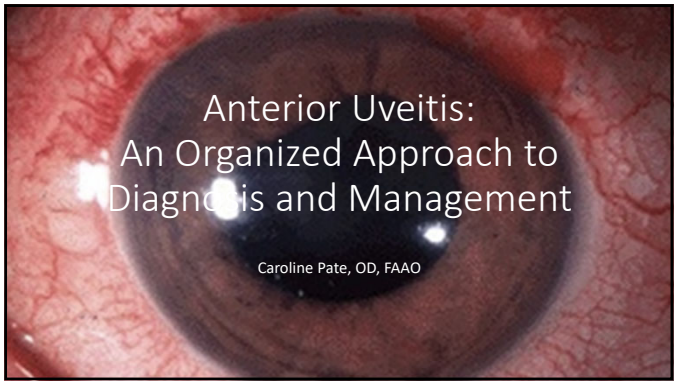

Anterior Uveitis: An Organized Approach to Diagnosis and Management

Caroline Pate, OD, FAAO

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No financial disclosures

Acknowledgments: Dr. Tammy Than

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Why Anterior Uveitis?

- Because its not uncommon
- Because these patients will show up as walk-ins or add-ons
- Hesitancy to manage/quick to refer
- *Anterior* uveitis – because covering all of uveitis would take more than 2 hrs
  - Uveitis involving the posterior segment should be managed by a retinal specialist

3

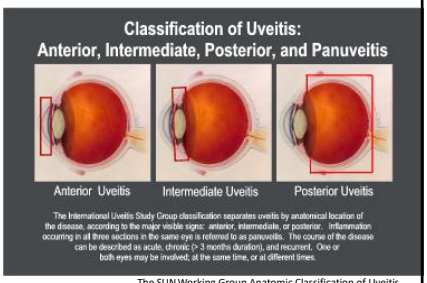
Classification: Anatomical

Anterior
- Iritis, cyclitis, iridocyclitis

Intermediate
- Pars Planitis

Posterior

Panuveitis



The SUN Working Group Anatomic Classification of Uveitis Am J Ophthalmol. 2005 Sep;140(3):509-16.

4

Epidemiology

- Uveitis – most common form of ocular inflammation
- Anterior uveitis accounts for ~90% of all uveitis
- Most commonly affects working age adults (20-59)
  - M=F
  - Special considerations in young & elderly
- Incidence varies greatly by geographic location

Foster, 2016, Dunn, 2015

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Epidemiology

- 3rd leading cause of blindness in the world
  - Accounts for 10-15% of all legal blindness (30,000 new cases annually) in US
- In the US, > $240 million spent annually on the treatment of uveitis and its complications

Foster, 2016; Dunn, 2015, Bajwa, 2015, Hunter 2011

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Pathophysiology

- Exact pathophysiology is not known
- Intraocular space is normally free of inflammatory cells because the BAB (anterior) and BRB (posterior) do their job
- Inflammation → tissue changes → vasodilation and ↑ vasopermeability

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Pathophysiology

- Extravasation
  - WBC (cells)
  - Protein (flare)
  - Larger MW proteins (fibrinogen → fibrin)
    - Keratic Precipitates
    - Synechia
      - Anterior
      - Posterior

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Pathophysiology

- Retinal Changes
  - Cystoid macular edema (CME)
  - Exudative retinal detachment (rare)

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What causes vision loss in uveitis?

- Band keratopathy
- Cataract
- Macular Edema*
- Epiretinal membrane*
- CNVM*
- Retinal vasculitis
- Retinal detachment
- Glaucoma
- Optic neuropathy

Series from Moorfields Eye Hospital – at 10-yr f/u

- 80% had VA > 20/50
- 90% had VA > 20/200
- CME, Macular scarring*, ERM = 79% of vision loss <20/50
- Macular scarring, CME, RD, = 71% of vision loss <20/200

Tomkins-Netzer, Ophthal, 2014

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What causes uveitis?

- Idiopathic → "Undifferentiated"
  - 35-40% (Foster, 2016)
  - 40-50% (Colmant, 2018)
- Trauma
- Post-operative
- Associated with ocular disease
- Associated with systemic disease
- Drug induced

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Principles of Uveitis Diagnosis

- Accurate diagnosis
- Accurate description/classification
- Understand the epidemiology and clinical characteristics of uveitic entities
- Targeted history and work up

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Anterior Uveitis: Diagnosis and Description

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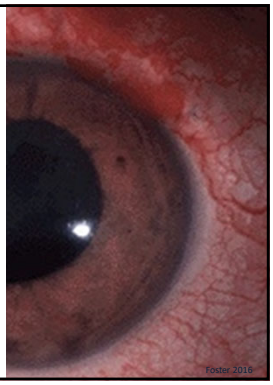
Clinical Presentation

- Symptoms
- Can be asymptomatic!
  - JIA (Juvenile Idiopathic Arthritis)
  - Fuch's
- Conjunctiva
- Pupils
- IOP



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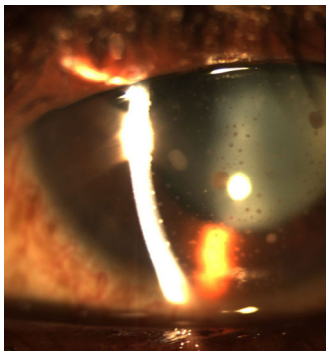
Clinical Examination - Cornea

- Keratic Precipitates
- Collection of inflammatory cells
- **Non-granulomatous:** fine, white deposits: collections of lymphocytes, plasma cells, and pigment
- **Granulomatous:** large, "greasy" appearance, "mutton-fat": collections of lymphocytes, plasma cells, and giant cells



