Clinical Decisions in Uveitis Management

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Uveitis Take Home Pearls

- Be a detective and find the cause
- Be aggressive with treatment
- Don't taper too soon
- Treat and follow

http://thedetectivechannel.com/

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Hypopyon

- HLA B27
- Bechet's
- Infectious uveitis
- CL Related

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What Diseases Comes to Mind?

- Behcet's
- SLE
- HSV
- Reiter
- Ulcerative colitis

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"The Common Eyeritis"

- 32YOWM, Red, Painful Eye OD, Photophobic, No discharge
- No previous episodes
- Ocular/Medical Hx: Unremarkable
- No other associated symptoms
- SLE: 2+ injection / 2+ cells

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What is Your Treatment?

- Which steroid should you use?
- What about cycloplegics?
- When do you prescribe an oral medication?
- Would you consider lab testing?
- When to schedule follow-up?

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JM 29 yowm

- RFV: Blurry VA OS for 2 days, yellow spot hourglass shape, constant, (-) headache, (-) N&V
- Medical Hx: Unremarkable
- BCVA
  - OD 20/20
  - OS 20/80 NI on Pinhole
- Subjective APD OS
- Entrance tests normal except for pain on EOMs in extreme gaze OS
- SLE: Trace Cells in AC and vitreous OS

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Differentials

- Atypical Mycobacterial Diseases
- Benign reactive conditions
- Cat scratch fever
- Coccidioidomycosis (Infectious Diseases)
- Leishmaniasis
- Lyme Disease
- Lymphogranuloma Venereum (LGV)
- Malignant neoplasms
- Nocardiosis
- Sarcoidosis
- Sporotrichosis
- Syphilis
- Toxoplasmosis

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- Assessment
  - Papillitis OS
  - Neuroretinitis OS
- Plan
  - Durezol QID OS
  - MRI of Head/Orbits with and without contrast
  - Order blood work to rule out infectious vs. neuro cause
  - F/u 2 weeks

Photo accessed from http://www.photoshoppix.com/modules/coppermine/albums/userpics/10008/normal_bad_cat.jpg

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Diagnostic Work Up

- MRI of Head and Orbits with and without contrast
- Lab Work
  - CBC with Differential
  - ESR
  - CRP
  - SMA-12
  - ANCA
  - RPR
  - Bartonella antibodies
  - Urinalysis
- Biopsy with PCR Testing
- Computed Tomography

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1 Week Follow Up Visit

- BCVA OS 20/CF1'
- No change to SLE
- Lab Results
  - Positive for *B. Henselae* IgM and IgG
  - MRI – slight protrusion and enhancement of optic nerve
- Discuss likely cause of condition and reassured VA should improve and restore to normal levels over 1-3 months.
- Antipyretics / analgesics prn
- Doxycycline 100mg BID PO x 2 weeks

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Anatomy and Physiology

- Uveal Tract
  - Iris – anterior extension of CB
  - Ciliary Body – Posterior extension of iris
    - Accommodation
    - 2 Layers of epithelium
      - Outer – RPE
      - Inner – sensory retina, produces aqueous
  - Choroid
    - Supplies nutrition for external retina
- Function is nourishment

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Uveitis Demography

- 3rd leading cause of preventable blindness in developed countries
- Prevalence of 38 per 100,000 population
- Mean age of onset is 30.7 years (+/-15)
- Approximately 85 causes of uveitis

Retrived from http://www.uveitis.ca/info.htm on March 18, 2011
Retrieved from http://www.uveitis.org/patient/glossary/t_z.html

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Uveitis Demography

- Age
- Sexual predilection
- Race
- Family History
- Geographic
- Other
  - Personality
  - Trauma
  - Exposure
  - Psychological
  - Social habits
  - Travel

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Classification of Uveitis

- Anatomical / structural location
- Etiology
- Acute vs. Chronic
- Non-granulomatous vs. Granulomatous
- Unilateral vs. Bilateral

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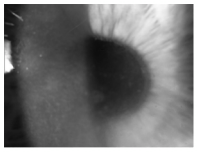
Anterior Uveitis

- Causes
  - Idiopathic
  - Traumatic
  - HLA-B27
  - Herpetic
- Can be recurrent, recalcitrant, granulomatous, or non-granulomatous



Retrieved from http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v4/v4c031.html

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Intermediate Uveitis

- 8-15% of all uveitis
- Involved pars plana, peripheral retina, vitreous
- Anterior vitreous cells
- Associated symptoms???

