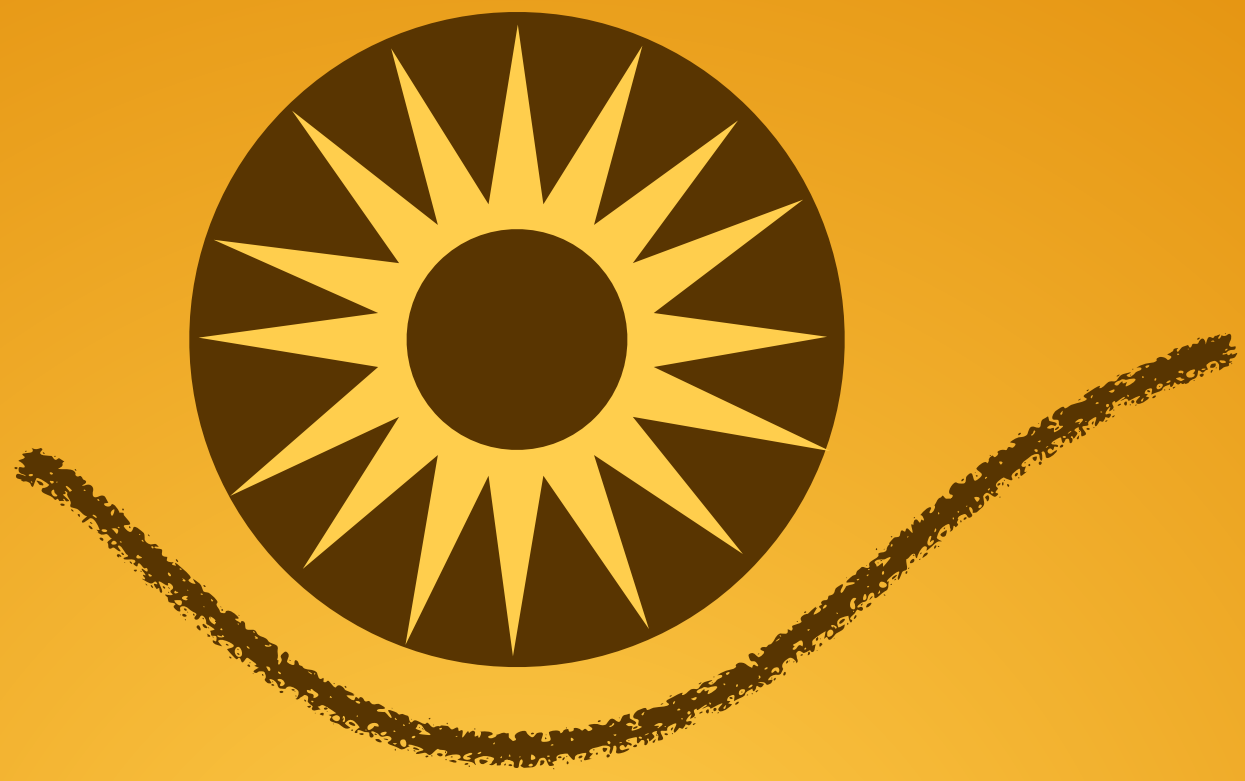
Ophthalmology PG Exam Notes



NOTES

2020

Uvea

Dhaval Patel MD

I notes 2020

(Ophthalmology PG Exam Notes)

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by inotesforPG.blogspot.com

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This is a compilation effort from my Post-graduation preparation notes and multiple other sources. Whole of the Manual is now revised from advices received from students from all over the world. Any contributions or comments are welcomed in the effort to improve this Manual.
This manual is made to serve the Exam purpose and as a Handy Reference tool only.

If you are reading this, just drop a comment or critic at:
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Dedication

To The **GOD**, the Almighty, for Giving me Imagination & Curiosity which keeps me always learning, for Giving me fine skills from which I can do my best for patients…

To My Grand-Mother; **Tejaben Patel**, for Training my childhood in such a disciplined way which has helped me to become what I am today…

To My Parents; **Bharat & Sudha Patel** and My Parents-In-Law; **Anil & Neela Patel**, for Trusting me, Motivating me and Helping me in my difficult times…

To My Wife; **Dr Dhara Patel**, for Believing in my strengths, Always supporting me in my all ventures, Bearing with me when I don't give her enough time while I am busy in my all ongoing projects and many more innumerable things which I always forget as usual…

To My Brother; **Dr Keyur Patel**, for helping me getting all the knowledge regarding Medical Science in the other continent…

To My Brother-In-Law; **Raj Patel**, for Bringing out Computer Science Kid within me and Teaching me in-numerous tips and tricks while dealing with computers…

To My Many **Friends and Relatives**; naming them all is not possible but they have helped me to Refine my life in one or the other way…

To All the **Ophthalmologists;** for pouring their knowledge and skills in this field which has now become one of the finest speciality in Medical field…

To **Patients;** for creating a demand which keeps all the ophthalmologists motivated to keep inventing and innovating methods, models and devices for their benefits…

I NOTES 2020

Ophthalmology PG Exam Notes

UVEA

If I have seen further than others,
It is by standing upon the shoulders of giants.
-Isaac Newton

Thank you GOD !

When I compiled first edition of this **iNotes** Manual in 2014, It was simple collection of few notes (*very much incomplete!*) which I prepared for my Post-graduate Ophthalmology Exams at AIIMS, New Delhi. Since then I am regularly receiving emails and messages regarding usefulness of these notes as a study material for Post-graduate students all across the world.

For last few years, I am getting emails asking that if I am going to bring any updated version of my **iNotes** as ophthalmology has advanced a lot in last 10 years. Hence from last one year I have started reading newer edition of books, recent question papers, gathered notes and presenting to you as completely new version as **iNotes 2020**.

In this edition of iNotes, I have tried to include clinical, practical and surgical tips which is going to be used in your future practice also so that this manual can be a handy book for you as a future reference too.

Also Remember, this is a "**Manual**" and not a "Complete Book", and Just like most of others, it is also far from Complete. One of the best way to utilise this for your exam preparation is to use this as a reference and make your personal manual by adding your own notes and topics asked in your university.

My Best wishes and Good luck to you All !!

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10-10–2020

INDEX

History of Uveitis

History of Uveitis Management

- Herbs
- Fever Therapy
- Leeches and Blood-letting
- Cycloplegia (1840)
- Corticosteroids (1949,Gordon)
- Nitrogen Mustard (1950, Roda-Perez)
- Methotrexate (1966, Wong)
- Other Antimetabolites and Alkylating Agents (1970 Onward)
- Biologic Response Modifiers (2001)
- Tolerance / Regulatory T Lymphocytes (2018)

Assessment of Uveitis

Patient History

- 90% of diagnoses can be made on the basis of the medical history alone
- Acute or chronic
- Accompanied by pain and redness, or by floaters and visual loss
- Visual disability and discomfort
- **Floaters and reduced vision** are the two most common complaints of patients with inflammation of the vitreous, retina, and choroid.
- **Questionnaire** developed by **Foster and MEEI**
- Family History
- HLA associations

Examination

- **UCVA and BCVA**
  - Cause of diminished vision: corneal opacity, anterior chamber inflammation, cataract, and vitreous haze
  - **Improvement in near vision** can precede an improvement in distance vision by several weeks in patients with chronic macular edema
  - Snellen eye chart
    - Ability to resolve high-contrast letters only
    - Not enough sensitivity if vision is poor
    - No lines between 20/100 and 20/200 or between 20/200 and 20/400.
    - Too few letters on the lines above 20/100.
    - Initial improvement might be missed with use of a standard Snellen chart.
  - ETDRS chart
    - Five letters per line starting with the 20/200 line
    - Every **three lines** represent a **doubling of the visual angle**
    - 20/40 to 20/20 = 20/80 to 20/40.
    - If patients cannot read the 20/200 line while sitting 4 m from the chart, they are moved to 1 m from the chart → 5/200
    - 1 and 4 m scales can be made continuous by adding 30 letters to the number read at 4 m. The scale of visual acuity is then linear and continuous from 5/200 (five letters) to 20/12.5 (95 letters).
  - Electronic visual acuity testing algorithm (E-ETDRS)
- **Skin**: Rashes, nodules, or vitiligo
- **Pupils and extraocular muscles:**

- Synechiae
- Iris atrophy
- RAPD
- Esotropia or exotropia resulting from long-standing visual loss may develop as a result of cataract, retinal, or optic nerve disease

- **IOP**:
  - Under anesthetic **without fluorescein**, done with a pneumotonometer, or preferably, performed at the end of the examination.
  - Elevated intraocular pressure or hypotony can occur as a result of intraocular inflammation
- **SLE**
  - Conjunctival hyperemia: CCC
  - Cornea
    - KP: aggregates of inflammatory cells
    - Base-down triangle configuration generally, diffuse in FHI
    - **Nongranulomatous**: small aggregates, neutrophils and lymphocytes
    - **'Mutton-fat' or 'granulomatous'**: larger granulomatous aggregates are composed of macrophages and giant cells
    - Interstitial keratitis may be associated with **syphilis or Cogan's syndrome**
  - Anterior chamber
    - Anterior chamber inflammation is a convenient but somewhat indirect measure of the inflammatory reaction
    - Cells
    - **Primarily lymphocytes** but a significant number of neutrophils may be present
    - Cells represent an **index of activity** but not a direct measure of the active inflammation
      - **CELLS Grading System**
        - ✓ **SUN-Standardization of uveitis nomenclature**
          - <1 -0
          - 1–5 -±
          - 6–15 -+1
          - 16–25 -+2
          - 26–50 -+3
          - >50 -+4
      - **Flare**:
        - ✓ Increased protein content in the anterior chamber
        - ✓ manifestation of a **breakdown of the blood–ocular barrier**

- ✓ When the slit beam is obliquely aimed across the anterior chamber, the ability to **visualize the path of the beam** is termed flare. This principle is known as TYNDALL EFFECT.
- ✓ **7 g of protein/100 mL of blood**, but only **11 mg of protein/ 100 mL of aqueous**.
- ✓ Chronic flare alone is not a sign of active inflammation. Damaged blood vessels may be leaky for a long time after the active inflammation has resolved.

Grading of Flare

- ✓ Nil -0
- ✓ Just detectable -+1
- ✓ Moderate (iris and lens details clear) +2
- ✓ Marked (iris and lens details hazy) +3
- ✓ Intense (fibrinous exudate) +4

- **Hypopyon** is a dramatic but short-lived finding in ocular inflammation that has been associated with Behçet's disease, endophthalmitis, and rifabutin toxicity in patients with AIDS.
- **Pseudohypopyon**, composed of tumor cells or hemorrhagic debris, can occur in some of the masquerade syndromes after vitreous hemorrhage.
- **Pink hypopyon**: Serratia marcescens endophthalmitis. Cytologic examination reveals no erythrocytes, and the pink color is due to the bacteria.

- Iris
  - Synechia
  - Fibrovascular membrane
  - Transillumination defects can be a clue to herpetic uveitis
  - Iris nodules: **Koeppe nodule** develops on the pupillary border, whereas the **Busacca's nodules** occur on the iris surface, **Berlin nodule** in the angle
- Anterior chamber angle
- Lens

Vitreous

- Grading of vitreous cells with use of Hruby lens
- **Cells in Retroilluminated Field**
  - 0–1 Clear 0+
  - 2–20 Few opacities Trace
  - 21–50 Scattered opacities 1+
  - 51–100 Moderate opacities 2+
  - 101–250 Many opacities 3+
  - >251 Dense opacities 4+

- **Vitreous haze is a better indicator** of active inflammation than are vitreous cells, because it combines the optical effect of cellular infiltration and protein leakage.

- **Retina and choroid**
  - Cystoid macular edema
  - Retinal vascular alterations: Vascular sheathing,
  - Retinal hemorrhages and cotton-wool spots
  - Choroidal lesions: grayish-yellow elevated masses,
- **Optic nerve**
  - Disc hyperemia, papillitis, or papilledema
  - Secondary glaucoma
  - Neovascularization

Diagnostic Testing in Uveitis

Lab Testing in Uveitis

- **Syphilis tests**
  - Screen with ***treponemal enzyme*** immunoassays (EIA), chemiluminescence immunoassays (CIA) or microbead immunoassays (MBIA) as initial screen
    - Qualitative
    - Persistent over lifetime
  - ***Nontreponemal tests*** to detect active infection:
    - Rapid plasma reagin (RPR) detects antibodies against cardiolipin, released by cells damaged by *T. pallidum*
    - Venereal disease research laboratory test (VDRL) is a microflocculation assay using nontreponemal antigen, cardiolipin
  - False-negative results in latent syphilis
    - VDRL testing is falsely negative in 30%
    - FTA-ABS is falsely negative in 1-2% of the cases
- **TB testing**
  - **Tuberculin skin test (TST**, also known as purified protein derivative (PPD) test)
  - Dosage
    - Purified protein derivative (PPD) simple protein precipitate of old tuberculin
    - 5-tuberculin unit (TU) dose of PPD
  - A positive TST is indicative of prior exposure to TB but not necessarily of active systemic infection
  - **Interferon-gamma (IFN-g) assays for latent TB infection**
    - QuantiFERON-TB Gold (Cellestis Ltd., Carnegie, Australia) assay

        - Uses whole blood
        - Enzyme-linked immunoabsorbent assay (ELISA)-based test
    - T SPOT-TB (Oxford Immunonotec, Oxford, UK)
        - Uses peripheral blood mononuclear cells
        - ELISPOT technology

- **HLA testing in uveitis**
    - HLA-A29: HLA-29 is present in 95-97% of patients with birdshot chorioretinopathy (BCR)
    - HLA-B27: HLA-B27 is present in 50-75% of Caucasian individuals with unilateral acute anterior uveitis (See Acute anterior uveitis)
    - HLA-B51 in Behçet disease
- **Urine β-2 microglobulin**
    - Elevated in up to 60% of patients with tubulointerstitial nephritis and uveitis syndrome (TINU)
    - Used for screening patients with bilateral acute anterior uveitis
    - Confirmatory biopsy necessary to make diagnosis of TINU
- **Antistreptolysin O titers (ASO)**
    - Patients with recent infection (throat skin)
    - Used to diagnose post-infectious uveitis
- **Antinuclear antibodies (ANA) testing in uveitis**
    - ANAs can be found in patients with a number of different autoimmune diseases
    - ANAs can be found in up to 25% of the normal population, usually in low titers.
    - Chronic iridocyclitis in a child with juvenile idiopathic arthritis (JIA)
    - Retinal vasculitis (SLE)
    - Scleritis
- **Antineutrophil cytoplasmic autoantibody (ANCA)**
    - Three patterns of neutrophil staining possible
        - c-ANCA: cytoplasmic staining: Antigenic specificity of c-ANCA has been identified as a 29 kDA neutral serine protease, proteinase 3 (PR-3)
        - p-ANCA: perinuclear staining: Autoantibodies against myeloperoxidase (MPO-ANCA)
        - Atypical patterns
    - Association with ANCA and active vasculitis
        - Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) 70-80% have positive **c-ANCA**, <10% have positive p-ANCA
        - Polyarteritis nodosa 60% have positive **p-ANCA**, 30% have positive c-ANCA
        - Microscopic polyangiitis c-ANCA or p-ANCA may be positive

- Churg-Strauss syndrome 50-80%have positive **p-ANCA**, c-ANCA rarely positive
- Idiopathic pauci-immune necrotizing vasculitis 50-80% have positive **p-ANCA**, c-ANCA rarely positive

- **Serum angiotensin converting enzyme (ACE) level**
  - Serum ACE activity is measured by kinetic spectrophotometry of furylacryloyl-phenylalanyl-glycylglycine hydrolysis
  - Any anterior, intermediate, posterior or panuveitis that necessitates work-up
- **HIV Testing**
  - Screening assays: Enzyme-linked immunoabsorbent assay (ELISA) tests, Results considered reactive or nonreactive
  - Confirmatory tests: Western blot or immunofluorescence assays, Results are termed positive, negative or indeterminate
- **Chest radiograph**
  - Indications: Tuberculosis suspect, Sarcoidosis suspect 90% sensitivity in active sarcoidosis
- **Chest CT:** TB, Sarcoidosis
- **Nuclear medicine and positron emission tomography**: Gallium scan for sarcoidosis, FDG-PET for tuberculosis
- **Intraocular Fluid examination:**
  - PCR: PCR may be performed on DNA or RNA (via reverse transcriptase, also known as RT-PCR). PCR may be performed in monoplex or in multiplex (ie, several primer sets analyzed simultaneously). PCR may be performed qualitatively or quantitatively (ie, qPCR). Detection of products may be by electrophoresis or by melt-curve analysis.
    - Viral PCR
      - Generally done in multiplex for HSV 1/2, VZV, CMV, (EBV)
      - Quantitative PCR
        - ✓ Utilizes SYBR dye or TaqMan probes
        - ✓ High utility in distinguishing latent virus from active infection
    - Pan-bacterial 16S PCR
      - Universal ribosomal sequence allows for amplification of most bacteria.
      - Subsequent sequencing required for identification of genus. Utility in corneal ulceration, endogenous endophthalmitis
    - Pan-fungal 5.8S/ITR/18S PCR:
      - Similar utility to pan-bacterial PCR
      - Fungi (28S rRNA gene)
    - Toxoplasma gondii

- *Mycobacterium* tuberculosis (65 kDA sAg)
- *Borrelia burgdorferi* (41 kDa flagellin gene)
- *Propionibacterium* (Pa1, rPa2, rPa3 antigens)
- Tropheryma whipplei (16S rRNA gene)
- Intraocular lymphoma (IgH gene, Myd88 L265P mutation)

- Culture: Culture of intraocular fluids remains the gold standard for diagnosis of endophthalmitis. Almost always vitreous specimens are obtained.
- Cytology: Cytology with PAP stain or H&E stain. Cytology remains the gold standard for the biopsy of lymphoma. Specimens can be obtained from the anterior chamber, vitreous cavity, or subretinal fluid. Selection of fluid source needs to balance the surgical risks of the procedure with the chance of identifying malignant cells in a particular anatomic location in specific patients. Thorough preoperative assessment including multimodality imaging should be used to identify the exact location of cellular infiltrate.
- Cytokine analysis for IL-6 and IL-10 can help distinguish lymphoma (high IL-10 to IL-6 ratio) from other inflammatory disease (low IL-10 to IL-6 ratio).
- Goldmann-Witmer testing
  - Widely used in Europe; limited availability in the United States
  - Newly recognized utility in ocular toxocariasis

- **ECG**

Conjunctival Biopsy

- **Indications**
  - Granulomatous disease sarcoidosis
  - Mucosa-associated lymphatic tissue (MALT) tumor/Conjunctival tumor (masquerading as follicular conjunctivitis or granulomatous disease)
  - Acquired immune deficiency syndrome (AIDS) related disease
    - Kaposi sarcoma
    - Molluscum contagiosum
  - Ocular mucous membrane pemphigoid
  - Exclude other infectious etiologies
- **Contraindications**
  - Prior history of ligneous conjunctivitis
  - Evident, active conjunctival infection

Vitreous Biopsy

- **Indications**

- Uveitis where neoplastic or infectious disease are suspected (either due to the clinical appearance or to failure to respond to conventional therapy)
  - Primary Vitreoretinal lymphoma (PVRL)
  - Viral infection (Herpes simplex, herpes zoster, cytomegalovirus, Epstein Barr, human herpesvirus-6)
  - Atypical toxoplasmosis
  - Mycobacterium tuberculosis
  - Whipple disease
- Microbiologic evaluation of endophthalmitis

- **Laboratory Testing for Diagnostic Tap**
  - Histology
  - Gram stain, culture, and sensitivity
  - Polymerase chain reaction (PCR)
    - Viral PCR/quantitative PCR
    - 16S universal bacterial PCR
    - 18S universal fungal PCR
    - Emerging deep sequencing techniques
  - Intraocular Antibody Testing
  - Cytokine Analysis

Chorioretinal Biopsy

- **Indications**
  - Intraocular lymphoma mostly confined to the subretinal space
  - Sight-threatening chorioretinitis of unknown etiology involving one eye or both eyes
    - Biopsy is performed in eye with worse visual potential
    - Includes cases with an atypical presentation, inconclusive system work up, inadequate response to conventional therapy
    - Useful to distinguish between cases of suspected infection or malignancy in which the biopsy has the potential to alter management
  - Suspected intraocular malignancy mostly confined to the subretinal space
- **Contraindications**
  - Disease in which there is a reasonable expectation that vitreous biopsy would provide sufficient material for cytologic examination
  - Chorioretinitis in which there is reasonable expectation that culture, or polymerase chain reaction analysis or antibody determinations of ocular fluid would be sufficient to make the diagnosis
  - Possible retinoblastoma in which intraocular biopsy may worsen the systemic prognosis

Imaging in Uveitis

- **Imaging purposes**
  - To establish diagnosis
  - To monitor treatment
  - To assess safety and efficacy of clinical trial interventions
- **Fluorescein angiography**
  - Cystoid macular edema
  - White dot syndrome
  - Vogt-Koyanagi-Harada (VKH) syndrome
  - Sympathetic ophthalmia
  - Posterior scleritis
  - Placoid syphilitic uveitis
  - Acute multifocal posterior pigment epitheliopathy
  - Serpiginous choroiditis
- **Indocyanine green angiography**
  - White dot syndrome
  - VKH syndrome
  - Sarcoid
  - Acute multifocal posterior pigment epitheliopathy
  - Serpiginous choroiditis
- **Color fundus photography**
  - Monitor change in chorioretinal lesions
  - Can use ultrawide-field imaging or small multifield standard photography
- **Ultrasonography**
  - Useful when media opacity precludes imaging by other methods
  - Particularly helpful for presurgical planning
- **Fundus autofluorescence**
  - Helpful to monitor retinal pigment epithelial cell absence or dysfunction
  - Monitor disease activity
  - Monitor disease progression
- **Optical coherence tomography**
  - Assess tissue thickness
    - Retinal thickness: Cystoid macular edema, Retinal thinning
    - Subretinal tissue thickness: Choroidal neovascularization, Subretinal fibrosis

        - Choroidal thickness: VKH syndrome, Posterior scleritis, Sympathetic ophthalmia
    - Assess morphological characteristics: Vitreoretinal interface changes
        - Epiretinal membrane
        - Vitreomacular traction
    - Assess retinal microstructure
    - Determine fluid: Intravitreal fluid, Subretinal fluid, Choroidal fluid
    - Hyper-reflective dots
    - Anterior chamber cells
    - Vitreous cells
- **Optical coherence angiography**
    - Determine vascular flow
    - Determine blood vessel location in depth slab

Speciality Referral in Uveitis

- **Rheumatology**: rheumatic disease, inflammatory arthritis, psoriasis, vasculitis
- **Dermatology**: psoriasis, other suspected associated cutaneous findings
- **Pulmonology**: nodules / adenopathy on chest imaging
- **Neurology**: demyelinating or other neurologic disease
- **Infectious disease**: assessment / management of suspected infectious uveitis
- **Oncologist/ocular oncologist**: suspected masquerade / malignancy

Differential Diagnosis

Acute or chronic uveitis

(<6 weeks, > 6 weeks)

Acute Uveitis

- Most cases of anterior uveitis: idiopathic, ankylosing spondylitis, Reiter's syndrome, Fuchs' heterochromic iridocyclitis
- Vogt–Koyanagi–Harada syndrome
- Toxoplasmosis
- White-dot syndromes: acute posterior multifocal placoid pigment epitheliopathy and multiple evanescent white-dot syndrome
- Acute retinal necrosis
- Postsurgical bacterial infection
- Trauma

Chronic Uveitis

- Juvenile rheumatoid arthritis
- Birdshot choroidopathy
- Serpiginous choroidopathy
- Tuberculous uveitis
- Postoperative uveitis (Propionibacterium acnes, fungal)
- Intraocular lymphoma
- Sympathetic ophthalmia
- Multifocal choroiditis
- Sarcoidosis
- Intermediate uveitis/pars planitis

Granulomatous or Nongranulomatous

Causes of granulomatous inflammation

- Sarcoidosis
- Sympathetic ophthalmia
- Uveitis associated with multiple sclerosis
- Lens-induced uveitis
- Intraocular foreign body
- Vogt–Koyanagi–Harada syndrome
- Syphilis

- Tuberculosis
- Other infectious agents

Unilateral or Bilateral

Causes of unilateral uveitis

- Sarcoidosis
- Postsurgical uveitis
- Intraocular foreign body
- Parasitic disease
- Acute retinal necrosis
- Behçet's disease

Location in the Eye

- **Causes of anterior uveitis**
  - Idiopathic
  - Ankylosing spondylitis
  - Reiter's syndrome
  - Inflammatory bowel disease
  - Psoriatic arthritis
  - Behçet's disease
  - HLA-B27-associated disease
  - Juvenile rheumatoid arthritis
  - Fuchs' heterochromic iridocyclitis
  - Sarcoidosis
  - Syphilis
  - Glaucomatocyclitic crisis
  - Masquerade syndromes
- **Causes of intermediate uveitis**
  - Sarcoidosis
  - Inflammatory bowel disease
  - Multiple sclerosis
  - Lyme disease
  - Pars planitis *(poorest prognosis among intermediate uveitis)*
- **Causes of posterior uveitis**
  - **FOCAL RETINITIS**

- Toxoplasmosis
- Onchocerciasis
- Cysticercosis
- Masquerade syndromes

- **MULTIFOCAL RETINITIS**
  - Syphilis
  - Herpes simplex virus
  - Cytomegalovirus
  - Sarcoidosis
  - Masquerade syndromes
  - Candidiasis
  - Meningococcus
- **FOCAL CHOROIDITIS**
  - Toxocariasis
  - Tuberculosis
  - Nocardiosis
  - Masquerade syndromes
- **MULTIFOCAL CHOROIDITIS**
  - Histoplasmosis
  - Sympathetic ophthalmia
  - Vogt–Koyanagi–Harada syndrome
  - Sarcoidosis
  - Serpiginous choroidopathy
  - Birdshot choroidopathy
  - Masquerade syndromes (metastatic tumor)

- **Causes of panuveitis**
  - Syphilis
  - Sarcoidosis
  - Vogt–Koyanagi–Harada syndrome
  - Infectious endophthalmitis
  - Behçet's disease
  - SO

