PROGRAM AGENDA

1:00 – 2:00 p.m.  **Update on Pseudotumor Cerebri Syndrome** –
Thomas J. Whittaker, JD, MD, Professor, Department of Ophthalmology, University of Kansas Medical Center

2:00 – 4:00 p.m.  **Anterior Uveitis: Common Infectious and Non-Infections Etiologies** – Dominick Opitz, O.D., F.A.A.O., Illinois College of Optometry, Chicago, IL

4:00 – 5:00 p.m.  **Detecting Functional Change in Progressing Glaucoma** –
Paul Munden, MD, Associate Professor, Department of Ophthalmology, University of Kansas Medical Center
Update on Pseudotumor Cerebri Syndrome
Thomas J. Whittaker MS JD MD

Financial Disclaimer
• I have no financial interest in any matter discussed in this presentation.

Update on Pseudotumor Cerebri Agenda
• Revised classification scheme
• Revised diagnostic criteria
  – With/without presence of papilledema
  – Opening pressure on LP—adults vs children
• Initial results of IIHTT—Idiopathic Intracranial Hypertension Treatment Trial
  – Diet and Diamox vs Diet and Placebo in treatment of IIH

Revised Classification and Diagnostic Criteria for PTCS
• New Classification—Umbrella Term “Pseudotumor Cerebri Syndrome” (PTCS) includes both
  – Primary Pseudotumor Cerebri
  – Secondary Pseudotumor Cerebri
• New criteria for diagnosis
  – “Same old/same old” modified Dandy criteria for cases with papilledema
  – New criteria for cases without papilledema
• New terminology: no longer benign idiopathic intracranial hypertension


Classification: Primary PTC
Primary pseudotumor cerebri—same old/same old
  – “Idiopathic intracranial hypertension (IIH)”
  • Includes patients with obesity, recent weight gain, polycystic ovarian syndrome, and thin children
  – Meets modified Dandy criteria of papilledema, normal neuroimaging, elevated intracranial pressure on LP, and normal CSF

Classification: Secondary PTC
• Cerebral venous abnormalities
  – Cerebral venous sinus thrombosis
  – Bilateral jugular venous thrombosis or surgical ligation
  – Middle ear or mastoid infection
  – Increased right heart pressure/Superior vena cava syndrome
  – Arteriovenous fistulas
  – Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage
  – Hypercoagulable states
• Medical Conditions
  – Endocrine disorders
    – Addison disease
    – Hyperparathyroidism
    – Hypercapnia
    – Sleep apnea
    – Pickwickian syndrome
    – Anemia
  – Renal failure
  – Turner syndrome
  – Down syndrome

• Medications
  – Antibiotics: Tetracycline, minocycline, doxycycline, sulfasalazine, sulfa drugs
  – Vitamin A and retinoids: Hypervitaminosis A, isotretinoin, all-trans retinoic acid for promyelocytic leukemia, excessive liver ingestion
  – Hormones: Human growth hormone, thyroxine (in children), leuprorelin acetate, levonorgestrel (Norplant system), anabolic steroids
  – Withdrawal from chronic corticosteroids
  – Lithium
  – Chlordecone
**Revised Criteria for Diagnosis**

A. Papilledema

B. Normal neurologic examination except for cranial nerve abnormalities

C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used

D. Normal CSF composition

E. Elevated lumbar puncture opening pressure (>250 mm CSF in adults and >280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture

A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

**Revised Diagnosis Criteria Without Papilledema**

In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if:

1. B–E from above are satisfied, and
2. In addition the patient has a unilateral or bilateral abducens nerve palsy

In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if:

1. B–E from above are satisfied, and
2. In addition at least 3 of the following neuroimaging criteria are satisfied:
   - i. Empty sella
   - ii. Flattening of the posterior aspect of the globe
   - iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
   - iv. Transverse venous sinus stenosis

**Initial results of the IIHTT**

Idiopathic Intracranial Hypertension Treatment Trial: a multicenter, double-blind, randomized, placebo-controlled study of acetazolamide in subjects with mild visual loss.

