Uveitis is the third leading cause of blindness in developed nations and accounts for 10-20% of blindness worldwide. Annual incidence of uveitis varies between 17 to 52 cases per 100,000 persons per year. Prevalence data suggest that uveitis may be found in up to 714 per 100,000 persons. While all age groups are affected, the peak onset occurs between 20 and 40 years of age, among working individuals, potentially greater personal and economic impact from visual loss than that of many age-related diseases.

Uveitis may be infectious or non-infectious, and is often associated with underlying systemic conditions. Specific diagnosis is of critical importance so that antimicrobial therapy is initiated when appropriate. Neoplastic disease is excluded or appropriately referred. Anti-inflammatory therapy is commenced for both ocular and systemic inflammatory disease.

Uveitis was initially considered a single disease entity. Approach to treatment varied little. Immunologic and microbiologic testing became more sophisticated. Though some diseases are local ocular immune phenomena, majority are systemic diseases with ocular manifestations. Pathogenesis of uveitis ranges from autoimmunity to neoplasia to viruses.
Several diseases are clinical diagnoses and require little laboratory analysis. Laboratory tests are rarely useful as screening tools. Knowledge of pretest probability is helpful:

- Avoids false positive results
- Avoids costly and unnecessary tests

Diagnostic test is only useful if it can confidently rule in or rule out a disease.

Laboratory testing for ocular inflammatory disease is frequently a challenge. The myriad of tests available, the complexities of their interpretation, and the underlying concern that one may miss an important systemic disease all play a role. Laboratory testing, although important, is not a substitute for a thorough history and physical examination of any patient with ocular inflammation:

- Obtaining an accurate and detailed history is the single most valuable tool in establishing a diagnosis of uveitis
- No amount of laboratory testing can compensate for an incomplete or inaccurate history

Laboratory testing is to identify etiology in order to direct specific treatment for the patient’s condition:

- i.e. Tuberculous uveitis should not be treated with corticosteroids alone

Identify associated systemic disease:

- such as the patient with tubulointerstitial nephritis and uveitis with elevated urinary β-2 microglobulin levels

Provide valuable prognostic information even when treatment is not influenced by the diagnosis:

- Knowing that a patient has HLA-B27-associated uveitis allows the clinician to counsel the patient about the likelihood of recurrent disease and vision loss.

Purpose of lab testing is to identify etiology in order to direct specific treatment for the patient’s condition.

- i.e. Tuberculous uveitis should not be treated with corticosteroids alone

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Provide valuable prognostic information even when treatment is not influenced by the diagnosis:

- Knowing that a patient has HLA-B27-associated uveitis allows the clinician to counsel the patient about the likelihood of recurrent disease and vision loss.

SUN:

- Disease is classified based on onset, duration, and course
- Onset of inflammation is considered either sudden or insidious
- Duration is divided into limited (≤3 months) and persistent (>3 months)
- Disease course can be described as acute, recurrent, or chronic
  - Acute anterior uveitis refers to an episode of sudden onset and limited duration
  - Recurrent uveitis describes repeated episodes of uveitis with periods of quiescence off all treatment for more than 3 months
  - In chronic uveitis, a patient is not free of inflammation for longer than 3 months while off treatment

SUN Descriptors of Uveitis:

<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden</td>
</tr>
<tr>
<td></td>
<td>Insidious</td>
</tr>
<tr>
<td>Duration</td>
<td>Limited ≤ 3 months</td>
</tr>
<tr>
<td></td>
<td>Persistent &gt; 3 months</td>
</tr>
<tr>
<td>Course</td>
<td>Acute: episode characterized by sudden onset and limited duration</td>
</tr>
<tr>
<td></td>
<td>Recurrent: repeated episodes separated by periods of inactivity without treatment ≤ 3 months in duration</td>
</tr>
<tr>
<td></td>
<td>Chronic: persistent uveitis with relapse in &gt; 3 months after discontinuing treatment</td>
</tr>
</tbody>
</table>

Classification:

- In 2005, the world’s major uveitis societies initiated a standardization of nomenclature process
- This project, termed SUN (Standardization of Uveitis Nomenclature), established language for describing the presentation, chronicity, anatomic location, and severity of uveitis and its response to treatment