Demographics

Age (yr)	Diagnostic Considerations
<5	Juvenile rheumatoid arthritis Toxocariasis Postviral neuroretinitis (Retinoblastoma) (Juvenile xanthogranuloma) Leukemia
5–15	Juvenile rheumatoid arthritis Pars planitis Toxocariasis Postviral neuroretinitis Sarcoidosis Leukemia
16–25	Pars planitis Ankylosing spondylitis Idiopathic anterior uveitis Toxoplasmosis Sarcoidosis Acute retinal necrosis
25–45	Ankylosing spondylitis Idiopathic anterior uveitis Fuchs' heterochromic iridocyclitis Idiopathic intermediate uveitis Toxoplasmosis Behçet's disease Idiopathic retinal vasculitis Sarcoidosis White-dot syndromes Vogt–Koyanagi–Harada syndrome AIDS, syphilis Serpiginous choroidopathy
45–65	Birdshot retinochoroiditis Idiopathic anterior uveitis Idiopathic intermediate uveitis Idiopathic retinal vasculitis Behçet's disease Serpiginous choroidopathy Acute retinal necrosis
>65	Idiopathic anterior uveitis Idiopathic intermediate uveitis Idiopathic retinal vasculitis Serpiginous choroidopathy (Masquerade syndromes)

Factor	Disease Risks
Female	Pauciarticular juvenile rheumatoid arthritis, chronic anterior uveitis
Male	Ankylosing spondylitis, sympathetic ophthalmia
American black	Sarcoidosis
Native American	Vogt–Koyanagi–Harada syndrome
Midwestern American	Presumed ocular histoplasmosis
Japanese	Vogt–Koyanagi–Harada syndrome Behçet's syndrome

Factor	Disease Risks
Mediterranean ancestry	Behçet's syndrome
Central American	Cysticercosis, onchocerciasis
South American	Cysticercosis, toxoplasmosis
West African	Onchocerciasis
Intravenous drug user	Fungal endophthalmitis, AIDS
Promiscuous sexual activity	AIDS, syphilis
Frequent hiking in wooded areas	Lyme disease

Symptoms and Signs

Symptom or Sign	Possible Associated Conditions
Headaches	Sarcoidosis, Vogt–Koyanagi–Harada syndrome
Neurosensory deafness	Vogt–Koyanagi–Harada syndrome, sarcoidosis
Cerebrospinal fluid pleocytosis	Vogt–Koyanagi–Harada syndrome, sarcoidosis, acute posterior multifocal placoid pigment epitheliopathy, Behçet's syndrome
Paresthesia, weakness	Intermediate uveitis associated with multiple sclerosis, Behçet's syndrome, steroid myopathy
Psychosis	Vogt–Koyanagi–Harada syndrome, sarcoidosis, Behçet's disease, steroid psychosis, systemic lupus erythematosus
Vitiligo, poliosis	Vogt–Koyanagi–Harada syndrome
Erythema nodosum	Behçet's syndrome, sarcoidosis
Skin nodules	Sarcoidosis, onchocerciasis
Alopecia	Vogt–Koyanagi–Harada syndrome
Skin rash	Behçet's syndrome, sarcoidosis, viral exanthem, syphilis, herpes zoster, psoriatic arthritis, Lyme disease
Oral ulcers	Behçet's syndrome, inflammatory bowel disease
Genital ulcers	Behçet's syndrome, Reiter's syndrome, sexually transmitted diseases
Salivary or lacrimal gland swelling	Sarcoidosis, lymphoma
Lymphoid organ enlargement	Sarcoidosis, AIDS
Diarrhea	Whipple's disease, inflammatory bowel disease
Cough, shortness of breath	Sarcoidosis, tuberculosis, malignancy
Sinusitis	Wegener's granulomatosis
Systemic vasculitis	Behçet's syndrome, sarcoidosis, relapsing polychondritis
Arthritis	Behçet's syndrome, Reiter's syndrome, sarcoidosis, juvenile rheumatoid arthritis, rheumatoid arthritis, Lyme disease, inflammatory bowel disease, Wegener's granulomatosus, systemic lupus erythematosus, other connective tissue diseases
Sacroiliitis	Ankylosing spondylitis, Reiter's syndrome, inflammatory bowel disease
Chemotherapy or other immunosuppression	Cytomegalovirus retinitis, *Candida* retinitis, other opportunistic organisms

- **Medications possibly causing uveitis**
  - Brimonidine
  - Latanoprost
  - Rifabutin
  - Terbinafine

- Trimethoprim

Classifications of Uveitis

- **STANDARDISATION OF UVEITIS NOMENCLATURE (SUN) Working Group Classification (SUN Working Group)**
  - International (35 centers, 13 countries) SUN Meeting 8-9 November 2004
  - Process
    - Survey prior to meeting
    - Consensus via nominal group techniques Manuscript in press
    - Endorsed by AUS & IUSG leadership

- **SUN Anatomic Classification**

Type	Primary site of inflammation	Includes
Anterior	Anterior chamber	Iritis, Iridocyclitis
Intermediate	Vitreous	Vitritis
		Pars planitis
Posterior	Retina or Choroid	Choroiditis
		Retinitis, Neuroretinitis
		Retinochoroditis
Panuveitis	AC, Vitreous, Retina or Choroid	

- **SUN Description of Uveitis**

Category	description	Comment
Onset	sudden	
	Insidious	
Duration	limited	≤3 months
	Persistant	> 3 months
Course	acute	Sudden onset, limited duration
	Recurrent	Episodes & ≥ 3 mos inactive off Rx
	Chronic	Persistent & prompt relapse off Rx

- **SUN Outcomes**
  - Inactive Uveitis: < 1 cell/field (i.e. a rare cell is inactive) Improved/worsened: 2 step change or
  - decreased/increase to inactive/4+
  - Remission: inactive off all Rx for ≥ 3 mo.
  - Corticosteroid-sparing: able to taper to ≤ 10 mg/day & uveitis inactive

Management Guidelines for Uveitis

Medical Therapy

- Goals of Therapy in Patients With Uveitis
  - Eliminate ocular inflammation
  - Reduce ocular and systemic morbidity
- Management can be grouped into
  - Corticosteroids
  - Immunomodulatory Agents
  - Other Therapy

Corticosteroids

Gordon's dictum – "Use enough, soon enough, taper and discontinue"

- Mechanism of action
  - Inhibits arachidonic acid release from phospholipids
  - Inhibit the transcription and action of cytokines
  - Limits B-and T-cell activity.

Preparation	Antiinflammatory potency
Hydrocortisone	1.0
Cortisone	0.8
Prednisolone	4.0
Prednisone	4.0
Dexamethasone	26
Methylprednisolone	5
Triamcinolone	5
Betamethasone	33

- **Topical application**
- **Periocular injections:**
  - **PST** 40 mg in 1 mL
  - **anecortave acetate**, a corticosteroid that has been modified so that its corticosteroid activity has been eliminated, is also injected periocularly. The interest in this molecule is **related to its retardation of blood vessel growth** through **inhibition of endothelial cell migration**.
- **Intraocular administration**
  - 2 mg of triamcinolone
  - Fluocinolone acetonide (FA) intravitreous implants
  - **Ozurdex** is a sustained-release biodegradable intravitreal implant containing dexamethasone.

- Systemic corticosteroids remain the initial drug of choice for most patients with severe bilateral endogenous sight-threatening uveitis. The striking **exception** to this rule is patients with **Behçet's disease**.

- **Steroid limitations: Poor outcomes as monotherapy in ophthalmology for:**
  - Adamantiades-Behçet disease
  - Juvenile idiopathic arthritis (JIA)
  - Wegener granulomatosis
  - Serpiginous
  - Birdshot
- **Steroid complications**
  - **Nonocular**
    - Endocrine (adrenal insufficiency, Cushing syndrome, growth failure, menstrual disorders)
    - Neuropsychiatric (pseudotumor cerebri, insomnia, mood swings, psychosis)
    - Gastrointestinal (peptic ulcer, intestinal perforation)
    - Musculoskeletal (osteoporosis, aseptic hip necrosis)
    - Cardiovascular (hypertension, sodium and fluid retention)
    - Metabolic (secondary diabetes mellitus, obesity, hyperlipidemia)
    - Dermatologic (acne, striae, hirsutism)
    - Immunologic (impaired inflammatory response, delayed tissue healing)
  - **Ocular:** Cataract, Glaucoma, Central serous retinopathy, Susceptibility to infection

- **Common immunosuppressive agents**

Agent	Usual dosage*
Prednisone	Oral: 1–2 mg/kg/day
Methylprednisolone	IV pulse: 1 g over 1–2 h
Intraocular triamcinolone	Intravitreal: 2–4 mg
Antimetabolites	
Methotrexate	Oral: 7.5–15 mg weekly; can be given intramuscularly
Azathioprine weight/day	Oral: 50–150 mg daily, 1–1.5 mg/kg, but up to 2.5 mg/kg body
Mycophenolate mofetil	Oral: 1 g twice per day
Alkylating agents	
Cyclophosphamide	Oral: 50–100 mg daily, up to 2.5 mg/kg body weight/day
	IV pulse: 750 mg/m^2 (adjusted to kidney function and white blood cell count)
Chlorambucil	Oral: 0.1–0.2 mg/kg/day
Ciclosporin	Oral: up to 5 mg/kg/day, usually given with prednisone, 10–20 mg/day

Agent	Usual dosage*
FK506	Oral: 0.10–0.15 mg/kg body weight/day
Daclizumab	IV or SC: 1–2 mg/kg
Etanercept	SC: 25 mg twice weekly; children 0.4 mg/kg twice weekly
Infliximab	SC: 3–10 mg/kg
Interferon-α	SC: 3–6 × 10^6 IU qd × 1 mo, then qod; 3 × 10^6 IU three times per week

Immunomodulatory Agents

- **Absolute Indications for Immunomodulatory Therapy**
  - Adamantiades-Behçets disease with retinal involvement
  - JIA
  - Vogt-Koyanagi-Harada
  - Necrotizing scleritis
  - Wegener granulomatosis
  - Polyarteritis nodosa
  - Relapsing polychondritis
  - Ocular cicatricial pemphigoid
  - Sympathetic ophthalmia
- **Relative Indications**
  - Intermediate uveitis
  - Severe vasculitis
  - Severe chronic iridocyclitis
- **Possible Indications**
  - Intermediate uveitis in children
  - Sarcoid-associated uveitis inadequately responsive to steroid
  - Keratoplasty with multiple rejections

- **Include 3 main categories of therapy:**
  1. **Antimetabolites**: Azathioprine, methotrexate, and mycophenolate mofetil
  2. **T-cell suppressors**: Cyclosporine and tacrolimus
  3. **Cytotoxic agents**: Cytotoxic agents are alkylating agents and include cyclophosphamide and chlorambucil.
- Most agents take several weeks to achieve efficacy; therefore, they initially are used in conjunction with oral corticosteroids. Once the disease is under control, corticosteroids can be tapered.

- **Azathioprine**
  - **Introduction**: It is a nucleoside analog which interferes with DNA replication and RNA transcription. Decreases peripheral T-and B-lymphocyte count and reduces lymphocyte activity. Metabolism is dependent on xanthine oxidase. It may decrease proliferation of immune cells, which results in lower autoimmune activity.
  - **Indications**: Behcet disease or chronic uveitis, especially with oral corticosteroids.
  - **Dose**: 1 mg/kg/ d orally initially; not to exceed 2.5-4 mg/kg/ d
  - **Side effects**
    - Causes GI upset
    - Alters liver function and renal function
    - Decreases the bone marrow function
    - Rarely causes pancreatitis
    - Increases risk of neoplasia
  - CBC and liver function tests should be done once every two weeks.

- **Methotrexate**
  - **Introduction**: It is a folic acid analog and inhibitor of dihydrofolate reductase, which is the enzyme responsible for the conversion of dihydrofolate to tetrahydrofolate. It arrests DNA replication, inhibiting rapidly dividing cells (e.g.leucocytes).
  - **Indications**: It is used to treat various ocular inflammatory diseases, including vasculitis, panuveitis, intermediate uveitis, and vitritis, Behcet disease or chronic uveitis, especially with oral corticosteroids.
  - **Dose**: 7.5-12.5 mg/wk PO initially; not to exceed 25 mg/wk; folate (1 mg/ d) is given concurrently to minimize nausea
  - **Side effects**
    - Increases fatigue
    - Causes GI upset
    - Alters liver, hematological and renal function
    - Rarely causes pneumonitis
  - CBC and liver function tests should be done once every two weeks.

- **Mycophenolate mofetil**
  - **Introduction**: It is a selective inhibitor of inosine monophosphate dehydrogenase, which interferes with guanosine nucleotide synthesis. It prevents lymphocyte proliferation, suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium, and decreases recruitment of leukocytes to sites of inflammation.
  - **Indications**: Various studies are ongoing to study effectivity in various inflammatory conditions.

- **Dose**: 500 mg orally bid initially; not to exceed 1.5 g bid
- **Side effects**
  - Increases chance of infection
  - Causes GI upset like nausea, vomiting and diarrhoea.
  - Alters liver, haematologic and renal function
  - Incidence of leucopenia, lymphoma, and non-melanoma skin cancers are reported
- CBC, renal and liver function tests should be done once every two weeks.

Cydosporine

- **Introduction**: It binds to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T -lymphocytes. This complex of cyclosporin and cyclophilin inhibits calcineurin which under normal circumstances is responsible for activating the transcription of interleukin2. It thus inhibits the transcription ofT lymphocytes that are in the GO and G1 phase of their cell cycle, which blocks replication and ability to produce lymphokines.
- **Indications**: Cyclosporine can be used in cases of uveitis which are not responding to treatment with steroids.
- **Dose**: 2.5-5 mg/kg/ d orally initially; not to exceed 10 mg/kg/ d
- **Side effects**
  - Causes gingival hyperplasia, tremors, myalgias and hirsuitism.
  - Nephrotoxic and Hepatotoxic
  - Can lead to hypertension
- CBC, renal and liver function tests should be done once evety two weeks.

Cyclophosphamide

- **Introduction**: It is chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of the active metabolites may involve crosslinking of DNA, which may interfere with growth of normal and neoplastic cells. It is cytotoxic to resting and dividing lymphocytes.
- **Indications**: The main indication is Wegner's granulomatosis. It can also be used as second line in management of cases not responding to steroids or other immunosuppresives.
- **Dose**: 2 mg/kg/ d orally initially; not to exceed 3 mg/kg/ d
- **Side effects:**
  - Causes haemorrhagic cystitis
  - Causes severe nausea, vomiting.
  - It can also lead to ovarian failure and testicular atrophy.

- CBC, renal, liver function tests and routine urine examination should be done once evety two weeks.

- **Biologicals: These are monoclonal antibodies against tumor necrosis factor (TNF).**
- ***TNF alpha Biological activities***
  - Induction of pro-inflammatory cytokines like IL-l, IL-6
  - Enhancement of leucocyte migration
  - Expression of adhesion molecules by endothelial cells and leucocytes
  - Activation of neutrophil and eosinophil functional activity

- **Infliximab**
  - **Introduction**: Infliximab is a genetically engineered fusion protein consisting of TNF receptors fused to the constant region of human immunoglobulin IgG 1. It is 75% humanised. It is a short-term immunosuppressive used in noninfectious uveitis.
  - **Indication**: Several investigatorsponsored trial and uncontrolled case series indicated that TNF antagonists, mainly infliximab is useful in ocular inflammation associated with Behcet's disease, Rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, Sarcoidosis, idiopathic uveitis, birdshot retinochoroiditis.
  - **Dosage**
    - Administered as 5-l Omg/kgintravenous infusion. Regime (1st doseDay 0, 2nd doseDay14, 3rd dose-Day 42) as intravenous infusion.
    - Methotrexate7.5 mg weekly and Folic acid 5 mg daily given to reduce immunogenicity.
  - **Mechanism of action**
    - • Neutralises 1NF-alpha activity, binds to soluble and membranous forms of1NF-alpha
    - • Rapid reduction of C-reactive protein
    - • Decreases pro-inflammatory cytokines-TNF-alpha, IL-6 & IL-l
  - **Side effects**
    - Anaphylactic reaction
    - Demyelination syndrome
    - Infusion related reactionhypersensitivity reaction
    - AutoimmunityLupus like syndromeAntibody to ds DNA
  - **Precautions**
    - Immunosuppression
    - Pregnancy & lactation
    - Extremes of age
    - Drug interactions

- Carcinogenesis, mutagenesis or impairment of fertility
- Known hypersensitivity to any murine proteins

- **Adalimumab**
  - It is a completely humanised monoclonal antibody against TNF-alpha. Thus, it has the potential to cause fewer side effects like anaphylactic reaction. Its role is being studied in various uveitic conditions especially childhood uveitis.

- **Etanercept (Enbrel)**
  - ENBREL was first approved 7 years ago for the treatment of moderate to severe rheumatoid arthritis (RA). It is a 1NF alpha inhibitor. It binds to both soluble and cell membrane associated TNF-alpha and inhibits their binding to cell-surface TNF-alpha receptors.
  - Its role was studied in childhood uveitis recently. The study showed that it is not effective in uveitis associated with juvenile arthritis, in fact it can provoke uveitis.

- **Sirolimus**
  - Lipophilic microcyclic lactone that is isolated from the actinomycete Streptomyces hygroscopicus, a fungus discovered at Rapa Nui
  - Mechanistic Target of Rapamycin (mTOR) Pathway
    - mTOR protein is an intracellular coordinator of ribosomal biogenesis, protein translation, and proper cell growth.
    - Potential role of the mTOR pathway in the pathogenesis of ocular inflammation: Modulates cellular responses to insulin, insulin-like growth factors, nutrient levels, hypoxia, and redox status
  - Phase 1 and 2 clinical trials
    - Sirolimus as a Therapeutic Approach for Uveitis (SAVE) study: subconjunctival and intravitreal sirolimus
    - Sirolimus as a Therapeutic Approach for Uveitis: Protocol 2 with Comparison of Two Doses of Intravitreal Sirolimus (SAVE-2) study
  - Phase 3 clinical trials
    - Sirolimus Study Assessing Double-Masked Uveitis Treatment-1 (SAKURA-1)
    - Sirolimus Study Assessing Double-Masked Uveitis Treatment-2 (SAKURA-2)

- **Upcoming Systemic Agents**
  - Tumor necrosis factor inhibitors
    - Relative efficacy of infliximab, adalimumab, and etanercept for uveitis
    - Golimumab, certolizumab
  - Anti-CD20

        - Rituximab
        - Use in granulomatosis with polyangiitis
        - Use in uveitis/scleritis
    - Anti-IL17: AIN457 clinical trial
    - IL-1 inhibitors: Gevokizumab, anakira, canakinumab, rilocept
    - IL-6 inhibitors: Toclizumab

Other Therapy

- Antiviral therapy
- Mydriatic and cycloplegic agents
    - Helps prevent the development of posterior synechiae and, in the extreme, iris bombe
    - Relieves discomfort/ pain
    - Gives unhindered view of the media and fundus
    - ***Avoid cyclopentolate*** (Cyclogyl), as this has been shown to be an effective chemoattractant for leukocytes.
- Antitoxoplasmosis therapy
- Immunostimulators
    - Levamisole
- Plasmapheresis
- NSAIDS

Novel Approaches to Medical Therapy

- **Iontophoresis Technology**
    - Use of electrical current to facilitate delivery of medication or ions into the tissue for therapeutic purposes
    - Based on the physical principle that like charges repel each other
    - Potential advantages
        - Safety
        - Avoids systemic toxicity
        - Physician-controlled dosing
    - Other speciality uses
        - Leduc demonstrated transcutaneous iontophoretic administration of strychnine in rabbits in early 1900s.
        - Clinical Applications
        - Dermatologic
            - Delivery of anesthetic through skin

        - Primary focal hyperhidrosis
    - Sweat test by pilocarpine iontophoresis for the diagnosis of cystic fibrosis
    - Administration of acetylcholine and sodium nitroprusside for assessing risk of development and progression of cardiovascular disease
    - Administration of nonsteroidal anti-inflammatory drugs or corticosteroids for musculoskeletal disorders
    - Administration of verapamil for treating Peyronie disease
    - Administration of vitamin C for treating melasma
  - Uveitis Uses
    - 1989: Lam et al showed transscleral dexamethasone delivery more effective than drops and subconjunctival injections.
    - 1997: Behar-Cohen et al developed rat uveitis model treated with iontophoresis of dexamethasone.
    - **Iontophoresis** system: First commercial ocular iontophoresis system developed by **EyeGate** Pharma
      - EGP-437 (dexamethasone phosphate formulated for iontophoresis
- **Contact lens**
  - Ability to absorb drugs and release over a period of time
  - Silicon-hydrogel loaded with vitamin E has been shown to increase dexamethasone release period to from 1 day to 7 to 9 days.
- **Nanoparticles**
  - Potential advantages: Ability to penetrate tissue better, more controlled release of drug over longer duration
  - Tamoxifen-loaded nanoparticles injected intravitreally have been shown to be effective in treating experimental autoimmune uveitis models whereas nonencapsulated tamoxifen had no effect.
  - Betamethasone-encapsulated particles have successfully treated EAU models.

Local Therapy

- **Ozurdex and Retisert**
  - FDA approved for intermediate and panuveitis
  - Multicenter Uveitis Steroid Treatment (MUST) trial results for Retisert
  - Intravitreal methotrexate for uveitis: Efficacy for cystoid macular edema
  - Intravitreal TNF inhibitors: infliximab
- **Sirolimus**
  - Periocular administration preliminary trial
  - Intravitreal trial: Sirolimus as Therapeutic Approach to Uveitis (SAVE) trial

Surgical Therapy

Disease needs to be clinically quiescent for at least 3 months

- Removal of band keratopathy
  - Calcium hydroxyapatite accumulates in Bowman's membrane
  - 1.7% solution of EDTA in water or saline applied to the cornea with cotton or a cellulose applicator.
  - Excimer laser
- Corneal transplantation
  - herpetic keratouveitis
- Cataract surgery
- Glaucoma surgery
- Laser treatment

Anterior Uveitis

- It accounts for around 60% of all the cases of uveitis
- **Definitions**
  - Anterior: “Primary site of inflammation is anterior chamber. Includes iritis, iridocyclitis and anterior cyclitis.”
  - 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”
  - Acute Anterior Uveitis (AAU): Iritis or iridocyclitis of sudden onset lasting less than 3 months

HLA B-27 Positive Anterior Uveitis

Uveitis in Spondyloarthropathies

- Group of seronegative spondyloarthropathies include: **(Mnemonic: PAIR)**
  - Ankylosing spondylitis
  - Reiter syndrome/Postinfectious or reactive arthritis
  - Inflammatmy bowel disease
  - Psoriatic arthritis
  - Undifferentiated spondyloarthropathy.
- These conditions are associated with both acute non-granulomatous anterior uveitis and HLA B 27 positivity.
- **HLA B-27 Association**: Human leucocyte antigen B-27 (HLA B-27) is a genome located on the short arm of chromosome 6. HLA B-27 positivity is present in around 8% of the Western population and 1% of the Asian population. But almost 50-60% of the patients with acute anterior uveitis are HLA B 27 positive.
- **Pathogenesis**: The actual role of HLA-B27 in triggering an inflammatory response causing disease is still not precisely known. It is believed to incite the immune reaction by molecular mimicry or acting as an arthritogenic peptide.
- **Clinical Features**
  - ***Symptoms***
    - Pain
    - Photophobia
    - Redness
    - Blurring of vision
  - ***Signs***
    - Circumcorneal congestion
    - Presence of fine keratic precipitates especially over the inferior part.

- Severe anterior chamber reaction, quite often fibrin and hypopyon formation occurs.

- **Natural Course**
  - There is a high frequency of recurrent episodes with a mean number of 0.6-3.3 attacks per year
  - Mean duration of each episode is 4-6 weeks.
  - The interval between acute attacks is about 14-25 months.
  - There may also be a decrease in the frequency of uveitis attacks with increasing duration of disease.

Ankylosing Spondylitis

- Ankylosing spondylitis is a chronic, usually progressive disease involving the articulations of the spine and adjacent soft tissues. The sacroiliac joints usually are affected. Involvement of the hip and shoulders commonly occurs, and peripheral joints are affected less frequently.
- **Epidemiology**: The disease begins most often in the third decade. Males are more commonly affected. HLA B 27 positivity is found in almost 90% of the patients with ankylosing spondylitis. Almost, 1 in 4 patients with HLA B 27 positivity will develop ankylosing spondylitis or anterior uveitis.
- **Clinical features**
  - ***Symptoms***: Lower back pain and stiffness which is worse after periods of inactivity. But very often, patients might not complain of back pain.
  - ***Signs***: Kyphoscoliosis
- **Investigations**
  - ***Radiological***· Radiographs of sacroiliac joints show sclerosis and narrowing of the joint space. This is followed by ligamentous ossification and osteoporosis. Both sacroiliac joints usually are involved, but findings may first appear on one side. Later on, there might be fusion of the lower vertebrae leading to loss of curvature and giving rise to 'bamboo spine' appearance.

Reactive Arthritis and Reiter's Syndrome

- Reactive arthritis (ReA) refers to spondyloarthropathies following enteric or urogenital infections and occurring in individuals who are HLA-B27 positive. Reiter's syndrome is included in this category.
- Reiter syndrome is described as a triad of
  - Arthritis
  - Nonspecific urethritis
  - Conjunctivitis, often accompanied by iritis.
- **Epidemiology**: It is generally seen in the young age group (20-40) If the disease is acquired secondary to a gastrointestinal infection, it is seen equally in both males and

females. If the disease is acquired secondary to a urogenital infection, it is more common in males. Almost, 75% of the patients with reactive arthritis are HLA B 27 positive.

- **Pathogenesis**: As described earlier, molecular mimicry is thought to be the cause for the inflammatory response. The bacteria that have been implicated include Salmonella species, Yersinia enterocolitica, Campylobacter jejuni, Chlamydia trachomatis, Chlamydia pneumoniae, Clostridium dilficile, and Ureaplasma urealyticum.
- **Clinical features**
  - ***Urethritis***: The syndrome usually begins with urethritis followed by conjunctivitis and rheumatological findings.
  - ***Conjunctivitis***: The conjunctivitis is usually minimal and lasts for only a few days or weeks. It is mucopurulent and papillary.
  - ***Arthritis***: Arthritis begins within 1 month of infection in 80% of patients. It usually is acute, asymmetric, oligoarticular, involving predominantly the joints of the lower extremities (e.g., knees, ankles, feet, wrists). The arthritis usually is quite painful. Dactylitis or sausage digit is a diffuse swelling of a solitary finger or toe. Plantar fascitis and Achilles tendonitis also are common. Sacroilitis is present in as many as 70% of patients.
  - ***Other features***: Punctate and subepithelial keratitis may occur rarely, leading to permanent corneal scars. Acute non-granulomatous iritis recurs frequently in this condition. It may become bilateral and chronic and may result in blindness. Mucocutaneous lesions like keratoderma blennorrhagicum, a scaly, erythematous, irritating disorder of the palms and soles of the feet, and circinate balanitis, a persistent, scaly, erythematous circumferential rash of the distal penis are known to occur.
- **Investigations**: ReA is a clinical diagnosis without definitive laboratory or radiographic findings. The diagnosis should be considered when an acute asymmetric inflammatory arthritis or tendonitis follows an episode of diarrhoea or dysuria.

