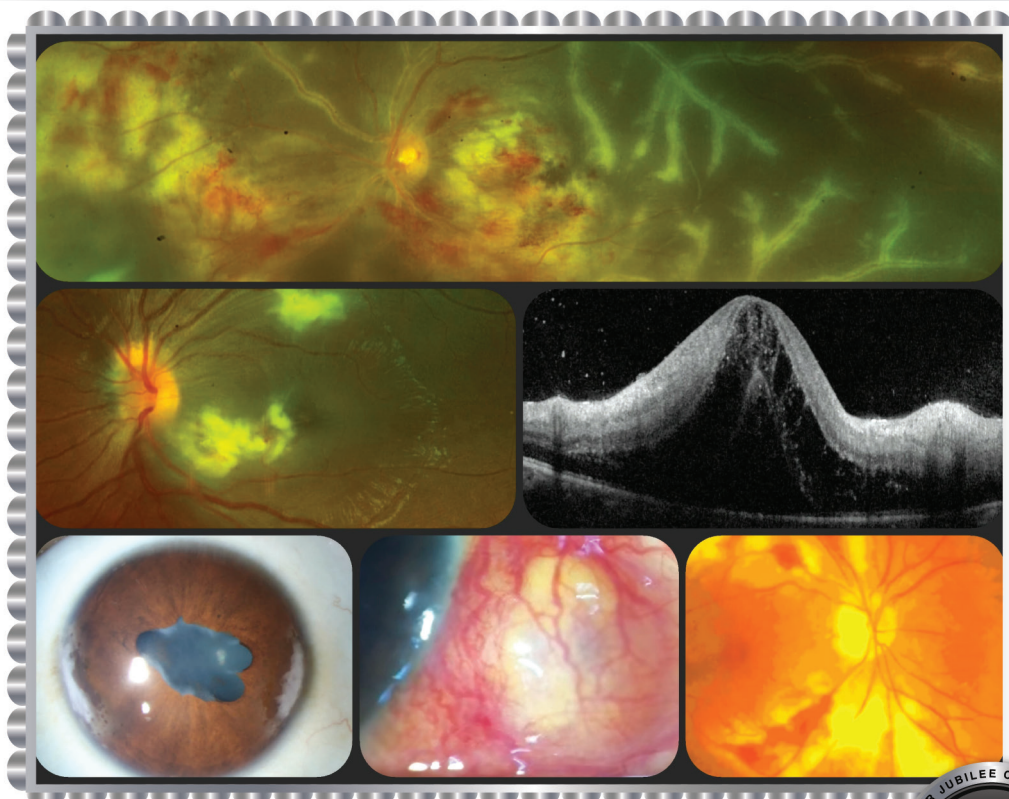
Uveitis Society (India)

READY RECKONER



SILVER JUBILEE CELEBRATION
25th ANNIVERSARY

President

Uveitis Society (India)

Dear Friends & Colleagues,

We are excited to introduce this ready reckoner in Uveitis to mark the 25th year celebrations of the Uveitis Society of India. This is designed to provide you with a practical guide that you can easily navigate and rely on in your clinical practice. It is designed to be your go to resource book for quick information and handy tips on how to proceed when you see a case of uveitis.

On behalf of the Uveitis Society of India, my sincere thanks to Dr. Mayur Moreker and his team for conceptualizing this idea and to all the authors who have contributed to this book. We do hope this book serves as a valuable tool for you in your daily practice while treating patients with uveitis.

Happy reading !!

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Dear Friends

Uveitis, is one disease, where similar signs or symptom(s) can be seen in more than one uveitic entity. This is one reason perhaps, why, artificial intelligence in uveitis is still a work in progress.

This could explain why artificial intelligence in uveitis is still in its early stages. However, if anything may come close to being a clinical help in your OPD daily, it is this "Ready reckoner".

Mayur and his team have put their heart and soul, to compile this, with the help of the Best in the business I 'reckon' that this 'readily' available tool will assist all of us in effectively managing any uveitis clinic. What better moment than as part of celebration of USI's silver jubilee.

Am delighted to have the easiest duty "writing the secretary's note" while enjoying the fantastic learning.

Our "ready reckoner" is not intended to be a replacement for a Uveitis textbook, but rather a 'guide' for the clinician

Heartfelt Thanks - Editorial team, all contributors, Hallmark events and all those who are part of this Am sure that this immediately available, convenient (tab-sized) tool will become an integral component of our clinics!

Best wishes

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Uveitis Society (India)

Dear Friends,

As we celebrate the Silver Jubilee of our Uveitis Society (India); I am delighted to introduce the "Uveitis Ready Reckoner"; conceptualized and executed by Dr. Mayur Moreker and his team, this booklet is "go-to" practical guide for the General Ophthalmologists as well as Uveitis Specialists for quick reference in a busy clinic.