Subjects had to meet the modified Dandy criteria for IIH, be aged 18-60, and have:

1. reproducible mild visual loss (~2 to ~7 dB perimetric mean deviation [PMD]),
2. bilateral papilledema,
3. elevated CSF opening pressure,
4. be untreated with regard to IIH, and
5. no secondary cause of increased intracranial pressure present.

**IIHTT Initial Results**

- 38 sites in North America enrolled 161 women and 4 men from March 2010 to November 2012 with follow up ending June 2013.
- Randomized to supervised diet either with acetazolamide or matching placebo
- Study drug–acetazolamide 250 mg, two tabs twice a day, with dosage increase of one tab/week up to 4 grams daily
- Subjects evaluated at screening, baseline, and 1,2,3,4,5, and 6 months after baseline

Study method details may be found in JAMA 311(16):1641-51 (2014).

**Baseline Symptoms in IIHTT**

![Baseline Symptoms in IIHTT](image)
Baseline Visual Field Defects in the \textit{IIHTT}

<table>
<thead>
<tr>
<th>Classification</th>
<th>Study Eye Total</th>
<th>Neuraxis Eye Total</th>
<th>Total Eyes Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed scores: Blind fields (90°)</td>
<td>172</td>
<td>744</td>
<td>916</td>
</tr>
<tr>
<td>With and without an enlarged optic disc (BH)</td>
<td>172</td>
<td>744</td>
<td>916</td>
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<tr>
<td>IIH without IIH defects</td>
<td>74</td>
<td>175</td>
<td>249</td>
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<tr>
<td>IIH without IIH defects</td>
<td>30</td>
<td>59</td>
<td>89</td>
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<tr>
<td>Observed dry eye</td>
<td>5</td>
<td>5</td>
<td>10</td>
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<tr>
<td>Other</td>
<td>30</td>
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<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>127</td>
<td>152</td>
</tr>
</tbody>
</table>

Table 2. Visual field defects in the IIHTT at baseline.

IIHTT results: PMD improvement

Figure 4. Results of pointwise linear regression show generalized improvement across the visual field.

Summary

- Classification scheme has changed:
  - Umbrella term is Pseudotumor Cerebri Syndrome
  - Good of PTC is now IIH or Primary PTC
  - Secondary PTC associated with various medications, medical conditions and venous abnormalities
- Diagnostic criteria changed a little
  - Good of PTC—same modified Dandy criteria
  - Note opening pressure—25 cm adults, 28 in children
  - PTCS without papilledema: different criteria require 6th nerve palsy or MRI abnormalities
- IIHTT initial results
  - Diamox works in larger doses, is safe, and well tolerated
  - Risk for treatment failures
  - Role for surgery/cerebral sinus stenosis stenting not yet evaluated

WHAT HAVE WE LEARNED FROM THE IIHTT:

1. Acetazolamide in IIH patients with mild visual loss produces a modest improvement in PMD over six months, much greater with moderate to high grade papilledema.
2. Acetazolamide has its greatest effect on visual field function and papilledema in the first month of escalating dosage.
3. Acetazolamide plus diet patients lost twice as much weight as placebo-plus-diet patients.
4. Risk factors for treatment failure: presence of high grade papilledema, lower ETDRS visual acuity measures at baseline, being Caucasian male. Treatment with the maximally tolerated dosage of acetazolamide appears to substantially reduce the risk of reaching IIHTT criteria of treatment failure.
5. IIH patients on acetazolamide as the only diuretic do not need potassium supplementation.
6. Perimetry performance failures were common—Dr. Keltner’s “bad hair days”—so repeat HVFs if it doesn’t make sense.
7. Perimetric mean deviation is an excellent measure for follow-up.

Resources:


Anterior Uveitis: Common Infectious and Non-Infections Etiologies

Dominick L. Opitz, O.D., F.A.A.O.
Associate Professor of Optometry
Senior Director, Ophthalmology Services and Practice Development
Illinois College of Optometry

Disclosures

• Shire
• B+L (Valeant)
• Allergan
• Glaukos

Outline

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

CASES

Clinical Approach to Uveitis

CLASSIFICATION OF 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)

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

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

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

What Causes Uveitis?

