nchhstp/atlas/](https://www.cdc.gov/nchhstp/atlas/).

Primary and Secondary Syphilis — Distribution of Cases by Sex and Sexual Behavior, United States, 2016

- Accounts for 1-2% of uveitis cases, but is considered the great masquerader
- Three stages of infections:
  - Primary, secondary, latent progressing to tertiary

Syphilis

Primary Syphilis

- The predominant lesion of primary syphilis is a chancre at the inoculation site.
- Chancres — erythematous papules at the inoculation site that later erode to form painless ulcers.
- The lesions appear 4 weeks after the initial infection and heal spontaneously in 1-2 months.

Primary Syphilis

- After *T. pallidum* penetrates the skin or mucous membrane, the organism enters the lymphatics and blood stream and disseminates shortly after contact.
- If left untreated, primary syphilis leads to secondary syphilis.
Secondary Syphilis

- The systemic treponemal load is largest in secondary syphilis.
- Generalized maculopapular (or pustular rash), and lymphadenopathy are the characteristic lesions in this stage.
- These lesions appear 4-10 weeks after the initial manifestation.

Secondary Syphilis

- Constitutional symptoms of fever, malaise, headache, nausea, anorexia, and joint pains often are present.
- The liver, kidneys, and/or GI tract may or may not be involved.
- Ocular involvement has been reported in 10% of cases, and cerebrospinal fluid (CSF) pleocytosis has been seen in a few cases.

Latent Syphilis

- Early Latent
  - Occur within 1 year after initial infection,
- Late Latent
  - After 1 year of the initial infection
- Most cases have been reported to stay at the latent stage with 30% converting to the tertiary stage.

Tertiary Syphilis

- 3 sub-groups:
  - Benign tertiary
    - Presents with gummatous lesions that are actually granulomas histologically; in the skin and the mucous membranes, the choroid, ciliary body, and iris
  - Cardiovascular
    - Presents with involvement of the coronary arteries or the aorta.
  - Neurosyphilis
    - Manifest with tabes dorsalis or general paresis
    - CNS is affected via the vascular pathways or via direct involvement of parenchyma.

Ocular Syphilis

- Rarely occurs before 6 months after the primary infections
- Most ocular involvement occurs during the secondary, latent or tertiary stages
- Uveitis may be acute, chronic or recurrent
  - Usually granulomatous, but may also be non-granulomatous

Making the Diagnosis

- Labs:
  - Non-treponemal serology tests
    - RPR or VDRL
      - Are antibodies present for treponema pallidum?
      - Indicate disease activity by quantifying amount of anticondrin antibody in serum
        - Reactive or nonreactive at dilutions of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, etc.
        - 50-75% can be nonreactive in early primary syphilis (<3 weeks)
        - 100% reactive 4+ weeks after exposure, secondary, early latent
        - Can be negative in late syphilis
    - Most often used as a screening test
Making the Diagnosis

- Labs:
  - Treponemal serology tests
    - FTA-ABS or MHA-TP
      - Reactive or nonreactive
    - Will test positive after primary infection indicating either active or past infection
- Referrals:
  - Internal medicine and/or infectious disease

Treatment for Syphilitic Uveitis

- Must determine what stage the infection is in before determining treatment:
  - Congenital:
  - Primary, secondary, or early latent:
    - Single dose IM PCN
  - Late Latent or tertiary:
    - IM PCN weekly x 3 doses
  - Neurosyphilis:
    - IV PCN q6hrs for 10-14 days
- Using oral steroids without PCN may lead to exacerbation of the disease!

Review

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
<th>Uveitis Present?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Chancer</td>
<td>No</td>
</tr>
<tr>
<td>Secondary</td>
<td>Rash, Lymphadenopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Latent</td>
<td>No evidence of systemic disease</td>
<td>Yes, most common</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Cardiovascular syphilis, neurosyphilis, benign tertiary syphilis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Foster CS. Diagnosis and treatment of uveitis

Infectious Uveitis

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Fungi</th>
<th>Parasites</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
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<td>Histoplasmosis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ocular necardiosis</td>
<td>West Nile Virus (WNV)</td>
<td>127</td>
<td></td>
<td></td>
</tr>
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<td>Bartonella ramsakae</td>
<td>Adenovirus</td>
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Tuberculosis