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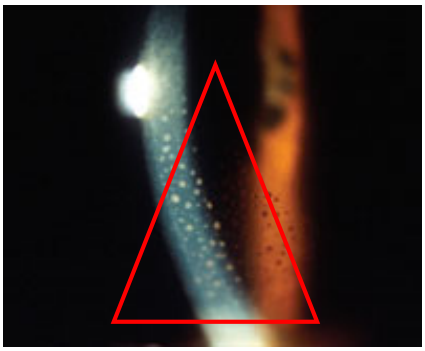

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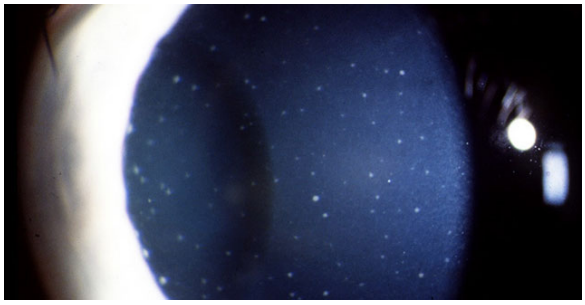

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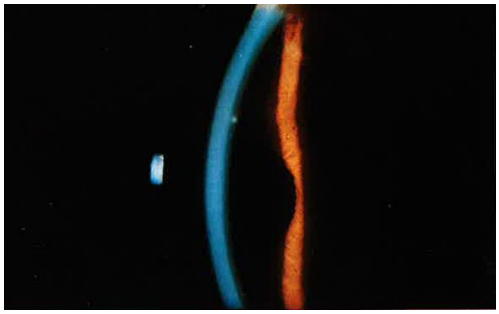

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Do KPs actually help us????

"MFKPs are typically associated with granulomatous inflammation"

Syphilis

Keratic precipitates (%)	
None	45
Fine	33
Round	11
Stellate	2
Mutton fat	9

Sarcoidosis

Keratic precipitates, %	
None	52
Fine	18
Round	6
Stellate	0
Mutton-fat	23

Tuberculosis

Keratic precipitates (%)	
None	88
Fine	5
Round	3
Stellate	0
Mutton fat	4

Spondyloarthritis/HLA-B27

Keratic precipitates,	
None	0
Fine	41
Round	54
Stellate	5
Mutton-fat	0
Other	0

Fuch's

Keratic precipitates (%)	
None	1
Fine	25
Round	7
Stellate	68
Mutton Fat	0
Other	0

SUN working group. *Am J Ophthalmol*. 2021;228:65-280

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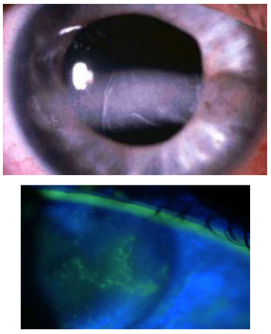
Clinical Examination - Cornea

- Edema
- Band keratopathy
  - Can be seen in chronic conditions
  - JIA
- Consider Herpes
  - Check for cornea hypoesthesia
  - Dendritic involvement ?



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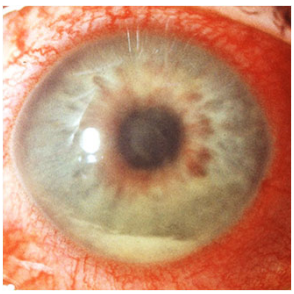
Clinical Examination – Anterior Chamber

- **Cells**: WBC/Leukocytes
- **Flare**: Protein = from vasodilation and ↑ permeability of inflamed blood vessels
  - Does not = active inflammation
- **Hypopyon**: layering of WBC



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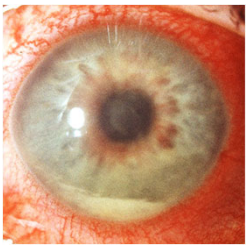
Hypopyon

- Differential diagnosis:
  - HLA-B27 anterior uveitis
  - Bechet's
  - Infectious
    - Endophthalmitis (post-surgical or endogenous)
    - Associated with corneal ulcer
  - Drug related (rifabutin)
  - Pseudo-hypopyon (malignant cells, lens induced, steroids)



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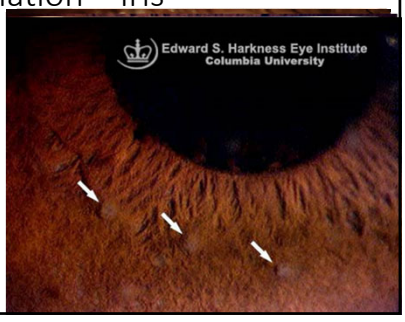
Clinical examination – Iris

- Examine for synechia
- Any atrophy?
- Inflammatory nodules
  - Associated with sarcoid, TB, syphilis
  - Koeppe
  - Busacca
  - Berlin



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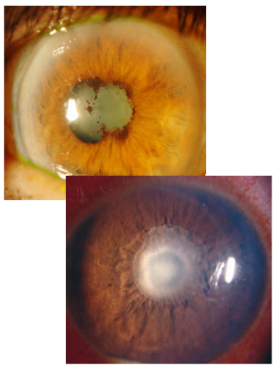

Posterior synechiae

- Sometimes this is all you get after dilation
- Complications
  - Poor view of posterior pole
  - Decreased vision
  - Secondary angle closure from iris bombe
  - Complicates cataract surgery
- "Occlusio pupillae"- fibrin growth over entire pupil

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Clinical examination - Lens

- Phakic patient
  - Inspect for signs of trauma
    - Vossius ring
    - Rosette cataract
  - May develop cataract secondary to chronic uveitis
- Pseudophakic patient
  - Residual lens material?

