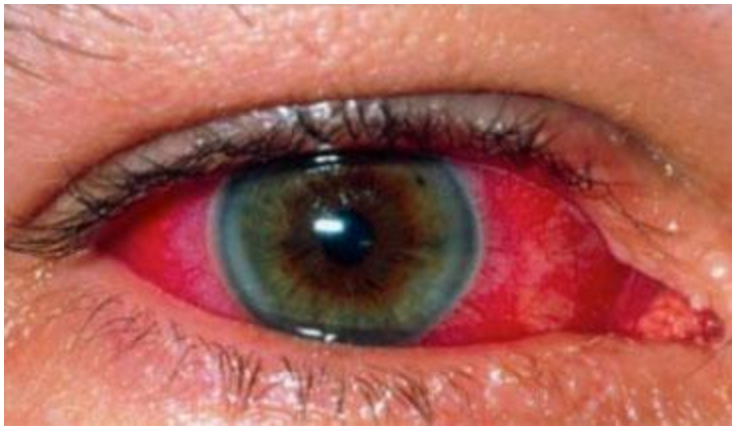
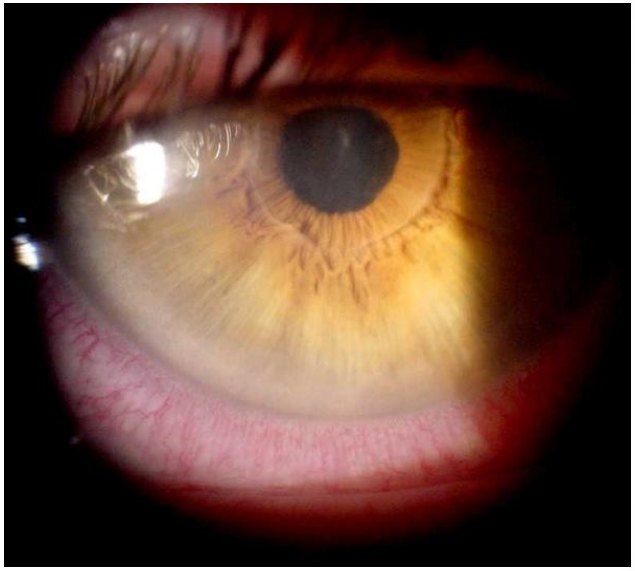
Work-up & Management of Uveitis



Introduction

- Uveitis is caused by disorders of diverse etiologies including wide spectrum of infectious and non infectious causes

- The inflammatory process primarily affects the uveal tissues with subsequent damage to the retina, optic nerve and vitreous



Middle East Afr J Ophthalmol. 2009 Oct-Dec; 16(4): 159–167

Prevalence

- According to previous studies, performed in the last decades, the prevalence of uveitis was estimated to be 17.5 to 22 per 100,000 population, however in recent reports, its prevalence is increased up to three times