- Granulomatous infection caused by *Mycobacterium tuberculosis*
- Primarily affect the lung, but may affect other systems (eye).
  - The bacterium likes highly oxygenated structures!
• 3 TB cases/100,000
• 67.1% were non-US born

• Ranked 16th among 50 States in TB rates (2.7/100,000)
• 86% of TB cases were non-US born

The Natural History of TB Infection

Exposure to TB

Non-Infection (70-90%)

Infection (10-30%)

Dormant TB (90%) well - never develop TB - NOT infectious

Active TB (10%) ill - 5% develop TB within 2 years - 5% develop TB many years later

Untreated - 50% die within 2 years

Tuberculosis In The Lung

A person may contract pulmonary tuberculosis from inhaling droplets from a cough or sneeze by an infected parent

Graduates in Lung Rate
Ocular Involvement

- May be due to active infection or immunologic reaction to the organism
  - Scleritis
  - Phlyctenulosis
  - interstitial keratitis
  - granulomatous uveitis (anterior and/or posterior)

Making the Dx of Tuberculosis

- Labs:
  - PPD (Purified Protein Derivative) skin test
    - Positive indicates exposure
    - Does not tell you if there is active infection
  - Interferron gamma/QuantiFerron
    - Used for those who have previously tested positive
  - Chest x-ray
  - Bacterial culture or PCR
- Referral:
  - Internal medicine and/or infectious disease

Treating TB

- Systemic treatment
  - Initial 2-month combination course:
    - Isoniazide (INH), rifampin, and pyrazinamide daily. Ethambutol is added in more resistant TB.
  - Continuation phase for an additional 4-7 months with isoniazide and rifampicin
  - For latent TB, 6-9 mos of isoniazide
- Ocular treatment:
  - Steroids ideally post-systemic treatment or in conjunction with systemic therapy

Infectious Uveitis

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| Lyme Disease   | Cytomegalovirus (CMV)                                                 | Aspergillosis                                                            | Diffuse unilateral subacute necrotizing retinopathy (DUSN)
| Endopitheliozis| Epstein-Barr virus (EBV)                                              | Cryptococcosis                                                          |                |
| Leptospirosis  | Rabesla                                                                | Coccidioidomycosis                                                      |                |
| Ocular         | West Nile Virus (WNV)                                                 | Coccioidomycosis                                                        |                |
| Nocardiosis    |                                                                      |                                                                          |                |
| Bartonella     | Adenovirus                                                             |                                                                        |                |
| henselae       |                                                                      |                                                                        |                |
| Moronucleosis  |                                                                      |                                                                        |                |
| Influenza      |                                                                      |                                                                        |                |

Lyme Disease

- Bacterial infection caused by the *Borrelia burgdorferi* spirochete and spread via tick bites.
- Animal reservoirs: deer, horses, cows, rodents, birds, cats, dogs.
- 8.2/100,000
- Men > females
- 2 age groups:
  - 5-14yo
  - 25-50yo
- Peak time for infection: May-August
- In most cases, the tick must be attached for 36 to 48 hours or more before the Lyme disease bacterium can be transmitted.

CDC by State

**Fact Facts**

- In 2014, 4% of confirmed Lyme disease cases were reported from 5 states:
  - Connecticut
  - New Jersey
  - Delaware
  - New York
  - Maine
  - Florida
  - Maryland
  - Rhode Island
  - Massachusetts
  - Vermont
  - Minnesota
  - Virginia
  - New Hampshire
  - Wisconsin

Lyme disease is the most commonly reported vector-borne illness in the United States. In 2014, it was the fifth most common notifiable vector-borne disease, whereas this disease does not occur nationwide and is concentrated heavily in the northeast and upper Midwest.
Reported cases of Lyme disease are most common among those aged 5-15.

Lyme disease cases by age and sex–United States, 2001-2010

Lyme Disease by Month

From left to right, an Ixodes scapularis larva, nymph, adult male tick, and adult female tick.

Illustrative examples of culture-confirmed erythema migrans.

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3 Stages of Lyme Disease

- **Stage 1:**
  - Macular rash (erythema migrans) at the site of the tick bite.
  - Within 2-28 days in 60-80%.
  - Rash may take “Bull’s Eye” pattern.
  - Symptoms:
    - Fever, malaise, fatigue, myalgias, arthralgias.