The Ready Reckoner contains chapters written and edited by various uveitis experts, who have provided practice-based tips on common uveitic diseases and entities that are encountered in the clinic. These tips include guidelines that will aid in diagnosis as well as management of uveitis patients. Some of the chapters are in a lucid format meant to give to-the-point answers to frequently asked questions. We hope that this quick guide will enhance the practitioner's ability to recognize and treat uveitic diseases and also pique the interest of those who may not see the entire spectrum of cases, but still would like to be up-to-date.

On behalf of the Scientific Committee of Uveitis Society (India), my sincere thanks to all the authors who have contributed to this book; and deepest gratitude to Dr. Mayur Moreker who worked tirelessly to produce a high-quality book that we can all be proud of. I am confident that this ready reckoner will serve as a valuable tool to you.

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Uveitis Society (India)

"Acquire the art of detachment; the virtue of method; and the quality of thoroughness; but above all the grace of humility". This aphorism from Sir William Osler is almost true, when it comes in the practice of uveitis. Uveitis is a conundrumto all of us. There can be nothing more humbling than trying to decode the interaction of the human immune system with what it perceives as "non-self" in the human eye. Further, as J.M. Barrie wrote, "Life is a long lesson in humility"; and so is the life of a uveitis enthusiast. This is so because of the dynamics of the tripartite interaction involving the immune system, what "triggers" it and what "modulates" it; is fast changing; making it difficult to answer all questions.

But, answering difficult questions on various topics in uveitis, and answering them to the point, was exactly what we called upon our team of talented young uveitis enthusiasts along with senior uveitis experts to do. As one reads through the proceeds of this ready reckoner, one realizes that each chapter contains answers to questions that crop up in the minds of ophthalmologists in a busy clinic, in a ready reckoner format.

Our Indian culture affirms the belief that our elders possess knowledge and experience. But above all, it is the wisdom accumulated over decades of their clinical practice. This ready reckoner affords the reader more than just a glimpse of this wisdom, with our legends & founding fathers expressing their views on various topics.

With contributions from the "junior-most" to the "senior-most", this ready reckoner symbolizes the profound connection between generations of uveitis enthusiasts and experts of our country. I personally bow down in all humility and reverence to all of them and I am blessed to be part of this editorial team. This ready reckoner celebrates the silver jubilee, it celebrates the 25 years of our society, with 25 chapters and one unique algorithm (as an icing on the cake!)

This effort would have been incomplete without the immense help and guidance of close to fifty contributors (authors and compilers) from all over our country. They can be easily represented by the "3S". The first S is our Uveitis Society (India) secretary, Sudharshan, who, along with our President Dr. Kalpana Babu and Scientific Committee Chairperson, Dr. Somasheila Murthy represent the encouragement of all the teachers, legends, seniors and office bearers of our esteemed society. The second S is my dear friend and brother, Samyak; who to me, represents all our authors; who have written and then checked, rechecked and then edited all the manuscripts. The third is Sampath who represents the unwavering support from the secretariat team of Hallmark Events with Veidhehi ji, Pramila and Vinay, for bringing this ready reckoner in its current form.

It is imperative that I wholeheartedly thank all our undergraduate, post graduate and fellowship teachers of ophthalmology; from whom we have learnt the science and art of ophthalmology and uveitis. Uveitis as a disease entity can be overwhelming to the most astute of ophthalmologists, which makes it almost mandatory that we thank all our patients and their families for all their interactions with us always as we continue to learn from them.

A show is incomplete without its audience and a book is unviable without its readers...So, a very special thanks to all the esteemed members of Uveitis Society (India) with the hope that this shall be a pleasant read and reckoner for all of us.

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Role of history taking and concepts for the management of rare epidemic and endemic infections

Somanath Anjana, S R Rathinam

Uveitis is the inflammation of the uveal tissue. It is an initial manifestation of a systemic disease occurring elsewhere in the body. It occurs due to infectious and non-infectious etiologies. Though the inflammatory process mainly affects the uvea, it consequently affects the vitreous, retina and optic nerve head as well, if untreated.

History taking: A detailed and elaborate history is necessary to reach a correct diagnosis and is the first step in the clinical workup of uveitis.With a good history we get clues and insights into the type of uveal disease with which one is suffering. About 70% of diagnosis can be made on the basis of detailed medical history and meticulous clinical work up. This is a challenge to the treating ophthalmologist.[1,2]

Age [3]:

Certain diseases have a predilection for certain age groups.

1. Children: Juvenile Rheumatoid Arthritis, Toxocariasis
2. Young adults: Bechet's, Human Leukocyte Associated antigen B27–associated uveitis, Fuch's uveitis.
3. Old age: Vogt Koyanagi Harada syndrome, Herpes Zoster Ophthalmicus , Tuberculosis and Leprosy

Gender

Certain conditions have a predilection for gender[4]:

1. Males - Ankylosing spondylitis, Reiter's, Bechet's, Sympathetic ophthalmia.
2. Females- Rheumatoid arthritis, Juvenile Rheumatoid Arthritis, Systemic lupus erythematosis.