Iranian Journal of Ophthalmology 2009;21(4):4-16

Classification of Uveitis

Table 5-1 The SUN Working Group Anatomical Classification of Uveitis

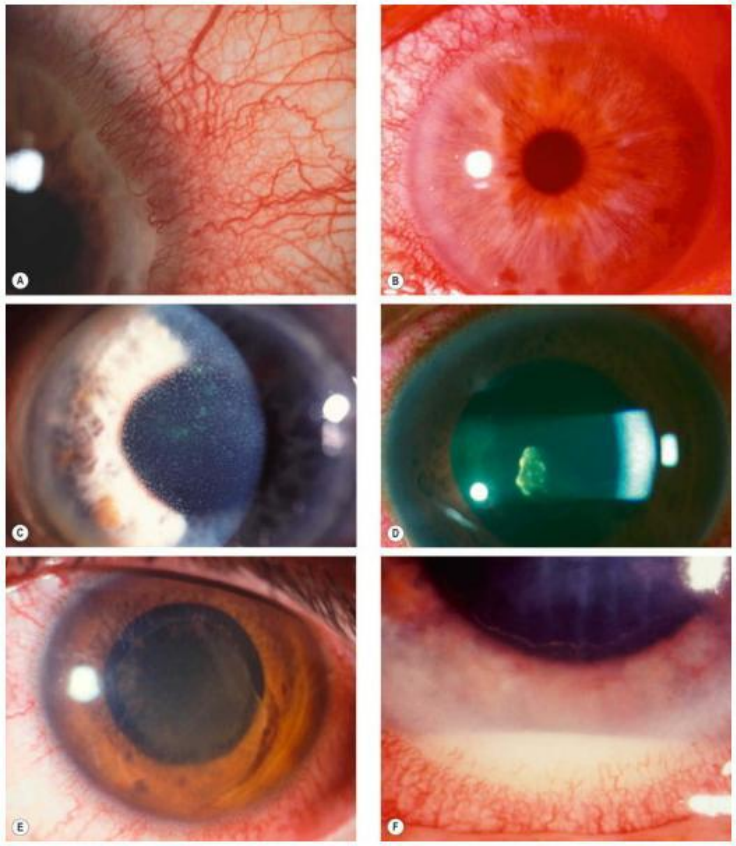
Type	Primary Site of Inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis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

Reprinted with permission from The Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):510.

Signs & Symptoms

Symptoms

- Redness
- Pain
- Photophobia
- Lacrimation
- Floaters
- Decreased vision



Signs

- Injection
- Keratic precipitate (KP)
- Iris nodule
- Koeppe, Busacca
- Cells (AC or Vitreous)
- Flares
- Posterior synechiae (PS)
- Choroiditis
- Retinitis
- Vasculitis

Signs of acute anterior uveitis. **(A)** Ciliary injection; **(B)** miosis; **(C)** endothelial dusting by cells; **(D)** aqueous flare and cells; **(E)** fibrinous exudate; **(F)** hypopyon

Clinical Work up in Uveitis

- Uveitis work up starts with an elaborate history-taking
- 70% of diagnosis can be made on the basis of detailed medical history and meticulous clinical work up alone
- Systemic history evaluation helps to offer possible systemic association with ocular involvement

History taking in uveitis

Demography	Age Gender Race Residence Occupation
Ocular history	Laterality Primary symptom Duration Onset Severity Course Associated findings
Systemic history	All systemic problems Associated other diseases
Treatment history	Details on dosage Response Treatment complications Compliance of the patient
Miscellaneous	Injury Surgery Migration Exposure to risk factors

Table 5-13 Medical History Factors in Diagnosis of Uveitis

Modifying Factors	Associated Factors Suggesting Systemic Conditions
Time course of disease	Immune system status
Acute	Systemic medications
Recurrent	Trauma history
Chronic	Travel history
Severity	Social history
Severe	Eating habits
Inactive	Pets
Distribution of uveitis	Sexual practices
Unilateral	Occupation
Bilateral	Drug use
Alternating	
Focal	
Multifocal	
Diffuse	
Patient's sex	
Patient's age	
Patient's race	

Extraocular examination

Poliosis	Vogt Koyanagi Harada's syndrome[12], Sympathetic ophthalmia
Loss of hair	Systemic lupus erythematosus, Vogt Koyanagi Harada's syndrome, and Syphilis.
Hypo-pigmentation of the skin	Leprosy, Sympathetic ophthalmia, and Vogt Koyanagi Harada's syndrome
Rash	Vasculitic disease, Systemic Lupus Erythematosus, Adamantiates Behcet's Disease, Syphilis
Erythema nodosum-Tender violaceous subcutaneous nodules in lower extremities	Inflammatory bowel disease, sarcoidosis, Tuberculosis and Behcet's disease.
Scaling of the skin	Systemic Lupus Erythematosus, Psoriatic arthritis, Syphilis, and Reiter's syndrome
Discoid lesions	Systemic Lupus Erythmatosus, Sarcoidosis, leprosy and Tuberculosis.
Nail abnormalities	Psoriatic arthritis, Reiter's syndrome, and Vasculitis
Oral and genital lesions	Behcet disease[13, 14], Reiter's and Syphilis
Oral ulcers alone	Systemic Lupus Erythematosus and Inflammatory Bowel Disease,
Urethral discharge	Reiter's syndrome, Syphilis, Herpes simplex, and Gonococcal urethritis
Epididymitis	Behcet'sdisease, Tuberculosis
Prostatitis	Reiter's syndrome, Ankylosing spondylitis, and Gonococcal disease
Nephritis	Vasculitis (Wegener's granulomatosis SLE, Behcet) sarcoidosis, tuberculosis
Arthralgias and arthritis	Seronegative spondyloarthropathies, juvenile rheumatoid arthritis, Behect's, sarcoidosis, Systemic Lupus Erythematosus, Relapsing polychondritis Leprosy reactions
Cartilage loss	Relapsing polychondritis, syphilis, and gonococcal disease, Leprosy, Wegener's granulomatosis