Inflammatory Bowel Disease

- Ulcerative colitis and Crohn disease are associated with acute anterior uveitis. Specifically, 2.4% of patients with Crohn disease and 5-12% of patients with ulcerative colitis develop acute anterior uveitis.
- Patients with uveitis and inflammatory bowel disease alone tend to be HLA B 27 negative.
- Almost, 50-60% of the patients with spondyloarthropathies and inflammatory bowel disease with uveitis are HLA B 27 positive.

Psoriatic Arthritis

- Psoriasis is a non-contagious disorder characterised by the presence of silvery white scales on the extensor surfaces of the body. Psoriasis precedes the onset of arthritis by months or years. Most patients have onychodystrophy, which includes onycholysis and ridging and pitting of nail beds.

- Twenty-five percent of patients develop a more severe symmetrical arthritis resembling rheumatoid arthritis. The proximal interphalangeal joints and distal interphalangeal joints commonly are involved with characteristic sausage-shaped digits.
- HLA B 27 positivity is present in cases where psoriatic arthritis is associated with spondylitis.

Management of HLA B27 Uveitis

- Aggressive early treatment to prevent permanent damage and development of chronicity
- Topical strong corticosteroid (eg, difluprednate 0.05%, prednisolone acetate 1%, q 1-2 h)
- Cycloplegia early to break synechiae and for comfort; may stop as disease remits.
- If hypopyon is present and vitreous is very cloudy, consider vitreous tap and culture.
- Oral prednisone (1 mg/kg/day) for severe cases when you are sure there is no infection
- Periocular corticosteroid injection for recalcitrant cases when glaucoma not a risk
- Explain to patient that attack of uveitis may persist for several months.
- Refractory or frequently recurring cases may be treated with nonbiologic immunomodulatory therapy or TNF inhibitors.
    - The TNF inhibitor etanercept is less efficacious than infliximab and adalimumab and may even be proinflammatory.

Juvenile Idiopathic Arthritis (JIA)

- Juvenile rheumatoid arthritis is also known as Juvenile idiopathic arthritis (JIA). JIA, as defined by the American Rheumatism Association (ARA), as the presence of arthritis (chronic, seronegative, and peripheral) before age 16 years, of at least 3 months duration, when other causes have been excluded.
- **Classification:** It is classified as
    - Oligoarticular onset JIA
    - Polyarticular onset JIA
    - Systemic onset JIA
    - Enthesitis-related arthritis: uveitis 7%-15%
    - Psoriatic arthritis: uveitis 10%-20%

- **Oligoarticular (Pauciarticular) Onset JIA (40-60%)**
    - This is common in girls (5:1).
    - Peak age of onset is at age 2 years.
    - Four or fewer joints are involved during the firstS months of the disease (often asymmetric). Oligoarticular onset commonly involves the knees and, less frequently, the ankles and wrists.
    - The arthritis may be evanescent, rarely destructive, and radiologically insignificant.

- Approximately, 75% of these patients test positive for antinuclear antibody (ANA). This mode of onset rarely is associated with systemic signs.
- A high risk for uveitis exists. (30%)

- **Polyarticular Onset JIA (20-40%)**
  - This is common in girls (3:1).
  - Peak age of onset is at age 3 years.
  - It involves 5 or more joints during the first 6 months of the disease.
  - Polyarticular onset- A commonly involves the small joints of the hand and, less frequently, the larger joints of the knee, ankle, or wrist. Asymmetric arthritis may be acute or chronic and may be destructive in 15% of patients.
  - Rheumatoid factor (RF) is present in 10% of children with this JIA subgroup. It is associated with subcutaneous nodules, erosions, and a poor prognosis.
  - Approximately 40% of these patients test positive for ANA. Systemic symptoms, including anorexia, anaemia, and growth retardation, are moderate.
  - An intermediate risk for uveitis exists. (5-10%)

- **Systemic Onset JIA (10-20%)**
  - This is equal frequency in boys and girls and can appear at any age.
  - Symmetric polyarthritis is present and may be destructive in 25% of patients. Hands, wrists, feet, ankles, elbows, knees, hips, shoulders, cervical spine, and jaw may be involved.
  - ANA is positive in only 10% of the patients. Systemic onset is associated with fever (high in evening and normal in morning), macular rash, leucocytosis, lymphadenopathy, and hepatomegaly. Pericarditis, pleuritis, splenomegaly and abdominal pain less commonly are observed.
  - A low risk for uveitis exists. (1%)

- **Enthesitis-related arthritis:** uveitis 7%-15%
- **Psoriatic arthritis:** uveitis 10%-20%

- **Risk Factors for Development of Uveitis in Patients with JIA**
  - Female gender
  - Pauciarticular variety
  - ANA positivity
- **Epidemiology:** Around 10% of the cases with JIA develop uveitis.
- **Clinical Features**
  - ***Symptoms***: Patients complain of mild pain, photophobia and blurring of vision. Many a times, the patient is asymptomatic.

- ***Signs***
  - Conjunctiva: Most patients have no conjunctival injection even during acute exacerbations.
  - Cornea:
    - Keratic precipitates -Small-medium, rarely mutton fat
    - Patient may develop band keratopathy with time
  - Anterior uveitis
    - Cells and flare; chronic flare (very common)
    - Non-granulomatous uveitis (>90%)
    - Bilateral (70-80%)
    - Chronic smoldering or recurrent disease in greater than 90%
  - Iris: Posterior synechiae; pupillary membrane; rarely may develop Koeppe nodules

- **Management**
  - **Screening guidelines**: Based on subtype, age, and laboratory testing
    - Initial screening, within 6 weeks of diagnosis of JIA
    - Oligoarticular JIA, enthesitis-related arthritis, psoriatic arthritis under 11 years of age: ophthalmic exam every 3-4 months
    - Polyarticular JIA, ANA positive, under 10 years of age: ophthalmic exam every 3-4 months
    - Polyarticular JIA, ANA negative, under 7 years of age: ophthalmic exam every 3-4 months
  - **Local**
    - Topical corticosteroids are used to treat initial flares and recurrent disease.
    - Long-term use is cautioned due to side effects.
    - One study showed that use of topical corticosteroids at dose of 3x/day or less was associated with lower risk of cataract development.
  - **Medical**
    - Systemic corticosteroids for complex disease, not responding to topical therapy but not acceptable for long-term therapy
    - Indication for systemic immunosuppressive therapy include active joint disease, recurrent or chronic uveitis, inadequate uveitis control, steroid responder
    - Goal: long-term inflammatory control
    - It includes the use of topical steroids and use of systemic steroids in cases which are not responding to topical therapy. But, most patient have a chronic course and use of steroids can give rise to severe complications like growth retardation, hypertension and diabetes mellitus. So, steroid sparing agents like Methotrexate are being tried in these patients.

- Multiple classes of immunosuppression
  - Antimetabolites: methotrexate (first-line therapy), azathioprine, mycophenolate mofetil
  - Biologics: adalimumab, infliximab, rituximab, tocilizumab, abatacept
  - Alkylating agents: cyclophosphamide, chlorambucil

- **Cataract extraction**
  - Cataract surgery is contraindicated in young patients with JIA due to the high chances of severe post-operative inflammation and cystoid macular oedema. Cataract surgery can be tried in older patients with JIA.
  - Heparin coated IOL should be used
  - Minimal intraoperative handling should be there
  - Combined lensectomy and vitrectomy can be tried in these patients
  - Post-operatively inflammation should be controlled aggressively and if required immunosuppressive therapy should be used.
- **Glaucoma surgery**
  - Failed topical treatment
  - Goniotomy, draining devices, trabeculectomy procedure
- **Band keratopathy**
  - EDTA chelation
  - Phototherapeutic keratectomy

Fuchs Uveitis Syndrome (FHI)

- Fuchs heterochromic iridocyclitis (FHI) is a chronic, unilateral iridocyclitis characterised by iris heterochromia.
- **Epidemiology**
  - It affects people between 20-60 years of age
  - Males and females are equally affected.
  - Nearly 2-3% of the patients with uveitis have Fuchs heterochromic iridocyclitis.
- **Pathogenesis**
  - Adrenergic dysfunction leading to iris hypopigmentation by reduced innervation to iris stromal melanocytes. Abnormal innervation to iris vasculature leads to breakdown in the blood-aqueous barrier with secondary leakage of proteins, cells, and inflammatory mediators into the anterior chamber.
  - Strong association between FHI and ocular toxoplasmosis has been documented. Rubella, HSV and Toxocara canis are some of the other organisms associated with Fuch's heterochromic iridocyclitis.
  - Higher interleukin 10 (IL-10) and interferon-gamma levels and lower IL-12 levels have been found in aqueous humor of patients with Fuch's heterochromic

iridocyclitis compared with immune associated uveitis. These findings point to T helper (Th1) subtype response in FHI.

- **Clinical Features**
  - ***Symptoms:*** The symptoms can vary from none to mild blurring of vision and discomfort.
  - ***Signs***
    - The classic triad of Fuch's heterochromic uveitis is heterochromia, cataract, and keratitic precipitates (KPs).
    - Conjunctiva and sclera: In most patients, there is no ciliary congestion or conjunctival hyperaemia.
    - Cornea: Small, nonpigmented, translucent, stellate KPswith filamentous projections distributed over the entire endothelial surface is pathognomic ofFuch's heterochromic iridocyclitis. Stellate KPs can also be seen in uveitis associated with toxoplasmosis, herpes simplex, herpes zoster, and cytomegalovirus (CMV).
    - Anterior chamber: There is minimal anterior chamber cells and flare. Paracentesis may result in the appearance of a filiform hemorrhage (Amsler sign).
    - Iris:
      - Heterochromia is present 75-90% cases. In unilateral cases, the hypopigmented eye is usually the affected eye. It is difficult to comment in bilateral cases (5-10%). Normally, a lighter coloured eye becomes darker when extensive loss of iris stroma occurs, exposing the darker pigment epithelial layer.
      - Iris sphincter atrophy may cause an irregular shaped pupil. White iris nodules may be seen along the pupillary border (Koeppe nodules) and in the iris stroma (Busacca nodules).
      - Fine vessels may be seen on the iris surface, especially in the angle. Neovascularisation of the iris and the anterior chamber angle (radial and circumferential) occurs in 6-22% of cases.
      - Posterior synechiae are never present. The presence of posterior synechiae should strongly suggest another diagnosis.
    - Trabecular meshwork: Fine blood vessels may be seen on the trabecular meshwork. These may bleed unexpectedly when the intraocular pressure suddenly drops during surgery or paracentesis.
    - Lens: Nearly, 80-90% of cases develop a posterior subcapsular cataract, which matures rapidly.
    - Vitreous: Fine vitreous opacities are observed.
    - Retina: The absence of cystoid macular oedema distinguishes Fuch's heterochromic iridocyclitis from other uveitis syndromes with chronic vitritis. Chorioretinal scars have been reported in some patients.
    - Intraocular pressure: Secondary glaucoma is a frequent complication and can be present in 15-59% of cases.

- **Management**
  - Inflammation: *There is no need for topical steroids, as it is ineffective in controlling inflammation.*
  - Cataract: The prognosis for Cataract surgery is generally good. Pre-op steroids are not required.
  - Glaucoma: Medical management is sufficient most of the time. If surgery is planned, trabeculectomy with Mitomycin C or valve implant is preferred.

Posner Schlossman Syndrome (Glaucomatocyclitic Crisis)

- It is characterised by recurrent episodes of unilateral uveitis associated with corneal oedema and increase in intraocular pressure out of proportion to the uveitis.
- **Epidemiology**
  - It typically affects people between the age of 20-50 yrs
  - Males and females are equally affected
  - Generally, only one eye is affected at one time
- **Pathogenesis**
  - The exact aetiology of glaucomatocyclitic crisis is not known.
  - Factors that have been postulated include the following:
    - Abnormal vascular process
    - Autonomic defect
    - Allergic condition
    - Cytomegalovirus (CMV)
    - Herpes simplex virus
    - Variation of developmental glaucoma
- **Clinical Features**
  - ***Symptoms***
    - It is characterised by recurrent episodes of unilateral uveitis with elevation of IOP which is out of proportion and lasts from a period of hours to days. Patient complains of blurring of vision with haloes and sometimes pain.
  - ***Signs***
    - Conjunctiva: The eye is quiet with no or minimal ciliary flush.
    - Cornea: If the IOP is above 40 mm Hg, the cornea can become edematous. Fine KP's can appear after 2-3 days of inflammation and resolve rapidly.
    - Anterior chamber: Minimal flare might be present and cells are generally absent.
    - Iris: Segmental ischaemia may be present.
    - IOP: It is generally elevated and in the range of 40-60 mm Hg. It is related to the number of days of uveitis and not to the severity of uveitis.

- Posterior synechiae may be present.

- **Management**
  - Inflammation: Prednisolone acetate 1% drops can be started and then tapered slowly.
  - Glaucoma: Medical management is sufficient most of the time. Topical beta blocker like Timolol 0.5% along with oral Diacetazolamide is sufficient to manage the acutely elevated IOP.

Lens Associated Uveitis

- Uveitis which results from immune reaction to lens material is called lens associated uveitis.
- This can occur either through leakage of lens material through intact capsule as occurs in hypermature cataract or following rupture of lens capsule (traumatic or surgical).
- **Pathogenesis**
  - It is thought to be an autoimmune reaction to lens protein because of altered tolerance. The first episode generally occurs insidiously but once the patient has got sensitized to the lens protein, e.g. following cataract surgery in one eye, the immune reaction occurs rapidly in the other eye following exposure to lens protein.
- **Clinical Features**
  - ***Symptoms***: Patient complains of redness, blurring of vision and pain.
  - ***Signs***
  - Both, granulomatous and non-granulomatous uveitis may occur.
  - The anterior chamber reaction may vary from mild to severe depending on the amount of lens protein.
  - Posterior synechiae formation occurs and IOP is quite often elevated.

Tubulointerstitial nephritis and uveitis syndrome (TINU)

- TINU was first described in 1975 by Dobrin et al.
- It is defined as occurrence of tubulointerstitial nephritis (TIN) and uveitis in a patient in the absence of other systemic diseases that can cause either interstitial nephritis or uveitis
- It is felt to be an immune-mediated process that can be caused by drugs or infections, but many cases remain idiopathic.
- TINU was originally felt to be mostly a bilateral, sudden-onset uveitis affecting children more than adults and more common in girls.
- It is increasingly being recognized that TINU can occur in any age range and can cause any type of uveitis; however, most cases are bilateral.
- **Symptoms**
  - TINU can be a life-threatening condition due to severe acute kidney injury.

- Most patients present with either nonspecific symptoms such as fever, rash, flank pain / tenderness, or fatigue, or they are completely asymptomatic except for ocular symptoms.

- **Diagnosis**: ***Diagnosis of exclusion***
  - Urine (not blood) beta 2 microglobulin is elevated as tubulointerstitial nephritis worsens.
  - There is felt to be an association with HLA-DQA1*01,DQB1*5, and DRB1*01, but HLA testing is not indicated.
  - Urinalysis can be normal or can show red blood cells / red blood cell casts.
  - Proteinuria can be present, but albuminuria is absent as glomerular pathology is not common.
  - Urinary and/or peripheral blood eosinophilia may be present.
  - Renal biopsy is needed to confirm the diagnosis.
  - Renal biopsy will show tubulointerstitial necrosis and/or fibrosis with preserved glomeruli, interstitial edema, and cellular infiltration of predominantly CD4-positive lymphocytes.
  - Need to exclude other systemic diseases that can cause both renal and ocular inflammation
- **Differential Diagnosis:**
  - Postinfectious or drug-induced uveitis
    - History of recent infection
    - Treatment with antibiotics prior to onset
  - Sarcoidosis
  - HLA-B27 uveitis
    - Typically alternating recurrent acute anterior uveitis
    - Lower back pain worse with inactivity
  - Inflammatory bowel disease
- **Treatment**
  - In cases with mild kidney dysfunction, oral steroids may be sufficient to control inflammation, but most patients will need long-term systemic immunosuppression to control the renal disease.
  - Ocular inflammation can be controlled with local therapy as needed

Intermediate Uveitis (IU)

- First described as chronic cyclitis by **Fuchs in 1908**.
- Clinical description: **Schepens** in 1950
- **Epidemiology**
  - **4–8%** of cases of uveitis
  - Has bimodal age distribution
  - 5-15 yrs: M>F
  - 20-40 yrs: F>M
  - It occurs equally in both the age groups.
  - It is bilateral in 70-90% of the cases. Of which it is asymmetrical in 25% cases
- **Etiology**
  - Multiple Sclerosis: In a study, 14.8% patients of intermediate uveitis had MS
  - Lyme disease: Caused by Borrelia Burgdorferi and spread by Investigationsodes Dam mini
  - Sarcoidosis: HTL V 1 infection: Mochizuki in his study found that 44.1% patients of IU had serology for HTLV 1
  - B Cell Lymphoma
  - Whipples Disease
  - HLA associations: HLA B 8, B 51; HLA DR 2(Subset 15 found in 64.3% patients of IU) HLA DR 17 ,DR-51
- **Clinical Features**
  - ***Symptoms***: Floaters and blurring of vision are the most common complaints. Rarely pain, redness or photopsiae. blurred vision and/or floaters
    - DOV due to moderate vitritis and cystoid macular edema
  - ***Signs***
    - minimal anterior segment inflammation (**exception** is patients with intermediate uveitis associated with **multiple sclerosis**, who typically develop a granulomatous anterior uveitis with formation of mutton-fat keratic precipitates.)
    - Posterior synechiae are rare and if present are broad based and difficult to break with dilatation. If posterior synechiae are present for more than 3-4 clock hours, the diagnosis of intermediate uveitis should be reconsidered.
    - Inferior vitreous snow balls. Vitreous strands.
    - Exudates may accumulate inferiorly to form snow bank.
    - The snow banks are of two types:
      - Smooth and shiny: Burned out pars planitis
      - Fluffy with attached snow halls: Active pars plani tis

- The snowbanks are commonly vascularised. These may bleed and give rise to Vitreous Haemorrhage. Peripheral retinal vasculitis is sometimes present inferiorly near the snow bank (8-30%).
- Cotton wool spots and retinal haemorrhage occur vety rarely. Seen generally after HTLVI infection.chronic cystoid macular edema, glaucoma, inflammatory changes in the retina, and retinal detachment, VH
- Autoimmune endotheliopathy is a rare finding associated with pars planitis
- **Glaucoma: 8-10%**
- **Macular edema: 28 – 50%**

- **Features of HTL V1 Intermediate Uveitis are:**
  - Increase in the CD4 to CD8 cells ratio
  - Increase in the soluble IL-2
  - Increase in the IL-6 and TNF-Alpha in the aqueous humor
  - The vasculitis rather than being peripheral often affects the posterior pole
  - Cotton wool spots and haemorrhages are more common
  - Cystoid macular edema is not as common as it is acute in onset and treated before becoming chronic
- **Complications**
  - CME: Occurs in 25% of the cases
  - Macular epiretinal gliosis
  - Secondaty cataract
  - Tractional retinal detachment
  - Cyclitic membrane formation: Due to massive proliferation of vascularised exudates onto and behind the posterior lens capsule. This can cause traction on the ciliary body region leading to Phthisis bulbi.
  - NVD, NVE, NVI
- **Investigations**
  - FFA:
    - Diffuse leakage in “fern-like” pattern
    - CME
    - Peripheral retinal nonperfusion
    - Retinal neovascularization with or without tractional membranes and vitreous hemorrhage
  - UBM: Can detect the presence of exudates in the pars plana region
  - ERG: Reduction in the B wave implicit time with duration of pars planitis >2 yrs
  - The work up of a case of intermediate uveitis involves the routine investigations done as part of uveitis work-up and in addition work up to r/ o aetiology
    - Multiple sclerosis : MRI

- Sarcoidosis: X-ray Chest, Serum ACE levels,Gallium Scan
- Serum HTLVI testing in patients from endemic areas like japan and Caribbean.

- **Differential Diagnosis**
  - **Unilateral Conditions Mimicking Intermediate Uveitis**
    - **Coat's**: Presence of telangiectatic vessels in the periphery with presence of hard exudates might mimick IU. Even the age of presentation is similar. The presence of snowballs and snowbanks goes in favour of IU.
    - **Intraocular tumours**: Retinoblastoma, malignant melanoma can disseminate into the vitreous and mimick IU. But the presence of a mass in the retina will help in distinguishing intraocular tumours from intermediate uveitis.
    - **Fuch's heterochromic iridocyclitis**: Might mimick IU but the presence of stellate comma shaped KP's all over the endothelium goes in favour of Fuch's.
    - **Retinal detachment**: Anterior vitreous cells might be present. But on 10, the detached retina is seen.
  - **Unilateral/Bilateral Conditions Mimicking Intermediate Uveitis**
    - Sarcoidosis
    - **Lyme's disease**: Cat scratch disease: More of retinal vasculitis and less of vitritis
  - **Bilateral Conditions**
    - **Senile vitritis**: Diagnosis of exclusion. Seen in older patients. No snowballs, snowbanks, retinal vasculitis but vitritis is present.
    - **Amyloidosis**: Causes vitritis but no snowbank, vasculitis or CME

- **Treatment**
  - Corticosteroids
  - Cycloplegics
  - Immunosuppressive agents
  - Surgery: cryotherapy and vitrectomy.

- Intermediate uveitis is a recurrent problem, it is not possible to decrease the number of episodes of IU. The treatment is directed towards decreasing the incidence of CME which is the major cause of visual loss in these patients.
- **Role of Topical Steroids**
  - Topical steroids are only used when there is severe AC reaction or posterior synechiae or acute endotheliopathy. Otherwise, there is no indication for using topical steroids.

- Kaplan has advised that only patients whose vision< 6/12 and who have developed CME should be treated. But, most clinicians treat if the vision has not improved at the end of 2 months even if there is no evidence of CME.
- ***Step 1***
  - Posterior sub-Tenon's injection of either 40 mg. Triamcinolone Acetonide or 40 mg Methyl Prednisolone every 6-8 weeks
  - ***Advantage of Triamcinolone over Methyl Prednisolone***
  - Smaller particle size
  - Lack of carrier vehicle. The vehicle of Methyl Prednisolone causes retinal and retinal pigment epithelium scarring
  - Well tolerated
  - ***Technique (Smith and Nozik)***
  - Ask the patient to look down.
  - A 4%1idocaine soaked cotton applicator is applied over the conjunctiva.
  - A 27 gauze 5/8 inch disposable needle with the bevel end up is used to enter the conjunctiva in the supero-temporal quadrant.
  - The needle is moved with broad side to side movement following the curve of the globe.
  - If the needle enters the sclera, the entire eyeball moves sideways with the movement of the needle.
  - Once the needle has reached posteriorly, the bevel is turned downwards and the drug is injected.
  - The anterior placement of the drug increases the chance of developing glaucoma and the incidence was found to be as high as 30% in one case series.
  - Other complications include ptosis, globe perforation and necrotizing scleritis.
  - If the disease is bilateral and severe, oral steroid is added in the dose of 1 mg/kg/day.
- ***Step 2: Cryotherapy and laser***
  - When corticosteroids fail, either cryotherapy or laser can be applied over the snowbank.
  - Aaberg did a study using cryopexy and found that quiescence of disease activity was seen in 78% cases and improvement in vision in 67% cases. The potential side-effect of cryopexy includes proliferative vitreoretinopathy and Retinal Detachment.
- ***Step 3: Vitrectomy***
  - It is done in cases not responding to both steroids and cryo/laser. It removes the inciting antigens, clears the inflammatory cells and decreases the vitreous traction thus reducing the cystoid macular oedema.
- ***Step 4: Immunosuppressive Therapy***

- Cyclophosphamide, Azathioprine, Methotrexate and Cyclosporine have all been tried in cases not responding to steroids or developing severe complications after starting steroids.
- Azathioprine is commonly used. It is available as 50 mg tablets. Azathioprine 150 mg/ day is used for the first 2 months. 100 mg/day is used for the next month 50 mg/ day is used for another month
- The blood Counts are Monitored. Newer immunosuppresives like Etanercept, Infliximab, Tacrolimus and Mycophenolate Mofetil are now becoming available.

Cataract Extraction in a Case of Uveitis

- The patient's eye should be quiet at least for a period of 3 months before the surgery.
- The patient should be given pre-operative oral steroids 40 mg/ day 3 days before the surgery and a posterior sub-Tenon's injection 3 days before the surgery.
- The cataract is operated by phacoemulsification and heparin coated PMMA lens is implanted.
- After, the wound is closed, peripheral pars plana vitrectomy is done and posterior capsulectomy is done.
- The chief complications of cataract surgery in these patients is the high incidence of CME and PCO formation.

Course and Outcome

- Several studies have tracked the progress of the disease. Notably, Smith has found in his large series of patients 59% had a chronic course, 31% had a smoldering course with periods of exacerbations and remissions while 10% had a benign self-limited course.
- The active inflammation generally persists for a period of 3 yrs and the disease burns out in a period of 5-15 yrs.
- If the macula is protected for this period, most patients end up with vision better than 6/12.
- Children have the worst prognosis.

Pars planitis / Idiopathic Intermediate Uveitis (IIU)

- The number of cases that really are pars planitis/ IIU are decreasing as we find other causes.
- Subset of patients with intermediate uveitis when a white opacity (commonly called a **snowbank**) occurs over the pars plana and ora serrata.
- **Features**
  - Although pars planitis probably does not represent a clinical entity distinct from intermediate uveitis, patients with pars planitis often have **worse vitreitis, more**

severe macular edema, and a worse prognosis than patients with intermediate uveitis who do not have a pars plana exudate.

- Inferior location of the exudate is attributed to gravity
- **Diffuse phlebitis** leads to breakdown of the blood–ocular barrier and release of inflammatory cells, cytokines, and other inflammatory mediators that settle inferiorly
- Snowballs are composed of **epithelioid cells and multinucleated giant cells**.
- Pars planitis in children can present as vitreous hemorrhage.
- Bilateral but very asymmetric disease can occur.