Demography [4]

Race and ancestry, can be predispositions to the development of specific diseases.

1. Caucausians : Ankylosing spondylitis, Reiter's disease
2. Black – Sarcoidosis
3. Orientals : Vogt Koyanagi Harada's syndrome, Bechet's syndrome .

Contact with pets / animals :

1. Cat- Toxocariasis, Toxoplasmosis
2. Cattle- Leptospirosis
3. Pigs- cysticercosis
4. Rats – leptospirosis

Plumbers and sewer workers are at an increased risk of leptospirosis, which is transmitted by a spirochete in sewage water and urine of rats, cattle or other animals. Meat handlers are also at risk of leptospirosis.[5]

Swimming in open water reservoirs may expose the individuals to water borne diseases that may result in uveitis. eg : leptospirosis and trematode induced uveitis[6].

Systemic conditions:

1. Diabetes mellitus
2. Renal failure

Immunosuppressed state

1	Demography	Age
		Gender
		Race
		Geographic location
		Occupation
		Socioeconomic status
2	Ocular history	Onset
		Laterality
		Course
		Duration
3	Systemic history	Duration
4	Treatment history	Medications
		Dose
		Duration
		Adverse effects
5	Others	Trauma , surgery

Extra ocular examination :

After history taking, examination of the patient is required.

The ophthalmologist can suspect certain clinical conditions to order appropriate tests

Table 2: Systemic signs seen in specific diseases

Poliosis	Vogt Koyanagi Harada's syndrome
	Sympathetic ophthalmia
Hypopigmentation of skin	Systemic lupus erythematosus
	Vogt Koyanagi Harada's syndrome
	Syphilis.
Erythema nodosum	Behcet's disease
	Sarcoid
	Inflammatory bowel disease
	TB
Scaling of skin	SLE

Arthralgia	Seronegative spondyloarthropathies
	Juvenile rheumatoid arthritis
	Relapsing polychondritis
	Behect's
	Sarcoidosis
	Systemic Lupus Erythematosus
Cartilage loss	Relapsing polychondritis
	Syphilis
	Gonococcal disease
	Wegener's granulomatosis

	Psoariasis
	Syphyllis
	Reiter's disease
Discoid lesions	SLE
	Sarcoid
	Leprosy
	Tuberculosis
Nail abnormalities	Psoariatic arthritis
	Reiter's syndrome
	Vasculitis
Oral and genital ulcers	Behcet's disease
	Syphyllis
	Reiter's disease
Oral ulcers	SLE
	Inflammatory Bowel disease
Urethral discharge	Reiter's disease
	Syphyllis
	Herpes simplex
	Gonococcal urethritis
Epidydmyitis	Behcet's disease
	Tuberculosis
Nephritis	Vasculitis (Wegener's granulomatosis SLE, Behcet)
	Sarcoidosis
	Tuberculosis

	leprosy
Sinusitis	Wegener's granulomatosis
	Sarcoidosis
	Mucormycosis
	Whipple's Disease
Cystitis	Retier's disease
	Whipple's disease
Lymph node involvement	Tuberculosis
	Sarcoidosis
	Lymphoma
Neuropathy	Leprosy
	Herpes zoster
	Sarcoidosis
	Multiple sclerosis
	Syphyllis
Hearing loss	Vogt koyanagi harada disease
	Sarcoidosis
	Vogt koyanagi harada disease
	Sarcoidosis
	Wegener's granulomatosis
Respiratory symptoms	Tuberculosis
	Sarcoidosis
	Wegener's granulomatosis
Bowel disease	Whipple's disease
	Crohn's disease
	Ulcerative colitis

Ocular symptoms :
1. Vision loss
2. Pain
3. Redness
4. Photophobia
5. Floaters
6. Pain on ocular movements

Ocular signs :
Conjunctiva, episclera, sclera and adnexa: A good day light examination and external examination with torch light is essential in every patient. Clues on infectious diseases like Hansen's disease or Herpes can be obtained on adnexal examination.
Inflammation of the conjunctiva and episclera: bright red in daylight and more in the fornix.

In cases of uveitis, the congestion of the perilimbal area is more than the palpebral and forniceal conjunctiva. In scleritis there is dilation of deep vascular plexus which is better seen with red free illumination with tenderness on palpation.