Nasopharyngeal manifestations including sinusitis	Wegener's granulomatosis, Sarcoidosis, Whipple's disease, and Mucormycosis.
Bladder (cystitis)	Whipple's disease and Reiter's disease.
Lymph nodes	Tuberculosis, Sarcoidosis, lymphoma
Neuropathy	Leprosy, Herpes zoster, Sarcoidosis, Multiple sclerosis, Syphilis and Sarcoidosis
Hearing loss	Vogt Koyanagi Harada's syndrome, Sarcoidosis.
Respiratory symptoms	Tuberculosis, Sarcoidosis, Wegener's granulomatosis (sinusitis)
Bowel disease	Whipples disease, Crohn's disease, Ulcerative colitis
Fever	Collagen vascular disease, Tuberculosis Leptospirosis

Reasons to investigate uveitis

- Come to a specific diagnosis
  - Infection
  - Auto Immunity
  - Allergy
  - Systemic Disease Associations.
- Confirm a clinical diagnosis, so as to institute appropriate treatment and avoid dangerous drug side effects
- Commence anti-metabolite or immunosuppressive therapy
- Identify complications
- To explain cause of poor vision
- Rule out masquerade syndromes/infections
- For academic and research purposes

Indications for investigations

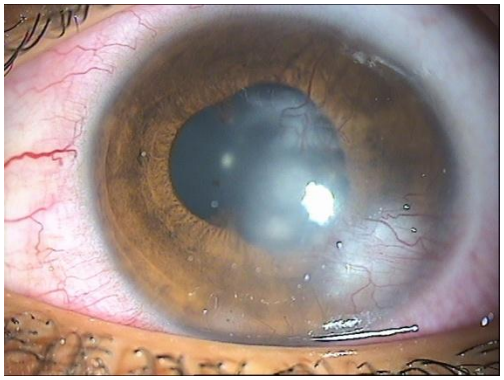
- ***To exclude the diagnosis of tumor, infection and presumed autoimmune disease***
- ***To evaluate the capacity of the eye to respond to therapy***
- ***To identify why the vision has not improved, i.e. non-responders, poor responders and early recurrences; irreversible changes e.g. subretinal fibrosis***

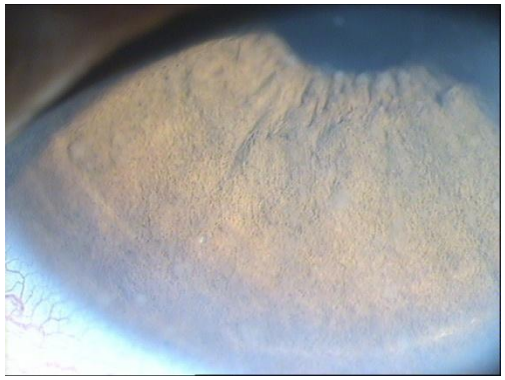
Selection of investigation

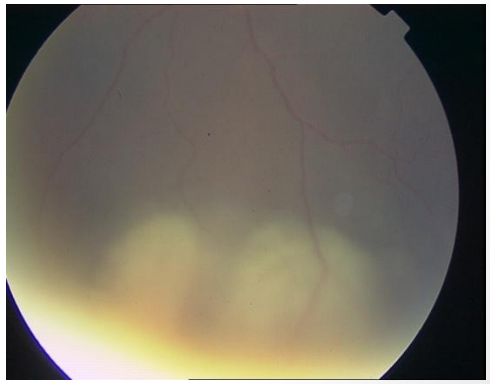
- ***Following points need to be considered before ordering the investigations.***
- **a) Age, sex and ethnic character of the subject.**
- **b) Type of uveitis i.e. anterior, posterior, and intermediate or pan-uveitis.**