### SUN Working Group for Anatomic Classification of Uveitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Primary Site of Inflammation</th>
<th>Includes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Uveitis</td>
<td>Anterior Chamber</td>
<td>Iritis, Anterior cyclitis, Iridocyclitis</td>
</tr>
<tr>
<td>Intermediate Uveitis</td>
<td>Vitreous</td>
<td>Focal, multifocal, or diffuse choroiditis, Retinoschisis, Retinal Neovascular.</td>
</tr>
<tr>
<td>Posterior Uveitis</td>
<td>Retina or Choroid</td>
<td>Posterior cyclitis, Hyalitis, Focal, multifocal, or diffuse choroiditis, Retinoschisis, Retinal Neovascular.</td>
</tr>
<tr>
<td>PanUveitis</td>
<td>Anterior chamber, vitreous, and retina or choroid</td>
<td></td>
</tr>
</tbody>
</table>

### Anterior Uveitis
- The most common form of uveitis
- Accounts for approximately 90% of all uveitis cases seen by general OD/MD
- May present with a wide range of symptoms
  - Their severity may vary with the underlying etiology, abruptness of onset, and tolerance of the patient
- Pain is often localized to the eye, but also can be referred to the periorbital region, forehead, or temple
- Blurred vision may be seen in cases of severe inflammation with fibrin or with reactive cystoid macular edema (CME)

### Intermediate Uveitis
- Defined as intraocular inflammation that predominantly involves peripheral retina, pars plana, and vitreous
- Patients typically present with painless blurred vision and floaters
- Photophobia and redness are not common
- May have mild to moderate anterior segment inflammation
- Anterior vitreous cells are present
- White clumps of inflammatory cells (snowballs) and whitish yellow exudate (snowbanking)

### Review of Systems
- The review of systems is essential in developing a differential diagnosis for uveitis and utilizes an extensive review from a patient questionnaire, supplemented by direct questioning
- Items of particular importance include:
  - History of oral or genital ulcers
  - Tinnitus or hearing loss
  - Headaches
  - Malaise
  - Chronic cough
  - Shortness of breath
  - Recent weight loss or gain
  - Fever, chills, or night sweats
  - Recent contact with individuals with known tubercular disease
  - Diarrhea or blood in the stool
  - Skin rashes
  - Arthritis (axial or peripheral)
  - High-risk sexual activities
  - Ingestion of game meats
  - Undercooked meats, or tainted water supplies
  - Presence and types of pets
  - Insect bites
  - Recent foreign travel

### Intermediate Uveitis
- Has an association with several systemic disorders
  - Initial diagnostic evaluation should exclude masquerade syndromes and infectious diseases
  - Diagnostic approach should focus on history and clinical exam

### Review of Systems
- It is important to observe the patient’s overall health, noting in particular signs such as pallor and nutritional status
- Examination of the skin, joints, and oral mucosa, as well as auscultation of the lungs and heart can be valuable in formulation of the differential diagnosis
- By the end of the initial interview, you should have a reasonably complete differential diagnosis in mind before examining the patient
Demographic information

- Certain types of uveitis or more common in particular age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Juvenile idiopathic arthritis</th>
<th>Toxocariasis</th>
<th>Post-viral</th>
<th>Retinoblastoma</th>
<th>Juvenile idiopathic arthritis</th>
<th>Toxocariasis</th>
<th>Post-viral</th>
<th>Retinoblastoma</th>
<th>Juvenile idiopathic arthritis</th>
<th>Toxocariasis</th>
<th>Post-viral</th>
<th>Retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 Years</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>5-15 Years</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
<td>Juvenile idiopathic arthritis</td>
<td>Toxocariasis</td>
<td>Post-viral</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>16-35 Years</td>
<td>HLA-B27 associated</td>
<td>Herpetic</td>
<td>HLA-B27 associated</td>
<td>IOL-associated uveitis</td>
<td>HLA-B27 associated</td>
<td>Herpetic</td>
<td>HLA-B27 associated</td>
<td>IOL-associated uveitis</td>
<td>HLA-B27 associated</td>
<td>Herpetic</td>
<td>HLA-B27 associated</td>
<td>IOL-associated uveitis</td>
</tr>
<tr>
<td>&gt;65 Years</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