Table 3: Ocular signs in anterior segment evaluation

Anatomic location	**Disease**
Forehead and adnexa	
Vesicles	Herpes zoster ophthalmicus
Poliosis	VKH
Madarosis	Leprosy
Nodules	Sarcoid ,leprosy
Conjunctiva	
Granuloma	Foreign body,sarcoid
Cornea	
Dendritic keratitis	Viral uveitis
Sclerokeratouveitis	Syphyllis ,tuberculosis,Hansen's and viral uveitis
Neurotrophic keratitis	Leprosy
Band keratopathy	Juvenile rheumatoid arthritis,Sarcoidosis
Iris	
Iris atrophy	Viral uveitis
Argyl Robertson pupil	Neurosyphyllis
Gonioscopy	
Peripheral anterior synechiae	Sarcoid ,tuberculosis
Iris nodules	Sarcoid ,tuberculosis
Hyphema	Herpetic uveitis
Foreign body	Traumatic uveitis

On slit lamp examination, uveitis can be classified as non-granulomatous and granulomatous uveitis.
In Fuch's uveitis keratic precipitates are stellate and uniform distribution of keratic precipitates are seen.

Table 4: Causes of granulomatous and non granulomatous uveitis.

Granulomatous uveitis- unilateral	Granulomatous uveitis- bilateral
Virus	Vogt Koyanagi Harada syndrome
Lens induced	Sarcoidosis
Sarcoid	Tuberculosis
Syphyllis	Phacoanaphylaxis
Tuberculosis	Sympathetic ophthalmia
Non granulomatous uveitis- unilateral	**Non Granulomatous uveitis- bilateral**
HLA B27 uveitis	Leptospirosis
Traumatic uveitis	Behcet's syndrome
Behcet's syndrome	TINU
Fuch's heterochromic uveitis	
Leptospirosis	
Drug induced	

Anterior chamber reaction: A slit beam of 1 mm x 1 mm is required for the assessment of the anterior chamber cells and flare. Presence of cells and flare is a marker for inflammation.

The SUN working group grading of anterior chamber cells and flare is as follows [7]

Grade	No of cells
0.5	01-May
1	Jun-15
2	16-25
3	26-50
4	>50

Flare	Description
0	Complete absence
1	Faint flare
2	Moderate flare
3	Marked flare
4	Intense

Iris examination:

- Presence of posterior synechiae: Adhesions between posterior surface of iris and lens. When the adhesions extend 360^0 around the pupillary border, it is known as seclusio pupillae. It affects the movement of aqueous from the posterior to the anterior chamber, a condition known as iris bombe. As pressure builds up posteriorly, the iris may bow forward, resulting in secondary angle closure.
- When there is membrane over the anterior lens surface over the pupillary area, it is known as oclusio pupillae.
- Adhesions between the posterior surface of the cornea and the anterior surface of the iris is known as peripheral anterior synechiae (PAS). This can lead to secondary angle closure.
- Iris atrophy is a diagnostic feature of Viral uveitis.
- Varicella zoster virus : sector iris atrophy due to a vascular occlusive vasculitis.
- Herpes simplex virus usually produces patchy iris atrophy.

- Other causes of iris atrophy :
  i. Anterior segment ischemia
  ii. Hansen's disease
  iii. Trauma
  iv. Previous attacks of angle-closure glaucoma.
- Iris nodules may be prominent in the iris stroma.
- Iris nodules seen at the pupillary margin: Koeppe's nodules
- Iris nodule on the surface of iris: Busacca's nodules.

Causes of iris nodules :

1. Sarcoidosis,
2. Tuberculosis
3. VKH syndrome
4. sympathetic ophthalmia
5. syphilis

Normal radial iris vessels can be seen dilated in acute inflammation producing iris hyperemia as in rubeosis irides. They disappear when inflammation is controlled.

Hetero-chromia of iris can be either hypochromic (abnormal eye is lighter than fellow eye) as seen in Fuch's heterochromic iridocyclitis or hyperchromic (abnormal eye is darker than fellow eye) as seen in melanosis of iris.

Anterior chamber angle :

Gonioscopic evaluation can show angle keratic precipitates as seen in sarcoidosis.

Inflammatory debris at the angle indicates, cause for increase in intraocular pressure due to occlusion of the trabecular meshwork .

In traumatic uveitis -Angle recession /angle recession glaucoma and foreign body in the angle can be seen.

Lens :

Most common type of cataract seen in uveitis is posterior subcapsular cataract.

Anterior lens opacities following extreme elevations in IOP (glaukomeflecken) provide insight into a history of acute uveitis glaucoma.

Intraocular pressure

i. Hypotony: Due to impaired production of the aqueous by the ciliary body.
ii. Elevated intraocular pressure: This is due to the accumulation of inflammatory material and debris in the trabecular meshwork, inflammation of the trabecular meshwork (trabeculitis), thereby causing obstruction to the flow of aqueous. Steroid medications can also increase intraocular pressure.