Selection of investigation

- **Specific eye findings like iris nodules, keratic precipitates, extent of fundus involvement, evidence of vasculitis and macular involvement.**

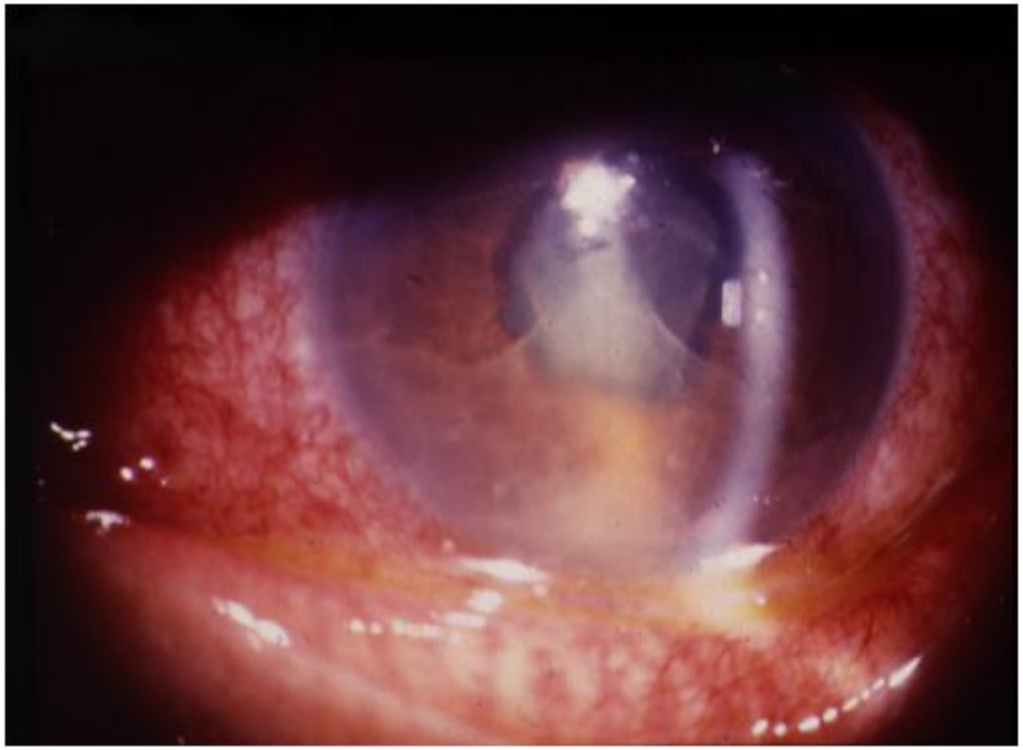






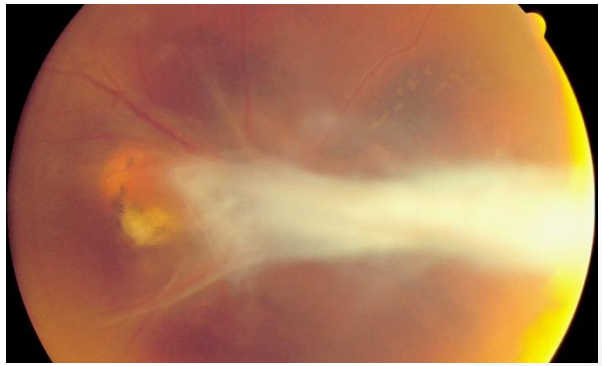
Selection of investigation

- **Response of eye to treatment i.e. the extent of visual loss.**



Selection of investigation

- **Whether the condition is active or healed i.e. change is reversible or not; typical example is toxoplasmic scar or inactive toxocara granuloma.**
- **Even if the diagnosis is confirmed, it will not benefit the patient as no treatment can improve the vision.**