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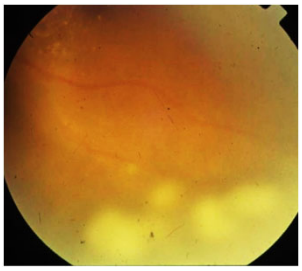
Clinical findings - Vitreous

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



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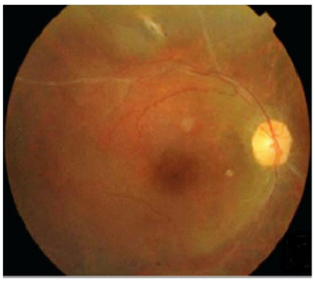
Clinical findings – Retina/Choroid

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



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

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

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Classification

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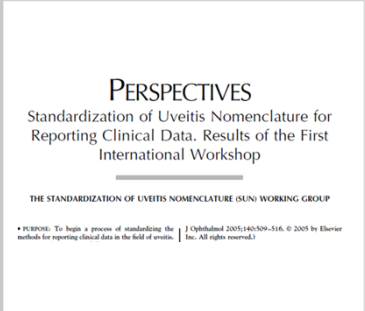
Classification

- Based on **S**tandardization of **U**veitis **N**omenclature for Reporting Clinical Data. Results of the First International Workshop.
- Characterized uveitis by:
  - Anatomic type/location
  - Onset/duration and clinical course
- Standardized evaluation



PERSPECTIVES

Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop

THE STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP

SUN Working Group Am J Ophthalmol. 2005 Sep;140(3):509-16. - Jabs AJO 2013

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SUN Classification – Important Descriptors

Onset
- Sudden
- Insidious

Duration
- Limited
  - ≤3 months duration
- Persistent
  - >3 months duration

Course
- Acute
  - Episode characterized by sudden onset and limited duration
- Recurrent
  - Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
- Chronic
  - Persistent uveitis with relapse in <3 months after discontinuing treatment

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Anatomical Classification

Type	Primary Site of Inflammation†	Includes
Anterior uveitis	Anterior chamber	Iritis
		Iridocyclitis
		Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis
		Posterior cyclitis
		Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis
		Chorioretinitis
		Retinochoroiditis
		Retinitis
		Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	

SUN Working Group. AJO 2005

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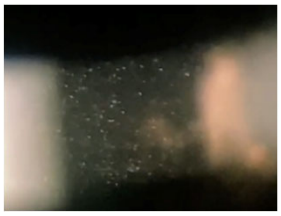
SUN Grading Scheme for Cells

- *1 x 1 mm beam*



Grade	Cells in Field
0	<1
0.5+ (trace)	1 – 5
1+	6 – 15
2+	16 – 25
3+	26 – 50
4+	> 50

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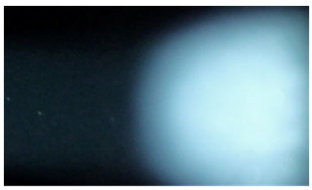
SUN Grading Scheme for Flare

- *1 x 1 mm beam*



Grade	Description
0	optically empty (compare bilaterally)
1+	Faint haze
2+	Moderate (Iris and lens detail clear)
3+	Marked (Iris and lens details hazy)
4+	Intense (fibrin; coagulated aqueous)

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Treatment of Anterior Uveitis

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Treatment of Anterior Uveitis - GOALS

- Preserve vision
- Relieve pain
- Reduce ocular inflammation
- Prevent sequelae
- Target the cause

- SUCCESS = induction of durable, corticosteroid-free remission

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Agents utilized

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

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Cycloplegics

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

- Options:
  - Cyclopentolate – not preferred due to short duration of action
  - Homatropine – pharmacy availability issues
  - Atropine – strongest cycloplegic

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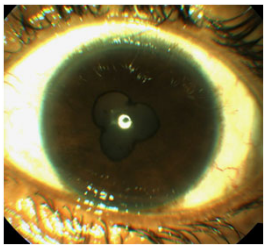
Mydriatics

- 10% phenylephrine can be useful in breaking synechia in-office
- In office concoction – soak cotton pledget in:
  - 10% phenylephrine
  - 1% atropine
  - 1% cyclopentolate



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Topical Corticosteroids

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

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HIT IT HARD AND TAPER SLOW

- Prednisolone acetate 1%
- Difluprednate 0.05%
- Need at least a 2 grade reduction in activity to begin tapering
  - e.g. improvement from 3+ cell to 1+ cell
- Weaker steroids – possible use as a taper

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Corneal Penetration and Anti-inflammatory Efficacy

Epithelium Intact		Epithelium Absent	
Pred Acetate 1%:	51%	Pred Acetate 1%:	53%
Pred Phosphate 1%:	28%	Pred Phosphate 1%:	53%

Musson, D G (1991). "Comparative corneal penetration of prednisolone sodium phosphate and prednisolone acetate in NZW rabbits.". *Journal of ocular pharmacology(8756-3320)*, 7 (2), p. 175

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Steroid dosing based on severity (prednisolone acetate)

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

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Ophthalmic steroid ointment

- Fluorometholone ophthalmic ointment 0.1%
- Loteprednol ophthalmic ointment 0.5%

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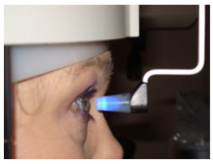
Ocular Side Effects of Treatment

- Iatrogenic (Steroid) OHT
  - Interference with phagocytosis in Schlemm's canal
  - Increased accumulation of glycosaminoglycans (GAGS) in TM
- Management…



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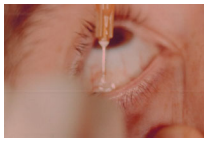
Periocular Steroids



- Subconjunctival or sub-Tenon's
- Triamcinolone or methylprednisolone
- Recalcitrant anterior uveitis, intermediate uveitis, posterior uveitis
- r/o "steroid responder"