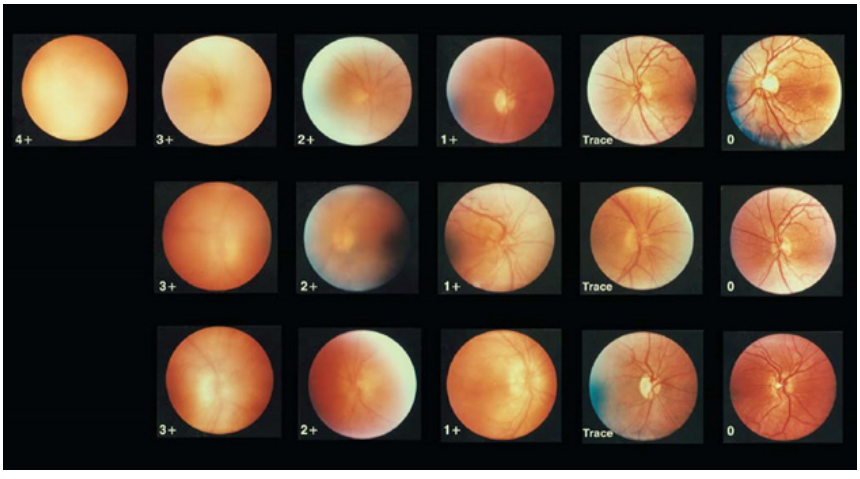
Causes of increase in intraocular pressure:

1. Posner-Schlossman's syndrome
2. Herpetic uveitis
3. Fuchs' heterochromic iridocyclitis
4. Uveitis with secondary angle closure glaucoma

Intermediate segment evaluation: The hallmark of intermediate uveitis is vitreous cell and vitreous haze.
Vitreous cells:[8]
Grading of vitreous cells :

Grade	Number of cells in the anterior vitreous high intensity 1 x 0.5 mm slit beam
0	0
0.5	1-5
1	6-10
2	11-20
3	21-50
4	>50

Vitreous haze:
Vitreous haze may be an indicator of disease activity than cell counts alone. The grading of vitreous haze is based on the clarity of view of the posterior segment on funduscopic examination.
The National Institutes of Health grading system for vitreous haze, which the SUN system adopted, employs a standardized set of fundus photographs that defines vitreous haze on a 0–4 scale.
Vitreous haze has been used in inclusion criteria in clinical trials for uveitis, and a 2-step improvement has been used as a principal outcome measure[8]



Additional signs of uveitis in the intermediate part of the eye includes:

1. snowballs: clumps of inflammatory cells in the vitreous
2. snow banking: exudates over the pars plana,prominent inferiorly
3. ciliary body detachment
4. retrolental membrane
5. vitreous strands or traction band

Posterior segment evaluation:

Optic disc:

1. Optic disc involvement takes the form of papillitis or disc edema, optic disc neovascularization, infiltration, and cupping.
2. Optic disc neovascularisation occurs in ischemic conditions and is characterized by sarcoidosis and leukemia can infiltrate the disc tissue, producing an appearance similar to papillitis.
3. Optic neuritis can occur in multiple sclerosis.
4. Optic disc granuloma is seen in sarcoidosis,toxoplasma uveitis,tuberculosis,toxocara uveitis .

Macula:

Chronic inflammation in the eye can lead to the following pathologies in the eye:

1. Cystoid Macular Edema (CME)
2. Macular lamellar holes
3. Inflammatory Choroidal Neovascularisation
4. Exudative macular detachment
5. Retina and choroid:
    - Retinochoroiditis
    - Chorioretinitis
    - Retinal vasculitis,Neovascularisation,Scars
    - Exudative retinal detachment

After history taking and complete ocular and systemic examination, we have certain descriptive terminologies in uveitis. Hence we will be able to give a specific name using the descriptive terminologies.

Table no 5: Descriptive terminologies used in uveitis :

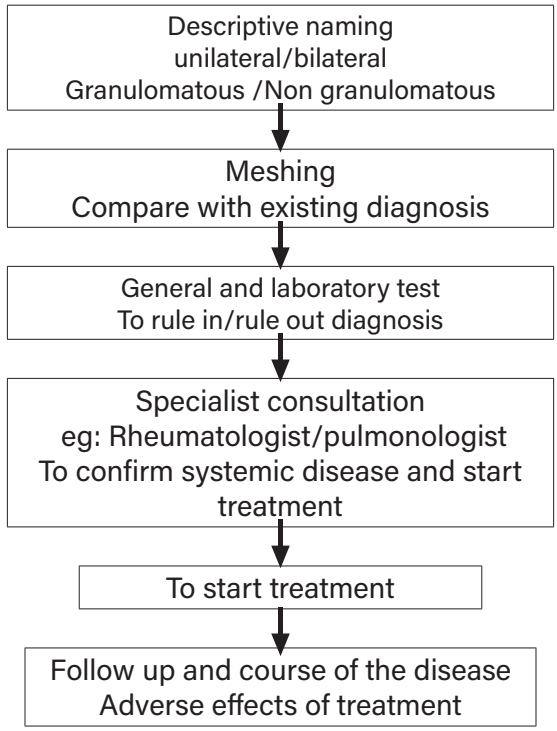
1	**Age**
	Pediatrics
	Young adults
	Geriatric
2	**Severity**
	Mild
	Moderate
	Severe
3	**Chronology**
	Acute
	Acute recurrent
	Chronic
4	**Pathology**
	Non granulomatous
	Granulomatous