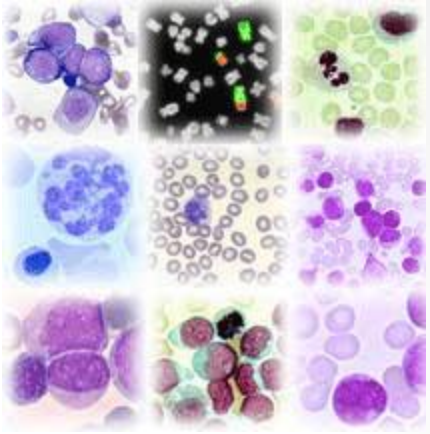
Choosing the Investigation

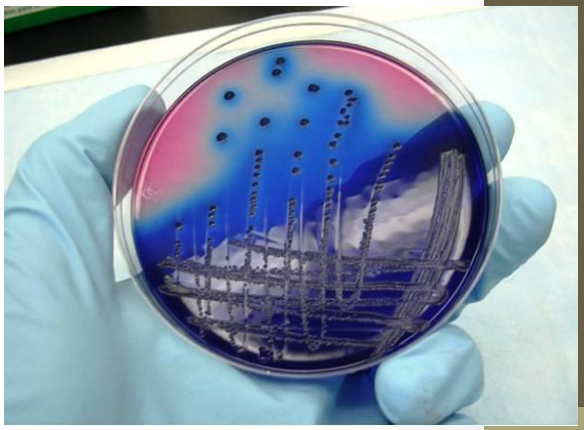
This depends on :

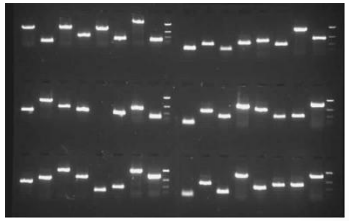
- *** Age, Sex and ethnicity.**
- *** Type of uveitis (anterior/intermediate/posterior)**
- *** Associated ocular and extraocular signs/symptoms.**
- *** Nature of uveitis (acute/chronic; unilateral/bilateral; active/healed)**

What investigations

- Hematological
- Immunological
- Microbiological
- Cytological
- Histopathological
- Radiological
- HLA typing
- Dermatological (skin tests)
- Ultrasonography
- ICG Angiography
- Systems review







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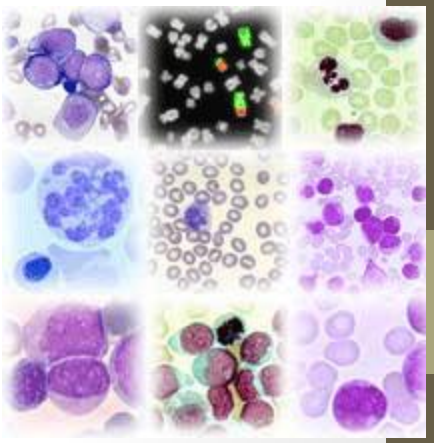
Hematological investigations when?

- Commencing antimetabolite or Immunosuppressive therapy.
- Suspicion of parasitic infestation
- Suspicion of leukemia
- ACE estimation in Sarcoidosis
- Factor V leiden mutation
- IgE levels



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Immunological investigations when?