- Do not administer if etiology is infectious

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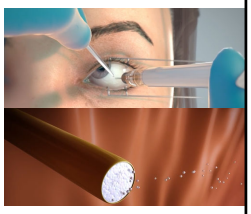
Uveitis Approved Steroid Implants

- All approved for noninfectious uveitis affecting posterior segment of the eye
- Retisert®-0.59mg fluocinolone acetonide
- Ozurdex™-0.70mg Dexamethasone
- Yutiq™- 0.18mg fluocinolone acetonide



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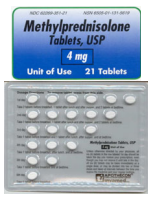
Oral Steroids

- Posterior, pan, or recalcitrant uveitis
- Must rule out infections (e.g., tuberculosis)
- Side effects
- Prophylactic acid reducer



- Prednisone
  - Start high and taper quickly
  - 1-2 mg/kg/day (~60-100 mg/day)
- Medrol Dosepak ?

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Immunomodulators

- Antimetabolites
  - Methotrexate, Azathioprine
- Inhibitors of T-lymphocytes Signaling
  - Cyclosporine, Tacrolimus
- Alkylating Agents
  - Cyclophosphamide, Chlorambucil
- Biologics
  - Adalimumab – FDA approval for uveitis
  - Infliximab – off label

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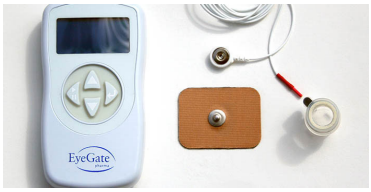
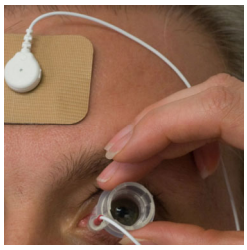
What's the future?

- EGP-437 Eyegate II Delivery System
- Trans-scleral iontophoresis





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Overall Management

- Re-evaluate 1-7 days
- Cycloplegic usually stopped before steroid
  - No need to taper
- Continue topical steroid until cells are gone
  - Taper
- Evaluate patient during taper and post-taper
  - IOP
- What's the etiology?

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Targeted history and diagnostic workup

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Why work up a uveitis patient?

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

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Infectious Diseases	• **Bacterial:** syphilis, tuberculosis, Lyme disease, cat-scratch disease, rickettsiosis, leptospirosis, brucellosis, Whipple's disease • **Parasitic**: toxoplasmosis, toxocariasis, Onchocerciasis • **Viral:** herpes virus, CMV, HTLV-1 • **Fungal:** candidiasis, histoplasmosis	**Ocular entities**	• Posner-Schlossman syndrome • Fuchs uveitis syndrome • Sympathetic ophthalmia • Phacoantigenic uveitis • Serpiginous choroiditis • Birdshot chorioretinopathy • Multifocal choroiditis • Placoid epitheliopathy • Pars planitis
Systemic Inflammatory Diseases	• HLA-B27-associated uveitis • Sarcoidosis • Behcet's disease • Vogt-Koyanagi-Harada disease • Juvenile idiopathic arthritis • Systemic lupus erythematosus • Multiple sclerosis • Tubulointerstitial nephritis and uveitis (TINU syndrome) • Chronic inflammatory bowel disease	**Drug-Induced**	• Rifabutin • Bisphosphonates • Fluoroquinolones
		Masqueraders	• **Trauma**, intraocular FB • **Tumors** (oculocerebral lymphoma, melanoma, retinoblastoma, metastases)

Adapted from Seve 2015

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Anatomic Location	Infectious	Systemic Disease	No Systemic Disease
Anterior uveitis	• CMV • HSV • Varicella zoster • Syphilis • TB • Lyme	• HLA-B27 assoc • Juvenile idiopathic arthritis–assoc • Behcet disease • Sarcoidosis • MS	• Fuchs uveitis syndrome • Post-traumatic
Intermediate	• Syphilis • Lyme disease	• Multiple sclerosis • Sarcoidosis	• Pars planitis
Posterior	• Toxoplasmic retinitis • CMV retinitis • Acute retinal necrosis • Progressive outer retinal necrosis • Diffuse unilateral subacute neuroretinitis • Syphilis • Lyme disease	• Sarcoidosis	• Serpiginous choroiditis • Acute posterior multifocal placoid pigment epitheliopathy • Multiple evanescent white dot • Birdshot chorioretinitis • Diffuse unilateral subacute neuroretinitis • Multifocal choroiditis with panuveitis • Punctate inner choroiditis • Relentless placoid choroiditis ("ampiginous")
Panuveitis	• Syphilis disease • Lyme disease • TB • ARN	• Behcet disease • Vogt-Koyanagi-Harada • Sarcoidosis	• Sympathetic ophthalmia

Adapted from Jabs AJO 2013

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Uveitis "Top 10" – Duane's Ophthalmology Most Commonly Encountered Causes

1. Traumatic
2. Post-surgical
3. Anterior Idiopathic/Undifferentiated
4. HLA-B27 associated uveitis
5. JIA associated uveitis
6. Fuch's uveitis syndrome
7. Posner-Schlossman syndrome
8. Herpetic anterior uveitis
9. Pars Planitis
10. TB/Sarcoid/Syphilis

Adapted from Duane's Ophthalmology

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Consider the presentation….