5	**Anatomy**
	Anterior
	Intermediate
	Posterior
	Panuveitis
6	**Laterality**
	Unilateral /unilateral alternating
	Bilateral/bilateral symmetrical / asymmetrically bilateral
7	**Etiology**
	Idiopathic
	Infectious
	Non infectious /immunologic
	Masquerade
	Traumatic

After the descriptive name for our uveitis patient, we compare with existing uveitis patterns that we know and this step is known as meshing step.
The list of etiologies are listed.
After arriving at the differential diagnosis we look for investigations to confirm or rule out the specific diagnosis

The final step is plan on treatment.

Flow chart 1: Systematic work up



Infectious causes of uveitis should be considered in all patients.
Clinicians should be aware of the rare endemic and epidemic causes of uveitis.
The diagnosis of these infections can be done based on the epidemiology data, ocular symptoms and signs.

Post fever retinitis

Post fever retinitis is a distinct subset of acute non-necrotizing retinitis following febrile illness caused by either bacteria or viruses. These manifestations may be the result of a direct invasion by the pathogen or by indirect invasion mediated through immune-mediated mechanisms.[9]

Causes :

i. Bacteria: Typhoid, rickettsia
i. Viral : chikungunya, dengue, West Nile virus

Clinical manifestations [10]:

Post fever retinitis manifests between 2 and 4 weeks after the fever in immunocompetent patients, irrespective of etiology.

Retinitis is unifocal to multifocal in distribution and has a predilection for the peripapillary retina often involving the macula - either direct involvement with retinitis or secondarily due to an exudative response - causing serous macular detachment.

- Cotton wool spots
- Hemorrhages
- Optic nerve is frequently involved. Depending on its proximity to the lesion ,optic nerve inflammation is seen.
- Following resolution of inflammation, pallor of the disc can occur.
- Retinal vasculitis

- Cystoid macula edema.

Investigations [10,11,12]:
Systemic : A battery of specific investigations is needed to identify the cause when the evaluation for fever is not done. However, it is not possible to do all serological investigations due to financial constraints and unavailability of gold standard test.

Intensive serological and laboratory work-up, including PCR tests on ocular fluids may not benefit the clinical course or alter the outcome.

Ocular:
- Optical coherence tomography
- FFA: to rule out macula ischemia

Treatment: [13]
- Self-limiting
- Steroids helps in hastening the resolution of inflammation and reducing the damage due to the inflammation. Steroids has to be tapered depending on the clinical response.
- Periocular steroids for macula edema.

Prognosis: The visual outcome is usually satisfactory with timely diagnosis and treatment.

Trematode Induced Uveitis

Trematode are a group of flatworms, which belong to the helminth class.

Trematode belonging to Procerovum Varium causes trematode induced uveitis.

Epidemiology :

Southeast Asian and Indian populations are exposed to 70 species of food-borne and waterborne trematodes. The burden of disease and current distribution of the parasites within the population are largely unknown due to lack of awareness and screening programs[14,15]

Life cycle [16]

Adult worms are seen in the conjunctival sac of Birds.

↓

Birds come in contact with water bodies.

↓

Adult worms release eggs.

↓

Eggs hatch. Release miracidia

↓

Miracidia mature to form cercariae in the intermediate host (snails).

(The cercariae emerge in large numbers during day-time, with a peak emergence in the afternoon (12 noon- 2pm). During the resting phase they remained suspended in the water. Slight disturbances of the water cause the cercariae to become active. The cercarial distribution is mainly confined to the upper layers of the water)

Cercariae have to reach eyes of birds. Instead, they reach human eye when these children swim in the pond where these infected snails live. Humans are the accidental host if infected with the cercariae [16]

Ocular Manifestations: [13,17]

Laterality: Unilateral. However bilateral involvement is seen in few cases.

Ocular signs :

- Visual acuity: Usually good.
- Recurrent episodes of inflammation or prolonged use of steroids can cause complicated cataract and retrocorneal membrane which may affect vision.
- Subconjunctival Granuloma: Usually seen in palpebral conjunctiva.
- Granuloma In lids: Mimics chalazion.
- Granulomatous keratic precipitates.
- Nodule: 2-5 mm in diameter
  - Most common location: Retro-corneal surface in the inferior quadrant.
  - Well circumscribed.
  - White in colour.
- Anterior chamber reaction

Differential Diagnosis:

- Ocular tuberculosis
- Sarcoidosis
- Foreign body granuloma
- Fungal granuloma
- Xanthelasma

Investigations:

- Complete blood count.
- Differential count.
- Erythrocyte Sedimentation Rate.
- Serum ACE.
- Mantoux Test.
- Radiology imaging of chest and abdomen: to rule out tuberculosis.
- Histopathology or molecular diagnostics [15,18]

Large granuloma: Excision or aspirated.