- Toxoplasma Retinochoroiditis (Active)
- AIDS
- Other Infectious Diseases CMV, HSV, VZV, Bartonella, Toxocara etc.
- Collagen Vascular Diseases
  - ANA, ANA profile (Scleritis and secondary infections)
  - ANCA (Scleritis)

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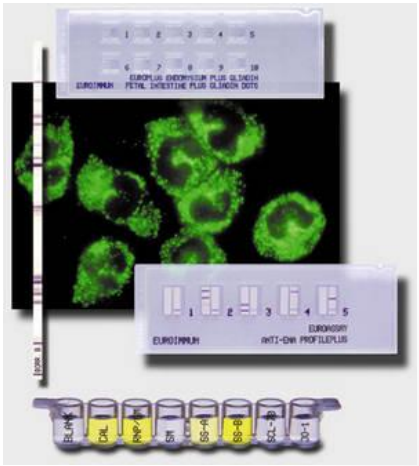
Some of the important serological investigations are



Rheumatoid Factor

- It is an antibody against the Fc portion of IgG, which is itself an antibody. RF and IgG join to form immune complexes which contribute to the disease process.
- **Has no role in the diagnosis of uveitic entities.**
- **However it forms the basis of dividing arthropathies into seropositive and seronegative.**

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Antinuclear Antibodies

- **Presence of ANA in the serum shows that there is possibility of an existing autoimmune disease and hence further investigations are warranted to identify the specific type.**

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Antinuclear Antibodies

- **Type of testing alters sensitivity and specificity of result (i.e. ELISA versus fluorescent detection on cellular substrates)**
- Positive ANA is helpful in evaluating risk for uveitis in pauciarticular chronic arthritis and has an almost universal presence in SLE.

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ANA alone is not a very good screening or diagnostic test

- Deane, Liard, Siegel, Baum: Pediatrics 1995, 95:892-5
- • ANA is positive in 113/500 consecutive children
- seen in clinic
- • 72/113 children have a clear, objective diagnosis
- • 31/113 with +ANA and no diagnosis remain
- without a diagnosis over mean f/u of 37 months
- Low titer ANA has poor positive predictive

power for diagnosis of rheumatic diseases

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Anti-DNA Antibodies

- Antibodies against ds-DNA are found in 40-80% cases of SLE and only rarely in other connective tissue disorders.
- Hence, it is considered to be relatively specific for SLE and the American Rheumatoid Arthritis Association considers it a criterion in the diagnosis of this disease.
- The normal reference range is 0.00-0.05 IU/ml or 70-200 units.
- They may also be useful in monitoring disease activity in these patients.
- A combination of positive ANA test, ds-DNA antibodies and hypocomplementaemia is said to have a diagnostic specificity of 100% for SLE.

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Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

- **ANCA are a group of autoantibodies that occur in a large majority of patients with systemic small vessel vasculitis.**
- **Most common conditions in which they are positive are Wegener's granulomatosis and microscopic polyarteritis nodosa.**
- **c-ANCA has a greater specificity than p-ANCA.**

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Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

- Diseases like PAN ,MPO or Wegener's Granulomatosis can very rarely cause retinal vessel inflammation.
- These diseases primarily affect sclera and adnexa.
- Manifestations are secondary to the associated renal induced hypertension (PAN,MPO).
- Direct infiltration of retina and optic nerve in case of Wegener‘s granulomatosis.

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Angiotensin Converting Enzyme (ACE)

- **Serum ACE levels are elevated in 85% of patients with active pulmonary disease due to sarcoidosis.**
- **However, it may also be increased in diabetes mellitus (24%), leprosy (53%), hyperthyroidism (81%), chronic renal disease, cirrhosis, amyloidosis and tuberculosis.**

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Angiotensin Converting Enzyme (ACE)

- **As it has a false positive rate of 2-4%, it is not considered a diagnostic test but a useful parameter to monitor disease activity and treatment response.**
- **SACE level is considered to be elevated if the value is above 35 U/ml in adults and 50U/ml in those below 19 years. (8 – 52 U/L)**
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Serum Globulin

- **75% of patients with sarcoidosis have elevated serum globulin levels.**
- **Due to this serum protein increases and albumin/globulin ratio decreases.**
- **Alterations in the serum protein values may act as the first clue to diagnosis of sarcoidosis in some patients. Subsequent serum electrophoresis may also reveal a characteristic "sarcoid-step" pattern. (Normal total serum protein = 6-8.6gm/dl; globulins = 2.3-3.5gm/dl).**
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Serum Lyzozyme

- **Sarcoidosis, serum lyzozyme is found to be elevated in 70% cases irrespective of whether the disease is active or inactive.**
- **However, increased levels may also be present in tuberculosis.**

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Serum C-reactive Protein (SCRP)

- The values of SCRP generally parallel that of ESR but the former is not influenced by anemia.
- It is a non-specific indicator of inflammatory activity in the body.
- It increases earlier and declines faster than ESR at the onset and resolution respectively of inflammation.
- Following steroid suppression in completely disappears.