- Consideration of gender, race, and ethnicity also useful when considering diagnosis
- Ankylosing spondylitis is more common in males
- Pauciarticular juvenile idiopathic arthritis (JIA) is more frequent in females
- Occupation may provide clues to infectious etiologies
- Slaughterhouse workers, butchers, veterinarians, and farmers may be exposed to tissues or milk products infected with Brucella
- Medical workers are at risk for tuberculosis, herpes simplex, HIV
- Current and past residences and recent travel
- A history of tick bites or traveling in wooded areas, particularly in endemic regions such as Connecticut or Wisconsin, raise possibility of Lyme disease
- Individuals residing in the southwestern United States, Mexico, or Central and South America may be exposed to coccidioidomycosis
- Leprosy should be considered in immigrants from developing regions

Ophthalmic Examination

- Evaluate Anterior Segment for:
  - Presence of scleritis
  - Presence of keratitis
  - Presence, distribution, and qualitative characteristics of KP
  - SUN scoring of anterior chamber cell and flare
  - Anterior and posterior synechiae
  - Lens opacity or lens precipitates
  - Vitreous haze score (standardized Nussenblatt scheme)

SUN Working Group Grading Scheme for Anterior Chamber - Cells

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cells in 1mm x 1mm slit beam</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>0.5+</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>1+</td>
<td>1-5</td>
</tr>
<tr>
<td>2+</td>
<td>6-15</td>
</tr>
<tr>
<td>3+</td>
<td>16-25</td>
</tr>
<tr>
<td>4+</td>
<td>26-50</td>
</tr>
</tbody>
</table>

SUN Working Group Grading Scheme for 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 but iris details clear</td>
</tr>
<tr>
<td>3+</td>
<td>Marked, iris details hazy</td>
</tr>
<tr>
<td>4+</td>
<td>Intense, plasmoid aqueous</td>
</tr>
</tbody>
</table>
Keratic Precipitates

- KP's are the most common corneal findings in anterior uveitis
- Consist of clusters of inflammatory cells that accumulate on the corneal endothelium, frequently in a triangular configuration (Arlt's triangle) base down
- Two types of KPs have been described clinically:
  - Non-granulomatous
    - Typically white or slightly pigmented and round in appearance
    - More commonly found over the middle and lower cornea (Fuchs' Heterochromic – diffuse)
  - Small to medium-sized KP are more common in acute non-granulomatous inflammation and are usually composed of lymphocytes.

Granulomatous
- These deposits are large, with irregular margins, and located on the middle and lower cornea
- They have a greasy appearance, and may coalesce
- Mutton-fat KPs are large collections of macrophages that typically occur in granulomatous inflammation
- The presence of mutton-fat KPs and iris nodules is strong evidence of a granulomatous inflammatory response

Forming the Differential

- Following the history and examination, a differential diagnosis should be established, which will guide the laboratory testing
  - Using anatomic location, onset, severity, pattern, duration, clinical pathology, patient demographics, and associated features will help guide testing
- An acute, severe non-granulomatous iridocyclitis in a 25-year-old white patient with morning back pain
  - Diagnosis of ankylosing spondylitis very likely
- 80-year-old patient who is experiencing an insidious, mild, chronic vitritis for the first time
  - Not likely to have an autoimmune process, but more likely have a malignancy or infection

Statistical Analysis

- The diagnostic evaluation is the final step in establishing a diagnosis
  - The approach is to select tests that have a high predictive value based on a likely diagnosis or narrow differential diagnosis
  - Lab analysis utilizes Bayesian statistics
  - Sensitivity is the probability a test will be positive if the patient has disease
  - Specificity is the probability a test will be negative if the patient does not have disease
  - Prevalence is the pretest probability in the patient’s population that he or she has the disease
    - Positive predictive value (PPV, the probability that the patient has disease if the test is positive)
    - Negative predictive value (NPV, the probability that the patient does not have disease given a negative test)

Laboratory Testing Guidelines

- There are no evidence-based guidelines for testing for uveitis
- First episodes of acute anterior uveitis, especially if mild, unilateral, non-granulomatous, and responsive to topical corticosteroids probably do not require diagnostic evaluation unless there is evidence for an underlying etiology
  - Diagnostic testing for first episodes of uveitis should be obtained when there is a high index of suspicion regarding an underlying cause
    - the inflammatory response appears granulomatous
    - or the inflammation fails to respond to therapy within a reasonable time
    - Diagnostic evaluation is also recommended for all patients with recurrent or chronic inflammation
  - There is no "standard" uveitis workup
    - The workup must be custom tailored for each patient depending on history, features of disease presentation, and risk factors
### Laboratory Testing Guidelines
- Testing need not be completed in one session.
- High-probability and high-morbidity diseases can be assessed initially, with less common conditions tested only if the initial workup is unrevealing.
- The evaluating doctor should order the appropriate laboratory tests rather than referring patients to their primary care provider or rheumatologist for a workup.
  - They are typically not familiar with the differential diagnosis of ocular inflammatory diseases, leading to incomplete workup and frustration for patients and physicians.