Retrieved from http://www.myretina.com/education/images/SNOWBALLS_001.jpg

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Posterior Uveitis

- Many systemic causes
- Many ocular diseases
- Consider infectious causes
- Common signs – retinal vasculitis

Retrieved from http://www.myvisiontest.com/newsarchive.php?action=tag&id=152

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Panuveitis

- Defined as inflammation of the entire uvea
  - Anterior, intermediate, and posterior
  - Most serious of all uveitis cases

The Ocular Immunology and Uveitis Foundation

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Etiology of Uveitis

- Idiopathic
- Autoimmune
- Infectious
- Infiltrative
- Traumatic
- Ischemic
- Iatrogenic
- Inherited

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Is it Acute or Chronic?

- Sudden or insidious
- Limited or persistent
- Recurrent
- Systemic history
- Response to therapy
- Bilateral

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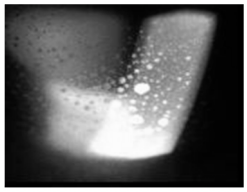
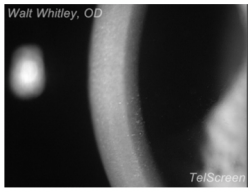
Histopathology

- Granulomatous
  - Mutton fat KPs
  - Iris nodules
  - Often chronic
- Nongranulomatous
  - Fine KPs
  - Often acute





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Khodadoust Line

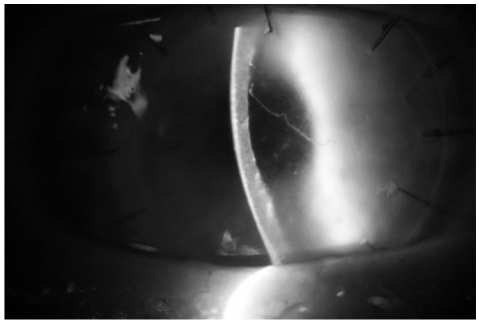

Photo Courtesy of Mitch Ibach, OD
Vance Thompson Vision

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Laterality

Photo accessed from http://eyewiki.aao.org/Fuchs_Heterochromic_Iridocyclitis_and_Secondary_Glaucoma

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Practical Diagnostic Approach

- Naming
  - Patient characteristics
- Meshing
  - Clinical characteristics
- History is Key!!
  - Medical, Ocular
  - Past, Family, Social

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Uveitis

- Classic Symptoms
  - Acute onset
  - Decreased vision
  - Redness
  - Photophobia
  - Pain
  - Excessive tearing

Retrieved from http://eyecaremanual.com/eye-conditions/photophobia/photophobia.html on 3/22/11.

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Clinical Signs

- VA
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Pupil
- IOP
- Lens
- Vitreous
- Disc edema
- Macular edema
- Periphlebitis

Photo accessed from http://www.medicinenet.com/image-collection/uveitis_picture/picture.htm

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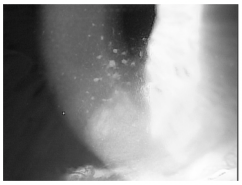
Case Example

- Referred for second opinion
- IOP improved to 32 mm Hg
- Dx: HSV Iridocyclitis OD
- Tx:
  - Valacyclovir 500 mg TID PO
  - Loteprednol etabonate QID OD
  - Timolol BID OD



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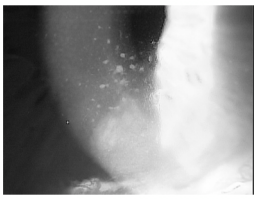
HSV Iridocyclitis

- Granulomatous vs. Non-granulomatous
- Presents with KPs, stromal edema, uveitis
- Trabeculitis
- Patchy iris defects



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SUN Working Group Grading Scheme Anterior Chamber Cells

Grade	Cells in Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	50+

Abbreviations: SUN, standardization of uveitis nomenclature.3 Field size is a 1-mm slit beam.