- Some eyes can be monitored without treatment (good visual acuity, no structural complications)
- **Management**
  - Topical steroids for anterior segment inflammation
  - Periocular steroid injections
  - Oral prednisone
  - Systemic immunomodulatory therapy
  - Vitrectomy and/or peripheral retinal ablation
  - Peripheral retinal ablation can induce remission of pars planitis in some patients.

Posterior Uveitis

- Involves retina and/or choroid as the primary site for inflammation but may have inflammation in the anterior chamber and/or vitreous. Fifteen percent to 30% of uveitis is classified as posterior uveitis.
- Toxoplasmosis and sarcoidosis are the most common diagnoses.
- Many diverse clinical presentations involving dots, spots, plaques, etc. A plethora of disease names, syndromes, acronyms, and eponyms. However, true understanding of the etiology may be lacking.
- May be localized to the eye or be associated with disease in other organs
- **Systemic Disease and Posterior Uveitis**
  - Always worthwhile to search for systemic disease associations, but do not be disappointed when there are none.
  - Causation, association, and unrelated coexistence have different implications when considering systemic disease. Syphilis is an example of a causative systemic disease; Behçet syndrome has associated inflammation in multiple organs; Hashimoto thyroiditis coexists in patients with posterior uveitis but is not clearly related.
  - To attempt to unify multiple patient symptoms into one diagnosis:
    Patients and doctors always want to know why a disease has occurred. Sometimes there is a clear etiologic agent (usually infectious), sometimes we can associate multiple symptoms into one umbrella diagnosis, and sometimes we have no answer.
  - To avoid undertreating non-ocular involvement
  - To access therapies that may be approved only for systemic diseases
  - To create collaborative interspecialty management to avoid duplication
- **Causes**
  - Mechanical: intraocular foreign body / ocular ischemic syndrome
  - Malignant: B cell lymphoma – may be localized only to the eye or involve the brain
  - Infectious: recurrent ocular toxoplasmosis / syphilis
  - Immune driven: multiple evanescent white dot syndrome (MEWDS), birdshot chorioretinopathy (BSCR) / sarcoidosis, Behçet
  - Genetic: ADNIV (CAPN5 mutation) / Blau syndrome (NOD2 mutation)
- **Tests**
  - Most patients should have a syphilis serology and radiographic chest imaging; both have a high PPV. Other testing when clinically appropriate.
  - HLA typing is most useful to confirm A29+ in BSCR, but only if the appearance is clinically consistent. Other HLA associations are weaker.
  - Viral serologies are rarely useful and are most useful when negative unless patient has systemic symptoms of active systemic infection.
  - TB Quanti-FERON testing has a PPV of 11% in uveitis overall, but a 95% PPV in clinical serpiginous choroiditis, hence serpiginous-like tuberculous choroiditis.

- Anti-neutrophil cytoplasmic antibody (ANCA) reasonable in retinal vasculitis (occlusive). ANA, ESR, and RF are rarely helpful. Atypical clinical appearance or response justifies more testing.

Panuveitis

- Sarcoidosis
- VKH
- Behcets

- **Sarcoidosis**
  - African Blacks
  - Granulomatous anterior uveitis
  - Vitritis, snow ball opacities
  - Vasculitis 'en tache de bougies' or candlewax appearance
  - Granulomas: Pre-retinal, Retinal, Choroidal and optic disc
  - Lung involvement
  - Skin: Lupus pernio
  - Investigations: X ray Chest, Serum ACE, Ca, Lysozyme

- **VogtKoyanagi-Harada disease**
  - Poliosis
  - Suiguira's sign
  - Exudative detachment 'clover leaf pattern'
  - Sunset fundus
  - Vasculitis
  - Alopecia, Vitiligo, Meningismus
  - CSF pleocytosis

- **Adamantiades-Behcet's disease**
  - Turkish, Japanese people_
  - Conjunctivitis, sub-conjunctival haemorrhages, filamentary keratitis

Specific Entities

Spirochetal Diseases

Syphilitic Uveitis

- This sexually transmitted bacterial disease, caused by *Treponema pallidum* and once considered on the wane, has reemerged in the last decade, especially in the United States, Canada, and several European countries.
- Up to 5% of patients with tertiary syphilis may develop ocular syphilis, and increasing numbers are being reported.
- Human immunodeficiency virus infection may coexist in 60%-70% of patients with syphilis, especially in men having sex with men.
- Uveitis is one of the most common manifestations of ocular syphilis but requires a very high index of suspicion because of a wide spectrum of clinical manifestations. Ocular syphilis may be the presenting symptom of HIV infection. Men are predominantly affected.
- **History**:
  - There are no pathognomonic signs of syphilitic uveitis. Since these patients frequently have neurosyphilis, they may complain of headache, deafness, nausea, and unsteady gait.
- Stages of syphilis infection and the classic manifestations associated with each stage include:
  - Primary disease: painless chancre
  - Secondary disease: palmar plantar rash
  - Latent: none
  - Tertiary: Cardiac and neurosyphilis
- **Features**:
  - Patients may present with bilateral anterior, intermediate, posterior, or panuveitis.
  - Patients with HIV infection may develop uveitis in early or late stages of syphilis and present more often with posterior uveitis. Patients with HIV infection and higher reagin titers also present with more severe inflammation.
  - Uveitis may have either acute or insidious onset and if untreated may run a chronic course. In posterior uveitis, patients may present with single or multifocal yellow, creamy, placoid lesions with overlying significant vitritis. Necrotizing retinitis may be seen uncommonly. There may be variable exudative retinal detachment. Uncommonly, punctate retinitis and preretinal infiltrates may be seen. Optic disc hyperemia and peripapillary retinal swelling may be significant, and late stages show optic atrophy. Posterior segment may show leopard skin lesions.
  - On fundus fluorescein angiography, the placoid lesions show hypofluorescence during the dye transit that becomes hyperfluorescent in the late frames. Retinal vessels may show occlusive changes. The retinal vessels show staining of the vessel walls.
- **Diagnosis**

- Treponemal-specific serologic or CSF testing, but can also be made by polymerase chain reaction from ocular samples.
- The CDC recommends “reverse sequence testing” with a treponemal-specific test performed first (FTA-ABS or Syphilis IgG ELISA), followed by a reflexive nontreponemal test (RPR).
- Lumbar puncture and CSF analysis should be used for the diagnosis and monitoring of neurosyphilis.
- All patients with syphilitic uveitis should be tested for HIV due to high rates of coinfection.

- **Management**:
  - The only 2 CDC-approved treatment options for syphilitic uveitis are:
    - 18-24 million units IV penicillin G daily for 2 weeks
    - 2.4 million units IM penicillin G plus 500 mg probenecid q.i.d. for 2 weeks
  - Systemic treatment of infection with an approved neurosyphilis regimen should begin immediately upon diagnosis; comanagement with an infectious disease specialist is beneficial to ensure an appropriate regimen and compliance.
  - Sexual partners need to be tested and treated.
  - Anti-inflammatory
    - Topical corticosteroids and cycloplegia can begin immediately for anterior manifestations.
    - Oral steroid pulse and taper for severe posterior inflammation or Jarisch-Herxheimer reaction may be required.

HIV-AIDS & CMV Retinitis

- Ocular manifestations of AIDS at some point affect 50–75% of infected persons worldwide
- HIV 1 >> 2
- Sexual transmission, Intravenous drug abuse, Perinatal, needle-stick injury
- Diagnosis of HIV infection is usually made by an enzyme-linked immunosorbent assay (**ELISA**) and is then confirmed by a **Western blot test**
- Persons with **HIV loads >30 000 copies/mL** have an **80%** likelihood of developing AIDS within 6 years. In contrast, those with HIV loads **<500 copies**/mL have a **5.4%** chance of developing AIDS.
- Most cases of P. jiroveci pneumonia occur when CD4+ counts fall to <200 cells/μL. Typically, CMV retinitis occurs when CD4+ counts are <50 cells/μL.
- HAART: many begin treatment when the CD4+ count drops to <350 cells/μL or if symptoms are present.
- **Ocular Manifestations of HIV-AIDS**
  - ***Adnexa***
    - Molluscum Contagiosum

- Herpes Zoster Ophthalmicus
- Kaposi's Sarcoma
- Conjunctival Squamous Cell Carcinoma
- Trichomegaly

- ***Anterior Segment***
  - Dry Eye
  - Anterior Uveitis
- ***Posterior Segment (four categories)***
  - Vasculopathy
    - Microvasculopathy
      - ✓ most common ocular manifestation
      - ✓ 40 -60 % HIV patients
      - ✓ inversely proportional to CD4+
      - ✓ recognized clinically as cotton-wool spots
      - ✓ pericyte necrosis, endothelial cell swelling, and thickened basement membranes
      - ✓ it is a marker for patients with severely compromised immune status
    - Large Vessel Disease
      - ✓ BRAO, BRVO, CRVO
      - ✓ An unusual frosted branch vasculitis has been associated with CMV retinitis in AIDS
  - Unusual malignancies
    - Non-Hodgkin's lymphoma: necrotizing retinitis, multifocal choroiditis, retinal vasculitis, vitritis, subretinal mass, and pseudo-hypopyon uveitis
  - Neuroophthalmologic abnormalities
  - Opportunistic infections.
    - Cytomegalovirus
    - Pneumocystis
    - Mycobacterium tuberculosis
    - Toxoplasma gondii
    - Mycobacterium avium complex
    - Varicella-zoster virus
    - Cryptococcus neoformans
    - Coccidioides immitis
    - Candida

CMV Retinitis

- Rarely occurring if the CD4+ count is >100 cells/μL and typically occurring when CD4+ counts are <50 cells/μL.
- Reaches the eye via the bloodstream
- Unusual to see more than three separate areas of CMV retinitis in an eye
- **Two types of clinical appearance**
- **Perivascular fluffy white lesion** with many scattered hemorrhages
- **Granular-appearing lesion** that has few associated hemorrhages and often has a central area of clearing, with atrophic retina and stippled retinal pigment epithelium
- **Diagnosis**
  - Based on clinical criteria.
  - PCR performed on a vitreous specimen or by culture of the virus from the vitreous or retina
- **Active CMV retinitis**:
  - Faint granular border of intraretinal infiltrates that represent the new foci of viral activity in normal retina
  - Grows at approximately 250 microns per week
  - Areas that have begun to atrophy are also seen as denoted by retinal pigment epithelial stippling
- **Progression**
  - New lesions that are not physically near an old one may form, probably by hematogenous spread
  - Old lesion spreads at its borders to involve new, previously uninfected retina
- **Treatment**
  - **Ganciclovir** and derivetives, foscarnet, cidofovir, and fomivirsen.
  - Intravitreal ganciclovir implant**: 1 μg of drug per hour for 8 months**
  - Current treatment**: Zone 1,2,3**

Herpes Infection (ARN & PORN)

- Herpetic anterior uveitis is commonly caused by herpes simplex virus (HSV) and varicella zoster virus (VZV), followed by cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus (HHV).
- It is characterized by a recurrent, granulomatous iridocyclitis, frequently associated with corneal involvement in the form of corneal scar or active keratitis. Iris atrophy and transiently raised IOP due to trabeculitis are common. Scleritis has been recently reported to be associated with herpetic infection. Posterior segment involvement may occur in the form of acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN). ARN

usually occurs in immunocompetent individuals and PORN in severely immunocompromised persons.

ARN

- 1971 in a report by **Urayama**
- Was called **Kirisawa's uveitis**
- Either sex and at any age
- **Etiology**
  - Initially believed to be an autoimmune
  - Experimental data support the **role of herpes virus infection** in the pathogenesis of ARN
- **Clinical Features**
  - Begin with unilateral, **33% bilateral** in 1-6 weeks
  - Pain, redness, floaters, and blurred vision
  - Anterior uveitis with or without keratic precipitates may occur
  - Vitritis → floaters
  - Earliest retinal lesions: **small, patchy, white-yellow areas** that tend to enlarge, increase in number, and coalesce over time, in **medperiphery**
  - Areas of clearing forming a **Swiss cheese pattern**
  - Retinal vasculitis
  - Optic neuropathy: Disc edema
  - Acute phase usually resolves in 2–3 months
  - TRD/ RRD and large breaks develops
- **Tests**
  - PCR may yield a positive result from the aqueous or vitreous fluid, but a negative PCR does not rule out the diagnosis. HSV and VZV have been known to be the common viruses causing ARN.
- **Diagnostic criteria by American Uveitis Society**
  1. One or more foci of retinal necrosis with discrete borders in the peripheral retina
  2. Rapid progression of disease if antiviral therapy has not been given
  3. Circumferential spread of disease
  4. Evidence of occlusive vasculopathy with arteriolar involvement
  5. Prominent inflammatory reaction in the vitreous and anterior chamber
- **Differential diagnosis**
  - Exogenous bacterial endophthalmitis
  - Fungal endophthalmitis
  - Behçet's disease

- Pars planitis
- Toxoplasmosis
- Syphilis
- Cytomegalovirus retinitis
- Sarcoidosis
- Intraocular lymphoma
- Progressive outer retinal necrosis syndrome

- **Treatment**
  - **10–14-day** course of intravenously administered **aciclovir 500 mg/m2** every 8 hours. Oral aciclovir 800 mg five times a day is then continued for an additional 6 weeks.
  - The patients should be monitored for renal function tests. In patients not responding to acyclovir, oral famciclovir or ganciclovir have been recommended. Other drugs that can be used include valaciclovir and foscarnet.
  - Oral corticosteroids are used to control active inflammation, and should be started at a high dose (1 mg/kg/day), and tapered gradually.
  - A low-dose aspirin (100 mg/day) is beneficial in view of occlusive retinal arteritis.
  - Vitreous surgery is indicated for retinal detachment or prophylactic for debulking the inflammatory cells and releasing vitreous traction.
  - The role of prophylactic laser photocoagulation is controversial.

PORN

- Progressive outer retinal necrosis
- Initially described in **immunocompromised** patients.
- **Clinical Features**
  - **Rapidly progressive necrotizing retinitis** with early patchy choroidal and deep retinal lesions which progressed relentlessly until patients were left with atrophic and necrotic retinas and pale optic nerves.
  - Unlike typical ARN there is little or **no vasculitis and less vitritis**, and in many patients **posterior pole** involvement occurs early in the course of disease
- **Differential Diagnosis**: ARN, other Differential Diagnosis of ARN
- **Etiology**:
  - Varicella-zoster virus and herpes simplex virus
- **Treatment**
  - High-dose intravenous aciclovir at a dosage of **10 mg/kg every 8 hours for 2 weeks** has also been used with inconsistent success
  - Induction doses of intravenous ganciclovir and foscarnet

Ocular Toxoplasmosis (OT)

- Caused by an obligate, intracellular protozoan parasite (*Toxoplasma gondii*) and the most important and frequent cause of infectious retinal disease and posterior uveitis.
- **50% of the adult** population is infected
- Most common cause of uveitis ?? in one study
- **Organism**
  - Cosmopolitan parasite
  - Humans can also be infected secondarily by ingesting meat (pork and lamb particularly, as well as chicken in endemic areas, but probably not beef)
  - Many antigens: **SAG 1** or p30 is most studied, **SAG 2** or p22.
- **Clinical Features**
  - Systemic
    - Lymphadenopathy in 90%
    - Fever, malaise, and sore throat
  - Ocular
    - Congenital:
      - Large atrophic scar, frequently in the macula
      - Reactivation sites will be 'satellite' lesions next to old atrophic lesions, indicative of previous toxoplasmic infections
    - Acquired
      - Organism has a propensity for neural tissue, it is important to bear in mind that the lesion classically begins in the retina
      - Scaffolding seen in vitreous of patient with severe recurrent ocular toxoplasmosis.
  - Decreased Vision
    - Vitreal inflammation
    - Infection involving the macula
    - Choroidal neovascularization
    - Retinal vein occlusion, papillitis, and florid disc neovascularization.
- A curious association between Fuchs' heterochromia and ocular toxoplasmosis was initially made by Toledo de Abreu
- **Diagnosis**
  - Antibody from the aqueous of patients with chronic toxoplasmosis stained more intensely to a 28-kDa antigen, believed to be the **GRA-2 antigen**, which is expressed in both tachyzoites and bradyzoites.

- Aqueous or vitreous paracentesis with Toxo PCR or with Goldmann-Witmer coefficient should be performed.
- Sabin–Feldman dye test
- ELISA

- **Therapy**
  - Immunocompetent person the disease is ultimately **self-limited**
  - Decision to treat generally would be based on the following **criteria**
    - A lesion within the temporal **arcade**;
    - A lesion **abutting the optic nerve** or threatening a large retinal vessel;
    - A lesion that has induced a large degree of **hemorrhage**;
    - A lesion that has induced enough of a vitreal inflammatory response that the **vision has dropped** below 20/40 in a previously 20/20 eye, or at least has sustained a two-line drop from the visual acuity before the acute infection;
    - A relative indication would be the case of **multiple recurrences** that develop marked vitreal condensation. Here one might be concerned that the continuation of this process might lead to retinal detachment.
  - Systemic steroids always associated to antitoxoplasmic drugs Pyrimethamine + sulfadiazine (or trimethoprim + sulfamethoxazole)
    - Systemic or intraocular clindamycin and combination of trimethoprim/ sulfamethoxazole have also been used.
  - **Folinic acid:** during pyrimethamine therapy

POHS: Presumed Ocular Histoplasmosis Syndrome

- Woods and Whalen (1953): Disciform macular detachment, peripheral spots
- Schlaegel and Kenny (1966): Peripapillary atrophy and pigmentary changes
- the only syndrome in the spectrum of ocular inflammation in which '**presumed'** has appeared in its name.
- ocular histoplasmosis syndrome is rather a distinct entity found almost exclusively in the United States, endemic in the Ohio and Mississippi River valley
- In fact the causative role of the fungus *Histoplasma capsulatum* is unclear, explaining why the term "presumed" has appeared in its name.
- Histoplasma capsulatum: Found in the soil, it is readily inhaled and phagocytosed.
- **Clinical Features**
  - White, 20–50 years of age
  - Multiple choroidal spots ('**histo' spots**): four to eight per eye, these choroidal scars are circular, depigmented, and atrophic; they have a disc diameter of 0.2–0.7 and may have a pigment clump centrally
  - CNVM

- Peripapillary changes
- Disciform scar
- No vitreous inflammatory disease
- HLA-B7 and HLA-DR2 positivity (macular disease)
- Maculopathy: RPED, CSCR

- **Differential Diagnosis**: Multifocal choroiditis, TB, sarcoidosis, outer toxoplasmosis
- **Treatment**
  - Amphotericin B has no role in the treatment of ocular histoplasmosis
  - Corticosteroids
  - 2-mg or a 6-mg fluocinolone acetonide implant
  - intravitreal injection of anti-VEGF agents
  - Laser and PDT
- **Prognosis**
  - If subfoveal CNVM develops, 75% of patients have worse than 20/200
  - Involvement of second eye is 10% at 5 years, 20% at 10 years
  - Macular scar in fellow eye is a bad prognostic sign

Toxocara canis

- T. canis is an ascarid (i.e., a member of the Ascariditae family) that can only complete its lifecycle in the **dog**.
- Humans enter the pathway when they ingest soil, food, or other materials contaminated with the eggs.
- **Ocular manifestations**
  - Average age of diagnosis is estimated to be **7.5 years** (2-31 years)
  - Granuloma either in the posterior pole or in the periphery.
  - Raised and whitish in colour, with a width of 0.75 to 2 or 3 disc diameters
  - Peripheral retinitis
  - 50% presented with a peripheral retinal granuloma and 25% as macular lesions
  - Optic nerve disease (very rare)
  - Endophthalmitis
- Fuchs' heterochromia has been reported associated with this entity, just as has been noted in cases of ocular toxoplasmosis
- **Differential Diagnosis**
  - RB (aqueous to serum LDH ratio is >1, phosphoglucose to isomerase ratio should be >2)
  - primary hyperplastic primary vitreous

- Coats' disease
- focal choroiditis from another cause, such as sarcoid
- retrolental fibroplasia.

- **Diagnosis**
  - eosinophilia and hyperglobulinemia
  - No eggs will be found in the stool
  - ELISA
- **Treatment**
  - The first is treatment with anthelmintic drugs such as **thiabendazole or diethylcarbamazine**
  - second is treatment with prednisone to reduce the secondary inflammatory response.
  - systemic **prednisone** (40 mg/day) with thiabendazole (2 g daily for 5 days)

Onchocerciasis

- River blindness
- One of the five major preventable causes of blindness (the others include cataract, trachoma, glaucoma, and xerophthalmia).
- Tissue-dwelling parasite, the nematode **Onchocerca volvulus**.
- Spread by the blackflies of the **Simulium** species
- Broad belt across western and central Africa
- **Clinical Features**
  - Microfilarial infestation in the cornea: punctate keratitis; the presence of 'snowflake' opacities
  - Iridocyclitis:
  - glaucoma and cataract
- **Diagnosis**
- **Treatment**
  - **DEC-C** is microfilaricidal, and with the massive killing of these organisms a severe systemic reaction occurs (**Mazzotti reaction**).
  - **Benzimidazoles**
  - **Ivermectin**: single oral dose of 150 µg/kg

Diffuse unilateral subacute neuroretinitis (DUSN)

- **Gass in 1977**: unilateral wipe-out syndrome.

- Later found to be related to a nematode in the subretinal space
- **Clinical Features**
  - Scattered **recurrent** deep gray-white retinal lesions with marked loss of central acuity
  - Progressive optic atrophy, narrowing of the retinal vessels, pigment epithelial stippling, and further visual field loss
  - Cause destruction of the retinal outer segments, visual loss is rarely reversible.
- **Worms of two sizes**
  - **Smaller** worm between **400 and 700** µm in length was seen in most patients who lived in southeastern United States
  - **Larger** (**1500–2000** µm) worm has been seen in patients residing in the northern and midwestern states
- **Treatment**
  - **Albendazole**, 400 mg/day for 30 days
  - Can be successfully destroyed by photocoagulation

Seasonal hyperacute panuveitis (SHAPU)

- Malla and Upadhyay and colleagues in Nepal
- Unilateral, children
- Contact with a **moth**
- **Clinical Features**
  - Very acutely with a red eye and leukocoria with little pain
  - Fibrinoid reaction in the anterior chamber, and often there is also a hypopyon
  - Hypotony and a very sudden decrease in vision.
- **No systemic abnormalities**. (normal ESR and RF)

Postsurgical Uveitis

- **Day 1 to Day 30**
  - Acute aerobic bacterial endophthalmitis
  - Sterile endophthalmitis
  - Increased activity of previous uveitis
  - Phacogenic (lens-related) uveitis
  - Toxic reaction to intraocular lens
- **DAY 15 to 2 YEARS**
  - Fungal endophthalmitis
  - Propionibacterium acnes or other anaerobic endophthalmitis

- Low virulence aerobic bacterial endophthalmitis
- Phacogenic (lens-related) uveitis
- Sympathetic ophthalmia
- Toxic reaction to intraocular lens
- Iris–ciliary body irritation related to physical contact with intraocular lens
- Glaucoma drainage device
- New onset of idiopathic uveitis

Sarcoidosis

- Multisystem granulomatous disease
- **Adrenal glands**, which produce corticosteroids, are the only organs consistently **spared** by this disease.
- Initially described as a dermatologic disease by **Hutchinson** in 1869
- **Boeck**: sarkoid → skin biopsies had a histology similar to that of sarcomas
- **Etiology**
  - Infectious, organic, and inorganic agents are possible antigens
  - CD4+ T cells that interact with APCs to initiate the formation and maintenance of granulomas.
  - Associations between both class I antigens (HLA-B8) and class II antigens (HLA-DRB1)
- **Clinical Features**
  - Respiratory symptoms
  - Generalized symptoms such as fever, fatigue, or weight loss.
  - Eye findings in about 25%
  - Anterior Segment
    - Acute nongranulomatous or chronic granulomatous iridocyclitis: 53% to 60%
    - Iris nodules 11%
    - Cataracts in patients with chronic sarcoid uveitis is 8–17%, and the prevalence of glaucoma varies from 11% to 23%.
  - Posterior Segment
    - 6–33% of patients with sarcoidosis
    - Vitritis
    - Vitreal snowballs
    - Macular edema
    - Perivenous sheathing: **'candle wax dripping'** (en taches de bougie) along the retinal veins

- Small yellow choroidal, and retinal pigment epithelial patches of inflammation: Deep yellow choroidal lesions consistent with **Dalen–Fuchs nodules** and mottling of the pigment epithelium occur in 36%
- Optic disc swelling
- Retinal neovascularization
- Large choroidal granulomas
- Subretinal neovascularization
- Optic neuropathy

- **International Workshop on Ocular Sarcoidosis (IWOS) Diagnostic Criteria**
  - Definite ocular sarcoidosis → Biopsy-supported diagnosis with compatible uveitis
  - Presumed ocular sarcoidosis → Biopsy n.d., bilateral hilar lymphadenopathy with compatible uveitis
  - Probable ocular sarcoidosis → Biopsy n.d., chest x-ray normal; 3 suggestive ocular signs and 2 positive investigational tests
  - Possible ocular sarcoidosis → Biopsy negative; 4 suggestive ocular findings and 2 positive investigations
- ***Clinical Signs Suggestive of Ocular Sarcoidosis***
  1. Mutton-fat keratic precipitates and/or iris nodules at pupillary margin or on stroma
  2. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae
  3. Snowballs/strings of pearls vitreous opacities
  4. Multifocal peripheral chorioretinal lesions (active and atrophic)
  5. Nodular and/or segmental periphlebitis (with or without candlewax exudate) and/or macroaneurysm
  6. Optic disc nodules/granuloma and/or solitary choroidal nodule
  7. Bilateral inflammation
- ***Laboratory Investigations in Suspected Ocular Sarcoidosis***
  1. Negative tuberculin test
  2. Elevated serum angiotensin converting enzyme and/or elevated serum lysozyme
  3. Chest x-ray: bilateral hilar lymphadenopathy
  4. Abnormal liver enzyme tests (any of: alkaline phosphatase, aspartate transaminases, alanine transaminases)
  5. Chest CT scan in patients with normal chest x-ray

- **Differential Diagnosis**
  - **Blau syndrome**: in children, familial granulomatosis, arthritis, uveitis, and skin rash
- **Diagnosis**:
  - Noncaseating epithelioid cell granulomas on biopsy.
  - 90% will have an abnormal chest X-ray

- 60% of patients with sarcoidosis have granulomas on a transbronchial lung biopsy
- Lacrimal gland biopsy
- Serum ACE levels are elevated in 60–90%
- Serum lysozyme levels may also be elevated
- Kveim skin test:
- Gallium scan:

- **Management**
  - The mainstay of therapy for both systemic and ocular sarcoidosis is **corticosteroids**.
  - Anterior segment disease may be managed with topical or periocular corticosteroid injections. Systemic therapy is typically required for bilateral posterior segment uveitis. Other immunosuppressive agents such as **methotrexate and infliximab** have demonstrated therapeutic benefit in the management of sarcoidosis and should be considered early for patients with chronic sarcoidosis requiring prolonged steroid therapy. **Cyclosporine and etanercept** do not appear to have benefit in the treatment of sarcoidosis.
  - The glaucoma should be treated medically with aqueous suppressants for as long as possible.
  - Argon laser trabeculoplasty is frequently ineffective.
  - Laser iridotomy and surgical iridectomy are the treatments of choice for patients with pupillary block.
  - If the intraocular pressure remains uncontrolled, surgical intervention with either a filtering procedure or a tube shunt is required.
  - Surgical success is improved if the intraocular inflammatory disease can be controlled prior to the surgical procedure.