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

- Non-infectious
  - Infectious
    - Bacterial
    - Viral
    - Fungal
    - Parasitic
    - Others
  
  - Masquerade (Neoplastic vs. Non-neoplastic)
    - 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

Presentation Points
- The condition
  - Signs, symptoms, etiology
- The type of uveitis
  - Acute, chronic, recurrent
  - Granulomatous vs non-gran
- The typical work-up
  - Labs
- Referrals
  - Who to best manage the systemic disease
- Treatment
  - Systemic
  - Ocular

Infectious Uveitis

Non-Infectious Etiologies

Masquerades

Underlying Causes of Anterior Uveitis

D. Opitz, O.D., F.A.A.O.
Non-Infectious Etiologies

**Acute**
- HLA-B27
- Ankylosing Spondylitis
- Reiter’s
- Inflammatory Bowel (Colitis, Crohn)
- Psoriatic Arthritis
- Lupus
- Wegener’s
- Polyarthritis
- Uveitis
- Fuchs’ Heterochromia
- Lens associated (phacolytic)
- Trauma and post-operative
- Drug induced (Ribabutin, Cidfovir)
- Juvenile Rheumatoid Arthritis (JRA)
- Juvenile Idiopathic Arthritis (JIA)
- Behcet’s
- Vogt-Koyanagi Harada Disease (VKH)
- Sarcoid
- Sympathetic Ophthalmia
- Idiopathic

**Chronic**
- Auto-immune Diseases
- Sarcoid
- Behcet’s
- JRA
- JIA
- VKH
- Sympathetic Ophthalmia
- Idiopathic

**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 spondylarthropathies (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 arthritis
    - CRAP
    - Chron’s/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
- 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

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

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.

Ankylosing Spondylitis

- Inflammation of the sacroiliac joints is the classic sign
  – the spinal column is also frequently involved.

Seronegative Spondyloarthropathies

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

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

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

www.espine.com

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

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

Reiter’s Syndrome

- 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

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.

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

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

Inflammatory Bowel Disease

- Includes:
  - Ileo-Colitis (Crohn's disease)
    - 2.4% will have anterior uveitis
  - Ulcerative Collitis
    - 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

What to Do if You Suspect Inflammatory Bowel Disease?

- Labs:
  - HLA-B27
- Referrals:
  - Internal Medicine
  - Gastrointerologist

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
    - Sulfasalzu and methotrexate reduce recurrence?
  - Properly educate patient
- Get systemic work-up
  - Appropriate referral to subspeciality
- We can make the diagnosis of an HLA-B27 related uveitis, but must rely on sub-specialty to confirm condition (ie: CRAP)
  - 50% of HLA-B27+ AAU will go on to develop one of the seronegative arthritis

Non-Infectious Etiologies

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>HLA-B27</td>
<td>Auto-immune Diseases</td>
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<tr>
<td>Ankylosing Spondylitis</td>
<td>Lupus</td>
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<td>Reiter’s</td>
<td>Wegner’s</td>
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<td>Inflammatory Bowel (Collitis, Crohn)</td>
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<td>Psoriatic Arthritis</td>
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<td>Tubulointerstitial Nephritis</td>
<td>Fuch’s Heterochromia</td>
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<td>Glaucomatocystic Crisis</td>
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<td>Trauma and post-operative</td>
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<td>Drug induced (Ribabutrin, Cidfovir)</td>
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<td>Sarcoidosis</td>
<td>Sympathetic Ophthalma</td>
</tr>
<tr>
<td>Idiopathic</td>
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</tbody>
</table>

Sarcoidosis

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

Sarcoid Presentation

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

Sarcoidosis

- Inflammation:
  - Chronic iritis in 3-10% of all uveitis cases
  - Uveitis may be acute, recurrent or chronic
  - Posterior uveitis (chorioretinitis, 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

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).
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