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SUN Working Group Grading Scheme Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris / lens details clear)
3+	Marked (iris / lens details hazy)
4+	Intense (fibrin / plastic aqueous)

Abbreviation: SUN, standardization of uveitis nomenclature.

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Anterior Synechiae

- Occurs in both acute and chronic uveitis
- Watch for angle closure
- Commonly found in:
  - Deeply pigmented eyes
  - Granulomatous disease
  - Traumatized eyes

Photo accessed from http://gonioscopy.org/PAS.html

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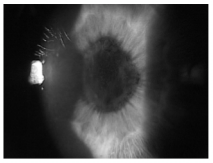
Posterior Synechiae

- Chronic anterior uveitis
- At location of Koeppe nodules
- Found in granulomatous and non-granulomatous forms
- Does not occur in pars planitis



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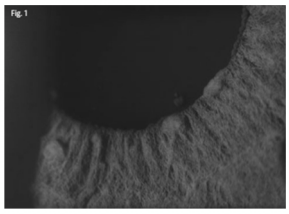
Iris Nodules

Koeppe Nodules **Bussaca Nodules**



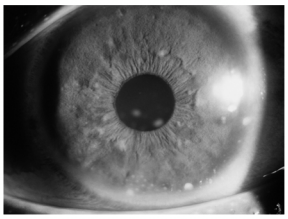


Photo accessed from http://www.aao.org/publications/eyenet/200804/am_rounds.cfm
Photo accessed from http://emedicine.medscape.com/article/1209505-clinical

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Grading of Vitreous Haze

- Grade 0 - Good view of NFL
- Grade 1 – Clear disc and vessels but hazy NFL
- Grade 2 – Disc and vessel hazy
- Grade 3 – Only disc visible
- Grade 4 – Disc not visible

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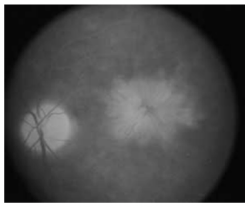
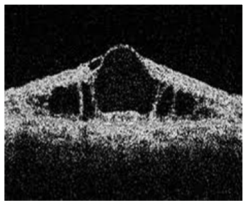
Ancillary Testing

- Fluorescein angiography
- Indocyanine green angiography
- Optical coherence tomography
- Ultrasound





Photos accessed from http://www.retinatexas.com/macular_edema.html

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Complications of Uveitis

- Evolution into chronic uveitis
- Macular edema
- Ocular hypertension
- Glaucoma
- Cataract

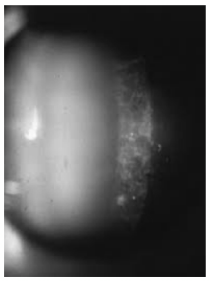

Photo accessed from http://www.opt.indiana.edu/NewHorizons/PSC.html

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Case Example

- 44yo Asian American c/o blurred VA, redness, tearing, peri-orbital edema starting 2-3 days prior
- Med Hx: Uncontrolled DM (Dx in 1998)
- Vasc: OD 20/60 PH 20/30
  OS 20/80 PH 20/40
- IOP: 21 / 18

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Case Example

- Acute, non-granulomatous, anterior uveitis OS
- Cause???
- Treatment
  - Ordered labs – CBC w/diff, ESR, SMA-12, HLA-B27, Urinalysis, FTA-ABS, RPR, Lyme Western Blot
  - Difluprednate q2h OS
  - Homatropine 5% TID OS
  - Doxycyline 100 mg BID po

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When Should Lab Tests Be Ordered?