Acute, unilateral (or bilateral) non-granulomatous AU

Chronic, bilateral (or unilateral), non-granulomatous AU

Granulomatous AU (unilateral or bilateral)

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Acute Non-Granulomatous Anterior Uveitis

- Idiopathic (most common)
- HLA-B27
  - Anklyosing spondylitis
  - Reactive arthritis
  - Inflammatory Bowel Dz
  - Psoriatic arthritis
- Behçet's disease
- Trauma
- Infections
  - HZV, HSV, CMV
  - Post operative endophthalmitis
  - Lyme Dz
  - Syphilis
- Lens Induced
- UGH (uveitis-glaucoma-hyphema)

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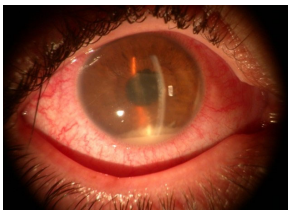
Case – 30 yo WM

- Similar episode 2 years ago in other eye
- No recent surgery or trauma
- ROS: + lower back pain worse in am
- Social hx: no recent tick bites, foreign travel, no drug use

- VA: OD20/100 OS: 20/20
- IOP: 11/15
- Pupils: OD poorly reactive, OS normal
- DFE: Hazy view OD but normal b-scan, OS normal



62

Autoimmune/inflammatory disorders

63

Seronegative spondyloarthropathies (SAs)

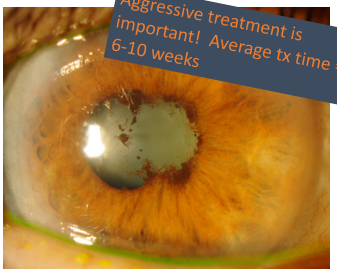
- Group of inflammatory rheumatic diseases that cause arthritis of the spine (Seronegative = negative RF)
  - **Ankylosing Spondylitis**
  - **Reactive arthritis**
  - **IBD (ulcerative colitis; Crohn disease)**
  - **Psoriatic arthritis**
- Hereditary; major gene that causes it is **HLA-B27**
- Can affect the joints of the arms and legs (e.g. hips and shoulders) as well as involve the skin, intestines and eyes
- Frequently undiagnosed; mean time to dx after onset of symptoms is 6 years

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

64

SA/HLA-B27 associated uveitis

- Accounts for ~20% of all uveitis
- Acute, rapid onset of unilateral pain and intense photophobia
- Non-granulomatous
- Moderate-severe A/C reaction (3-4+ cells, plasmoid aqueous, fibrin, +/-hypopyon)
- Posterior synechiae common

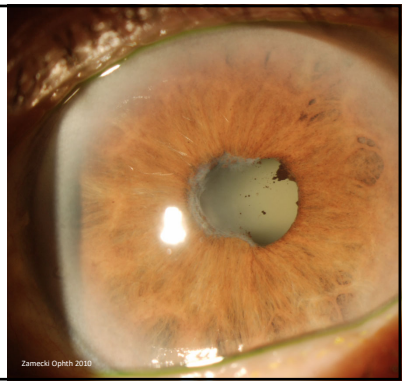


Zamecki Ophth 2010; Chang Surv 2005

65

SA/HLA-B27 associated uveitis

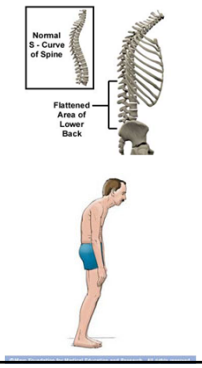
- Of **recurrent, acute, unilateral alternating anterior uveitis**: 80% will have a SA or be HLA-B27 positive
- Of patients with uveitis and (+) HLA-B27, 60-76% will have an associated SA
  - And about half of these SAs will have been undiagnosed or misdiagnosed



66

Anklyosing Spondylitis

- Aggressive inflammatory arthropathy
- Onset usually in 20s
- Rare in AA
- M>F (females less severe)
- **<u>Lower back pain</u>**
  - Worse after inactivity
- "Bamboo spine"
- 25% have anterior uveitis
  - May present years before skeletal signs
  - High rate of recurrence
    - Can alternate between two eyes
  - Resolution between attacks



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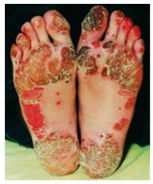
Reactive Arthritis

- Formerly known as Reiter's syndrome
- "Can't see, can't pee, can't climb a tree"
  - Conjunctivitis/Uveitis
  - Urethritis
  - Arthritis – lower joints affected
  - Only 1/3 have all 3
- Dermal skin lesions
- More common in men
- 75-90% HLA-B27+
- Often follows genitourinary infection



68

Other SA/HLA-B27 conditions

- Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Crohn's disease
    - Diarrhea, bloody stools, cramping
    - GI referral
- Psoriatic arthritis
  - Arthritis of upper extremities
  - Characteristic skin lesions – red patches with silvery scales

69

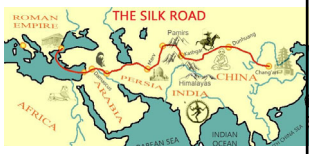
Rheumatoid arthritis

- Uveitis misconception
- Psoriatic, reactive and JIA true etiologies
- Common cause of Scleritis/Episcleritis

70

Behçet's disease

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

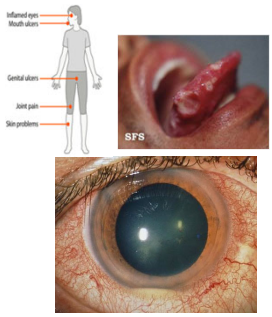


KAÇMAZ, AJO 2008

71

Behçet's disease

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



Reiff, 2013 KAÇMAZ, AJO 2008

72

Behçet's disease

- Diagnosis based on specific clinical findings, as there is no specific lab test
- Associated with HLA-B51
- Males > Females
  - Although reverse may be true in US and Western Europe
- Usually bilateral (80%)
- In 20% of cases, ocular involvement may be the initial manifestation
  - Panuveitis most common (up to 89% - Arevalo 2015)
  - Posterior seg involved in ~ 70% of patients
- Acute inflammation of retinal arteries and veins