Sympathetic Ophthalmia (SO)

- Bilateral granulomatous uveitis that occurs after either intentional or unintentional penetrating trauma to one eye.
- 0.19% post trauma
- 0.015% post intraocular surgery
- Trauma to one eye (the exciting eye) will result in an inflammatory response not only in that eye but also in the contralateral eye (the sympathizing eye)
- 80% of patients some 3 months after injury to the exciting eye and in 90% within 1 year of trauma
- Bacterial endophthalmitis following penetrating injury or surgery cannot prevent development of SO.
- Early systemic corticosteroid administration following the trauma cannot prevent development of SO.

- **Clinical Features**
  - Acute anterior uveitis: granulomatous, with mutton-fat keratic precipitates
  - Moderate to severe vitritis
  - Dalen–Fuchs nodule:
    - Not pathognomonic
    - multiple white-yellow lesions in the periphery
  - Swelling of the disc
  - Subretinal neovascularization
- **Sequelae**
  - Secondary glaucoma and cataract
  - Retinal and optic atrophy
  - Disc neovascularization
- **Investigations**
  - FA: initial blockage of Dalen–Fuchs nodules with ultimate hyperfluorescence of the lesion
  - ICG: pattern of hypofluorescence in the intermediate phase of the angiogram, followed by a fading, and the second was a hypofluorescent pattern that persisted throughout the course of the study
  - **High level of serum β2-microglobulin**
  - Strong association between HLA-DR4, DRw53, and Bw54 haplotypes and both VKH and sympathetic ophthalmia
  - Cellular immune response to both **S-antigen and interphotoreceptor retinoid-binding protein (IRBP)**
- One of the classic findings in both sympathetic ophthalmia and the Vogt–Koyanagi–Harada syndrome is the preservation of the choriocapillaris.
- **Treatment**
  - Although in the past enucleation of the unsalvageable traumatized globe was recommended to prevent the development of SO, recent surgical advances and effective immunosuppressive treatment modalities suggest that prophylactic enucleation following open globe injury may not be required, and anatomic reconstruction is recommended.
  - There is no clear evidence for enucleation of the exciting eye to improve visual prognosis in the sympathizing eye once SO develops.
  - Effective anti-inflammatory treatment of SO includes primarily high-dose systemic corticosteroids and usually additional immunomodulatory agent(s). The immunomodulatory agents are required for sparing the corticosteroid or effectively suppressing the ocular inflammation. (at least 1–1.5 mg/kg of prednisone or equivalent on a daily basis.)
  - The immunomodulatory agents include cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, cyclophosphamide, and biologicals such as anti-TNF agents.

- Surgery for either glaucoma or cataract

Vogt-Koyanagi-Harada Syndrome (VKH)

- Vogt–Koyanagi–Harada syndrome (VKH)
- **Mohammad-al-Ghafiqi:** disease with poliosis, neuralgias, and hearing changes
- **Alfred Vogt:** 1906:
- **Koyanagi** in 1929
- **Harada** in 1926, described an essentially posterior uveitis with an exudative retinal detachment associated with a ***pleocytosis in the cerebrospinal fluid (CSF).***
- ***Vogt-Koyanagi: severe, acute, granulomatous, anterior uveitis with skin (25%) and ear (25%) involvement***
- ***Harada: granulomatous, posterior uveitis with CNS involvement***
- **Clinical Features**
  - Systemic findings
    - Prodromal stage: in which the patient may complain of headache, orbital pain, stiff neck, and vertigo. There may also be a fever.
    - CNS: Lumber puncture shows pleocytosis in 84%
    - Auditory difficulties: Dysacousia in 74%
    - Skin Lesion:
      - Sensitivity to touch of both hair and skin 72%
      - Vitiligo and poliosis: 63 – 90%
      - Alopecia: 70–73%
  - Ocular findings
    - Granulomatous uveitis, with mutton-fat keratic precipitates on the corneal endothelium
    - Perilimbal vitiligo (**Sugiura's sign**)
    - Nodules may be noted on the pupillary margin, as well as in the iris stroma
    - Glaucoma
    - Swelling of the optic nerve head is seen early in 87%
    - Retinal edema
    - Exudative nonrhegmatogenous retinal detachment
    - Dalen–Fuchs nodules
    - Neovascularization of the retina and optic nerve
    - Subretinal neovascularization of the macula
    - 'Sunset glow' appearance to the fundus: characteristic depigmentation of the posterior portion of the globe occurs

- Blond fundus: mottled appearance as well as a profound loss of pigment

- **Phases of VKH**
  - Prodromal phase: headache, nausea, vertigo, meningismus, fever, and orbital pain
  - Acute phase: bilateral uveitis most evident in the posterior pole and usually associated with swelling and hyperemia of the optic nerve head and serous detachment (s) of the retina
  - Convalescent/chronic phase: Depigmentation of the choroid, resulting in display of bright orangered appearance of the fundus (sunset glow fundus), nummular chorioretinal scars, and in some patients vitiligo and/or poliosis
  - Chronic recurrent phase: Characterized by acute episodes of granulomatous anterior uveitis or pan-uveitis with exacerbations usually resistant to corticosteroid therapy. This phase is also marked by complications such as subretinal fibrosis, subretinal neovascular membranes, and cataract.
- **Revised criteria for diagnosis of VKH**
  - Complete VKH: Criteria 1–5 must be present
  - Incomplete VKH: Criteria 1–3 and either 4 or 5 must be present
  - Probable VKH (isolated ocular disease): Criteria 1–3 must be present
- ***Criteria***
  1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
  2. No clinical or laboratory evidence suggestive of other ocular disease entities
  3. Bilateral ocular involvement
     - Early manifestations: Evidence of diffuse choroiditis → focal areas of subretinal fluid bullous serous retinal detachments
     - Late manifestations: suggestive of prior presence of 3a, Ocular depigmentation
  4. Neurological/auditory findings
     - Meningismus
     - Tinnitus
     - Cerebrospinal fluid plenocytosis
  5. Intergumentory finding
     - Alopecia
     - Poliosis
     - Vitiligo
- **Investigations**
  - FA
    - Multiple pinpoint areas of leakage are noted at the level of the RPE
    - Large confluent area of leakage
    - Late leakage of the disc

        - Early choroidal stromal vessel hyperfluorescence and hypofluorescent dark dots.
        - Fuzzy vascular pattern to the large stromal vessels and disc hyperfluorescence.
    - ERG
    - EOG
    - OCT
        - Troughs of RPE undulations
        - Choroidal folds
- **Therapy**
    - In the acute phase the treatment, lasting for 6 months or longer with gradual taper of systemic corticosteroids, is important in preventing chronic and recurrent phases of the disease.
    - Systemic high-dose corticosteroids are the mainstay of treatment during the acute phase, and the chronic phase requires immunomodulatory agents. However, treatment approaches vary: some recommending combination of systemic corticosteroids with mycophenolate mofetil or other steroid-sparing agent, azathioprine, or methotrexate, and others preferring to administer corticosteroids.
    - In the United States most centers use the oral route of corticosteroid administration (1 to 2 mg/Kg), whereas in Japan and Europe intravenous corticosteroid administration is preferred. Both routes of administration are found useful in treating the uveitis, with no significant difference in outcome.
    - The patients who do not respond to systemic corticosteroids are managed with a combination of corticosteroids and cyclosporine or other immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide), including biologicals such as anti-TNFα.
    - Intravitreal delivery of corticosteroids (triamcinolone, 4 mg/0.1 ml) have been used in the treatment; however, such an approach may not prevent development or treatment of extraocular manifestations.

Difference between VKH and SO

- Presence of penetrating injury in SO and absence of such trauma in VKH
- VKH develops predominantly in pigmented individuals of various ethnic and racial groups: Asians, Latinos, Middle-Eastern and South Europeans. There is no such proclivity in the development of SO.
- VKH is relatively more common in women, and SO is more common in men.
- In patients with VKH, average age at presentation varies from 32 to 35 years, and in contrast in SO the average age is 46 years.
- Extraocular changes (vitiligo, poliosis, and tinnitus) are reported frequently in patients with VKH, and such changes including depigmented ocular fundus (sunset glow fundus) are rare in SO.

Behcet's Disease

- Named after Hulusi Behçet, a Turkish dermatologist who first described the triad of recurrent oral aphthous ulcers, genital ulcers, and hypopyon uveitis
- Also known as Adamantiades-Behçet syndrome or Silk Road disease
- Multisystemic small-vessel vasculitis characterized by obliteration of arteries, veins, and capillaries
- Most common manifestations include mucous membrane lesions of the GI tract, ocular inflammation, and inflammatory arthritis. Cardiovascular and neurological system involvement can lead to fatal consequences of aneurysm or obliterative cerebral vasculitis.
- As the name suggests, there is a much higher prevalence in countries along the Silk Road, the ancient trade route between Europe, the Middle East, and Asia. Rare in United States and Africa but it is well documented that cases occur.
- Young adults (25-35 years), no gender predilection, but a more severe course in males
- Over half of Behçet disease patients will have ocular features.
- **Etiopathogenesis**
  - HLA-B51 is present in 50%-80% but is not an essential diagnostic marker.
  - The lack of patients in large populations (eg, Brazil) suggests environmental factors must interact with HLA-B51 in susceptible populations. Putative factors include mycobacterial heat shock protein and organophosphates.
  - Immune response
    - Pathogens activate both innate and adaptive immunity.
    - Consequent interaction of T-lymphocytes (Th1 and Th17 phenotype) with activated neutrophils
    - Resultant tissue damage (pathergy skin test, hypopyon, pseudofolliculitis, vascular involvement)
  - Genome wide-association study (GWAS) outcomes
    - Polymorphisms in loci of genes encoding interleukin-10 (IL-10), IL-23R, IL12RB2, STAT4 confer risk in Turkish, Japanese, and Chinese populations.
    - Nonsynonymous variants in the toll-like receptor 4 (TLR4) gene and the Familial Mediterranean Fever (MEFV) gene mutation confer risk in the Turkish population.
    - Other susceptibility genes: endoplasmic reticulum aminopeptidase 1 (ERAP1) and C-C chemokine receptor type 1 (CCR1)-CCR3
- **Ocular features**
  - Chronic recurrent nongranulomatous uveitis
  - 60% develop panuveitis, but anterior, intermediate, posterior uveitis can also occur.
  - Hypopyon:
    - Smooth-layered, shifts with gravity
    - Maybe white-eyed despite severe inflammation: so-called "cold hypopyon"
    - Transient

- Implies severe posterior segment involvement
- Incidence: 5%-30% of eyes (True incidence may be higher as it is transient.)
- Five times increased risk of hypopyon in BD in a nonendemic population

- Retinal vasculitis can affect arteries, veins, and the capillary bed (ferning). There can be chorioretinal infiltrates and frank ischemic retina due to multifocal occlusive and necrotizing retinal vasculitis.
- Other findings include cystoid macula edema, optic nerve head edema, retinal hemorrhages, distinct retinal artery, and retinal vein occlusions.
- Less common anterior findings: recurrent conjunctivitis, episcleritis, scleritis
- End stage: obliterated white retinal arterioles with chorioretinal atrophy and optic disk pallor
- Complications: neovascularization, cataract and glaucoma

- **Diagnosis**
  - **CRITERIA OF THE INTERNATIONAL STUDY GROUP 1990**
    - Recurrent oral aphthous ulcers; Small or large aphthous or herpetiform ulcerations, recurring at least 3 times in a 12 month period ***Plus 2 of the following:***
      - Recurrent genital ulcers: Aphthous ulcerations or scarring
      - Eye lesions: Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination or retinal vasculitis observed by an ophthalmologist
      - Skin lesions: Erythema nodosum, pseudofolliculitis, papulopustulous lesions or acneiform papules in postadolescent patients without steroid treatment
      - Positive pathergy testing: Intracutaneous stick with 21G needle on the forearm (inside), read physician after 24–48 h
  - **CRITERIA of Behçet's Disease Research Committee of Japan**
    - Major criteria
      - Recurrent oral aphthous ulcers
      - Skin lesions (erythema nodosum, folliculitis)
      - Genital ulcers
      - Iridocyclitis (with hypopyon)
      - Posterior uveitis with retinal vasculitis
    - Minor criteria
      - Arthritis
      - Epididymitis
      - GI involvement
      - Vascular involvement (thrombosis)
      - Neurologic symptoms

- **Management**
  - Anterior uveitis
    - Topical steroids
    - Periocular steroid injections
  - Posterior segment–involving uveitis
    - Intravitreal steroid injection
    - Oral corticosteroids
    - Colchicine: Efficacious for mucocutaneous signs, efficacy not shown for BU
    - Conventional IMT
      - Azathioprine and/or cyclosporine A: Efficacy proven in randomized controlled trials (RCTs)
      - Mycophenolate mofetil: Effective in uncontrolled studies including BU patients
      - Tacrolimus: Limited data
      - Cyclophosphamide: Intravenous monthly pulses inferior to cyclosporine A
      - Chlorambucil: Efficacious in open-label trials, used as last resort until biologic era
    - Biologic Agents
      - Antitumor necrosis factor alpha (Anti-TNFα) agents
        - ✓ Infliximab: Suggested as first-line IMT for BU based on systematic review of published data
        - ✓ Adalimumab: Suggested as first-line IMT for BU based on systematic review of published data
        - ✓ Etanercept: Associated with development of uveitis in other diseases
        - ✓ Golimumab: Data limited to 1 case refractory to other TNF-α blockers
        - ✓ Certolizumab: Not studied in BU
      - Interferon-alpha (IFN-α)
        - ✓ Efficacy shown in open-label trials
        - ✓ Response rate: 85%-98%
        - ✓ A low-dose regimen is better tolerated.
        - ✓ Potential to induce durable remission after discontinuation
        - ✓ Better “general perception of health” than those treated with conventional IMT
      - Others
        - ✓ Gevokizumab (IL-1β regulating monoclonal antibody), rituximab (B cell antigen CD20 antibody), and tocilizumab

(antiIL6 receptor antibody) were found effective in case reports or small pilot studies.

- ✓ Daclizumab (anti-IL2R antibody) and secukinumab (anti-IL17A antibody) were found ineffective in RCTs.

- **Prognosis**
  - Systemically: Good in absence of neurological or cardiovascular involvement
  - Ocular: With stronger first-line therapy such as biologics, prognosis may have improved, with 10%-15% deteriorating to VA <20/200 after 5 years. Thirty years ago this figure was 50%+.

Retinal Vasculitis

- Retinal vasculitis is an inflammatory disease of the blood vessels of the retina that may be associated with primary ocular conditions or with inflammatory or infectious diseases in other parts of the body (systemic diseases). It has been defined as the vascular leakage and staining of vessel walls on fluorescein angiography, with or without the clinical appearance of fluffy, white perivascular infiltrates in an eye with evidence of inflammatory cells in the vitreous body or aqueous humor
- **Primary causes**
  - Localized to the eye
    - Idiopathic
    - Intermediate uveitis of the pars planitis type
    - Frosted branch angiitis
    - Idiopathic retinal vasculitis, aneurysms and neuroretinitis (**IRVAN**)
  - Involving the eye and other organs (primary systemic associations)
    - Giant cell arteritis
    - Takayasu arteritis
    - Polyarteritis nodosa
    - Wegener's granulomatosis
- **Secondary vasculitis**
  - Localized to the eye:
    - Ocular sarcoidosis
    - Birdshot chorioretinoapthy retinal vasculitis
    - Necrotic herpetic retinopathies (herpes simplex, varicella zoster virus)
    - Toxoplasmic retinochoroiditis
    - Tuberculosis
    - DUSN (Diffuse unilateral subacute neuroretinitis)
    - Primary ocular lymphoma
  - Associated with systemic involvement

- Sarcoidosis
- Behçet's disease
- Multiple sclerosis
- Systemic lupus erythematosis (SLE)
- Spodylarthritis with HLA-associated uveitis
- Inflammatory bowel diseases
- Relapsing polychondritis
- Tuberculosis
- Syphilis
- Lyme disease
- Viral (Cytomegalovirus, HIV, West Nile)

✦ **Arteritis & Phlebitis**

✣ ***Primarily arteritis***

- Systemic lupus erythematosus
- Polyarteritis nodosa
- Syphilis
- Acute retinal necrosis
- Progressive outer retinal necrosis
- Idiopathic retinal vasculitis and renal
- Chug-Strauss syndrome

✣ ***Primarily phlebitis***

- Sarcoidosis
- Multiple sclerosis
- Behcet disease
- Birdshot chorioretinopathy
- HIV paraviral syndrome
- Eales disease

✣ ***Arteritis and phlebitis***

- Toxoplasmosis
- Relapsing polychondritis
- Granulomatosis with polyangiitis
- Crohn disease
- Frosted branch angiitis

✦ **Clinical Features**

✣ The classic symptom of retinal vasculitis is a painless decrease in vision. Other symptoms may include floaters from accompanying vitritis, a blind spot from

ischemia-induced scotomas, metamorphopsia (change in shape of an object) in case of macular involvement or altered color perception. Retinal vasculitis can also be asymptomatic.

- Retinal examination typically reveals sheathing (a whitish-yellow cuff of material surrounding the blood vessel) of the affected retinal vasculature associated with variable vitritis (inflammatory cells behind the lens in the vitreous body). It involves noncontiguous portions of the vessel.
- Inflammation may involve retinal arteries, veins or capillaries, but peripheral venous involvement is commonly recognized. Arterioles are preferentially involved in syphilis.
- The location and appearance of vascular lesions may have a limited diagnostic utility. "Candlewax drippings" seen as dense, focal, nonocclusive periphlebitis are associated with sarcoidosis, but its appearance is neither pathognomonic nor present in all patients with the disease.
- The occlusive phlebitis of Behçet's syndrome tends to manifest in the posterior pole, although peripheral retinal vasculitis may occur. Presence of a choroiditis lesion (active or healed) underlying the retinal vessels is a common observation in vasculitis of tubercular origin. Additional evidence of ocular inflammation such as cells in the aqueous humor may accompany retinal vasculitis.
- Narrowing of the retinal blood vessels, vitreous hemorrhage, and new blood vessel growth are present as complications of retinal vasculitis.

- **Investigations**
  - Optical coherence tomography
  - Ultrasonograhy
  - Indocyanine green angiography
  - Ultrasound biomicroscopy
  - Few laboratory studies that should be done in all patients with isolated retinal vasculitis are:
    - Full blood counts
    - Erythrocyte sedimentation rate
    - Mantoux test
    - Chest X-ray to rule out sarcoidosis or tuberculosis (Computed tomography if required)
    - Syphilis serology (Treponema pallidum hemagglutination test)
  - Suspecting a specific etiology
    - Toxoplasmosis serology
    - HIV
    - Lyme disease serology
    - X-ray of sacro-iliac joint
    - C-reactive protein
    - Serum Angiotensin-Converting-Enzyme

- Human leukocyte antigen (HLA) typing
- ANA, ANCA

- **Management**
  - The management of retinal vasculitis is to reduce inflammation, thereby reducing the risk of permanent harm to the retina or irreversible damage to the macula.
  - Systemic prednisone, 1 mg/kg/day, is the first-line drug for those patients in whom infection is not suspected. It is tapered in 5-mg steps each week to 5 mg a day maintenance. If the disease is not controlled on 5 mg a day, a second-line immunomodulatory agent is preferable to long-term steroid treatment. This requires prompt referral to a specialist, skilled in the use of these drugs and their complications.
  - Patients with infection require the appropriate antimicrobial therapy for their condition. In India, cases of Eales disease (a subset of patients with idiopathic ischemic retinal vasculitis) routinely receive antituberculous chemotherapy along with steroid and retinal laser. Intraocular injections of steroids, antiviral, and anti-VEGF drugs have increasing roles in managing aspects of retinal vasculitis.
  - Retinal photocoagulation is used in ischemic cases to control neovascularization and has a limited role in persistent neovascular snowbanks in eyes with pars planitis. Vitrectomy is required for cases of prolonged or recurrent vitreous hemorrhage and for secondary complications such as epiretinal membranes.

Lupus-associated retinal vasculitis

- Systemic lupus erythematosus (SLE) is a chronic, autoimmune, multisystem connective tissue disorder with prominent autoantibody production and relapsing and remitting clinical course.
- **Epidemiology**
  - The incidence of SLE ranges from 1.8-20 cases per 100,000 per year and is 9 times higher in women.
  - While SLE is more common in people of African and Asian descent, thromboembolic events are more common in white patients.
  - Average age of onset is 30.
  - Ocular manifestations occur in up to one-third of patients.
- **Pathogenesis**
  - A. SLE is a complex disease process, with dysregulation of the immune system at multiple levels, including defects in the innate and adaptive immune systems, apoptotic clearance, cytokines, T-cell signaling, and B-cell immunity.
  - Two major theories exist on how antibody overproduction causes tissue damage:
    - Immune complex deposition in end-organ capillary beds activates immune / inflammatory responses.
    - Autoantibodies cross-react with normal proteins, causing tissue damage.

- The exact mechanism of vascular occlusion is unclear; however, some suggest that immune-complex deposition, complement activation with microvascular thrombosis, and fibrinoid degeneration of the vascular wall are involved.

- **Ocular Features**
  - SLE can affect the periorbita, ocular adnexa, eye, and optic nerve.
  - The most common manifestation is keratoconjunctivitis sicca, which can be found in up to one-third of patients. The majority of patients endorse at least 1 dry eye symptom.
  - Uveitis is uncommon as an isolated manifestation of SLE.
  - Scleritis is rarely necrotizing but can manifest as nodular or diffuse and anterior and/or posterior. The scleritis typically presents as painful and can be potentially vision threating, requiring prompt treatment.
  - The most visually devastating complications occur secondary to optic nerve involvement and retinal vasculopathy.
  - Lupus retinopathy is a common manifestation of systemic disease, occurring in up to 29% of patients. The most common pattern of retinopathy is microangiopathy similar to diabetes, with the earliest findings being cotton-wool spots and retinal hemorrhages. A strong correlation exists between the presence of retinopathy and central nervous system (CNS) disease.
  - Retinal edema, hard exudates, microaneurysms, arterial narrowing, venous engorgement, and vascular tortuosity have all been reported.
  - Retinal vasculitis with inflammation of the arterioles or venules tends to have poorer visual outcomes and often presents in an acute fashion. Fluorescein angiography frequently demonstrates arterial and capillary nonperfusion, leakage from neovascular fronds, and staining of the walls of involved vessels. Retinal vascular complications are typically bilateral but can present unilaterally.
  - Central retinal vein occlusion and arterial occlusive disease have been reported.
  - Lupus choroidopathy with exudative retinal detachments is rare. It is generally seen in patients with highly active disease, including CNS vasculitis and nephropathy, as well as uncontrolled blood pressure.
  - Optic nerve disease is a rare manifestation of SLE, presenting as optic neuritis and ischemic optic neuropathy with vision typically worse than 20/200.

- **Diagnosis**
  - Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus: Requires ≥ 4 criteria (at least 1 clinical and 1 immunologic) or biopsy-proven lupus nephritis with positive ANA or anti-dsDNA.
  - Ocular involvement may be clinically silent, and so all patients with SLE should undergo careful eye examination. In addition to a complete ophthalmic examination (ocular vital signs, slit-lamp biomicroscopy, and dilated fundus examination), one or more special tests may be required, including multimodal imaging (OCT, fluorescein and/or indocyanine green angiography, autofluorescence imaging), visual field testing, and electroretinography.

- **Management**

- Significant ocular involvement including orbital inflammation, scleritis, peripheral ulcerative keratitis, retinal vasculitis, choroiditis, and optic nerve involvement warrant systemic therapy.
- Corticosteroids are the mainstay of acute treatment because they are fast acting and effective. Highdose steroids should only be used short term.
- Antimalarials such as chloroquine and, more commonly, hydroxychloroquine are highly effective in curtailing future flares with fewer side effects than alkylating agents. However, these therapies can cause irreversible vision loss secondary to druginduced maculopathy, for which patients require screening and monitoring according to the 2016 AAO guidelines.
- Early and aggressive treatment is warranted for patients with retinal vasculitis given the correlation with CNS vasculitis to prevent high level of morbidity and mortality.
- Periocular steroid injections have a role in unilateral or asymmetric disease; however, they should be used with caution and avoided in patients with scleritis.
- Steroid-sparing immunosuppressive agents are used in a large proportion of patients due to treatment failure or harmful side effects of corticosteroids. Methotrexate, mycophenolate mofetil, cyclosporine A, azathioprine, chroambucil, and cyclophosphamide have all been used with varying degrees of success.
- Recently, newer biologic agents targeting specific molecules in Band T-cell activation have been employed with clinical improvement.

Eales Disease

- Eales' disease is an idiopathic retinal periphlebitis that primarily affects the peripheral retina in young adults. Retinal changes are characterized by periphlebitis, peripheral non-perfusion and neovascularization leading to visual loss. The disease afflicts people worldwide but for unknown reasons is more common in the Indian subcontinent. Eales' disease appears to be an immunologic reaction that may be triggered by an exogenous exposure.
- A syndrome of recurrent retinal and vitreous hemorrhage in young men, associated with constipation and epistaxis, was first described by **Henry Eales** in **1880**.
- **Etiopathogenesis**
  - Mycobacterium tuberculosis DNA has been detected by polymerase chain reaction, in the vitreous of such patients. However, the role of mycobacterium genome in the pathogenesis is yet to be ascertained.
  - Retinal S-antigen and Inter-photoreceptor Retinoid Binding Protein plays a role in the etiopathogenesis of this condition.
  - An extraneous agent results in the exposure of normally sequestered uveitopathogenic antigens of the immune system, leading to an immune response in the eye that may initiate the disease process.
  - Oxidative stress plays an important role in the pathogenesis of Eales' disease.
  - Retinal photoreceptors and platelets have been shown to be an easy target of oxidants because of high proportion of polyunsaturated fatty acids. The decreased

membrane fluidity in platelets suggests alterations in the physiological events, which may result in alterations in functioning of retinal photoreceptors.