- Bilateral cases
- Atypical age group
- Recurrent uveitis
- Recalcitrant cases
- Hyperacute cases
- Worsens with tapering
- VA worsens
- Immunosuppressed

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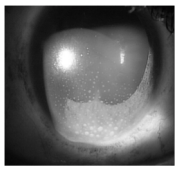
Uveitis: Common Systemic Associations

- Most common cause
  - Idiopathic : 38-70%
- Other systemic causes
  - HLA-B27 related disease
  - Sarcoidosis
  - Systemic Lupus Erythematosus
  - Rheumatoid Arthritis
  - Behcets Disease



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Lab Testing

- Minimum lab testing
  - CBC with differential
  - Erythrocyte sedimentation rate (ESR)
  - Angiotensin converting enzyme (ACE)
  - Venereal disease research laboratory (VDRL)
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Lyme titers in endemic areas
  - HLA-B27
  - Antinuclear antibody (ANA)
  - Urinalysis
  - Chest X-ray
  - PPD

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Considerations

- Joint pain???
- Breathing problems??
- Retrobulbar eye pain???
- Skin lesions???
- Retinal scars???

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Condition	Clinical Features	Test Indicated
Ankylosing spondylitis	Young male, low back pain, chest pain	HLA-B27, sacroiliac X-ray
Reiter's syndrome	Young male, arthritis, urethritis, conjunctivitis	HLA-B27, ESR, CRP
Juvenile idiopathic arthritis	Slight male predilection, sacroiliitis common	ANA, RF, knee radiograph
Inflammatory bowel disease	Ulcerative colitis, diarrhea, abdominal cramps	HLA-B27, GI referral for endoscopy
Sarcoidosis	African Americans, females, vasculitis, vitritis	ACE, chest X-ray or CT scan
Tuberculosis	Prolonged cough, fever, chills, night sweats, weight loss	PPD, chest X-ray
Syphilis	Hx of sexual contact with infected person, rash, fever, malaise, headache, joint pain	FTA-ABS, VDRL, RPR
Toxoplasmosis	Immunocompromised status, exposure to cats, hx of eating raw meat, punched-out retinal lesions	Toxoplasma IgG or IgM for acute acquired cases
Lyme disease	Recent tick bite	Lyme Western Blot

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Complete Blood Count (CBC)

- Order with differential
- Used to evaluate general health status
- Helps differentiate infection vs. inflammation
- Additionally, a CBC can detect a white blood cell malignancy such as leukemia or lymphoma

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Erythrocyte Sedimentation Rate (ESR)

- Westergren ESR is best
- Order STAT
- Normal values
  - 0-13 mm/hr (males)
  - 0-20 mm/hr (females)
- > 50 mm/hr is suggestive of temporal arteritis
- If elevated, start oral prednisone 60 – 100 mg / day
- Temporal artery biopsy to confirm within one week

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C-Reactive Protein

- Ordered in conjunction with ESR
- Checks inflammatory component of enzymes secreted from the liver
- Consider ESR & CRP in autoimmune conditions
- For GCA, 99% sensitivity with ESR and CRP

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Angiotensin Converting Enzyme (ACE)

- Produced by a variety of cells including granulomatous cells
- Serum ACE levels reflect the total amount of granulomatous tissue in the body
- Screen for sarcoidosis
  - 75% sensitive
  - 95% specific
- False positives include:
  - TB
  - Lymphomas
  - Leprosy
- Consider serum lysozyme / calcium assay

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Sarcoidosis

- Often young, African American females
- Granuloma forming disease
- Enlarged lymph nodes
- Shortness of breath
- Fatigue
- Diagnostic Testing
  - Chest X-ray
  - Elevated ACE
  - PPD: TB vs. Sarcoid
  - Biopsy of nodule

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Purified Protein Derivative (PPD)

- Skin test to screen for tuberculosis
- Intradermal injection of 0.1ml of soluble antigen from a given TB organism in forearm
  - Positive test – 5 – 15 induration in 2-3 days
- Specificity increased with chest x-ray
- False positives include prior exposure to TB

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Screening Tests for Syphilis