- **Stage 2:**
  - Occurs weeks-months following exposure where the spirochete spreads to the skin, CNS, joints, heart, and eyes.
  - Neurological involvement in 30-40% (meningitis, encephalitis, Bell’s Palsy).
  - Ocular include anterior, posterior, intermediate and pan uveitis.
  - 25% of new onset Bell’s is from Lyme.

- **Stage 3 or persistent disease**
  - Occurs 5 or more months after the infection.
  - Multiple cranial nerve involvement (II, III, IV, V, VI, VII).
  - Keratitis is most common ocular finding in stage 3 followed by episcleritis.

Lyme Disease

- **Stage 2:**
  - Occurs weeks-months following exposure where the spirochete spreads to the skin, CNS, joints, heart, and eyes.
  - Neurological involvement in 30-40% (meningitis, encephalitis, Bell’s Palsy).
  - Ocular include anterior, posterior, intermediate and pan uveitis.
  - 25% of new onset Bell’s is from Lyme.

Clinical Manifestations of Confirmed Lyme Disease Cases—United States, 2001-2010

- **Centers:** 1%
- **Meningitis/Encephalitis:** 13%
- **Arthralgia:** 13%
- **Bells Palsy:** 9%
- **Erythema Migrans:** 9%

This figure represents the breakdown of reported Lyme disease cases from 2001 to 2010 by disease manifestation. The majority of cases are the erythema migrans (EM) rash. Other manifestations are less common, some patients have more than one manifestation.

Recommended antimicrobial regimens for treatment of patients with Lyme disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day*</td>
<td>50 mg per kg per day divided q6h up to 500 mg 3 times per day</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day*</td>
<td>Not recommended for children age 8 years or less. Use doxycycline 200 mg/day in adults and 100 mg/day in children 8 years of age and older</td>
</tr>
<tr>
<td>Carbampenem</td>
<td>500 mg twice per day</td>
<td>500 mg per kg per day divided q6h up to 5000 mg per day</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously every 12 hours</td>
<td>2 g intravenously every 12 hours in children 2-18 years of age. Use 500 mg intravenously every 12 hours in children 0-2 years of age</td>
</tr>
<tr>
<td>Penicillin</td>
<td>500,000 U q6h</td>
<td>500,000 U q6h for children 0-12 years of age</td>
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</tbody>
</table>

*Although a higher dosage given twice per day might be equally as effective, in view of the severity of disease or efficacy, multiple administrations is not recommended.


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If you Suspect Lyme…

- Labs:
  - Lyme (IFA) immunosorbent assay
  - ELISA
  - Western blot series
  - PCR
- Systemic treatment:
  - Doxycycline except in children or pregnant
    - Adults: 100 mg bid for 10-21 days
    - Kids over 8 years old: 4 mg/kg per day bid with max of 100 mg per dose
  - Amoxicillin in kids, pregnant
    - Adults: 500 mg bid for 14-21 days
    - Kids: 50 mg/kg per day bid with max dose of 500 mg/dose
  - Cefuroxime axetil
    - Adults: 500 mg bid 14-21 days
    - 50 mg/kg per day bid with max dose of 500 mg per dose
- Ocular Treatment:
  - Topical steroids for uveitis after or in conjunction with systemic treatment

Infectious Uveitis

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<tr>
<th>Infectious</th>
<th>Etiology</th>
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Most Common Infectious Underlying Etiology for AU

- Viral Etiologies
  - HSV & VZV = up to 10%
  - CMV
    - HIV negative: 22.8% of AU associated with raised IOP*
  - Rubella
    - Fuch’s Heterochromia Iridocyclitis

Clinical Features of Viral AU?

- May vary depending on the Virus
- 50-90% of all types of viral AU:
  - Elevated IOP
  - Iris atrophy
  - KP
  - Unilateral

HSV and VZV Clinical Features

- Corneal scars
- Corneal hypo-aesthesia
- Sectoral iris atrophy
- Elevated IOP
- KP
  - Can be granulomatous, but usually smaller KP (non-granulomatous)
  - Located centrally or in Arlt’s Triangle
  - Medium to fine KP have been seen
- Often confused with Posner–Shlieosman syndrome (PS5)
### Comparison of Herpetic Uveitis

**HSV**  
- **Location:**  
  - 61% anterior with keratitis  
  - 20% without keratitis  
- **Type:**  
  - Non Granulomatous 80%  
  - Granulomatous 20%  
- **Course:**  
  - Acute: 11%  
  - Chronic: 18%  
  - Recurrent: 71%  
- **Iris Atrophy:** 41%  
- **Unilateral vs. Bilateral:** 82:18  