<table>
<thead>
<tr>
<th>Infection</th>
<th>Viral</th>
<th>Fungal</th>
<th>Parasitic</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>Herpes Simplex virus (HSV)</td>
<td>Histoplasmosis</td>
<td>Toxoplasmosis</td>
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<tr>
<td>Tuberculosis</td>
<td>Varicella-zoster virus (VZV)</td>
<td>Candidiasis</td>
<td>Toxocariasis</td>
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<td>Lyme Disease</td>
<td>Cytomegalovirus (CMV)</td>
<td>Aspergillosis</td>
<td>Cysticercosis</td>
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<td>Endophthalmitis</td>
<td>Epstein-Barr virus (EBV)</td>
<td>Cryptococcosis</td>
<td>Diffuse unilateral subacute retinitis (DUSR)</td>
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<td>coccidioidomycosis</td>
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<td>Ocular necrotizing</td>
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<td>Mononucleosis</td>
<td>Influenza</td>
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</table>

**Syphilis**

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

**CDC Primary and Secondary Syphilis**

- In US:
  - 2000: 2.1 cases per 100,000
  - 2011: 4.5 per 100,000
  - 2013: 5.3 per 100,000
- In Illinois (ranked 9th of 50 States)
  - 8.2 per 100,000
- In CA (2nd)
  - 9.3 per 100,000
- Georgia (1st)
  - 10.3 per 100,000
- District of Columbia
  - 26.6 per 100,000
- Wyoming (50th)
  - 0.2 per 100,000
- Kansas (41st)
  - 1.9 per 100,000

- It is associated with multiple ocular manifestations that occur in both the acquired and congenital forms.

- Transmission occurs via sexual contact or transplacental.
Syphilis

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

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 bloodstream 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 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 anticardiolipin 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 wks)
    - 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:
    - IV penicillin
  - Primary, secondary, or early latent:
    - Single dose IM PCN
  - Late Latent or tertiary:
    - IM PCN weekly x 3 doses
  - Neurosyphilis:
    - IV PCN q4hrs 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>
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<th>Viral</th>
<th>Fungal</th>
<th>Parasitic</th>
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<td>Lyme Disease</td>
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<tr>
<td>Oropharyngitis (CMV)</td>
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<td>Aspergillus</td>
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<tr>
<td>Endophthalmitis</td>
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<tr>
<td>West Nile Virus (WNV)</td>
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<tr>
<td>Bartonella henselae</td>
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<td>Mononucleosis</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!
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
  - interferon gamma/QuantiFerron
    - Used for those who have previously tested PPD
  - Chest x-ray
  - Bacterial culture or PCR

- Referral:
  - Internal medicine and/or infectious disease

• 86% of TB cases in 2014 had known HIV status at TB diagnosis.
• All TB patients should have counseling and testing for HIV infection

Treating TB

- Systemic treatment
  - Initial 2-month combination course:
    - Isoniazide (INH), rifampin, and pyrazinamide daily.
    - Ethambutol added in more resistant TB.
  - Continuation phase for an additional 4-7 months with isoniazide and rifampin
  - 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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<td>Rubella</td>
<td>coccidioidomycosis</td>
<td>Choriocarcioma</td>
<td></td>
</tr>
</tbody>
</table>

| Ocular nocardiosis | West Nile Virus (WNV) |
| Bartonella henselae | adenovirus |
| | meningococcal |
| | 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:
  - 5-14 yo
  - 25-50 yo
- 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

<table>
<thead>
<tr>
<th>Fast Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2014, 46% of confirmed Lyme disease cases were reported from Florida.</td>
</tr>
<tr>
<td>Connecticut</td>
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<tr>
<td>Delaware</td>
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<tr>
<td>Maine</td>
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<tr>
<td>Maryland</td>
</tr>
<tr>
<td>Massachusetts</td>
</tr>
<tr>
<td>Minnesota</td>
</tr>
<tr>
<td>New Hampshire</td>
</tr>
</tbody>
</table>

Lyme disease is the most commonly reported vectorborne illness in the United States. In 2014, it was the fifth most common nationally reportable disease. However, the disease does not occur nationwide and is concentrated heavily in the Northeast and upper Midwest.
From left to right, an Ixodes scapularis larva, nymph, adult male tick, and adult female tick.

Illustrative examples of culture-confirmed erythema migrans.

Reported cases of Lyme disease are most common among those aged 5–15.