- Venereal Disease Research Lab (VDRL)
  - VDRL may become non-reactive in latent syphilis or after successful treatment
  - False positives may occur in:
    - Pregnancy
    - Infectious mononucleosis
    - Systemic lupus erythamatosis
- Rapid Plasma Reagin (RPR)
  - Alternative to VDRL

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Fluorescent Treponemal Antibody Absorption (FTA-ABS)

- Detects specific antibodies against T pallidum
- Confirms diagnosis of syphilis
  - More specific than VDRL
  - More sensitive in primary syphilis
- Test may remain positive for life
- Reactive:
  - Primary syphilis 95%
  - Secondary 100%
  - Late latent 100%
  - Tertiary 96%
  - False positives may occur in pregnancy and SLE

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Syphillis

- STD caused by T pallidum / great imitator / any tissue and organ
- Sexually active / multiple partners
- Systemic Sx – Depends on stage – primary painless ulcer / secondary skin rash palms, soles, trunk / tertiary neurosyphillis
- All types of ocular inflammation
- Labs
  - VDRL / RPR
  - FTA – ABS
  - ESR elevated
- Tx – penicillin therapy
- Good prognosis if treated early

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Lyme Titer

- Ordered based on suspicion
- Erythema migrans is the only manifestation of Lyme disease in the United States for which clinical diagnosis should be made in the absence of laboratory confirmation
- A patient with a significantly characteristic symptom with the appropriate history of possible exposure should be started on antibiotics after appropriate laboratory studies have been drawn

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Tx for Lyme Disease

- Early infection or nonspecific symptoms with positive Lyme titers in the adult may be treated with oral doxycycline (100 mg twice daily for 14 days) or amoxicillin (500 mg three times a day for 14 days)
- Severe infection in adults with definitive ocular, neuroophthalmic, neurological, or cardiac involvement may be treated with penicillin G (24 million units, intravenous, daily in four divided doses for 21 days) or intravenous ceftriaxone (2 g/day in two divided doses for 21days.

Wormser et. Al. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesios is: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical infectious diseases. Vol. 43. Issue 9.*

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Human Leukocyte Antigen

- Positive in several conditions
  - Ankylosing spondylitis
  - Reiter's syndrome
  - Inflammatory bowel disease
  - Psoriatic arthritis
  - Behcet's disease
- HLA-B27 typing may yield false positives
- Most useful for patients with acute, unilateral anterior uveitis

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HLA-B27

- Ankylosing spondylitis
  - Affects males 20-40yo
  - Sacroiliac joint- lower back pain
  - HLA-B27 – 88%
- Inflammatory bowel disease
  - Bloody stool, abdominal pain
  - Weight loss
  - HLA-B27 – 60%

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HLA-B27

- Reactive Arthritis
  - Triad: Urethritis, Arthritis, Uveitis
  - More commonly affects men in 30-40yo
  - HLA-B27 – 88%
- Psoriatic arthritis
  - Skin lesions precede joint inflammation
  - Red, painful, swollen joints
  - Worse in the am
  - HLA-B27 – 70%

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Behcet Disease

- Often Japanese or Middle eastern men 20-40yo
- Triad: Sores on mouth & genitals, uveitis
- Arthritis, skin problems, inflammation of spine
- Diagnosis
  - Positive Behcetine (pathergy) test
  - Recurrent mouth and genital sores
  - Rule out disease with similar presentation

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Antinuclear Antibody (ANA)

- In autoimmune diseases, plasma cells produce antibodies directed against the body's tissues
- Positive values (titers < 1:20) are associated with connective tissue diseases
  - Systemic lupus erythematosis
  - Tuberculosis
  - Chronic hepatitis
  - Lymphoma
  - Sjogrens
  - Scleraderma
- Helpful in children to r/o JRA

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Systemic Lupus Erythematosus

- African American women 20-40yo
- Rash, arthritis, fever
- Malaise, fatigue, hair loss, chest pain
- Vasculitis, kidney disease
- Diagnostic testing
  - ANA
  - CBC - decreased complement levels
  - ESR
  - Chest X-ray, Kidney biopsy

http://images.medicinenet.com/images/image_collection/skin/systemic-lupus-erythematosus.jpg