Reiff, 2013; KAÇMAZ, AJO 2008

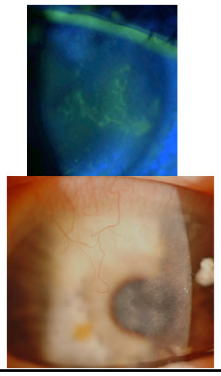
73

Infectious disorders

74

Herpetic Uveitis

- HSV
  - h/o unilateral red eye
  - Blur, photophobia, pain, redness
  - May have active corneal disease
    - Use Rose Bengal stain!
  - Reduced corneal sensitivity
- Usually secondary to keratitis but *may present without corneal involvement*
- HSV – uveitis usually with stromal or disciform keratitis



75

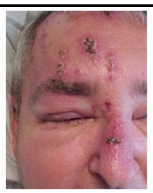
HSV Keratouveitis – how to stay out of trouble

- ALWAYS look at the cornea – in most **non-herpetic** uveitis, the anterior part of the cornea is NOT involved and there is NO corneal edema
- Clues to consider HSV:
  - Multiple episodes in same eye
  - High/asymmetric IOP
  - Fine, stellate KPs
- Consider dendrite masqueraders: e.g. epithelial regeneration line after a corneal abrasion
- If cornea is compromised/when in doubt, do NOT use a steroid

76

Herpes Zoster

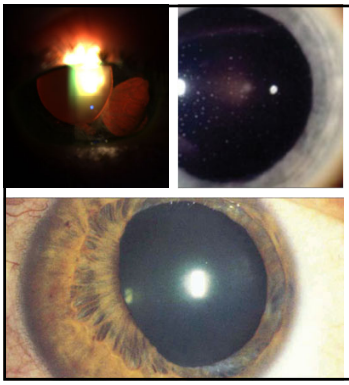
- Most common > age 50 OR immunosuppressed
- In one population-based study, **2.5%** of all pts with HZ had ocular involvement
- ~1/3 of cases involving the ocular dermatome had ocular involvement



Ocular findings:
- Keratitis: 76%
- Iritis/uveitis: 47%
- Conjunctivitis: 35%
- Severe eye pain: 14%
- Increased IOP: 12%

Yawn et al Mayo Clin Proc 2013

77



HZ uveitis

- Occurs in ~ 47% of pts with HZO
- Usually starts 1-3 weeks after rash
- Unilateral; usually mild and transient
- Increased IOP
- Diffuse small KP
- Iris atrophy (sectoral or diffuse) and irregular pupil

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Chronic, Nongranulomatous Anterior Uveitis

- Juvenile Idiopathic Arthritis (JIA)
- Fuchs' Uveitis Syndrome
- Autoimmune disease

79

Juvenile Idiopathic Arthritis (JIA)

- Formerly known as JRA
- **80% of pediatric uveitis cases are associated with JIA**
  - Most prevalent systemic disorder in children with uveitis
- Children < 16 yrs; F>M
- Chronic bilateral anterior uveitis – usually **ASYMPTOMATIC**
  - Slow, chronic onset
- Fine or no KP with posterior synechiae
- Band keratopathy

Ayuso, Surv Ophthalmol 2014

80

Juvenile Idiopathic Arthritis (JIA)

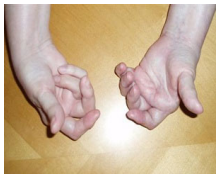
- Group of clinically distinct arthritic disorders characterized by:
  - Asymmetric arthritis
  - Early age of onset
  - Female predilection
  - (+) ANA
- Multifactorial autoimmune disorder to which patients are genetically predisposed and may be influenced by environmental factors and infections

Ayuso, Surv Ophthalmol 2014

81

Juvenile Idiopathic Arthritis (JIA)

- Oligoarticular JIA
  - 50%
  - ≤ 4 joints
  - F>M
  - **30% develop AU**
- Polyarticular JIA
  - 20%
  - ≥ 5 joints
  - May have uveitis
- Systemic JIA
  - 30%
  - Uveitis is *extremely rare*



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Other childhood uveitis

TINU (tubulointerstitial nephritis and uveitis syndrome)

- Rare; 1st reported 1975
- Mean age 14-15, 3x F>M
- Presents with ant uveitis, later followed by acute interstitial nephritis
- Responds well to corticosteroid therapy
- Urinalysis: + Beta-2 microglobulin

Pars Planitis

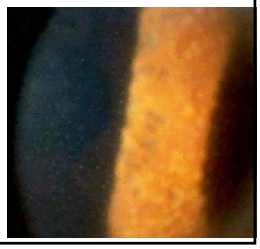
- Typically children and adolescents; M > F
- Usually bilateral
- Subset of idiopathic intermediate uveitis, with snow banking or snowball formation at the pars plana
- Rarely associated with a systemic disease

Reiff 2013

83

Fuch's uveitis syndrome (FUS)

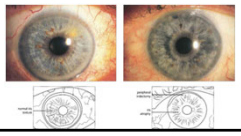
- Unilateral (90%), recurrent low grade uveitis, little injection or pain
- Iris heterochromia or atrophy
- NO posterior synechiae
- **Fine/stellate diffuse KP over entire endothelium**



84

Fuchs' uveitis syndrome (FUS)

- **Glaucoma, cataract**
- Vitreous opacities, iris nodules, abnormal vessels in angle, chorioretinal scars
- Does not tend to respond well to topical steroids!