Lyme disease cases are most often detected from June through October; a smaller but steady increase occurs from December through March.

The graph displays the number of reported cases of Lyme disease from 1995 through 2014.

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

---

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis/Encephalitis</td>
<td>586</td>
</tr>
<tr>
<td>Bell’s Palsy</td>
<td>249</td>
</tr>
</tbody>
</table>
| Arthritis | 84%

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 uncommon; 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 adult</th>
<th>Dosage for child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day*</td>
<td>25 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg once per day</td>
<td>2 mg/kg per day</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg once per day</td>
<td>25 mg/kg every 12 hours</td>
</tr>
<tr>
<td>Intravenous regimens</td>
<td>For recommended dosing regimens see table 3</td>
<td>For recommended dosing regimens see table 3</td>
</tr>
<tr>
<td>Oral regimens</td>
<td>For recommended dosing regimens see table 3</td>
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<tr>
<td>Intravenous regimens</td>
<td>2 g intravenously once per day in a single dose intermittent for 14 days</td>
<td>2 g intravenously divided every 8 hours for 14 days</td>
</tr>
<tr>
<td>Oral regimens</td>
<td>2 g intravenously divided every 8 hours</td>
<td>100-200 mg/kg divided every 8 hours for 14 days</td>
</tr>
<tr>
<td>Penicillin</td>
<td>18-36 million units per day divided every 6 hours</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Clinical Infectious Diseases Society of America</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Although a higher dosage given twice per day may be equally effective, it poses the risk of adverse effects; no studies have been conducted in children on twice-a-day regimens.*
Recommended therapy for patients with Lyme disease.

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/day
  - Cefuroxime axetil
    - Adults: 500 mg bid 14-21 days
    - 30 mg/kg per day bid with max dose of 500 mg.
- Ocular Treatment:
  - Topical steroids for uveitis after or in conjunction with systemic treatment

Infectious Uveitis

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<td>Onchocerciaasis</td>
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<td>VZV</td>
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<tr>
<td>Bartonella henselae</td>
<td>Adenovirus</td>
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<tr>
<td>Microsporidiosis</td>
<td>Mononucleosis</td>
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<td>Influenza</td>
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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 Ants’ Triangle
  - Medium to fine KP have been seen
- Often confused with Posner-Schlossman syndrome (PSS)
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
  - Famciclovir, 500 mg three times per day
- Maintenance/prophylaxis to reduce recurrence:
  - Acyclovir, 400 mg twice per day
  - Famciclovir, 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.


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


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

Rubella Anterior Uveitis

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

Is it Possible to Differentiate Between Infectious and Non-Infectious KP?

- In vivo confocal microscopy
  - Classify KP based on appearance
    - Globular
    - Infiltrating
    - Infectious
  - Smooth-rounded
  - Granulomatous
  - Stippled
  - Dendritiform
  - **more common in infectious uveitis
  - **Sensitivity/specificity=84% and 93%

**REFERENCES:**

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!

dopitz@ico.edu
Detecting Functional Change in Progressing Glaucoma.

Guided Progression Analysis (GPA)

Paul M Munden, MD MBA
Associate Professor
University of Kansas Department of Ophthalmology

Glaucoma

- Many different conditions having in common a characteristic optic neuropathy usually associated with a higher than normal intraocular pressure.

Glaucoma: Diagnosis

- Characteristic optic nerve changes on clinical examination
- Characteristic Nerve Fiber Layer (NFL) changes on optic nerve OCT (structure)
- Characteristic field loss on automated perimetry (functional)

Glaucoma: Diagnosis

- Clinical examination
  - Increased vertical cup to disc ratio
  - Focal notching and rim thinning
  - ISNT guideline
  - Concentric increase in cup to disc ratio
  - Disc hemorrhage

Glaucoma: Diagnosis

- Nerve Fiber Layer Changes
  - Thinning or loss of NFL in characteristic locations

Glaucoma: Diagnosis

- Visual Field Loss
  - Correlation to NFL anatomic structure
  - Arcuate Defects
  - Nasal Step
  - Cecocentral scotoma (LTG)
Glaucoma: Diagnosis