### Syphilis
- Caused by Treponema pallidum.
  - Spirochete that cannot be cultured under normal conditions.
- Mainstays of testing are direct and indirect treponemal antibody tests.
  - The direct tests are seroconversion markers (i.e., once a patient has been exposed to syphilis, these markers remain forever positive).
    - Fluorescent treponemal antibody (FTA-ABS).
    - Treponema pallidum particle agglutination assay (TPPA).
    - Microhemagglutination assay (MHA-TP).
- Direct tests are more useful for ruling out syphilis than establishing the diagnosis.

### Syphilis
- Indirect treponemal antibody tests vary with disease load and become undetectable in fully treated disease.
  - Rapid plasmin reagent (RPR).
  - Venereal Disease Research laboratory (VDRL).
- Recommend a direct treponemal test first, and if positive, follow by one of the indirect tests.
- Patient with positive FTA-ABS / TPPA and positive RPR or VDRL test results has active syphilis necessitating treatment.
- Patient who is FTA-ABS/TPPA positive and RPR or VDRL negative:
  - Previously treated syphilis.
  - False-positive FTA-ABS.
  - Latent syphilis.
  - Neurosyphilis.

### Laboratory Testing Guidelines
- Several nonspecific tests prove worthwhile:
  - Complete blood count (CBC) with differential.
    - Identifies systemic infection (with leukocytosis), parasitic infection (with eosinophilia), leukemia, or certain immunocompromised states.
  - Metabolic panel.
    - Renal or hepatic dysfunction and undiagnosed hyperglycemia.
    - Results essential for initiating therapy with oral corticosteroids or steroid-sparing medications.
  - Non-specific tests of inflammation, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
    - Rarely of utility in the diagnosis of uveitic disease.

### Syphilis
- Several newer modalities of testing for syphilis are now available.
- Commercial testing for anti-syphilis IgG, has lower false-negative and false-positive rates than indirect testing.
  - If syphilis IgG is negative, patient is not exposed to disease.
  - If syphilis IgG is positive, follow with RPR; if RPR is negative, check TPPA or FTA-ABS.
- Polymerase chain reaction (PCR) diagnostics are capable of detecting Treponema pallidum DNA in order to make a diagnosis from biopsy specimens (such as vitreous).
Syphilis

- Ocular syphilis cases increased from 2014 to 2015 in most jurisdictions studied, according to a surveillance report published November 4 in the *Morbidity and Mortality Weekly Report*.
- The investigators also recommend that all patients with inflammatory eye disease of unknown cause be tested for syphilis, regardless of risk factors.

Tuberculosis

- Tuberculosis (TB) is endemic in most of the world
  - More than 2 billion people have been infected with *Mycobacterium tuberculosis* (mTB)
  - Difficult to culture in laboratory
  - Definitive diagnosis only through observation of mTB
    - on biopsy material with acid fast stains
    - PCR amplification of mTB DNA
  - Often necessary to resort to indirect means
  - Chest X-rays may be normal in up to 15%

- The tuberculin skin test (TST) is the mainstay of diagnosis worldwide:
  - Mantoux test
  - Purified protein derivative (PPD)
  - To be read 48 hours after intradermal administration of the protein derivative:
    - Extent of induration
    - >5 mm are positive
    - ≤5 mm induration are negative
    - Intermediate values (5 to 30 mm)
  - Most positive PPD tests are not associated with active disease but will reflect exposure or latent disease
  - Millions of false positive due to *Bacille Calmette-Guerin Vaccine*

  - Interferon gamma release assays (IGRAs)
    - QuantIFERON TB-Gold test
    - T-SPOT TB test
    - Peripheral blood leukocytes are purified and mixed with a very specific set of mTB peptides that do not include Bacille Calmette-Guerin (BCG) vaccine cross-reacting proteins
    - Sensitivity is comparable to the TST and specificity is higher due to loss of BCG cross-reactivity
    - Considerably more expensive than TST testing