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Rheumatoid Factor (RF)

- Differentiates RA from other chronic arthritides
- Positive values (titers > 1:80) occur in approximately 70% of patients with rheumatoid arthritis
- Positive in only 5% of patients with JRA
- Can be positive in the following
  - Sjogren's
  - SLE
  - Syphilis
  - Chronic infections
  - Sarcoidosis
  - Liver disease

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Rheumatoid Arthritis

- Middle aged women
- Arthritis affecting both sides equally
- Morning stiffness
- Inflammation of joints and tissue
- Diagnostic Testing
  - Positive rheumatoid factor
  - Anti-CCP present
  - Elevated CBC
  - Joint X-ray

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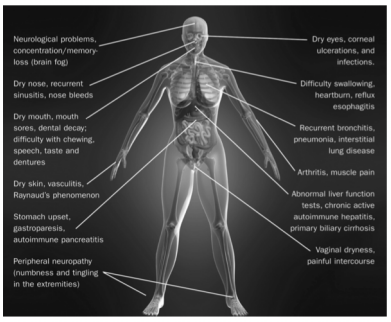
Sjögren's Is More than Dry Eye[1]



1. http://www.sjogrens.org/home/about-sjogrens-syndrome/symptoms

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Sjogrens Syndrome

- Chronic automimmune disease in which WBC attack moisture producing glands
- Diagnosis
  - (+) ANA
  - (+) RF
  - (+) SS-A (Ro)
  - (+) SS-B (La)
  - ESR
  - Immunoglobins

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Recent Clinical Findings for Sjögren's

Current Screening	New SS Panel
• Combined serology sensitivity & specificity is around 40-60%	• Combined serology sensitivity & specificity is 87% and 82.5% respectively • Cumulative specificity of 92.2% for CA6, SP-1, and PSP
• None of the serology test diagnose SS early • Misses approximately 25-35 % cases	• Approximately 50% of the **early & new** cases are identified (Ro and La Negative) • Picks up additional cases
• All serology tests identifies are non-organ specific auto-antibodies and could occur in other autoimmune diseases	• Comprises of both organ/non-organ specific auto-antibodies

1. Tincani A, et al. Novel aspects of Sjögren's Syndrome in 2012. BMC Med Apr 4 2013;11:93. doi: 10.1186/1741-7015-11-93. 2. Shen L, et al. Novel autoantibodies in Sjogren's Syndrome. Clin Immunol 2012;145:251-255. 3. Huang Y, et al. The immune factors involved in the pathogenesis, diagnosis, and treatment of Sjogren's Syndrome. Clin Dev Immunol 2013; Article ID 160491. doi:10.1155/2013/160491.
4. Ramos-Casals M, Brito-Zeron P, Siso-Almirall A, Bosch X. Primary Sjogren's Syndrome. BMJ 2012;344:e3821

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Plaquenil (hydroxychloroquine sulfate)

- Indicated for the treatment of discoid and systemic lupus erythematosus, rheumatoid arthritis, and malaria
- Primary risk factors
  - Duration > 5 years
  - Cumulative dose >1000g
  - Age
  - Systemic – High BMI, liver, kidney dysfunction
  - Ocular – retina or macular changes

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Plaquenil Examinations

- Complete dilated examination
- Central visual field testing 10-2
- Fundus photography for co-existing retinal disease
- Spectral domain OCT, FAF, mfERG (if available)

Accessed from http://www.kellogg.umich.edu/theeyeshaveit/side-effects/chloroquine.html

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Urinalysis

- Can disclose evidence of diseases, even some that have not caused significant signs or symptoms
- Commonly a part of routine health screening
  - Urinary tract or kidney infection
  - Evaluate causes of kidney failure
  - Screen for progression of some chronic conditions such as diabetes mellitus and high blood pressure
- Useful in the diagnosis of tubulointerstitial nephritis

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Radiology

- Chest
  - Sarcoidosis
  - TB
- SI Joint
  - Ankylosing spondylitis
  - Reiter's
  - Ulcerative colitis
- Large Joints
  - JRA
  - Reiter's
  - Bechet's