Along with histopathological examination, bacterial and fungal culture needs to be done.

When there is no history of swimming: molecular diagnostics or histopathology is beneficial.

Treatment:

- Lesions smaller than 3 mm:

Topical steroids

Oral steroids: After ruling out other infectious causes.

- Lesions larger than 3 mm:

Excision biopsy

Post op period: oral and topical steroids to be continued.

Recurrences of new granuloma can occur if the patient comes in contact with the same water resources.

Leptospirosis uveitis

Leptospirosis is a widespread zoonosis secondary to the infection by genus Leptospira. It is a gram-negative spirochete.

Epidemiology :

Leptospirosis is prevalent in the tropical and subtropical countries[19]. Most of the cases are not reported due to lack of awareness and non-availability of diagnostic investigations.

According to the WHO guidelines, in tropical countries the incidence rate is 10-100/1, 00,000 and during an epidemic it may increase to over 100/1, 00,000.[20]

Risk factors:

- Occupational exposure: Farmers, gardeners, meat or animal handling, veterinary professional
- Poor socioeconomic conditions
- Recreational activities: Swimming/water sports
- Household: Infestation by infected rodents, contact with pets/dogs.
- Floods/rainfall

Transmission:

Rodents: Reservoir of the organisms.

↓

Shed the organisms in urine.

↓

Human infection: exposure to risk factors.

Systemic Manifestations:

Incubation period of leptospirosis: 5 -14 days.

The systemic manifestation of leptospirosis has two phases:

A. The acute phase or the anicteric phase: Seen in first week.

This phase is characterised by:

- Fever
- Myalgia
- Headache
- Abdominal pain
- Nausea and vomiting.

B. The immune phase or icteric phase or Weil's Syndrome. The symptoms of immunological phase are manifested in the second week.

This phase which is characterised by:

- Jaundice
- Renal failure
- Fever
- headache
- myalgia.

Many organs are affected in leptospirosis, but the kidneys are often affected which causes renal failure and is most common cause of death.

Ocular manifestations:

The severity of systemic presentation has no influence over the ocular severity[21,22].

There are a few ocular features which are characteristic of the disease to make a diagnosis.

Ocular manifestations in the initial bacteraemia phase are :

- conjunctival congestion
- chemosis without discharge
- subconjunctival haemorrhage
- yellow sclera.

In immunological phase ocular manifestations are:

- Non-granulomatous keratic precipitates on endothelium with moderate to severe anterior chamber inflammation.
- Hypopyon is one of the presenting features, when inflammation is severe.
- Develop cataract early in the course of the disease.
- Vitritis with veil like membranes are present in the posterior segment. Persistence of the membrane even after the inflammation is resolved is seen in few patients.
- Papilitis and vasculitis mainly involving the veins .
- Absence of retinitis and choroiditis in the above setting usually marks the diagnosis.

Differential diagnosis:

- Behcet's disease : Presence of non-granulomatous uveitis, hypopyon and vasculitis may mimic leptospirosis.
- HLA-B27 anterior uveitis can be misdiagnosed as leptospirosis, but alternating presentation and prominent fibrinous reaction differentiates from leptospirosis .
- Endogenous endopthalmitis : History of fever, management with intravenous fluids and the ocular presentation may mimic leptospirosis.

Investigations:

Leptospira are present in the blood up to 4-7 days after onset of infection. Leptospira specific IgM antibodies are produced after 7 days and clear the bacteria from the blood. These IgM antibodies can persist for many months after initial presentation.[23]

The diagnosis can be made by:

- Direct methods : Microscopy, culture or molecular methods.

In microscopy, Dark field- phase contrast method is used. The leptospires are seen as thin, bright actively mobile rods.

To be visible on microscopy minimum of 10 leptospires /ml is necessary.

Warthin-Starry stain is used in histochemical staining.

- The culture media is not much of use as it takes 3 months to culture these organisms.
- Indirect serological methods: Detection of IgM antibodies by MAT and ELISA.

Micro Agglutination Test (MAT) is the gold standard test. It is a highly sensitive assay. It can be performed only in laboratories where maintenance of strains for preparing live

antigens is possible. A disadvantage of this test is elevated titres of MAT in a population where leptospirosis is common .

Other laboratory findings are:

- elevated WBC count
- elevated ESR.
- Impaired liver/renal function tests depending on the systemic presentation.

Treatment:

Systemic disease:

- Patients with mild disease - Doxycycline 100 mg orally twice per day
- Patient presenting with severe systemic disease: Intravenous penicillin or third generation cephalosporin.

Monitoring and supportive care like dialysis and mechanical ventilation may be needed in cases of organ failure.

- Ocular disease:

Patients diagnosed with uveitis: Depending on the site of inflammation needs topical, oral or periocular steroids along with oral antibiotic- doxycycline 100 mg twice daily for two weeks.