- Chest x-ray is a useful adjunct to skin testing
- However, it is important to recognize that most cases of uveitic TB from paucibacillary or miliary disease are not accompanied by pulmonary disease
  - A negative chest x-ray in the setting of positive PPD and suspicious disease (e.g., serpiginoid uveitis or panuveitis) does not rule out TB
  - Such cases can be problematic since treatment commits the patient to 9 months or more of a multidrug regimen with significant potential toxicity
  - In such cases, it is worth obtaining vitreous biopsy for PCR

- Diagnostic gold standard for sarcoidosis is the histopathologic identification of noncaseating, non-necrotizing granulomas
- Optimal testing unclear
  - core diagnostic test remains the chest x-ray
  - Radiographic evidence of hilar adenopathy or interstitial fibrosis necessitates referral to a pulmonologist for pulmonary function tests, bronchoscopy, or mediastinoscopy
Sarcoidosis

- Several serum enzyme or electrolyte tests have limited utility in the diagnosis of sarcoidosis
  - ACE test measures serum concentration of this enzyme produced by macrophages
    - present in higher levels in patients with a high systemic granuloma load
  - Studied for ocular sarcoidosis un uveitis patients
    - 84% sensitivity and 95% specificity
    - PPV only 47%
    - NPV even lower
  - Because ACE levels are not specific for sarcoidosis, a positive test never makes the diagnosis

- Serum lysozyme
  - PPV 12%

- Urinary 24 hour calcium testing
  - result of elevated levels of 1,25 dihydroxyvitamin D3 produced by macrophages in sarcoid granulomas

- Although the utility of these indirect tests for sarcoidosis is extremely limited, their diagnostic accuracy improves substantially when combined with positive imaging studies such as chest radiography or high-resolution chest CT

Lyme Disease

- Caused by the spirochete bacterium Borrelia burgdorferi
- Geography is a dominant feature
  - Lyme risk varies corresponding to the habitat of its vector (ticks of the Ixodes genus)
    - highest probabilities in the Northeast and northern Midwest
    - minimal disease in the mountain states
- Serologic testing, with screening ELISA followed by confirmatory Western blot screening, is the mainstay of diagnosis
- A significant proportion of certain populations have previous exposure to Lyme
  - Ex ~6% of outdoor workers in New Jersey are seropositive for Lyme exposure

- PCR diagnostics are capable of detecting Borrelia burgdorferi
  - sensitivity and specificity of this test for ocular disease remain unknown

Human Leukocyte Antigen Testing

- Human leukocyte antigen disease
  - HLA – disease associations are simply associations between a major histocompatibility complex molecule, and a clinical condition
  - Testing for HLA can provide supportive evidence for a particular diagnosis but cannot make a definitive diagnosis
  - Statistically it is the increased frequency of an HLA haplotype in persons with that disease, as compared to the frequency in a disease free population
  - The ratio of these two frequencies is the “relative risk”

- Ocular disease associations with HLA Testing
  - HLA-B27  HLA-A29
  - HLA-B51  HLA-DRB1*0102
  - HLA-A*02:101:01:02N
- Human leukocyte antigen disease associations
  - HLA-B27
  - HLA-A29
  - HLA-B51
  - HLA-DRB1*0102
  - HLA-A*02:101:01:02N

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- Ocular disease associations with HLA Testing
  - HLA-B27  HLA-A29
  - HLA-B51  HLA-DRB1*0102
Approximately 50% of acute anterior uveitis cases are associated with HLA-B27.

- Prevalence of this allele in the general United States population is about 8%.
- False-positive rate of 8%.
- HLA-B27 is not a single allele but a family of at least 31 different alleles that encode for HLA-B27 subtypes.
- HLA-B2701 to HLA-B2728.
- There is a varied distribution of these HLA-B27 subtypes in different populations.
- Accounts for the varying strengths of HLA-B27-disease association observed in different ethnic groups.

HLA-B27 positivity is associated with a number of presumed autoimmune diseases (seronegative spondyloarthropathy):

- Ankylosing spondylitis.
- Reactive arthritis.
- Psoriatic arthritis.
- Inflammatory bowel disease.

Acute, unilateral, sudden onset, non-granulomatous, anterior uveitis, particularly with hypopyon, is characteristic of HLA-B27-positive uveitis.

- Tendency towards recurrent attacks and more severe inflammation, including hypopyon formation.
- Males are affected more frequently than females.
- 2.5:1.
- 20-40 years of age.
- Patients should be questioned carefully for history of:
  - Axial arthritis.
  - Lower back stiffness and pain (worse on waking).
  - Sacroiliac films can be diagnostic of ankylosing spondylitis.
  - Relatively low sensitivity.
  - A positive review of systems should prompt referral to a rheumatologist for workup.