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Biopsy

- Conjunctival and lacrimal gland – sarcoid
- Aqueous samples – Viral retinitis
- Vitreous biopsy – infectious endophthalmitis
- Retinal/choroid
  - Dx not established
  - No response to therapy
  - Further deterioration despite therapy
  - Exclusion of malignancy or infection

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Plan for Treatment

- Protect vision
- Reduce scarring
- Reduce pain
- Decrease inflammation
- Find the cause

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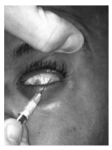
Treatments for Uveitis

- Steroids
  - Topical
  - Local
  - Systemic
- Cycloplegics
- Analgesics
- Immunosuppressants
- Calcineurin inhibitors
- Biological blockers
- Glaucoma medications



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Systemic Therapy for Inflammatory Disease

- Acute inflammatory episodes typically necessitate steroid treatment (topical, periocular, intraocular, systemic)
- Steroids exhibit great efficacy (especially in anterior uveitis), but come with significant side effects, limiting chronic use
  - Cataract, glaucoma, herpetic reactivation, increased infection
  - Gastric ulcer, reactivation of latent disease, hyperglycemia, osteoporosis, Cushing syndrome
- MUST Study
  - Local and implant steroids effective for uveitis treatment
  - High incidence of local ocular SE and systemic complications

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Steroid Pulse Therapy

- QID to Q 1 Hour for 7 to 10 Days
- Zero Tolerance for AC Cells
- Avoids Surface Toxicity
- Quick & Dirty
- Hit It Hard and Fast: Aggressive
- **Treat and Follow**

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Don't Forget the Cycloplegics

- Comfort
- Break synechiae
- Stabilize blood-aqueous barrier

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Break the Synechia

- Phenylephrine
  - Adrenergic agonist
  - 2.5, 10% concentration
  - Not a cycloplege
  - Can potentially release more pigment cells
- Goniosynechialysis
  - On-off pressure using goniolens

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Non-Therapeutic Treatments

- Hot compress
- Sunglasses / Hats
- Stay indoors
- Low lighting
- Plus for near
- Patching

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Importance to Treat and Follow

- Mild – 4 to 7 days
- Moderate – 2 to 4 days
- Severe – 1 to 2 days
- Once resolved - q1-6 months

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Current and Future Treatments for Uveitis

- Retisert – fluocinolone intravitreal implant
- Ozurdex – dexamethasome intravitreal implant
- Iluvien – fluocinolone intravitreal implant
- Humira - Adalimumab injection / TNF inhibitor
- Luveniq – voclosporin orally / calcineurin inhibitor
- Dexamethasone anterior segment iontophoresis

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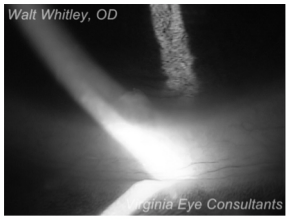
Case Example

- 62 yowm, cataract sx three weeks prior
- VAsc OD: 20/25
- IOP OD: 15 mmHg
- SLE: Mild K edema / 1 + cells / IOL centered



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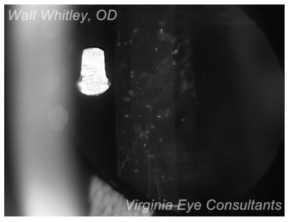
Case Example

- 77 yowf
- S/P Phaco OS 6 months prior
- VAsc: 20/30
- IOP: 12 mmHg
- SLE: tr cells



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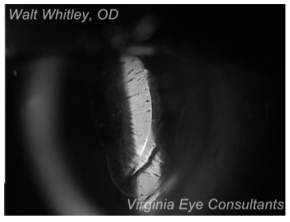
Case Example

- 68 yowm
- s/p ACIOL OD
- Mild low grade inflammation



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Take Home Pearls

- Be Aggressive with treatment
- Don’t taper too soon
- Be a detective and find the cause
- Treat and follow

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