**VZV**  
- **Location:**  
  - 58% anterior with keratitis  
  - 17% without keratitis  
- **Type:**  
  - Non Granulomatous: 96%  
  - Granulomatous: 4%  
- **Course:**  
  - Acute: 20%  
  - Chronic: 42%  
  - Recurrent: 38%  
- **Iris Atrophy:** 25%  
- **Unilateral:** 100%  
- **Past h/o zoster**

### Treatment of HSV Uveitis

- **Topical Steroids**  
  - ie: 1% prednisolone acetate ophthalmic suspension QID  
- **Concurrent anti-viral!!**  
  - Viroptic® (1% trifluridine ophthalmic solution) QID  
  - Zirgan® (ganciclovir ophthalmic gel) 0.15% QID  
  - **oral anti-viral (**preferred**)**  
    - Valacyclovir 500mg BID  
    - Acyclovir 400-800mg 5x/day  
    - Less ocular toxicity with oral antivirals  
    - contraindications (pregnancy).  
- **Cycloplegic agents**  
- **Long-term/Chronic oral antivirals to reduce recurrence rates.**  
  - Year or more of tx

### Subgroup HEDS Study: The Role of Oral Acyclovir

- **45% decrease in recurrence in ALL forms of HSV (epithelial, stroma, iridocyclitis)**  
- Effect was best demonstrated in patients with multiple recurrences  
- **NO decrease in incidence of changing to stromal HSV**  
- **NO effect acutely but decreased recurrence**

### Treatment of zoster (HZV/VZV) Uveitis

- **Anti-viral therapy**  
  - valacyclovir (Valtrex)  
  - Acyclovir  
- **Steroids helpful, but relapses high if not treated concurrently with anti-virals**  
- **Control IOP**  
  - up to 90% have high IOP  
  - **How to lower IOP?**

### Anti-Viral Dosing?

- **HEDS* interpretation for active ocular disease:**  
  - *acyclovir, 400 mg five times per day  
  - valacyclovir, 1000 mg twice per day  
  - famciclovir 250 mg three times per day.  
- **Maintenance/prophylaxis to reduce recurrence:**  
  - acyclovir, 400 mg twice per day  
  - valacyclovir, 500 mg daily.

### Treatment of zoster (HZV/VZV) Uveitis

- **Treat Inflammation**  
- **Treat with Antivirals**  
- **Control IOP**  
  - up to 90% have high IOP  
  - **How to lower IOP?**  
  - Can I use a PGA?
Will PGA Re-activate HSV?

- **Purpose:**
  - To determine the reactivation rate of HSV keratitis for pts treated with PGA
- **Results:**
  - the rate of HSV was 0.11%
  - Similar rate to normal population (0.15%)
  - No correlation with an increased risk from the use of PGA.

References:

CMV AU Features

- Patchy or diffuse iris atrophy
- No posterior Synechiae
- Posterior Segment is usually spared
  - Different clinical presentation from CMV retinitis which occurs in immunocompromised pts.
- Thought to be an underlying cause of PSS

References:

Treatment of CMV Uveitis

- Studies comparing oral and topical ganciclovir
  - 75% of pt treated with orals responded BUT 3 out of 4 relapsed
  - 66% responded to topical ganciclovir
  - 25% of chronic recurred
- Recommendation:
  - Topical ganciclovir for suspected CMV AU in combination with topical steroids

References:
Rubella Anterior Uveitis

- KP
  - Fine, diffuse, stellate KP
- Diffuse Iris Atrophy and/or Heterochromia
- No PAS
- PSC
- Vitritis
- Posterior Seg involvement
  - Sectorial peripheral retinal vascular leakage
  - CME
  - Disc hyperfluorescence on FA.
- AKA: Fuch’s Heterochromia Uveitis

Treatment for Rubella Uveitis

- Respond poorly to steroids.
- Primary goal is to control IOP and prevent loss of vision
  - Glaucomatous optic atrophy
  - PSC
    - CE/IOL
    - CME risks

Recommendation

- A virus cause should be suspected in cases of unilateral anterior uveitis with iris atrophy and elevated IOPs
- Judicious use of corticosteroids if aqueous analysis (PCR) is not available.
- Concurrent anti-virals is appropriate and recommended

Thank You!

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