- Automated Perimetry
- Humphrey Visual Field Analyzer
- Stat PAC
- Single Field Analysis

Glaucoma: Progression

- NFL loss is irreversible and permanent
- Untreated or inadequately treated glaucoma will progress
- Goal is to lower IOP to a level sufficient to prevent further damage
- Monitor and test patient at regular intervals to detect progression or confirm stability

Untreated Glaucoma: Visual Disability

- Population Survey
  - St. Lucia, West Indies
  - 10 year resurvey
  - 205 untreated glaucoma patients and suspects
  - 16% progressed to blindness in at least 1 eye
  - 9% progressed to blindness in both eyes
  - More than 50% that progressed to end-stage had minimal or no visual field loss at baseline

Treated Glaucoma: Visual Disability

- Retrospective Study
- Olmstead County, MN
- 20 year follow-up
- 295 newly diagnosed treated patients.
  - IOP not optimally controlled
- Probability of blindness after 20 years (Kaplan-Meier)
  - BCVA 20/200 or worse, <20 degrees visual field
  - One eye - 27% (95% CI 20-33%)
  - Both eyes - 9% (95% CI 5-14%)


Glaucma: Detecting Progression

- **Structural** Changes from Baseline
  - Serial Disc Photography
  - Visual Inspection
- Serial Optic Nerve OCT
  - Visual Inspection
  - Image analysis software guidance

- **Functional** Changes from Baseline
  - Serial Automated Visual Field Testing

Glaucma: Visual Field Progression

- Difficult to detect "real" change!
- Inherent variability in test to test performance
- OHTS
  - 86% initial "abnormal" VF had subsequent "normal" VF
  - 66% two "abnormal" VF had subsequent "normal" VF
  - 12% three "abnormal" VF had subsequent "normal" VF
- CNTG
  - As many as 4 to 6 abnormal VF necessary to confirm progression

Glaucoma: Visual Field Progression

- Difficult to detect change!
- Inspection of serial fields
  - Which fields compare?
  - What parameters?

Visual Field: Test-Retest Variability

- Frequency of seeing curve
  - Scotoma depth and location
- Overall VF status
  - Less variability with minimal or severe loss
- Test strategy
  - Full threshold-SITA standard-SITA fast
- Patient Factors
  - Learning effect
  - Physical limitations
  - "Bad Hair Day"
- External Factors
  - Inexperienced technicians
  - Room temperature
  - Chair position/comfort

Is there a tool to help us?

Is there a way to distinguish true visual field progression from normal variability?
Guided Progression Analysis (GPA)

- HVF Analyzer software package
- Identify and measure statistically significant VF progression for glaucoma patients
- Compares two designated baseline VF tests with up to 14 follow-up visual field tests.
- Reports progression when VF results fall outside expected range of test-retest variability

Guided Progression Analysis (GPA)

- GPA Normative Database
  - 363 subjects
  - Diverse by gender and ethnicity
  - Mild to Severe glaucoma
  - Excludes first time test takers
  - 4 clinic visits in 1 month
  - 3 fields per visit
  - Full Threshold, SITA Standard, SITA Fast

Guided Progression Analysis (GPA)

Event Analysis
- Progression analysis plot
- Pointwise variability in Pattern Deviation plot
- Identifies individual points or groups of points that are statistically worse
- Based on ENG trial criteria

Trend Analysis
- Visual Field Index (VFI) regression analysis
- VFI values are plotted to determine rate of progression and statistical significance
- Provides a visual trend of the progression pattern and predicts VFI loss over time

Guided Progression Analysis (GPA)

Using GPA

- Software Activation
- Set up Print Out Options
- GPA reports
- Select Baseline Fields
  - Use VFI plot to help select similar baseline fields
  - Oldest two automatically chosen unless:
    - Learning effect
    - False Positives > 15%
  - Select new baseline fields after change in treatment or confirmed progression from baseline
- Compares subsequent fields to baseline fields
  - Statistical analysis to determine likely progression