Strongly associated with Birdshot chorioretinitis:

- Bilateral multifocal choroiditis typically associated with visual field loss, reduced electroretinogram, and cystoid macular edema.
- Occurs nearly exclusively in patients who are HLA-A29 positive.
- Negative test for A29 makes this diagnosis exceedingly unlikely.
- A29 also has an allele frequency of about 8%.
- False positives are relatively common.

Other HLA correlations with inflammatory eye diseases:

- HLA-B7, DR15 - Presumed Ocular Histoplasmosis Syndrome.
- HLA-DQW7 Bw62, DR4 - Acute Retinal Necrosis.

- Association with HLA alleles is only relative risk factor.
  - Indicates a higher probability of developing disease.
  - Not a definitive diagnostic marker.

HLA-B51 is associated with an approximately 6-fold increased relative risk of Behcet’s Disease.

- The allele is found in only 39% of Behcet’s Disease vs. 18% control.
- Positive test does not prove disease nor does a negative test rule out disease.
Rheumatologic diseases are commonly associated with acute anterior uveitis, scleritis, and retinal vasculitis. The mainstay of testing is serology and radiographic analysis when indicated. Approximately 37% of patients with anterior scleritis will have serology suggestive of collagen vascular disease. Primarily rheumatoid arthritis (RA) definitive diagnosis of RA requires documentation of the arthritic component of disease. Serologic evidence can provide strong support.

Rheumatoid Factor, RF (an anti-IgG antibody) sensitivity of 0.28 specificity of 0.88 making the test more useful for ruling out disease than confirming it. Falsely positive in: Sjögren syndrome, Chronic viral infection, Hepatitis, Systemic lupus erythematosus.

ACPA (anti-citrullinated protein antibody test) has been more recently used as a biomarker for rheumatoid arthritis due to greater specificity. Positive predictive value is ~65% Negative predictive value is ~92%.

Chronic anterior uveitis frequently associated with juvenile idiopathic arthritis (JIA) typically bilateral and asymptomatic. Associated with very high rates of complications. Most commonly associated with the pauci-articular form of JIA (fewer than 5 joints involved). Majority of these patients will have positive antinuclear antibody (ANA) titers, but negative rheumatoid factor.

Granulomatosis with polyangiitis GPA (formerly Wegener granulomatosis), a systemic vasculitis, is an uncommon cause of scleritis, retinal vasculitis, and orbital inflammatory disease. The cytoplasmic anti-neutrophil cytoplasmic antibody, or cANCA is positive in most patients with WG. The pANCA test (anti-myeloperoxidase) is associated with the other systemic vasculitides. Both tests are commonly ordered in scleritis because of the very high morbidity and mortality of these systemic vasculitides if left untreated.

Systemic lupus erythematosus (SLE) can cause scleritis and retinal vasculitis. Testing is more problematic. SLE is a clinical diagnosis based on 11 diagnostic criteria. Only 1 of 11 is a lab test (ANA). Approximately 5% of the population is ANA-positive at moderate titer. Anti-dsDNA is more specific. Only 0.5% of the population positive at baseline. ~60% of patients with SLE. Anti-histone antibodies are also relatively specific for SLE. Patient suspected of having SLE based on systemic findings should be referred to a rheumatologist for evaluation.
Rheumatologic Disease

- Tubulointerstitial nephritis and uveitis (TINU) syndrome
  - It consists of interstitial nephritis, which can be drug-related, infection-related or idiopathic, and bilateral symptomatic anterior uveitis
  - Usually seen in children and young adults, with a female to male ratio of 3:1
  - It is probably an underdiagnosed disorder
  - Ocular symptoms generally follow renal involvement in most patients, but can also precede or occur simultaneously
  - The long-term prognosis is good in most cases
  - Screened for by urinalysis and urinary beta-2-microglobulin
    - This protein, which is the coreceptor for HLA class 1, spills into the urine in patients with interstitial nephritis
    - A positive result warrants referral to a nephrologist for possible renal biopsy and to help guide therapy.