- The natural course of Eales' disease is quite variable with temporary and even permanent remission in some cases and relentless progression to blindness in others.
- **Clinical Features**
- Eales' disease is characterized by retinal phlebitis, peripheral nonperfusion, and retinal neovascularization.
  - **Retinal Phlebitis:** Intraocular inflammation is a common manifestation of Eales' disease. Signs and symptoms of inflammation occur at varying times in the course of the disease, but are less common in late stages. Fundus examination in the early stages of the disease reveals venous dilatation in the periphery with tortuosity and discontinuity of veins. Perivascular exudates are seen along the peripheral veins. Vascular sheathing ranges from thin white lines limiting the blood column on both sides to heavy exudative sheathing. The thin white lines tend to be continuous, and the heavy exudative sheathing is usually segmental. Superficial flame-shaped haemorrhages are often located in the areas of sheathed vessels. Though not initially involved, at a later stage the arteries also attenuate in the periphery. The involved vessels become obliterated and an avascular area develops in the periphery which is better visualized by fluorescein angiography. Areas of vascular sheathing frequently leak fluorescein dye; however, the sheathing does not always correspond to the staining. The intensity of the dye leakage seen with fluorescein angiography is not always proportional to the activity of the inflammatory process.
  - **Peripheral Non-perfusion:** Most patients with Eales' disease develop varying degrees of peripheral retinal nonperfusion. Intraretinal haemorrhages often first appear in the affected area, followed by an increase in vascular tortuosity with frequent collateral formation around occluded vessels. Fine solid white lines representing the remains of obliterated large vessels are commonly seen in the area of nonperfusion. These fine lines retain configuration of normal retinal vasculature. This junction between the anteroperipheral nonperfusion and the posterior perfused retina is usually sharply demarcated. The vascular abnormalities at the junction between the perfused and nonperfused zones include microaneurysms, veno-venous shunts, venous beading and occasionally hard exudates and cotton-wool spots.
  - **Neovascularization**: Neovascularization is observed in upto 80% of patients with Eales' disease. The new vessels can form either on the disc (NVD) or elsewhere on the retina (NVE). The NVE, however, is usually more common than NVD and is usually located at the junction between the perfused and nonperfused retina. Bleeding from neovascularization is common, usually recurrent, and is one of the major causes of visual loss. A few days after vitreous haemorrhage, blood settles in the lower vitreous, and fundus details become visible again. In favourable cases, there may not be any recurrence after the first episode of vitreous haemorrhage. In recurrent bleeding, the fundus shows evidence of old blood, with signs of fibrous organization, retinitis proliferans or even tractional retinal detachment. Some patients may develop uveitis, complicated cataract, rubeosis iridis, and secondary neovascular glaucoma in the late stage of the disease.
  - Other vitreous abnormalities seen in Eales' disease are vitreous condensation and posterior vitreous detachment.

- The macula is usually not involved primarily in Eales' disease despite extensive peripheral nonperfusion. This preserves the central vision. However, in some patients the nonperfusion extends to the macula or macular oedema develops. In eyes after recurrent vitreous haemorrhages with extensive fibrosis, the optic disc becomes pale, arteries and veins become narrow, leading eventually to secondary optic atrophy.

- **Classification**
  - **Charmis** in 1965 classified Eales' disease into four stages on the basis of its evolution and prognosis.
    - Stage I is the very early stage of evolution and is characterized by mild periphlebitis of small peripheral retinal capillaries, as detected by ophthalmoscopy.
    - Perivasculitis of the venous capillary system is widespread and larger veins are also affected in stage II.
    - New vessel formation with abundant haemorrhage in the retina and vitreous is seen in stage III
    - Stage IV is the end result of massive and recurrent vitreous haemorrhages with retinitis proliferans and tractional RD.

- **Investigations**
  - MANTOUX
  - CHEST X-RAY
  - VDRL
  - ESR
  - ANCA ANA CRP
  - ACE , SERUM CA LEVEL
  - SEROLOGY TITRE FOR TOXOPLASMA
  - HIV
  - COMPLETE HAEMOGRAM , BT CT
  - Hb Electrophoresis
  - FFA to r/o
  - Active or healed vasculitis
  - CNP area
  - NVD, NVE
  - ? Macula
  - OCT to r/o
  - CME Epiretinal membrane, subclinical macular hole
  - USG to r/o RD and PVD status
- **Management**

- Active Vasculitis
  - Systemic steroids up to 2 mg/kg of prednisolone have been advocated in the active phase. These can be tapered over 6–8 weeks.
  - Subtenon injections of triamcinolone have also been used in a dose of 0.5–1 ml (40mg/ml).
  - The use of antimetabolites has been reported in one eyed patients and in central disease. Low dose oral methotrexate pulse therapy (at a dose of 12.5 mg/week) for 12 weeks has been reported recently but needs more evaluation
- IF VIREOUS HAEMORRAGE
  - Treat other eye
  - Rest
  - Look for cells and flare
- MONITOR
  - visual acuity
  - IOP
  - Ant segmentcells and flare
  - OCT – before and after treatment
  - FFA after 6-8 weeks and look for dye leakage
- Role of ATT
  - Clinical suspectsmassive infiltration, nodule formation and obliteration of venous segment give 450 isoniazid and 300 ethambutol x 9 months
- PHOTOCOAGULATION
  - Never treat active vasculitis
  - NVE – moderately overlapping burns
  - NVE raised anchoring and feeder vessels
  - Gross CNP – sectoral
  - NVD PRP
- ARC
  - Small undilating pupil
  - Media hazy due to cataract
  - Vitreous haemorrhage
  - Adjunct to photocoagulation
- Time for Surgical Intervention
  - Study demonstrated the importance of early vitrectomy for persistent haemorrhage.
  - delaying vitrectomy is believed to allow the development of cystoid macular edema, macular scar and macular pucker.

        - Operate between 3 to 6 months
        - Indication
            - Nonresolving vitreous haemorrhage
            - TRD involving posterior pole
            - Multiple vitreous membranes with or without TRD
            - Combined TRD and RRD
- **Good prognosis factors**
    - Fewer episodes and shorter duration of vit haemorrhage
    - PVD is completed
    - Prior photocoagulation
- **Bad prognosis factors**
    - Multifocal attachment
    - TRD involving macula

Tuberculosis (TB)

- About one third of the world's population has latent **tuberculosis**, caused by *Mycobacterium* ***tuberculosis***.
- From this pool, roughly 9 million cases of active **tuberculosis** emerge annually, resulting in 2-3 million deaths.
- Treatment of active Tuberculosis gives cure rates above 95% provided that the strain of Mycobacterium tuberculosis is not multidrug resistant and that compliance is adequate. Non-adherence to treatment may decrease cure rates to 79% and increase the prevalence of multidrug resistant strains
- Globally, the most common opportunistic infection and the leading cause of death related to HIV infection is **tuberculosis**. The two main approaches to **tuberculosis** control are casefinding combined with treatment of active cases, and prevention of disease in infected people.
- The tubercle bacillus was discovered by Robert Koch in 1882
- **Pathogenesis**
    - Both types of response are cell-mediated and there has been considerable controversy about whether protective and immunopathological responses are manifestations of the same mechanism, differing only in degree
    - The characteristic histological lesion of tuberculosis is the granuloma, which consists of a chronic, compact aggregate of activated macrophages (epithelioid cells), some of which fuse to form multinucleate giant cells
    - *Mycobacterium* ***tuberculosis*** uses a trick to invade cells. The body's immune system normally tags any invading bacteria with proteins that alert macrophages to consume it. One of these proteins, C2a, then floats in the blood with no known function. *M* ***tuberculosis*** manages to associate with this discarded C2a protein and use it to create a new label that helps the bacteria adhere to the macrophage and

enter it. Once inside the macrophage, the mycobacteria multiply until the cell ruptures and the bacteria are then released to repeat the process.

- Mechanisms involved in the manifestations of ocular tuberculosis
  - Immune reaction to tubercular antigens: Phlyctenulosis, Vitritis, Anterior uveitis, Interstitial keratitis, Retinal vasculitis
  - Tissue invasion by Mycobacterium tuberculosis: Endogenous Endophthalmitis, Chorioretinitis, Nodular scleritis
  - Immune reaction and tissue invasion: Cyclitis, Choroiditis, Multifocal choroiditis, Chorioretinitis

- **Investigations**
  - CXR
  - Culture Sputum / urine culture / stain for AAFB (acid and alkali fast bacilli). Ziehl Neelsen stain or auramine-phenol fluorescent test are confirmatory
  - The tuberculin skin test (TST) is the most common laboratory test performed.
    - Tuberculin hypersensitivity
    - Mantoux: Old Tuberculin = PPD (purified protein derivative)
  - Interferon-gamma release assays (IGRAs):
    - QuantiFERON-TB Gold In-Tube (QFT) (Cellestis, Inc.; Australia) and
    - ELISpotPLUS (T-SPOT.TB, Oxford Immunotec; Abingdon, UK) have found significant use in detection of TB uveitis.
    - These measure interferon-gamma response produced by the T cells after antigenic stimulation. The diagnostic accuracy is known to improve with their use.
  - Real-time PCR and multitargeted PCR (MPCR) are newer diagnostic aids for TB uveitis.
    - MPCR uses 3 target genes simultaneously for diagnosis of TB, namely, **IS6110, MPB64, and protein b.** Using 3 primers in intraocular fluids has shown a high sensitivity and specificity for diagnosing TB uveitis.
  - Biopsy

- **Ocular Manifestations**
  - Eyelids → Localized mass
  - Conjunctivae → Conjunctival granuloma
  - Sclera → Focal necrotizing scleritis, nodular scleritis, sclerokeratitis
  - Cornea → Interstitial keratitis, phlyctenulosis
  - Ciliary body → Cyclitis caseating granuloma
  - Uvea → Anterior granulomatous, uveitis
  - Vitreous → Vitritis
  - Choroid → Multifocal choroditis, chorioretinitis, peripapillary choroiditis, tubercles
  - Retina → Retinitis retinochoroiditis, retinal vasculitis

- Optic nerve → Papillitis, optic neuritis, retrobulbar neuritis
- Orbit → Granuloma, localized mass
- Lacrimal gland → Granuloma, localized mass

- **Diagnosis of ocular tuberculosis**
  - Presumed ocular tuberculosis
    - Clinical findings: uveitis, choroiditis, cyclitis
    - Positive purified protein derivative (PPD) skin test
    - Exclusion of other causes
    - Response to antituberculous multidrug combination therapy in 2–4 weeks
  - Definitive ocular tuberculosis
    - Clinical findings
    - Demonstrating caseating granuloma and acid-fast bacilli by histopathology of ocular tissue biopsy specimen
    - Isolation of Mycobacterium tuberculosis on Lowestein–Jensen medium
    - Demonstration of Mycobacterium tuberculosis DNA by PCR
- **Management**
  - Antitubercular therapy is highly effective in reducing the recurrences of uveitis in patients with manifest TB.
  - The World Health Organization recommends that new patients with both pulmonary TB and extrapulmonary TB to be treated with a 4-drug regimen (isoniazid, 5 mg/kg/day; rifampicin, 10 mg/kg/day; ethambutol, 15 mg/kg/day; and pyrazinamide, 20-25 mg/kg/day). Ethambutol and pyrazinamide are stopped after 2 months. Isoniazid and rifampicin are continued for 4-6 months.
  - Corticosteroids seem to have a potential benefit in patients with tubercular pericarditis and meningitis, similarly; steroids are used in ocular TB as well. More evidence is required on the dose and duration of corticosteroids in ocular infections.
  - Antibiotic sensitivity tests and minimum inhibitory concentration of drug in ocular TB are not studied well.
  - In patients with coexisting HIV and systemic TB, initiation of concomitant antitubercular and antiretroviral therapy may result in exacerbation of inflammation and clinical deterioration. Either addition of corticosteroids or delaying the administration of highly active antiretroviral therapy (HAART) for the first 2 months of antituberculosis treatment is advised.
- **Drug-Resistant TB**
  - The possibility of drug-resistant TB is not always considered in ocular TB. Detection of drug resistance is not attempted because drug susceptibility testing is possible only in culture isolates. Difficulties in isolating the organisms from ocular TB make this assay difficult. This has serious implications specifically in uveitis; when a trial of antitubercular treatment fails in presumed ocular TB, there is a very high possibility for the uveitis specialist to assume a nontubercular etiology and to start corticosteroids or immunosuppressive treatment to control inflammation.

- Drug susceptibility testing can be performed on all positive mycobacterial cultures by 1% proportional method on Middlebrook 7H10 agar for all antitubercular drugs. Conventional methods for mycobacteria culture and drug susceptibility testing (DST) are elaborate and time consuming. In such situations molecular diagnostic studies to rule out drug resistance may be of help.
- Drug-resistant strains have evolved mainly due to incomplete or improper treatment of TB patients. Multidrug-resistant (MDR)-TB and extensively drug-resistant tuberculosis (XDRTB) have been reported in 45 countries, and they are considered as a global threat. Most cases are missed due to insufficient laboratory infrastructure for diagnosis. MDRand XDR-TB are generally thought to have high mortality rates. At present, MDRTB is treated by a combination of 8 to 10 drugs with therapies lasting up to 18-24 months; only 4 of these drugs were actually developed to treat TB. With the correct combination and rational use of available antituberculosis drugs, better prognosis can be obtained.

Leprosy

- Important and neglected cause of blindness
- Ocular disease: Chronic anterior uveitis with iris pearls (represent miliary lepromas), vitreous opacities, retinal detachment, extensive iris atrophy, and intractable glaucoma. Posterior uveal involvement is rare.
- Treatment of iridocyclitis is mandatory, as well as protection of anesthetic corneas from exposure, erosion, and ulceration in the face of lagophthalmos.

Intraocular Lymphoma

- **Intraocular lymphoma is comprised of the following:**
  - Vitreoretinal lymphoma
    - 95% of the time diffuse large B-cell lymphoma (DLBCL)
      - Primary (PVRL)
      - Secondary (Either associated with primary CNS lymphoma or systemic DLBCL)
    - 5% of the time T-cell lymphoma
      - Rare; many times associated with mycosis fungoides.
  - Choroidal lymphoma,
    - usually B-cell lymphoma and mainly small B-cell lymphoma
    - 20% diffuse large B-cell
  - Iridial lymphoma
    - usually seen in immunocompromised patients
    - involves many times Epstein-Barr virus–driven diffuse large B-cell lymphoma
- **History and clinical symptoms:** insidious onset, floaters, decreased vision, history of CNS lymphoma or systemic lymphoma

- **Clinical Findings**
  - Vitritis
  - Retinal or retinal pigment epithelial (RPE) infiltration
  - Subretinal lesions
  - Optic nerve edema with infiltrative disease
- **Diagnosis and treatment**
  - Vitreous biopsy for cytopathology, flow cytometry, and gene rearrangement (ie, IgH gene rearrangement in B-cell lymphoma; T-cell receptor gene rearrangement in T-cell lymphoma)
  - Cytokine levels for interleukin-10 to interleukin-6 ratio (IL-10: IL-6 ratio > 1)
  - Management with neuro-oncologist, oncologist

PVRL: Primary Vitreoretinal Lymphoma

- Primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL).
- PVRL may affect the subretinal space, the vitreous, and the optic nerve.
- Immunocompetent and immunodeficient patients may develop PVRL. Historically, reactivation of latent Epstein-Barr virus has mediated the development of PVRL in immunodeficient patients, while most immunocompetent cases have not been related to an infectious pathogen.
- Classically, immunocompetent patients may develop disease in their fifth to sixth decades of life, while immunodeficient patients developed disease much earlier. However, with the use of antiretroviral therapy in AIDS patients, the incidence of PCNSL and PVRL has declined.
- There is a slight female preponderance of disease.
- **Clinical Symptoms and Signs**
  - Patients typically complain of floaters and blurry vision.
  - Vitritis, anterior chamber cell, or subretinal involvement may be seen.
  - The vitritis responds to systemic and local steroids, which allows this entity to masquerade as a noninfectious uveitis.
  - When subretinal lesions exist, OCT can identify hyper-reflective lesion between retinal pigment epithelium and Bruch membrane.
- **Differential Diagnosis:**
  - Intermediate uveitis
  - Tuberculosis
  - Syphilis
- **Diagnosis**
  - Cytopathology or molecular testing of ocular tissue (aqueous, vitreous, or chorioretinal biopsy)

- Some centers use interleukin level (IL) in aqueous humor and the vitreous as supportive evidence of the diagnosis of intraocular lymphoma. In fact, the sensitivity is high (80% to 90%) for IL-10 measurement and/or the ratio of IL10:IL6
- As the majority of large, diffuse vitreoretinal B-cell lymphomas have shown Myd99-L2655P mutation, this PCR test has proven to be very useful as an ancillary diagnostic tool in scarcely cellular specimens.
- MRI brain to evaluate for CNS disease

- **Primary vitreoretinal lymphoma (PVRL) Management**
  - Without CNS or systemic involvement
    - Only 1 eye involved: Use local therapy—whether it is local intravitreal methotrexate and rituximab alone or carefully given between 30-35 Gy external beam is still in contention.
    - Both eyes involved: There is still a preference toward local therapy, although systemic treatment may not be excluded. Addition of intravitreal chemotherapeutic agents in addition to the systemic therapy would be considered.
  - With CNS involvement
    - High-dose methotrexate-based therapy (possibly with systemic rituximab) in conjunction with local therapy given the limited penetration of systemic agents into the vitreous cavity
    - Consideration of whole-brain radiotherapy in conjunction with ocular radiotherapy in those who have failed systemic therapy and are too debilitated or do not meet criteria for more aggressive therapy such as ASCT

Lymphocytic Choriomeningitis Virus (LCMV)

- Single strand, RNA, Arena virus, rodent reservoirs
- Symptomatic maternal illness in 2/3 of cases
- Transplacental transmission, maternal viremia
- IgG, IgM by IFA, western blot, ELISA (CDC)
- **Systemic findings**
  - Macrocephaly, microcephaly Hydrocephalus, intracranial calcifications Neurologic abnormalities, seizures, mild MR
- **Ocular findings**
  - Chorioretinal scars
  - Optic atrophy, strabismus, nystagmus
- **Differential Diagnosis**: toxoplasmosis
- Serology
- Pattern of calcification

Cat-Scratch Disease (CSD)

- Bartonella henselae
- Highest age-specific incidence < 10 yrs old
- Systemic disease
  - Erythematous papule inoculation site
  - Flu-like illness, regional adenopathy
- Ocular disease (5-10%)
  - Parinaud's oculoglandular syndrome
  - Neuroretinitis, retinochoroiditis
- Clinical diagnosis, confirmatory serology
  - IFA titers 1:64, EIA, western blot, PCR
- Broad differential diagnosis
  - Syphilis, Lyme, TB, DUSN, Toxoplasma, Toxocara, leptospirosis, mumps, HSV, VZV
  - Sarcoidosis
  - HTN,DM, AION, pseudotumor, leukemic
- No definitive treatment guidelines
  - doxycycline, erythromycin, rifampin, TMP-SMX, cipro

Lyme Disease

- Tick-borne: Borrelia burgdorferi
- Northeast, Mid-Atlantic, and upper Midwest Peak incidence: ages 5-9 and 50-59 years
- **Systemic stages**
  - Early: erythema migrans
  - Disseminated: fever, meningitis, Bell's palsy, arrhythmia, arthritis Persistent: arthritis, neurologic syndromes
- **Protean ocular manifestations**
  - Conjunctivitis, anterior uveitis, keratitis
  - Intermediate uveitis
  - Posterior uveitis (vitritis, retinal vasculitis, choroiditis, neuroretinitis), panuveitis
- Clinical diagnosis, supportive serology, PCR
- **Differential Diagnosis:** JIA
- **Treatment**: IV antibiotics at neurological doses ceftriaxone,cefotaxime, penicillin G, 14-28 days doxycycline

CINCA/NOMID

(Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome)

- Systemic:
  - Polyarthropathy, meningitis, migratory skin rash Sensorineural hearing loss, characteristic habitus
  - Perilimbal injection, CNS disease, polyarthropathy
- Ocular:
  - Optic disc changes, chronic anterior uveitis
  - Absence of posterior synechiae, cataract, glaucoma
- Mean onset 4.5 years.
- Monocular VA loss
- Differential Diagnosis : JIA

Blau Syndrome

- **Presentation**
  - Skin lesions
  - Arthritis (possible diagnosis of JIA)
  - Fever
  - Onset before 4 years of age (joint and skin)
  - Ocular pain, photophobia, redness, blurred vision
  - Family history
- **Clinical examination**
  - Joint manifestations: symmetric polyarthritis of wrists; metacarpophalangeal joint, metatarsophalangeal joint, proximal interphalangeal joint of hands and feet, ankles
  - Skin manifestations: tender, papulonodular rash; firm, subcutaneous nodules
  - Uveitis
    - Bilateral > unilateral
    - Granulomatous panuveitis
    - Band keratopathy
    - Granulomatous inflammation of conjunctiva and lacrimal glands
- **Differential diagnosis**
  - Early onset sarcoidosis (EOS)
  - JIA (if anterior uveitis)
  - TB
- **Diagnostic evaluation**

- Genetic testing for CARD15/NOD gene
- Specific treponemal antibody testing
- Chest x-ray
- Serum angiotensin converting enzyme (ACE) and lysozyme
- TB testing (PPD or INF-γ release assay)
- ANA, rheumatoid factor (if considering JIA)
- Referral to rheumatologist

Ocular Masquerade Syndromes (OMS)

- Masquerade syndromes are disorders that occur with intraocular inflammation and are often misdiagnosed as a chronic idiopathic uveitis.
- The term "Masquerade Syndrome" was first used in 1967 to describe a case of conjunctival carcinoma that manifested as chronic conjunctivitis. Today, it is used to describe disorders that stimulate chronic uveitis
- The most common features of this entity are bilateral asymmetrical involvement, the presence of aqueous and/ or vitreous cells, older age, history of systemic or ocular malignancy, the absence of other inflammatory signs such as ocular pain, keratic precipitates and synechiae, and initial response and eventual resistance to corticosteroids.
- **Types**
  - Non-malignant ocular disorders masquerading as uveitis
    - Intraocular foreign body
    - Retinal detachment
    - Myopic degeneration
    - Pigment dispersion syndrome
    - Multiple sclerosis
    - Intraocular infections
  - Malignant ocular disorders masquerading as uveitis
    - Intraocular lymphomas
    - Non-Hodgkin's lymphoma of central nervous system
    - Systemic non-Hodgkin's lymphoma metastatic to eye
    - Hodgkin's lymphoma
    - Carcinoma metastatic to eye
- The importance of OMS arises from the possibility of life rescue with the early recognition and prompt treatment of underlying malignancy. Thus, in each case with non-responsiveness to treatment with corticosteroids for possible uveitis, OMS should be considered.

White Spot Syndromes (WSS)

- Heterogeneous group of chorioretinal inflammatory diseases
  - Overlapping clinical features
  - Multiple, well-circumscribed, white-yellow lesions
  - Outer retina, retinal pigment epithelium (RPE), choriocapillaris / choroid
- **Differential diagnosis:**
  - Presumed ocular histoplasmosis (POHS)
  - Syphilis
  - Tuberculosis
  - Toxoplasmosis
  - Pneumocystis choroidopathy
  - Candidiasis
  - Necrotizing viral retinopathy
  - Ophthalmomyiasis
  - Sarcoidosis
  - Diffuse unilateral subacute neuroretinitis (DUSN)
  - Sympathetic ophthalmia
  - Vogt-Koyanagi-Harada syndrome (VKH)
  - Intraocular lymphoma
- **Shared Fearures**
  - Age: < 50 years, except BSCR, serpiginous
  - Sex: ♀ **(Female)** predominance BSCR, MEWDS, MCP, PIC
  - Bilateral: except DUSN, MEWDS, ARPE
  - Photopsias, blurred visual acuity (VA), nyctalopia, floaters, visual field loss (blind spot enlargement)
  - Viral syndrome preceding ocular disease: MFC, PIC, APMPPE, ARPE, MEWDS
- **Etiology**:
  - Autoimmune in birdshot chorioretinopathy, AZOOR, MEWDS

Birdshot Retinochoroidopathy (BSRC)

- Ryan and Maumenee in 1980
- Gass in 1981 who called it vitiliginous chorioretinitis.
- Lesions are scattered around the optic disc and radiate to the equator in a “shotgun” pattern.

- Fits into the broad scheme of 'white-dot syndromes' However this disorder seems to have better-defined boundaries
- 0.6–1.5% of patients referred to tertiary centers for uveitis, or 6–7.9% of patients with posterior uveitis
- **HLA-A29***02 subtype is most commonly associated with BCR
- **Pathogenesis**
  - Immunogenetics
    - HLA-A-29 + (80%-98%) 7% general white population
      - HLA A29*02 (Caucasian)
      - HLA A29*01 (Asian)
  - Retinal autoimmunity
    - Lymphocyte proliferation to retinal S antigen
    - Similarity between birdshot retinochoroidopathy and experimental autoimmune uveitis
    - Mixed T and B cells in choroidal lesions, no organisms
  - Mechanism
    - ↑ expression self peptides to T cells A29 molecule?
    - Polymorphisms in linkage disequilibrium with HLA-A29?
    - Molecular mimicry with microbial antigen?
      - Antigen specific vs. nonspecific bystander activation
      - Borrelia burgdorferi
- **Clinical Features**
  - blurred vision, floaters, and photopsias
  - Severe nyctalopia despite normal visual acuity
  - **OCULAR EXAMINATION FINDINGS**
    - Quiet anterior chamber
    - Vitreal inflammation but no snowbanking
    - Retinal vascular leakage and cystoid macular edema
    - Typical birdshot lesions are ill-defined, cream-colored choroidal lesions, most often seen in the nasal postequatorial fundus and exhibiting a radial distribution from the nerve.
    - Bilateral
    - Low to moderate risk of subretinal neovascularization
    - **Supportive findings include**: HLA-A29 positive, retinal vasculitis, and CME
  - Exclusion criteria include: presence of significant keratic precipitates, posterior synechiae, or diagnosis of infectious, neoplastic, or inflammatory disease that may cause multifocal choroidal lesions.
- **Additional Tests**

- Abnormal electroretinogram and electrooculogram findings
- Evidence of retinal autoimmunity
- HLA-A29+
  - One of the strongest associations between HLA type and disease in all of medicine
  - 7% of the white population is positive for HLA-A29.
  - HLA-A29 positivity in the absence of characteristic clinical findings of birdshot chorioretinopathy should not result in a diagnosis of birdshot chorioretinopathy.