- Exact etiology unknown
  - Likely associated with rubella virus
  - Quentin and Reiber (2004) found evidence of intraocular production of antibodies against rubella virus in all 52 of their FUS pts
  - Since vaccination program against rubella started in US, sharp decline in FUS cases

Cunningham 2009, Rothova 2007

85

Granulomatous Anterior Uveitis (unilateral or bilateral)

- RARELY EVER IDIOPATHIC
- Most common causes:
  - Sarcoid
  - Syphilis
  - TB

86

Sarcoidosis

- Multisystem granulomatous inflammatory autoimmune disease of unknown etiology
  - Young, AA females in US
  - #2 systemic etiology of uveitis in U.S.
- Lungs (95%), lymphatics, eyes (25-60%), skin (25%), nervous system, cardiac, liver, laryngeal

Jamilloux 2004; Ianuzzi NEJM 2007

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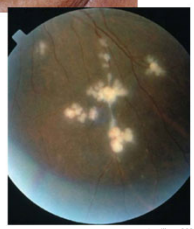
Ocular Sarcoid

- Up to 25–60% of patients have ocular involvement
  - Nodules/Ant Seg Granulomas
  - Chronic dacryoadenitis
  - Uveitis
  - Posterior Segment
    - Candle wax drippings
    - Vitritis
    - CME



Jamilloux 2004

88

Ocular Sarcoid Uveitis

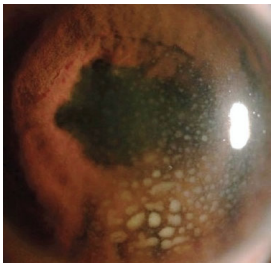
- Can produce any type of uveitis
  - Ant uveitis: 41–75%
  - Intermediate: 6–10%
  - Posterior: 28%
  - Panuveitis: 9–30%

Jamilloux 2004

89

Ocular sarcoid - Anterior segment

- Bilateral
- Granulomatous
  - Large mutton-fat KP's
- Anterior and posterior synechiae
- Nodules
  - Koeppe
  - Busacca
  - Berlin



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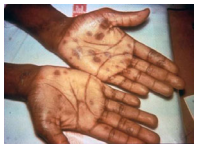
Syphilis

- A chronic, multistage sexually transmitted disease caused by the spirochete *Treponema pallidum*
  - Primary: sores at original site of infection "chancre"
  - Secondary: skin rash, swollen lymph nodes, fever
  - Latent: no symptoms
  - Tertiary: neurologic, sometimes cardiovascular involvement
- **Ocular syphilis can occur during any stage**
- Standard uveitis treatment + Penicillin G



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

91

Ocular Syphilis

- Can involve almost any eye structure
  - Posterior uveitis and panuveitis most common
  - Anterior uveitis
  - Optic neuropathy
  - Retinal vasculitis
  - Interstitial keratitis
- CDC reports rise in rate of cases every year since 2000
  - Majority in HIV+ MSM
- Cases of ocular syphilis should be reported to state/local health department within 24 hours of dx

www.cdc.gov/std/syphilis/stats.htm

92

Tuberculosis

- Infectious disease caused by *mycobacterium tuberculosis*
  - ¼ of the world's population is infected with TB
  - Rare in US
  - Six countries account for **60%** of the total cases: India, Indonesia, China, Nigeria, Pakistan and South Africa

www.cdc.gov/tuberculosis

95

Tuberculosis

Latent TB Infection

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

TB Disease

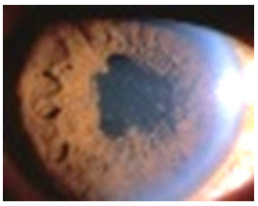
- Feel sick: cough, weakness or fatigue weight loss, chills, fever, sweating at night
- Can spread to others
- Chest X-ray/Sputum culture to Dx
- Requires treatment to prevent spread

https://www.cdc.gov/tb http://www.who.int/mediacentre/factsheets/fs104/en/

96

Ocular Tuberculosis

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



Figueira 2016; Ang BJO 2016

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Ocular Entities

98

Posner-Schlossman Syndrome
Glaucomatocyclitic crisis

- Mild unilateral non-granulomatous anterior uveitis with **markedly elevated IOP**
  - recurrences may affect either eye
  - at risk for OAG
- Minimal symptoms, open angles
  - Mild hyperemia
  - Mild corneal edema
  - Sentinel KPs
  - May also have diffuse iris atrophy
- **Unlike Fuchs, responds well to steroids**
  - **Cycloplegia often not necessary**
  - **Avoid PG for IOP control**

Megaw et al Surv Ophthalmol 2017

99

Drug-Induced uveitis

- Rare – incidence <1%
- Medication History…
  - Prostaglandins
  - Bisphosphonates
    - Boniva/Actonel/Fosamax

Guillén 2016; Eadie 2015

100

Traumatic Uveitis

- Classic findings:
  - Follows blunt trauma
  - Timing (2-7 days after injury)
  - Vision is typically good unless there is other damage to the eye
- Treatment:
  - Cycloplegia
  - Topical steroids
  - Look for other signs of ocular trauma in the eye (hyphema, iris tears, cataract, retinal problems)
  - Follow up 5-7 days

103

Masqueraders

- **Trauma** – intraocular FB
- **Tumors**
  - Lymphoma
  - Retinoblastoma
- **Endophthalmitis**
- **Retinal Detachment**

104

Ask the right systemic questions to help guide your differentials!

- Joint problems?
- Lower back pain?
- Pain on urination?
- Digestive problems?
  - Cramping, diarrhea, bloody stool?
- Lung/breathing problems?
- Rashes/skin problems?
- Any recent foreign travel?
- Been hiking/camping? Possible exposure to ticks?
- Any other systemic or autoimmune disease?

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Laboratory Testing

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When to test?

- Bilateral
- Recurrent
- Intermediate, posterior, or panuveitis
- Obvious systemic complaints
- Intense inflammation

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Laboratory Testing

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

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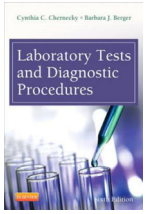
If You Order Tests...