There are no standard diagnostic criteria for TINU

- The diagnosis is one of exclusion, after conditions known to cause interstitial nephritis and uveitis are ruled out
- Bilateral anterior uveitis, with or without intermediate or posterior findings, is the most common clinical presentation
- Ocular inflammation can develop anytime from less than 2 months before or 12 months after the onset of acute interstitial nephritis.

Testing for Viral Disease

- Serology is of little value unless negative
  - Most patients have had exposure—therefore likely seropositive
- Viral cultures have very poor yield and slow to return results
- Detection of local antibody or viral DNA has improved diagnostic yield
- Goldmann-Witmer Coefficient (GWC)
  - Measurement of ratio of aqueous to systemic antibody titers
  - More common in Europe
  - Replaced by PCR testing for viral DNA

Testing for Viral Disease

- Polymerase Chain Reaction (PCR)
  - Biochemical technique for creating analytical quantities of nucleic acids from small starting quantities
  - Incapable of distinguishing active vs. latent infections
  - Capable of detection of fewer than 10 copies of viral DNA from aqueous or vitreous
  - Quantitative real-time PCR will provide titer-like data on amounts of viral DNA in samples
Testing for Parasitic Disease

- Need to be considered in differentials, but mostly for a few well-defined scenarios
  - Retinochoroiditis with dense vitritis and choroidal scars
  - Ocular toxoplasmosis
  - Unilateral panuveitis, peripheral granuloma, epiretinal traction to optic nerve
    * Ocular toxocariasis
  - Insidious, progressive unilateral vision loss, focal loss of RPE
  - Diffuse Unilateral Subacute Neuroretinitis (DUSN)
  - Caused by nematodes

Testing for Parasitic Disease

- Serologic testing has different roles
  - 30% of Americans are seropositive for Toxoplasma gondii
  - Negative serology effectively rules out disease
  - Definitive diagnosis of T. gondii made either by GWC or PCR of vitreous
  - Toxocara canis and Toxocara catis not routinely tested in US
  - Older literature suggests 25% of children in US have positive titers
  - Cases of negative serum titers but positive ocular titers have been seen
  - Therefore, negative serology does not rule out toxocariasis

Testing for Parasitic Disease

- DUSN
  - Caused by nematodes Baylisascaris procyonis and Ancylostoma caninum
  - Similar syndromes worldwide (India and southeast Asia)
  - Many nematodes cause phenotypically similar disease, and negative serologic titers do not rule out disease

Testing for Masquerade Syndromes

- Most cases of uveitis are infectious, auto-immune, or auto-inflammatory in nature
- Must be vigilant for occasional masquerade syndrome
  - Intraocular lymphoma (adults)
  - Head MRI
  - Lumbar puncture
  - Vitreous biopsy
  - Retinoblastoma with vitreous seeding (children)
  - Clinical appearance (leukocoria)
  - Imaging (B-scan, CT)

Additional Testing

- A few clinical presentations of uveitis suggest specific testing
  - Pars planitis or intermediate uveitis
    * Insidious onset uveitis primarily affecting vitreous cavity
    * Inferior Pars plana snowbank
    * In addition to sarcoidosis, syphilis, and TB
    * Must have high clinical suspicion of demyelinating disease
      * Present in 15-20%
      * MRI of brain needed if neurologic symptoms elicited during history
  - Neuroretinitis in one or both eyes is typical for cat scratch disease
  - Serological testing is confirmatory and helps guide proper antibiotic therapy
  - More challenging to test for panuveitis
    * Bechet disease, VKH, sympathetic ophthalmia, multifocal choroiditis
      * All clinically defined syndromes without clear etiologies
      * Diagnosis cannot be made through lab testing
    * White dot syndromes including acute posterior multifocal placoid pigment epitheliopathy (APMPEP), serpiginous choroiditis, punctate inner choroidopathy, relentless plaid choriretinitis, and multiple evanescent white dot syndrome
      * Do not have specific tests to establish these diagnoses
      * Lab testing is used to rule out an infectious and other similar etiologies
Case Study

• TD, 38 year old white male
• Referred to me by his PCP
• Patient complains of:
  • Redness, pain, photophobia OD x 6 days
  • Tobramycin QID not effective
• Reports unremarkable medical and ocular history
• Entering VA 20/20 OD, OS
• PERRL

Case Study, Day 1

• Slit lamp exam
  • 3+ cell OD, fine KP
  • Minimal injection
  • IOP 12 mm OD, OS
• Fundus exam
  • Unremarkable OU
• Diagnosis: ??