- **Investigations**
  - FFA:
    - hypofluoresce in the early phase and there can be diffuse hyperfluorescence in the late phases
    - increased transit time, leakage from retinal vasculature leading to CME, optic disc hyperfluorescence
  - ICGA
    - In the active disease, the birdshot lesions appear hypofluorescent during the intermediate phase
    - Late in the ICGA, there is diffuse choroidal hyperfluorescence
  - OCT: CME
  - FAF: clinical choroidal lesions did not always correspond to the FAF defects suggests that the choroid and RPE may be affected independently
  - ERG: negative ERG pattern: greater decrease in b-wave amplitude versus a-wave amplitude
  - EOG: Decreased Arden ratios, representing RPE dysfunction
  - Visual field: peripheral constriction, enlarged blind spot, central or paracentral scotomas, and generalized diminished sensitivity

- **Treatment**
  - Initial treatment with prednisone 1 mg/kg day
    - Up to 60 mg daily for 3-4 weeks
    - Taper off if possible, and if not, < 10 mg/day
  - Initial treatment with antimetabolite
    - CellCept (Mycophenolate Mofetil) 1 gm b.i.d.; maximum 1.5 gm b.i.d. failing prednisone taper
    - Methotrexate 15 mg/weekly with 1 mg folic acid daily; maximum 25 mg/ weekly failing prednisone taper
    - Consider initial combined CSA/ mycophenolate mofetil
  - Adjunctive periocular/intravitreal steroid for CME

- Add CSA (2.5-5.0 mg/kg/day) or tacrolimus (0.10– 0.15 mg/kg/day) to antimetabolite with significant inflammatory recurrence/failure prednisone taper.
- Advance to TNF inhibitor (infliximab, adalimumab) failing combined IMT with significant inflammatory recurrence/failure prednisone taper. Discontinue CSA/ tacrolimus.
- **Daclizumab**, a monoclonal antibody against the alpha-subunit of the IL-2 receptor of T cells, has recently been found to have value in treating BCR
- Consider fluocinolone acetonide implant. Systemic steroid/IMT failure or intolerance

Placoid diseases

- APMPPE, SC, RPC, PPM

APMPPE: Acute posterior multifocal placoid pigment epitheliopathy

- 1968 by Gass
- M = F
- 20 and 50 with the mean age of onset being 26
- **Etiology**:
  - Associated with multiple conditions: Lyme disease, pulmonary TB, group A streptococcal infection, hepatitis B vaccine, mumps, sarcoid, Wegner granulomatosis, ulcerative colitis, systemic necrotizing vasculitis; viral prodrome
  - HLA-B7 (40%) and HLA-DR2 (57%)
- **Pathogenesis**
  - Gass: abnormalities were primarily at the level of the **RPE**
  - Van Buskirk: alternate theory **that choroidal perfusion was the primary problem** and that the hypofluorescence seen with angiography was due to lack of perfusion of the choriocapillaris
  - Fishman: **diffuse RPE process** was implicated in the acute phase of the disease. It also confirmed the transitory nature of this process as the EOG could normalize
- **Clinical Features**
  - Rapid onset of central vision loss that may be described as blurred vision, paracentral scotoma, metamorphopsia, “spots” in the vision, and photopsias
  - Bilateral >> unilateral
  - Multiple round and confluent cream colored, flat lesions with indistinct margins scattered in the posterior pole.
  - Lesions are not found anterior to the equator
  - The placoid lesions tend to clear centrally initially leaving hypopigmentation. Later there is mild pigment mottling
  - Improvement of the visual symptoms within 2–4 weeks

- Relatively good prognosis

- **Investigations**
  - FFA
    - Early phase as nonfluorescent
    - Later in the angiogram there is a progressive, irregular staining of the lesions
    - As the process becomes inactive, hyperfluorescence corresponding to window defects in the RPE develops and staining is no longer evident
  - ICGA
    - Acute lesions show early hypofluorescence
    - As the disease heals, the hypofluorescence in the late phase becomes less defined and smaller
    - Support to the theory of choroidal ischemia as an underlying factor in the pathogenesis of APMPPE
  - OCT
    - Mild hyperreflective area above the RPE in the photoreceptor layer corresponding to the placoid lesions
  - FAF
    - Centrally there was intense hyperautofluorescence, and the depigmented halo was hypoautofluorescent, implying atrophy
  - The electroretinogram is normal to minimally subnormal.
  - EOG: abnormal light:dark ratios suggesting a diffuse RPE problem

- **Stages of Disease by OCT:**
  - **Stage 1a hyperacute phase:** Demarcated domeshaped elevation of the inner segment/outer segment (IS/OS) junction, ± SRF (yellowish-gray fundus lesion)
  - **Stage 1b acute phase (2-4 days later):** Flattening of dome, thickening of IS/OS junction, increased reflectivity of ONL
  - **Stage 2 subacute phase (2 weeks later):** + SRF with separation of IS/OS junction and RPE, fading of hyper-reflectivity of ONL
  - **Stage 3 late phase (from 1.5-6 months later):** Disruption of IS/OS junction, increased hyperreflectivity of RPE
  - **Stage 4 resolution phase (~ 3 months after onset):** Two bands of IS/OS junction and RPE regain normal appearance, except for minimal persistent irregularity in RPE

- **Systemic associations**
  - Cerebral vasculitis
  - Meningo-encephalitis
  - Stroke
  - CN VI palsy

- **Varient of APMPPE: Ampiginous choroiditis (RPC)**
  - Variant of APMPPE and serpiginous choroiditis = relentless placoid chorioretinitis (RPC)
  - Distinguishing features on presentation
  - Distribution of lesions – periphery (mid and far) and macula
  - Morphology of lesions
  - Mild vitritis (25%)
  - Prolonged relapsing course: 35%-65% within 6 months to 5 years
  - Complications differed
    - Present: subretinal fibrosis and epiretinal membrane
    - Absent: episcleritis, optic disc swelling, CNV, subretinal fluid, retinal detachment
  - Possible association with systemic autoimmune disease

- **Management of APMPPE or Ampiginous Choroiditis**
  - Kaplan's modification of Occam's razor: "Treat the cause *and* If you don't know the cause, invoke autoimmunity and inflammation as the cause."
    - Acute suppression of immunity (ie, corticosteroids)
    - Chronic suppression of immunity: Immunomodulatory therapy (IMT)—alkylating agents, antimetabolites, T cell inhibitors, biologics
    - Ampiginous choroidopathy: forme fruste of serpiginous choroidopathy
  - Treatment recommendations
    - If central macular involved or VA ≤ 20/25: Systemic corticosteroids with IMT monotherapy (methotrexate, mycophenolate mofetil or azathioprine)
    - If VA > 20/25 and central macular not threatened: Watchful waiting
    - If patient older than 50 years of age (has a lesion resembling serpiginous choroidopathy): Very watchful waiting
    - In either case, follow the patient closely, with judicious use of serial OCT examinations (remembering that Medicare and insurance companies will probably not pay for the studies)

SC: Serpiginous choroiditis

- Also known as
  - Helicoid peripapillary chorioretinal degeneration
  - Geographic helicoid peripapillary choroidopathy GHPC
  - Geographical choroidopathy
- Disease of healthy individuals
- 30 and 70

- M >> F
- Higher prevalence of **HLA-B7**
- **Pathogenesis**
  - Autoimmune Etiology
    - Favorable response to immunosuppressive agents
    - HLA association: HLA-B7, HLA-A2, HLA-B8, and HLA-DW3.
    - T-cell immune response to retinal S-antigen
  - Infectious Etiology: Primarily presents as multifocal serpiginoid choroiditis.
    - Tuberculosis
      - Hutchinson reported infectious etiology over a century ago.
      - Case reports based on tuberculin skin test (TST) and interferon gamma release assays
      - Association with pulmonary tuberculosis
      - Molecular studies (PCR)
      - Response to anti-TB agents
      - Geographic distribution
    - Herpes infection (VZV and HSV)
      - Association with herpes zoster ophthalmicus
      - Molecular studies (PCR)
      - Response to antiviral agents
  - Idiopathic
    - Histopathology
    - Molecular studies (PCR)
  - Vascular
- **Differential Diagnosis**
  - Ampiginous
  - Relentless placoid chorioretinitis
  - Others
- **Clinical Features**
  - Asymptomatic until the lesions affect the fovea
  - Bilateral but asymmetric presentation
  - Classic, 80%
    - Geographic patches of gray or creamy yellow placoid lesions in the peripapillary region.
    - Progresses in a centrifugal manner with finger-like or serpentine projections
    - Chronic → chorioretinal atrophy, subretinal fibrosis, and RPE clumping

- Macular serpiginous choroiditis, 20%
  - No difference in the lesions except for location.
  - Generally a poorer prognosis
- Non-granulomatous anterior uveitis
- CNV, which affects 13–20% of eyes, vein occlusions, retinal vasculitis, usually a periphlebitis, CME, and bilateral full-thickness macular holes
- Multiple recurrences at intervals of months to years

- **Investigations**
  - FFA: hypofluorescence during the early phase
  - ICGA
    - better staging of SC
    - better identification of the active lesions
    - persistence of choroidal activity even when the signs of retinal activity had disappeared
  - OCT: retinal atrophy with disruption of the photoreceptor layers in affected area
- **Systemic associations:** Crohn's disease, SLE, celiac disease, and extrapyramidal dystonia
- **Treatment**
  - Steroids
  - Immunosuppressant's

Relentless placoid chorioretinitis RPC

- In 2000 by Jones and colleagues
- Resembling both APMPPE and serpiginous choroiditis
- Clinical Features
  - Sudden painless blurring, metamorphopsia, floaters, or can be asymptomatic.
  - Bilateral posterior creamy-white lesions at the level of the RPE
  - Hallmark of this disease is the eventual presence of numerous (>50 to hundreds) lesions with involvement anterior and posterior to the equator
- Investigations
  - FFA, ICGA, FAF, OCT

Persistent placoid maculopathy PPM

- Resembles macular serpiginous choroiditis but differs in its clinical course and visual prognosis
- CNV is a common feature of PPM, and usually the major cause of visual loss.

Acute Retinal Pigment Epitheliitis (ARPE)

- Krill and Deutman (1972)
- Benign, self-limiting inflammation RPE Otherwise healthy young adults
- Clusters small grey macular spots
- Surrounding yellow halo depigmentation
- Acute visual disturbance with complete recovery
- **Epidemiology**
  - Average age 29 years (16-40) Younger than AMD pts
  - Male = female
- **Pathogenesis**
  - unknown
  - Possibly viral
- **Presentation**
  - Acute, unilateral (75%) ↓ VA (20/20-20/200)
  - Central metamorphopsia and/or scotoma
- **Ophthalmic Findings**
  - Quite AC
  - Mild vitritis
  - 2-4 clusters of 2-6 dots
  - Subtle, small, discrete Hyperpigmented lesions
  - Yellow halo (acute stage)
  - Fine subfoveal pigment clumping ON, vessels, retina WNL
  - SRF, retinal edema absent
- **Ancillary Tests**
  - IVFA: Early hypo-fluorescence grey black dot with surrounding hyper-fluorescent halo Late fading
  - VF: Central scotoma
  - Electrophysiology ERG: WNL, EOG: Abnormal
- **Differential Diagnosis**
  - AMN: Viral prodrome, bilateral, reddish petaloid lesions, IVFA
  - APMPPE: Bilateral, lesion size/evolution, IVFA, systemic associations
  - CSCR: NSD, IVFA, Evolution from ARPE
  - Viral retinitides: Rubella, “salt and pepper” retinopathy, systemic findings
- **Course and Treatment**
  - Prognosis: Resolution VA (20/20), VF 6-12 weeks Recurrent, bilateral cases rare
  - Treatment: None

Progressive subretinal fibrosis and uveitis syndrome (PSFU)

- Also known as diffuse subretinal fibrosis syndrome
- Young, healthy, and myopic
- **Clinical Features**
  - Unilateral decreased vision, floaters, possibly photopsias, scotomas, and metamorphopsia.
  - Numerous small (100–500 μm) yellow spots are seen at the level of the choriocapillaris, RPE, and deep retina

AZOOR Complex

- Gass has used the term AZOOR complex to encompass the following entities: MEWDS, multifocal choroiditis, punctate inner choroidopathy (PIC), acute idiopathic blind-spot enlargement, acute macular neuroretinopathy, acute annular outer retinopathy, and AZOOR (acute zonal occult outer retinopathy).
- ♀ (female) predominance
- Zones of VF loss contiguous with BS photopsias
- ↓ ERG amplitudes

MEWDS: Multiple evanescent white dot syndrome

- Jampol and colleagues (1984)
- Acute, multifocal, usually unilateral retinopathy affecting young adults
- Female predominance (75%).
- Mean age of 27 years
- **Pathogenesis**
  - Unknown
  - Possible viral association
- **Clinical Features**
  - Acute onset of blurred vision in one eye
  - Blind spot or “spots” in their periphery correlating to a temporal scotoma.
  - Small (100–200 μμ) white spots are seen at the level of the RPE or deep retina
  - Mostly concentrated in the paramacular area, usually sparing the fovea itself
  - Classic macular appearance is a granularity
  - Mild iritis may be present. Vitritis may be seen but is often absent
  - Usually a self-limited disease
  - Recovery of visual function occurs over several weeks (3–10 weeks

- **Investigations**
  - FFA: early and late hyperfluorescence of the white dots in a wreath-like pattern; diffuse, but patchy, late staining at the level of the RPE and retina; and disc capillary leakage
  - ICGA
    - no abnormalities of large choroidal vessels in the early phase
    - hypofluorescent lesions are evident in the late phase
  - OCT
    - dome-shaped reflective lesion in the subretinal space was seen corresponding to a clinical white dot
    - disturbance in the photoreceptor inner/outer segment (IS–OS) junction
  - FAF
- **Differential Diagnosis**
  - APMPPE: Bilateral, larger lesions with pigment, IVFA
  - MFC: Bilateral, Vitritis, CME, chronicity, spot evolution, NL ERG
  - BRC: Bilateral, CME, vasculitis, spot evolution, ERG/EOG static
  - ARPE: Bilateral, central hyperpigmentation, yellow halo
  - Sarcoid: Bilateral, vitritis, phlebitis, RPE perturbation
- **Course and Treatment**
  - Prognosis
    - Spontaneous visual recovery in 2 to 10 weeks White spots disappear
    - Persistent macular RPE granularity
    - Rarely recurs
    - Associated ocular conditions
    - MEWDS before/after MFC (Bryan et al, Retina 2002; 22) AMN before/after MEWDS (Gass et al, Archives 1989; 107)
  - Treatment: none

PIC: Punctate inner choroidopathy

- Watzke (1984)
- Disease of young, relatively healthy, myopic women
- **Clinical Features**
  - Scotomas were the presenting complaint in 91% of patients, followed by blurred vision (86%), photopsias (73%), floaters (69%), metamorphopsia (65%), and decreased peripheral vision (26%).
  - Most (85%) presented with unilateral symptoms
  - Gray or yellow, small round lesions are seen scattered throughout the posterior pole

- **Investigations**
  - FFA: Hyperfluorescent in the arterial phase or may appear as blocked fluorescence
  - ICGA: Hypofluoresce in the early, middle, and late phases of ICGA
  - OCT: Associated with CNV, outer retinal irregularity

MFCPU: Multifocal choroiditis and panuveitis

- Nozik and Dorsch (1973), Dreyer and Gass (1984)
- Caucasian myopic women
- 20-60 years
- **Clinical Features**
  - Decreased central vision, photopsias, floaters, metamorphopsia, paracentral or temporal scotomas, ocular discomfort, and photophobia
  - Yellow round or oval lesions, ranging in number from one to scores
  - 50 to 1000 µm
  - Posterior pole, peripapillary region, and midperiphery
  - Can also be arranged in linear scars parallel to the ora
  - Become atrophic with a variable amount of pigment ("punched out" appearance).
  - The peripapillary region may have a characteristic subretinal fibrosis that has been described as a "napkin ring" configuration
  - Mild to moderate anterior uveitis
- **Investigations**
  - FFA
    - Acute phase, the clinical lesions appear hypofluorescent
    - CNV may be present in the peripapillary or macular
  - ICGA: Hypofluorescent round spots that may be far more numerous than seen on clinical examination
  - Spectral domain OCT: subretinal / sub-RPE elevation with hyperreflectivity of subretinal space and disruption of ellipsoid zone
  - Autofluorescence: hyperautofluorescent ring around hypoautofluorescent center
  - OCT-A
    - Network of hyper-reflective vessels on outer retinal and choriocapillaris images
    - May not be able to distinguish between clinically active and inactive CNV lesions
- **Treatment of MFC and Inflammatory CNV**
  - Anti-VEGF therapy: Use in pregnancy has been reported, but no definitive guidelines available and potential for maternal / fetal complications (spontaneous abortion, pre-eclampsia) still needs to be considered.

- Corticosteroids
- Steroid-sparing immunosuppression

AZOOR: Acute zonal occult outer retinopathy

- Gass (1993)
- Acute loss one or more zones of outer retinal function associated with photopsia, minimal funduscopic changes and ERG abnormalities affecting one or both eyes.
- linked to the white spot syndromes although it has no white spots
- predominance of Caucasians
- predominance of women
- young
- **Clinical Features**
  - abrupt onset of a scotoma related to outer retinal dysfunction
  - photopsias
  - area of involvement will show retinal atrophy and mottling
  - area of involvement is often peripapillary but usually the central vision is good unless a scotoma extends to the fovea.
  - may resemble sectoral retinitis pigmentosa, DUSN
- **Investigations**
  - FFA: window defects and abnormalities at the level of the pigment epithelium become apparent
  - ICGA: normal or may show hypofluorescence
  - OCT: absence or irregularity of the IS–OS photoreceptor line
  - VF: Scotomas (usually peripheral and temporal) develop often in continuity with the optic disc
- **Treatment**: Steroids (peri-intra and systemic), immunosuppressives; for secondary CNVM: antiVEGF

Acute annular occult outer retinopathy

Patients develop a scotoma with a grey–white line in the fundus between normal retina and involved retina. This line of activity fades. The areas of involvement subsequently may show evolution similar to AZOOR with RPE changes and retinal thinning.

AIBSE: Acute idiopathic blind spot enlargement

- Described by Fletcher in 1987 as acute enlargement of the blind spot with normal fundi (without optic disc edema) and electroretinographic changes
- Sudden onset of photopsias and a temporal scotoma involving the blind spot.

- Primarily young women
- **Clinical Features**
  - Loss of vision
  - Blurring, awareness of a loss of part of their visual field, or “looking through a film
  - Photopsias, swirling movement within a scotoma, colored lights, or after “flash bulb” phenomena
  - Normal fundus and normal optic disc appearance
  - Afferent pupillary defects and dyschromatopsia
  - Photostress recovery has been noted to be prolonged
- **Diagnosis**
  - Visual field testing: enlarged blind spot
  - ERG normal/subnormal
- **Differential**: Overlapping features in AIBSE, MEWS, PIC, MCP, POHS, AMN, SFU
- **Treatment**: None
- **Prognosis**: Self-limited. Some protracted cases described

AMN: Acute macular neuroretinopathy

- Bos and Deutman (1975)
- Rare condition characterized by sudden onset of visual impairment and multifocal scotomas that correspond rather precisely to reddish, flat, or depressed circumscribed lesions in the macula
- **Epidemiology**
  - Rare 41 cases reported in literature Women (83%) > men
  - 27 years (20-53)
- **Clinical Features**
  - Decreased vision and paracentral scotomas. A viral prodrome or drug use
  - Several small lesions are seen surrounding the fovea at the level of the outer retina
  - Round, oval, or petaloid
  - Unilateral or bilateral
  - Several days after the development of scotomas
- **Investigations**
  - FFA ICGA: normal
  - OCT
    - High reflectivity band corresponding to the retinal pigment epithelium–choriocapillaris complex
    - Distortion of the IS–OS junction and focal thinning of the outer retina
- **Differential Diagnosis**

- Sub-retinal hemorrhage APMPPE
- ARPE
- CSCR

- **Treatment and Prognosis**
  - No treatment
  - Minimal decline visual acuity
  - Frequent persistence of symptoms
  - Scotomata may become less dense, smaller Persist despite resolution fundus lesions (9 years)

Misc

Mosquito-Borne Uveitis

- **Mosquito vectors**
  - Culex: West Nile virus (WNV)
  - Aedis: dengue, chikungunya, Zika
- **Associated Systemic Features**
  - Incubation up to 2 weeks
    - 80% asymptomatic
    - 20% symptomatic: fever, headache, myalgia, arthralgia, malaise
  - WNV: 5% of symptomatic have encephalopathy, most likely to have eye findings
  - Dengue: Hemorrhage common, can be fatal
  - Chikungunya: Arthritis common, severe and lasting
  - Zika: mild, except in newborns / children
- **Ocular Manifestations**
  - Anterior inflammation, mild; vitreous inflammation, mild
  - Multifocal retinochoroiditis / retinal vasculitis
    - WNV: curvilinear pattern, signate lesions with dark center and pale surround
    - Dengue: prominent vasculitis ± hemorrhage
    - Chikungunya: prominent vasculitis / neuroretinitis
    - Zika: retinal pigment epithelium (unilateral acute idiopathic maculopathy), focal chorioretinal scars, and RPE disruption
- **Imaging**
  - Wide-field color, fluorescein angiography (FA), fundus autofluorescence most useful: location and pattern of lesions
  - OCT/OCT angiography: RPE and retinal vascular involvement
  - FA: activity, ischemia
- **Complications**
  - Scars / atrophy
  - Vascular occlusion / ischemia
  - Cystoid macular edema
- **Diagnosis**: Serological Tests
  - PCR early
  - Antibody testing late (cross-reactive to other antiflavivirus antibodies)
- **Treatment**: Supportive
  - Fluids
  - Pain control

- Corticosteroids

Emerging Infectious Diseases (EID)

- Diseases whose incidence in humans have increased during the last two decades or which threaten to increase in the near future
- **Overview of EIDs:**
  - 54% of EIDs are due to bacteria, and many are due to drug-resistant microbes.
  - Ebola virus disease in the Democratic Republic of Congo (DRC): Ongoing in eastern DRC, 3 Ebola outbreaks over last 3 years in DRC
  - Middle East respiratory syndrome coronavirus (MERS-CoV) in Oman, Saudi Arabia, and the United Kingdom
  - Plague in Madagascar
  - Cholera in Kenya, Nigeria, and Zambia
- **2018 WHO Priority diseases**
  - Filovirus diseases (Ebola and Marburg), Crimea Congo hemorrhagic fever, Emerging coronaviruses: MERS-CoV and SARS, Lassa fever virus, Nipah and henipaviral diseases, Rift Valley fever, Zika, Disease X

- **Ebola virus disease (EVD)**
  - West African EVD outbreak was the largest in history, with 28,600 affected and over 11,300 deaths, including >800 health care workers.
  - Three EVD outbreaks within the DRC from 2017 to 2019
  - Caused by 1 of 5 strains of Ebola virus, Zaire Ebola virus is the most fatal strain.
  - Clinical features: severe diarrhea, vomiting, electrolyte abnormalities, hypotension, encephalopathy in late stages
  - **Ophthalmic features during acute EVD**
    - Subconjunctival hemorrhage
    - Conjunctivitis
    - Anterior uveitis
    - Vision loss of unclear etiology
  - **Ophthalmic features during EVD convalescence**
    - Spectrum of eye disease ranging from anterior uveitis to aggressive, sight-threatening panuveitis
    - Associated with Ebola virus persistence (Ocular immune privilege plays a role.)
    - Uveitis identified in 13%-34% of West African EVD survivors
    - Severe vision impairment or blindness observed in nearly 40% of EVD survivors

- Other features: iris heterochromia, anterior uveitis, intermediate uveitis, chorioretinal scarring, posterior synechiae, dense white uveitic cataract
- Ebola Virus Persistence in Ocular Tissues and Fluids (EVICT) Study showed no evidence of Ebola virus RNA persistence in aqueous humor by RT-PCR at >19 months after acute Ebola virus infection.
- Risk of Ebola virus in vitreous/retina remains unknown and under investigation.

Ebola vaccine development:

- Promising results from Merck rVSV-EBOV vaccine trial (Ebola Ca Suffit) during West African EVD outbreak
- Recombination, replication competent vesicular stomatitis virus-based candidate vaccine expressing Zaire Ebolavirus surface glycoprotein
- Substantial protection against EVD, with no cases identified 10 days after vaccination in randomized and nonrandomized clusters of patients in vaccine trial

Marburg virus disease

Clinical features

- Incubation period from 2 to 21 days
- High fever, severe headache, and severe malaise with muscle aches and pains; severe watery diarrhea, abdominal pain and cramping
- Severe hemorrhagic manifestations between 5 and 7 days, with hematemesis, bleeding from gums, mucous membranes, shock, and severe blood loss, with death between 8 and 9 days

Ophthalmic features

- Acute hypertensive anterior uveitis following clearance of Marburg virus from bloodstream (described from Johannesburg outbreak in 1975)
- Keratic precipitates
- Elevated IOP
- Marburg virus culture of aqueous humor positive during acute anterior uveitis with inclusion bodies in cytoplasm of Vero cells
- Negative virus culture 2 weeks after initial Marburg virus-positive culture

Lassa virus/Lassa hemorrhagic fever

Clinical features

- Rodent-borne arenavirus responsible for Lassa viral hemorrhagic fever endemic to West Africa
- Mild disease or unrecognized in 80% of patients
- 20% of patients show severe disease, including facial swelling, hepatic and renal abnormalities, pulmonary edema, and hemorrhage

- Case fatality rate is ~1%; and among hospitalized patients, >15%.