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Management of Uveitis

The goal of treatment is to rapidly resolve the inflammation, resulting in the return of vision

Table 1 Topical corticosteroids used in anterior uveitis

Drug	%
Dexamethasone	0.1
Prednisolone acetate	1.0
Prednisolone phosphate	1.0
Fluoromethalone	0.1
Loteprednol	0.2, 0.5
Rimexalone	1

Table 2 Commonly used topical mydriatics/cycloplegics

		Mydriasis		Cycloplegia	
Drug	%	Maximal-Hours	Recovery	Maximal-Hours	Recovery-Days
Atropine	1.0	30-40	7-10 days	1-3	7-12
Homatropine	1.0	40-60	1-3 days	0.5-1	1-3
Cyclopentolate	0.5-1	30-60	1 days	0.5-1	1
Tropicamide	0.5-1	20-40	3-6 hours	1/2	<1/4
Phenylephrine	0.5-1	20-60	3-6 hours	None	None

Table 5. Biologic-Modifying Agents Used to Treat Uveitis

Medication	Dose	Considerations	Side Effects
Adalimumab (antibody against TNF alpha)	Subcutaneous 40 mg every 2 wk to weekly	Can be used in combination with agents such as methotrexate	Injection-site reactions, upper respiratory, sinus, and urinary tract infections, GI upset, high cholesterol, and hypertension
Daclizumab (antibody against interleukin 2 receptor)	IV 1-4 mg/kg every 14 days	Has shown promise in treating uveitis	Headache, nausea, lymphadenopathy, skin reactions
Infliximab (antibody against TNF alpha)	IV 5 mg/kg at wk 0, 2, 6, then every 8 wk	Associated with a greater risk of cancer and overall mortality	Infections, demyelinating disease, heart failure, anaphylactic reactions
Interferon alfa-2a (modulates immune response)	3 million units three times per wk subcutaneously	Used for uveitis in Behcet's syndrome	Leukopenia, thrombocytopenia, flulike symptoms, psychosis, depression
Rituximab (CD20-directed cytolytic antibody)	IV infusion 375 mg/m^2 every wk for 4 wk	Experience reported from the Massachusetts Eye Research and Surgery Institution	Nausea, headache, fatigue, rash, flulike symptoms

GI: gastrointestinal; TNF: tumor necrosis factor. Source: References 1, 25.

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Conclusion

- **Uveitis is the most common form of ocular inflammation**
- **The highest incidence is seen in persons 25 to 44 years of age, and the condition and may be more prevalent in men than women and in girls versus boys**
- **The course of uveitis is characterized as sudden or insidious and may be limited in duration, lasting 3 months or less, or persistent, lasting longer than 3 months**
- **The goals of therapy are to resolve inflammation, spare vision, and, in the case of chronic or persistent uveitis, bring about a cure**
- **First-line therapy for treating acute uveitis consists of topical or systemic steroids**
- **In the acute setting, cycloplegic ocular drops such as homatropine may be used to relieve pain and prevent photophobia and synechiae formation**
- **Steroids should be used for the shortest duration possible and slowly tapered to prevent an ocular inflammation flare**
- **If high-dose (adult dose 60-80 mg/day) oral prednisone has not produced a response or resolved the uveitis within 2 to 4 weeks, an immunosuppressive agent such as methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, chlorambucil, or leflunomide should be added**
- **Finally, if the uveitis is resistant to the immunosuppressive agents, then biologic-modifying agents such as adalimumab, infliximab, daclizumab, rituximab, or interferon alfa-2a may be required**

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