Permitted Baseline and Follow-up Configurations for GPA

<table>
<thead>
<tr>
<th>If the Key Exam is:</th>
<th>And Baseline Exams are:</th>
<th>Follow-up Exams must be:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITA Standard</td>
<td>SITA Standard</td>
<td>All SITA Standard</td>
</tr>
<tr>
<td>SITA Standard</td>
<td>Full Threshold</td>
<td>Any combination of SITA Standard and Full Threshold</td>
</tr>
<tr>
<td>SITA Fast</td>
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</tr>
</tbody>
</table>

Note: GPA supports the inclusion of Control 18-2 and 24-2 in the same analysis. GPA will analyze all tests in the same case as if they were 24-2 tests. GPA does not support further fields or Control 16-6 tests for either Baseline or Follow-up.
Guided Progression Analysis (GPA)

GPA Reports

- **Full GPA Report**
  - The whole ball of wax.
  - Baseline page with grayscale and indices including VFI plot
  - All follow-up exams (up to 14) with Progression Probability Analysis and GPA alert

- **GPA Last 3 Follow-Up**
  - Full GPA lite
  - Baseline page and three most recent follow-up exams

Guided Progression Analysis (GPA)

GPA Reports

- **Single Field Analysis with GPA**
  - Standard SFA with greyscale and key indices
  - Separate GPA information box with Progression Analysis Probability plot
  - No VFI plot or linear regression analysis

- **GPA Summary Report**
  - Baseline fields with grayscale and indices at bottom
  - VFI plot and VFI bar in center
  - Current visual field with grayscale and indices at bottom
  - Progression Analysis Probability Plot and GPA alert at bottom

Guided Progression Analysis (GPA)

Interpreting Reports - Event Analysis

- **Deviation from Baseline Plot**
  - Compares pattern deviation of f/u test to average pattern deviation of baseline tests at each point

- **Progression Analysis Probability Plot**
  - Point by point statistical significance of values in Deviation from Baseline Plot
    - Single dot - no significant change
    - Open triangle - P < 5% (.05,1/20) real deterioration at the point
    - Average of 2-3 points (out of 76) by chance alone
    - Half filled triangle - P < 0.5% same point, two consecutive tests
    - Solid triangle - P < 5% same point, three consecutive tests.
    - X - Data out of range for analysis.
      - Areas of deep or absolute defect.
Guided Progression Analysis (GPA) Interpreting Reports - Event Analysis

- **GPA Alert**
  - Alerts to deterioration in consecutive tests
  - Applies to whole field, not individual points
  - No Progression Detected
  - Possible Progression - 3 or more points, 2 consecutive tests
  - Likely Progression - 3 or more points, 3 consecutive tests
  - EMGT criteria

Guided Progression Analysis (GPA) Interpreting Reports - Trend Analysis

- **VFI Plot**
  - Graphs VFI values as a function of patient age
  - Linear regression analysis of VFI over time
    - At least 5 exams over 2 years
    - Not drawn when slope is positive
      - Learning Effect
      - Not drawn when 95% confidence level on slope >5%
  - **VFI Bar**
    - Histogram indicates current VFI value and 2 - 5 year VFI projection of the linear progression line.
    - VFI 50% in better eye or less correlates with significant VRQOL impairment

Guided Progression Analysis (GPA) Interpretation

- Statistically based software package to help identify glaucoma progression
- Requires sufficient number of fields
  - At least 5 for event analysis
  - At least 5 over 2 years for trend analysis
- Choose good baseline fields
- Garbage in, Garbage out
- Reset after progression or intervention
- Systematic Inspection of Report
  - Assess the triangles
  - Check defect depth, location, RNFL anatomy correlation
  - If progression called, check fields for reliability

Guided Progression Analysis (GPA) Interpretation

- GPA vs “Experts”
  - “Level of agreement between majority expert consensus of subjective determination of visual field progression and GPA is “fair.” In cases of disagreement with GPA, the expert consensus was usually progression. Access to GPA results after initial classification changed expert consensus in 11 of 100 cases.”

Guided Progression Analysis (GPA) Summary

- Not a substitute for clinical judgment
- Aid to analysis, helps differentiate variability from progression
- Correlate with other clinical findings
- Treat the patient not the test!