- **Treatment**
  - Supportive care
  - Intravenous ribavarin considered investigational
- **Ophthalmic features**
  - Conjunctivitis observed in acute phase of illness
  - Lassa virus identified in anterior uvea of infected guinea pigs

- **Zika virus (Flavivirus) Diseases**
  - Acquired Zika infection (AZI)
    - Disease features
      - Maculopapular rash, arthritis, nonpurulent conjunctivitis
      - Symptoms present in only 20% of patients
      - Confirmation of Zika virus infection by ZIKV RNA with RT-PCR, serology (IgM), or plaque-reduction assay
    - Ocular findings in AZI
      - Conjunctivitis
      - Acute hypertensive anterior uveitis
      - Unilateral acute idiopathic maculopathy
      - Bilateral posterior uveitis
  - Congenital Zika syndrome (CZS)
    - Disease features
      - Severe microcephaly with partially collapsed skull
      - Brain abnormalities: thin cerebral cortices and subcortical calcifications
      - Congenital contractures: clubfoot, arthrogryposis
      - Early hypertonia, symptoms of extrapyramidal involvement
      - Hearing loss
    - Ocular findings in CZS
      - Most common posterior segment disease findings: pigment mottling and chorioretinal atrophy, commonly seen in macular region (first described in Pernambuco in NE Brazil, then other states in Brazil, and subsequently Colombia and Venezuela)
      - OCT findings: discontinuity of ellipsoid zone and hyper-reflectivity under RPE, retinal and choroidal thinning, colobomatous-like appearance
      - Posterior segment disease findings: optic nerve and retinal vascular disease

- Other findings: iris coloboma, lens subluxation, cataract, glaucoma, and microphthalmia
- Ventura et al described 32 infants with CZS where all children showed cortical or cerebral visual impairment (CVI) due to brain damage, often affecting visual processing centers or visual pathways of the brain

- Treatment
  - Multidisciplinary care with trained physicians and therapists given that children with CZS present with severe and multiple disabilities
  - Ophthalmologists play a key role, in assessment of visual function, visual milestones, and functional vision assessment
  - Children may need magnifying glasses, patching, visual stimulation therapy, and in select cases, strabismus surgery

West Nile virus

- Disease features
  - First isolated in 1937 in West Nile district of Uganda.
  - Single-stranded RNA flavivirus, zoonotic disease transmitted by *Culex* mosquito
  - Subclinical infection in 80%/febrile illness in 20%
  - Severe neurologic disease (meningoencephalitis) in less than 1% of patients, most frequently associated with medical comorbidities (elderly patients, diabetics)
- Ophthalmic features
  - Multifocal chorioretinitis = most common manifestation (80%)
  - Active lesions: circular, deep, creamy lesions
  - Inactive lesions: “target-like” lesions with central pigmentation and hypopigmented halo
  - Other manifestations: anterior uveitis, retinal vasculitis, optic neuritis, neuroretinitis

Dengue Virus Diseases

- Clinical features
  - 25% of dengue virus infections are symptomatic; 5% present with severe, life-threatening disease called *severe* dengue
  - Transmission via *Aedes* species of mosquito
  - Acute onset of fever, headache, body aches, and truncal rash spreading centrifugally
  - Severe dengue is dengue with any of the following symptoms: severe plasma leakage leading to shock, fluid accumulation with respiratory

distress, severe bleeding, or severe organ impairment including elevated transaminases >1000 IU/L, impaired consciousness or cardiac involvement.

- Ophthalmic features
  - Onset of ocular symptoms within 2-5 days of fever, typically 1 day after the peak of thrombocytopenia
  - Ocular symptoms include eye pain, blurred vision, photophobia, and floaters
  - Dengue maculopathy: well-recognized and thought to be serotype and geography-related (DENV-1 epidemic caused 10% incidence of maculopathy and no cases during DENV-2 epidemic.)
  - Dengue retinopathy including retinal vasculopathy and macular edema may threaten vision.

- **Yellow fever Virus**
  - Clinical features
    - Described as the original viral hemorrhagic fever
    - Severe yellow fever: pan-systemic viral sepsis with viremia, fever, prostration, hepatic, renal and myocardial injury, shock, and case fatality rate ranging from 20% to 50%
    - Symptoms include fevers, chills, headache, lower back pain, **Faget sign** (increased temperature with decreased heart rate), epigastric pain, and dehydration
    - Hepatic-induced coagulopathy produces severe hemorrhage, petechiae, ecchymosis, and hematemesis
  - Ophthalmic findings
    - Retinal nerve fiber layer infarcts in >50% of patients
    - Superficial hemorrhages and deep grayish lesions at level of outer retina and choroid
    - Elevated aspartate aminotransferase (AST) levels, total bilirubin levels, serum creatinine, severe thrombocytopenia and *severe Yellow fever* classification associated with retinopathy

- **Rubella (German measles)**
  - Eliminated from the U.S. in 2004 but remains a problem in other parts of the world; <10 cases per year in the U.S., primarily from acquired infection
  - Last major Rubella epidemic in the U.S. in 1964-65, with an estimated 12.5 million people with rubella, 20,000 with congenital rubella syndrome (CRS)
  - Signs/symptoms: low-grade fever, headache, conjunctivitis, lymphadenopathy, cough, rhinorrhea, facial and truncal rash
  - *Congenital rubella syndrome*: salt-and-pepper retinopathy, cataract in association with sensorineural hearing loss and cardiovascular defects

- Rubella persistence may lead to Fuchs heterochromic iridocyclitis, diagnosed via metagenomic deep sequencing (MDS), RT-PCR, intraocular antibody testing and Goldmann-Witmer coefficient assay in Europe only

- **Measles (Rubeola)**
  - High fever (Temperature may be more than 104 degrees), cough, runny nose and watery eyes
  - Tiny white spots (Koplik spots) 2-3 days after symptoms
  - Measles rash with small raised bumps on top of flat red spots 3-5 days after symptoms (begins on face at hairline and spreads downward to neck, trunk, arms, legs, and feet)
  - Measles posterior uveitis presents with painless visual loss associated with optic disc swelling, arteriolar attenuation, diffuse retinal edema, and stellate macular lesions
  - Optic disc pallor, vascular sheathing, and pigmentary retinopathy with disease resolution
  - Findings of measles posterior uveitis/retinopathy associated with subacute sclerosing panencephalitis (SSPE) or measles encephalitis

Surgery in Infectious Retinitis

- **Cytomegalovirus Retinitis (CMVR)**
  - Most frequent ocular opportunistic infection in acquired immunodeficiency syndrome (AIDS) patients (CD4+ < 50 cells/μL)
  - It occurred in 30% of AIDS patients in the pre– combination antiretroviral therapy (cART) era.
  - It occurred in < 1% of patients in the cART era. (cART: protease inhibitors and/or nucleoside reverse transcriptase inhibitors and/or antinucleoside analogue inhibitors regimes)
- **Retinal detachment (RD)**
  - RD develops in 20% of patients with CMVR.
  - The current rate of detachment may be reduced by improved therapies for CMVR.
  - The number of new patients acquiring CMVR has fallen, resulting in a lower incidence of these detachments.
  - Extent of retinitis and activity are risk factors.
  - For longer patient survival we need to select surgical strategies that will provide the best longterm visual outcome.
- **Surgical Management**

- Vitrectomy with planned removal of silicone oil, scleral buckle, vitrectomy with gas tamponade, and laser demarcation are strategies that may provide excellent visual and anatomic results for RDs with various characteristics.
- The final selection of the surgical approach depends on the mechanical factors of the detachment and patient factors such as immune status, expected survival, control of retinitis, and visual needs.
- Cataract surgery
- Vitrectomy + laser + silicone oil
- Polymerase chain reaction (PCR) and inflammation
  - Sample preparation for PCR
  - The choice of biopsy site must be guided by disease suspicion; individual patient factors such as media opacity, anterior chamber depth, or coexistence of vitreous pathologic conditions; and the comfort level of the ophthalmologist with anterior chamber paracentesis or vitreous biopsy.
  - Very little tissue is needed for PCR; samples as small as 1 µL can be processed for testing.
  - Typically, 50to 100-µL samples are ideal, as they allow for possible retesting if necessary.

Acute Retina Necrosis (ARN) and AIDS

- Retinal detachment
  - 50% to 75% of untreated eyes, usually within 1 to 2 months following the onset of ARN symptoms
  - Vitreous inflammation can lead to vitreous organization and proliferative vitreoretinopathy with subsequent tractional retinal detachment.
- Surgical Management
  - Vitrectomy
    - Prophylactic vitreous surgery could be a possible choice for patients who have poorly or nonresponsive, progressive retinal lesions, especially when they become close to the posterior pole.
    - Vitreous surgery has been recognized as a procedure that is indicated for cases with RD, one of the main late-stage complications.
    - Reports on the vitreous fluid obtained from the patients with ARN indicate the presence of inflammatory cytokines (interleukin [IL]-6 and IL-10 and interferon gamma), suggesting that the removal of these inflammatory cytokines induces a remission of retinal lesions.
    - Silicone oil tamponade is ideal for RD and as a tamponade for short-term usage only.

        - Endolaser photocoagulation is applied at the time of vitrectomy on normal retina to surround the posterior edge of necrotic lesions by 2 to 3 adjacent rows.
    - Other Options
        - Silicone oil surgery
        - Silicone oil removal (+phacoemulsification) Vitrectomy with gas tamponade
        - Scleral buckle
        - Laser demarcation
    - As in the repair of any RDs, surgical success requires permanent closure of retinal holes and relaxation of vitreous traction that might cause new tears.
    - Pars plana vitrectomy with silicone oil injection obviously accomplishes these objectives; even failed cases with open inferior breaks will generally have the RD well enough demarcated that the macula remains attached.
    - If good adhesion is achieved, oil removal can be considered at a later date combined with phacoemulsification.

Role of Vitrectomy in Uveitis

Diagnostic Vitrectomy

- **Infections**: culture and polymerase chain reaction
    - Endophthalmitis
        - Chronic postoperative
        - Endogenous
- **Malignancies**
    - Intraocular lymphoma: clinical appearance
        - Cytology
        - Flow cytometry
        - Gene rearrangements
    - Vitreoretinal metastatic disease: Histopathology
- **Other conditions**
    - Amyloid: clinical appearance
        - Formalin-fixed paraffin sections
            - Congo red
            - Polarized microscopy for birefringence
            - Immunostaining for amyloid
    - Chorioretinal lesions of uncertain etiology: Chorioretinal biopsy

Therapeutic Vitrectomy for Uveitis

- **Vitrectomy for Repair of Structural Complications of Uveitis**
  - Vitreous opacification, debris, and hemorrhage
  - Lens-induced uveitis
  - Epiretinal membranes and cystoid macular edema (CME)
  - Traction or rhegmatogenous retinal detachment
  - Hypotony and cyclitic membranes
  - Uveitic glaucoma and posterior tube placement
- **Vitrectomy for Control of Uveitis Activity**
  - Theoretic mechanism of action
  - Removal of ocular autoantigens: Type II collagen and lens antigens
  - Removal of autoreactive immune cells and cytokines (IL-1, IL-2, TNF-a, etc.)
  - Alter the immunologic milieu with aqueous humor: ACAID
    - Anti-inflammatory cytokines: TGF-B and VIP
    - Inhibition of complement fixation
    - Apoptosis
- **Clinical evidence for Vitrectomy**
  - Kaplan suggested PPV for intermediate uveitis over immunosuppression (1992).
  - Improved vision by PPV and “cells disappeared from the aqueous” Algreve et al (1981)
  - PPV, gas tamponade, and posterior tube placement controlled both IOP and uveitis complications. Patronas (2012)

Vitrectomy for Vision

- Nonclearing vitreous opacities
  - Healed infections: toxoplasmosis
  - Fuchs uveitis syndrome
- Combined with cataract surgery
- Macular disease: cystoid macular edema and epiretinal membrane

Managing Glaucoma in Patients With Uveitis

- In a patient with uveitis, glaucoma should not be considered synonymous with elevated IOP, but the diagnosis should be reserved for those situations where there is either glaucomatous disc damage or visual field loss.
- A patient with elevated IOP due to synechial angle closure secondary to uveitis is mostly classified as having uveitic glaucoma without evidence of optic disc changes or visual field loss, because these changes are inevitable without appropriate intervention.
- The overall prevalence of uveitic glaucoma ranges between 10% and 20%, but is much more common in chronic uveitis and can be as high as 46%.
- **Uveitic Conditions Most Commonly Associated With Glaucoma**
  - Juvenile idiopathic arthritis
  - Fuchs heterochromic iridocyclitis
  - Sarcoid uveitis
  - Intermediate uveitis / pars planitis
  - Viral iridocyclitis
  - Glaucomatocyclitic crisis (Posner-Schlossman syndrome)
  - Recent studies suggest uveitis with iris transillumination, pigment dispersion, and severe early IOP rise as a possible adverse drug reaction of systemic fluoroquinolone treatment, particularly moxifloxacin.
- **Medical Management**
  - Drugs
    - Beta-blockers
    - Topical and oral carbonic anhydrase inhibitors
    - Alpha-2 agonists
    - Prostaglandin (PG) agonists
      - Initially thought to have a propensity to increase the activity of uveitis
      - PG agonists were shown to be effective in lowering IOP in patients with uveitic glaucoma, in whom the uveitis is controlled on IMT, without increasing the rate of flare-ups of uveitis.
    - Hyperosmotic drugs
  - Uveitic glaucoma patients often require more than one drug to control their IOP.
  - Most of the patients respond to medical treatment; only 4% to 30% of patients require surgical treatment.
- **Laser Therapy**
  - **Argon and/or Nd:YAG laser iridotomy**
    - Indicated for pupillary block glaucoma due to a secluded pupil from extensive posterior synechiae or fibrin membrane
    - In some cases, a surgical iridectomy may be required if the laser iridotomy closes secondary to intense inflammation.

- **Argon laser trabeculoplasty**
  - Usually not useful in uveitic eyes
  - Has been shown to have low success rates in uveitic glaucoma patients because of angle alterations
- **Transscleral laser cyclophotocoagulation**
  - Reserved for cases where all other efforts to lower IOP have failed.
  - Should be used cautiously because the risk of permanent hypotony is increased with a cyclodestructive procedure in uveitic eyes with compromised ciliary epithelium function

Surgical Therapy

- **Glaucoma filtration surgery**
- Filtration surgery is indicated when IOP is uncontrolled on maximum tolerated IOP-lowering therapy.
- Long-term success of trabeculectomy has increased with antimetabolic agents such as intraoperative mitomycin C (MMC) and intra-/ postoperative 5-fluorouracil.
- Success rate of MMC trabeculectomy for uveitic glaucoma ranges from 50% to 90% with various criteria of success.
- **Glaucoma drainage devices**
- Used with increasing frequency in uveitic glaucoma, either as the initial glaucoma surgery or when trabeculectomy fails
- Success rate is upto 94% at 1year and 50% at 4 years with various criteria of success.
- IOP control is especially favorable in JIA-associated glaucoma.
- **Ex-PRESS mini glaucoma shunt**
- A miniature stainless steel shunt developed for use as an alternative procedure to trabeculectomy
- A nonvalved, flow-restricting implant with a 400-µm (27-gauge) external diameter, a 50or 200-µm inner diameter, and a rounded and beveled tip
- The procedure is similar to a standard trabeculectomy.
- Main advantages are ease of insertion, formation of a standard size filtration opening, and elimination of the iridectomy, which may reduce inflammation.
- Disadvantages are necessity of a filtration bleb and antifibrotic use, fibrosis over the opening, and possible device-related complications.
- Not studied in uveitic glaucoma

Other Surgical Therapy

- **Goniotomy**
- A low-risk and effective first-line surgery for young patients with refractory glaucoma associated with chronic uveitis
- Outcome is adversely affected by increased age, peripheral anterior synechiae, prior surgeries, and aphakia.

- **Deep sclerectomy**
- Not proven to be superior to trabeculectomy
- Nonpenetrating surgery is associated with less inflammation during the early postoperative period.

Tatoo Induced Uveitis

- Tattoo Pigments
  - Black ink ingredients include soot, carbon, ash, nickel, and iron.
  - Tattoo pigments migrate into lymph nodes.
- Common Features
  - Bilateral intraocular inflammation
  - Anterior uveitis is more common than panuveitis.
  - Black ink tattoos
  - Granulomatous and nongranulomatous
- Histopathologic findings:
  - This includes non-necrotizing granulomas.
  - Immunopathology evaluation could be more consistent with delayed type hypersensitivity, especially in cases where tattoo swelling precedes uveitis.
- Treatment Options
  - Some cases are responsive to treatment with topical and/or oral steroids with taper.
  - Most cases tend to be chronic or recurrent. Chronic immunosuppression is recommended for these cases.
  - Management could include removal of tattoo; however, uveitis could still persist. If tattoos are extensive, expense and need for skin grafting may preclude this option. If removal of tattoo is pro-inflammatory, it could worsen the course of inflammation.
- Coincident Uveitis and Tattoo Induration
  - First described in 1952: bilateral anterior uveitis, tattoo granulomas, systemic sarcoidosis
  - 1969. Case series of 3: Three of 3 cases were bilateral anterior uveitis, 1/3 with retinitis tattoo granulomas, *no* systemic sarcoidosis.
  - 2014. Case series of 7. Five of 7 bilateral nongranuomatous anterior uveitis, tattoo granulomas. Two of 7 bilateral granulomatous panuveitis. *No* systemic sarcoidosis.
  - Tattoo swelling may proceed or occur simultaneously with uveitis.

Drug-Induced Uveitis

- Although uncommon, drug-induced uveitis is well recognized and associated with an increasing number of pharmacotherapeutics.
- Drug-induced uveitis is easily overlooked. A detailed medical / drug history is essential.

- While the mechanisms of drug-induced uveitis are largely unknown, agents known to act through direct modulation of the immune system are believed to induce uveitis as an equally direct, albeit unwanted, consequence of that immunomodulation (eg, TNF inhibitors, checkpoint inhibitors).
- **Systemic Agents**
  - **Immune checkpoint inhibitors**
    - **Ipilimumab** (anti-CTLA-4; Yervoy), pembrolizumab (Keytruda), and nivolumab (Opdivo); both anti-PD-1
      - One percent of patients develop uveitis.
      - Over 50 cases to date
      - Over 90% treated for metastatic malignant melanoma.
      - Sixty percent have other non-ocular autoimmune complications. Anterior uveitis is most common; uncommon, orbital inflammation. Most bilateral.
    - **Atezolizumab, avelumab, and durvalumab** antiPD-L1 (no reported cases of uveitis yet)
  - **MEK inhibitor (trametinib [Mekinist]) and BRAF inhibitors (vemurafenib [Zelboraf] and dabrafenib [Tafinlar])**
    - For metastatic melanoma
    - Anterior, intermediate, or panuveitis
    - Most bilateral
  - Cidofovir
    - For cytomegalovirus retinitis
    - Nongranulomatous anterior uveitis and hypotony
    - Hypotony may persist.
  - Rifabutin
    - As prophylaxis for Mycobacterium avium complex (MAC)
    - Anterior ± hypopyon.
  - Sulfonamides
    - Antibiotics / anticonvulsants / diuretics
    - Nongranulomatous anterior uveitis
  - Bisphosphonates
    - For osteoporosis
    - Uveitis, scleritis, episcleritis, orbital inflammation
    - Implicated agents include pamidronate (Aredia), etidronate (Didronel), risedronate (Actonel and Atelvia), alendronate (Fosamax and Binosto), and zoledronic acid (Reclast). Pamidronate most common.
  - Tumor necrosis factor inhibitors

        - Especially etanercept (Enbrel), but also infliximab (Remicade) and adalimumab (Humira)
- **Intravitreal Agents**
    - Anti-VEGF agents: < 1%
    - Cidofovir
- **Topical Agents**
    - Metipranolol
        - Nonselective beta-blocker
        - Granulomatous anterior uveitis
    - Brimonidine
        - Selective alpha2-adrenergic agonist
        - Granulomatous anterior uveitis
    - Prostaglandin agonists: latanoprost, travoprost, bimatoprost
- **Vaccines**
    - Human papillomavirus vaccine (Gardasil)
        - Anterior ± papillitis
        - Vogt-Koyanagi-Harada–like
        - Ampiginous
    - BCG
    - Varicella virus vaccine
    - Hepatitis B vaccine
    - Hepatitis A vaccine

Intraocular Medulloepithelioma

- Congenital, nonhereditary tumor of the nonpigmented ciliary epithelium, usually diagnosed in childhood
- Second most common primary intraocular neoplasm during the first decade of life
- Commonly used clinical name: diktyoma
- **Epidemiology**
    - No reliable population-based information on incidence or prevalence
    - No sex or racial predilection
    - Median age of 2-5 years
        - 11 cases reported in persons older than 20 years
        - Oldest documented case is 79 years.
        - Most cases in adults are malignant.

- **Pathology**
  - Classified into nonteratoid and teratoid medulloepitheliomas, benign or malignant
  - Most commonly, pseudostratified epithelium resembling medullary epithelium of the embryonic neural tube or developing neurosensory retina, surrounded by loose mesenchymal tissue rich in hyaluronic acid (eg, combination of primitive neuroepithelium and hypocellular stroma)
  - When the medullary epithelium folds so that the vitreous surface faces inward, it creates cysts rich in hyaluronic acid. Such proliferating cysts can be a part of the mass or detach from the main tumor and appear as free-floating cysts in the anterior or posterior segment of the eye.
  - Both Homer Wright and Flexner-Wintersteiner rosettes can be observed among undifferentiated neuroblasts. Calcification is uncommon.
  - The term “teratoid medulloepithelioma” applies when heteroplastic tissue is present. Mature hyaline cartilage is the most common heteroplastic element, but neuroglial tissue resembling disorganized brain and rhabdomyoblasts have also been described. More than a third of contain heteroplastic elements, usually hyaline cartilage, rhabdomyoblasts, or brainlike tissue. Those with heteroplastic tissue are designated teratoid medulloepitheliomas.
- **Clinical Features**
  - Irregularly shaped ciliary body and/or iris masses with smooth surfaces and gray to fleshy pink color. Intrinsic vessels are occasionally noted, visible on or close to the surface.
  - Approximately half of cases have cysts noted within the lesion or in the anterior chamber. Malignant retrolental membranes have also been described.
  - Frequent ocular associations of subluxation of the lens, cataract, or glaucoma
  - Typically, tumors are slow growing and not visible until they enlarge enough to protrude into the pupil, distort the iris, or invade the adjacent tissues.
  - Differential diagnosis includes acquired neoplasms of the nonpigmented or pigmented ciliary body epithelium, adenomatous hyperplasia, Fuchs adenoma and carcinoma, and metastatic tumors such as neuroblastoma.
  - 20% may show signs of persistent fetal vasculature.
- **Management**
  - Surgical enucleation has been the standard therapy for intraocular medulloepithelioma once the diagnosis has been established.
  - Globe-conserving therapies have been more commonly employed over the past 2 decades.
  - Surgical excision (iridocyclectomy) has been utilized with varying degrees of success, but because it has an unacceptably high recurrence rate overall it is generally not recommended.
  - Brachytherapy has been used successfully in recent series and is the most effective globe-sparing therapy. Fine needle aspiration biopsy (FNAB) may be performed prior to brachytherapy but is not considered to be necessary in all cases.

- The polymorphic nature of medulloepithelioma means that sample variation can affect the accuracy of aspiration cytology. The risk of tumor seeding with FNAB is unknown, but risks are likely similar to those with retinoblastoma.
- Treatment options include careful observation for documentation of growth, brachytherapy, or enucleation. FNAB can be used to confirm the diagnosis before brachytherapy or enucleation.

Tips of Managing Uveitis

- The use of short-term intraocular or periocular steroids to treat chronic disease. The problem of reacting to reactivations rather than prevention.
- Topical therapy to treat posterior pole disease. The phakic patient's eye will not usually permit enough steroid to get to the posterior pole.
- Triamcinolone therapy in severe uveitis; risk of infection. Intraocular injections can certainly be helpful but beware of infections. A good history and evaluation is critical.
- Behçet vs. acute retinal necrosis. Under the right circumstances these can be similar, with serious consequences if a mistake is made.
- Undertreating anterior segment disease in children. We always wish to minimize, particularly when it comes to children, whether to add systemic medication or surgery. This can have a very negative effect on outcome.
- Following intraocular inflammation with no therapy if vision remains good because of good vision. We know that it is a matter of time before the vision will decrease.
- No therapy for relatively mild, chronic disease such as birdshot.
- PPD positivity and ocular disease masquerading a masquerade. It's not always easy, but don't fall back on systemic tests if your clinical impression tells you otherwise.
- MRI: Repeat and repeat.
- Avastin to treat active uveitis.

Pattern Recognition of the Uveitis

- Toxoplasmosis: unilateral, focal retinochoroiditis
- VZV/HSV anterior uveitis: corneal scars, iris atrophy, IOP increased, diffuse keratic precipitates (KPs)
- Late-onset endophthalmitis: pseudophakia, history, capsular opacities
- Aspergillus endophthalmitis: necrotic granuloma in posterior pole and "hyaloidal hypopyon"
- CMV retinitis: one of four patterns – "pizza pie," granular, brushfire, frosted branch angiitis
- Toxocariasis: peripheral granuloma, focal macular granuloma, diffuse endophthalmitis

- Bartonellosis: Focal choroiditis or neuroretinitis
- Necrotizing herpetic retinitis: VZV, HSV 1& 2
  - Acute retinal necrosis (ARN): peripheral areas of confluent retinal necrosis, occlusive retinal arteritis, vitritis and anterior chamber reaction, immunocompetent host
  - Progressive outer retinal necrosis (PORN): areas of confluent retinitis in periphery, minimal vitreous haze and inflammation, immunocompromised host (esp. HIV)
- Tuberculous uveitis: tuberculous serpiginoid choroiditis
- Hypopyon
  - Congealed and immobile; think infection or HLAB27
  - Mobile: consider Behçet disease
- Choroidal Spots Descriptors
  - Ameboid: Serpiginous
  - Placoid: APMPPE
  - Yellow-orange ovoid: BSCR
  - Punched-out: MFCPU
  - Punctate: PIC
  - Evanescent white: MEWDS
- Presentation Characterisation
  - Unilateral alternating RAAU: HLA-B27-associated uveitis
  - Bilateral CAU in a child: JIA-associated uveitis
  - Unilateral CAU: FHIC, HSV CAU
  - Bilateral chronic intermediate uveitis: Pars planitis, sarcoidosis, MS-associated uveitis
  - Unilateral recurrent focal retinitis: Toxoplasmosis
  - Chronic focal retinitis in a patient with AIDS: Cytomegalovirus retinitis
  - Acute peripheral multifocal retinitis: Acute retinal necrosis
  - Bilateral chronic multifocal choroiditis: BSCR, MFCPU,PIC
  - Acute multifocal choroiditis: APMPPE, MEWDS, PIC