• Plan
  • Start Pred Forte Q1H OD
  • FML ointment QHS OD
  • Atropine 1% daily OD
  • RTO x 1 day

Case Study, Day 2

• Patient slightly more comfortable
• VA 20/20 OD, OS
• Pupils: Dilated OD
  • 2+ to 3 cell, fine KP
• IOP 13 mm OU

• Continue current treatment: RTO x 3-4 days
• Blood work requested

Case Study, Day 7

Rescheduled visit for Day 5
Significant improvement in signs and symptoms
Discontinued atropine, starting tapering steroid

Case Study

• Blood work
  • CRP: normal
  • ESR: normal
  • ANA: negative
  • RF: normal
  • Lyme serology: normal
  • HLA B27: ??

• Resubmitted for blood draw

Blood test results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>normal</td>
</tr>
<tr>
<td>ESR</td>
<td>normal</td>
</tr>
<tr>
<td>ANA (Anti-nuclear antibody)</td>
<td>negative</td>
</tr>
<tr>
<td>RF (Rheumatoid factor)</td>
<td>normal</td>
</tr>
<tr>
<td>Lyme serology</td>
<td>normal</td>
</tr>
<tr>
<td>HLA B27</td>
<td>??</td>
</tr>
</tbody>
</table>

HLA B27: HLA-B27 is a genetic marker associated with various autoimmune diseases, including ankylosing spondylitis. The result of HLA B27 in this case is unknown (?).
**Next steps**

- Recommend establishing relationship with subspecialist
- Educate patient on potential chronic, recurrent nature
- Long term options with recurrences?
  - Anecdotal evidence that Restasis may have some benefits in preventing or reducing frequency of recurrences
  - Topical cyclosporine A 0.05% for recurrent anterior uveitis
  - Prabhu SS, Shtein RM, Michelotti MM, Cooney TM
  - Poster Presentation ASCRS 2014

**Case Example**

- 64 yo WF referred for high pressure
  - C/O blurred vision, dry eye, photophobia, pain and redness for approx. 9 months
  - Was seen 2 weeks ago and was told has high eye pressure, approx 31, and needs additional follow up because not coming down
  - Was seen by retina and referring OD
  - Inquired why seeing Retina. Stated had an injection in OS month prior for bleeding, thinks AMD
  - Initially referred for blurry vision OS

**Case Study**

- Best corrected VA
  - 20/30 OD, 20/25 OS
- Pupils, EOM’s, CVF – WNL
- SLE
  - L/L – Cl OU
  - Conj – Cl OU
  - Cornea – band keratopathy OU
  - AC – 2+ cell DU
  - Iris – Cl OU no synechiae
  - Lens – 1+ NS OU
  - Ta OD 32, OS 22
- C/D - OD .45/.45, OS .4/.4
- Macula
  - OD: ERM, Thickening
  - OS: Thickening
- Vitreous: 1+ cell OD, Tr cell OS, Ig floaters OD
- Periphery – White spots OD>OS
First time I have seen the patient, but was very suspicious for underlying systemic etiology
- Bilateral Panuveitis (Anterior and posterior segments involved)
- Secondary increase in intraocular pressure
- Retinal involvement
- CME
- Multifocal Choroiditis

Although currently seeing a retinal specialist, they were treating OS, and I felt her OD was much worse
- Also felt the swelling they were treating her for was not AMD

Plan
- Started Pred Forte and Cosopt, back for full GLC workup
  - Ran labs with a high suspicion for Birdshot Chorioretinopathy
    - Spoke w retina Dr and told them my suspicion and what I was doing
    - CBC, HLA-A29, HLA-B27 (low risk), RA, ACPR, cANCA, pANCA, FTA-ABS
    - No hx of exposure to Lyme or TB, wrong demographic for Sarcoid
- Came back positive for HLA-A29
  - Sent to Rheumatology and started on CellCept, which has controlled her ocular inflammation and helped bring her IOP down, and reduce retinal swelling
  - Follow up with retina for continued tx of CME
Conclusion

- Lab work should be guided by a thorough patient history, clinical exam, and review of systems
- Always remember diseases with significant systemic ramifications
  - Tuberculosis, syphilis, Sarcoidosis, Lyme Disease
- Most patients with unexplained uveitis should undergo lab workup
- Very few lab tests for uveitis are definitive
  - Most are supportive
  - Be vigilant for false positive results
  - Consider retesting if disease does not follow anticipated course

Thank you

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