- Interpret
  - Get a good reference book!
  - Commercial lab websites (labcorp, quest)
- Communicate
- Treat
- Refer



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Lab Testing in Anterior Uveitis

- Often Freebie if…
  - First occurrence
  - Acute
  - Mild
  - Unilateral
  - Nongranulomatous

110

No lab testing also…

- Evidence of HS, HZ
- Post-operative
- Trauma
- Known systemic disease
- Corresponds with new medication

- Remember – high % are idiopathic…

111

Suggested initial labs

- No universal recommended approach
- **Anterior Uveitis**
  - HLA-B27
  - ACE
  - Lysozyme
  - FTA-ABS
  - RPR or VDRL

- **Intermediate Uveitis**
  - ACE
  - Lysozyme
  - *Borrelia burgdorferi* IgG/IgM antibodies
  - RPR/FTA-ABS

- **Posterior Uveitis**
  - ACE
  - Lysozyme
  - ANA
  - ANCA
  - *Borrelia burgdorferi* IgG/IgM antibodies
  - *Bartonella henselae* IgG/IgM antibodies
  - FTA-ABS
  - RPR
  - *Toxoplasmosis gondii* IgG/IgM antibodies

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HLA-B27

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

113

ACE (Angiotensin Converting Enzyme)

- Helps confirm dx of sarcoidosis
  - ACE elevated in 60% of sarcoid patients

- Best for patients > 20 YO
- 12 hour fast before test

- Normal under 67 U/L
  - Over 100 U/L = highly suggestive

- Sensitivity and specificity only 60% and 70%

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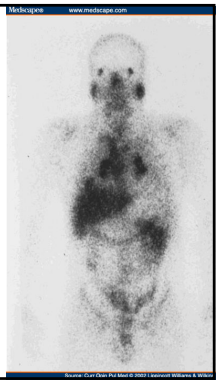
Sarcoidosis: Other Lab Tests

- **Chest X-Ray / CT scan**
- Liver enzymes
- Conjunctival or lacrimal gland biopsy
- Serum lysozyme
- Serum calcium
- Gallium scan – poor predictive value
  - Nuclear medicine test
  - Radioactive gallium citrate is injected
  - Hot spots at site of inflammation



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Syphilis Testing

Treponemal-Based
- FTA-ABS (fluorescent treponemal antibody absorption)
- MHA-TP (microhemagglutination treponemal pallidum)

Nonspecific
- RPR (rapid plasma reagin)
- VDRL (venereal disease research laboratory)

116

Syphilis

RPR or VDRL	FTA-ABS or MHA-TP	Interpretation
+	+	Active Syphilis
-	+	Adequate Treatment (Inactive)
+	-	False positive
-	-	No exposure

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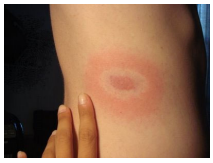
Lyme Disease

- Endemic?
- Exposed?
- *Borrelia burgdorferi* : IgG/IgM antibody titers (lyme)
- Western blot confirmation



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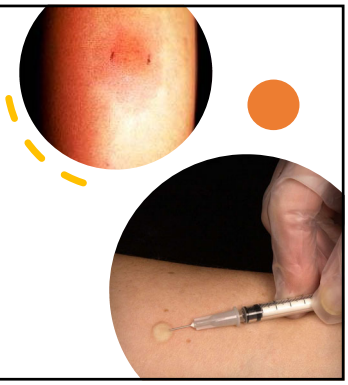
TB Testing

- Depends…
- Prevalence?
- Previous exposure?
- Risk Factors

- PPD
- QuantiFERON Gold



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Targeted laboratory testing

120

ANA (Antinuclear antibody)

- Evaluates immune system
- Screening test for SLE
  - 95%
- Sensitive but not specific
- Normal: nonreactive
- Results in 4-5 days

- SLE- 95 %
- Scleroderma- 60-90%
- Rheumatoid arthritis- 41%
- Sjogren's syndrome- 48%

- JIA with uveitis – 80% positive
  - 2/3 with oligoarticular JIA

121

p-ANCA

- Perinuclear-Antineutrophil cytoplasmic antibody
- ↑ in Crohn disease

- c-ANCA (antineutrophil cytoplasmic antibody C)
  - Autoimmune vasculitis

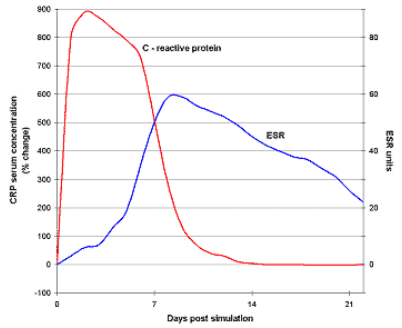
- Normal – titer <1:40

122

Non-specific tests

- CBC with differential
- Erythrocyte Sedimentation Rate (ESR)
  - M: age/2
  - F: (age+10)/2
- C-Reactive Protein

123



http://www.bing.com/images/search?q=fibrinogen+and+esr&view=detail&id=71753E2D1520B868B1884F9107224B803B1FFB20&first=1&FORM=IDFRIR

124

Other Diagnostic Procedures

- Radiologic Studies
  - Chest X-Ray / CT Scan
  - Sacroiliac joint
  - Other affected joints

- Anterior chamber tap

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Keep in Mind…

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

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Anterior Uveitis – Takeaway pearls

- Treatment often straightforward but may require persistence
  - Always overtreat rather than undertreat
  - Remember to hit it hard and taper slow
- DFE!
- Etiology not always so simple
  - Don't be afraid to order labs
- Look and listen for clues

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