Prevention:

- Use of protective wear by farmers, livestock workers, butchers and sewage workers
- Use of gloves and protective footwear during gardening/farming is considered safe.
- Prophylactic medication can be taken by people travelling to pilgrimage places and taking dip in the river or stagnant water bodies. It is also advisable in people participating in recreational sports.
- Use of boiled water
- Measures to control rodents can also decrease the indirect contact with the organism.

Prognosis:

Ocular manifestation responds well to the treatment.

Patients usually regain visual acuity after ocular inflammation resolved, except in cases of persistence of vitreous membrane.

Cataract due to leptospirosis uveitis has good visual prognosis, when operated after control of inflammation.

Though the prognosis of these epidemic and endemic ocular infections is good, they can be vision threatening if not treated appropriately.

Personal protection (prevention of mosquito bites and use of protective clothing), control of rat reservoirs and improvement of sanitary conditions can prevent these infections.

References :

1. *Smith RE, Nozik RA: Uveitis: A clinical approach to diagnosis and management, Baltimore, Williams and Wilkins: 1989.*
2. *Cunningham ET, Nozik RA. Uveitis: Diagnostic approach and ancillary analysis. In: Duane's Clinical Ophthalmology, Vol 37. Philadelphia: Lippincott-Raven: 1997:1–25*
3. *Cunningham ET. Uveitis in children. Ocular Immunology and Inflammation 2000;8:251-261.*
4. *Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. Indian J Ophthalmol. 2007;55:173–83*
5. *Rathinam SR. Ocular leptospirosis. Curr Opin Ophthalmol. 2002;13:381–6*
6. *Rathinam SR, Usha KR, Rao NA. Presumed trematode-induced granulomatous anterior uveitis: A newly recognized cause of intraocular inflammation in children from south India. Am J Ophthalmol. 2002;133:773–9*
7. *Jabs DA, Nussenblatt RB, Rosenbaum JT Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol.2005;140:509–16*
8. *Nussenblatt RB, Palestine AG, Chan C, Roberge F. Standardization of vitreal inflammatory activityin intermediate and posterior uveitis.Ophthalmology.1985; 92:467–471.*
9. *Anchal, Bhavik. Commentary: Post fever retinitis and vasculitis. Indian Journal of Ophthalmology 66(12):p 1844, December 2018.*
10. *Karkhur, S., Soni, D. Clinical spectrum, disease course and management outcome of post-fever retinitis cases: experience from a tertiary eye institute in central India. Int Ophthalmol 42, 2697–2709 (2022)*
11. *Sivakumar RR, Prajna L, Arya LK, Muraly P, Shukla J, Saxena D, et al Molecular diagnosis and ocular imaging of West Nile virus retinitis and neuroretinitis Ophthalmology. 2013;120:1820–6*
12. *Lalitha P, Rathinam S, Banushree K, Maheshkumar S, Vijayakumar R, Sathe P. Ocular involvement associated with an epidemic outbreak of chikungunya virus infection Am J Ophthalmol. 2007;144:552–6*
13. *Kawali A, Mahendradas P, Mohan A, Mallavarapu M, Shetty B. Epidemic Retinitis.Ocul Immunol Inflamm. 2019;27(4):571-577.*
14. *Vedhanayaki R, Rathinam SR.Trematode granuloma in children. Journal of Ophthalmology and Related Sciences 2020;4(1):1-5*
15. *Rathinam SR, Arya LK, Usha KR, Prajna L, Tandon V. Novel Etiological Agent: Molecular Evidence for Trematode-Induced Anterior Uveitis in Children. Arch Ophthalmol. 2012;130(11):1481–1484. doi:10.1001/archophthalmol.2012.729*
16. *Umadevi K, Madhavi R. Observations on the morphology and life-cycle of Procerovum varium (Onji & Nishio, 1916) (Trematoda: Heterophyidae). Syst Parasitol. 2000;46(3):215-225.*
17. *Rathinam SR, Usha KR, Rao NA. Presumed trematode-induced granulomatous anterior uveitis: a newly recognized cause of intraocular inflammation in children from south India. Am J Ophthalmol. 2002;133(6):773-779.*
18. *Rajesh Vedhanayaki; Sivakumar, Rathinam; Thundikandy, Radhika. Trematode Granuloma: Journey of the Worm from the River Bed to the Agar Plate. TNOA Journal of Ophthalmic Science and Research 62(2):p 157-161, Apr–Jun 2024.*
19. *Hartskeerl RA, Collares-Pereira M, Ellis WA (2011) Emergence, control and re-emerging leptospirosis: dynamics of infection in the changing world. Clin Microbiol Infect.doi: 10.1111/j.1469-0691.2011.03474.x*
20. *World Health Organization. (ý2003)ý. Human leptospirosis : guidance for diagnosis, surveillance and control. Geneva : World Health Organization. http://www.who.int/iris/handle/10665/42667*
21. *Rathinam SR, Balakrishnan V, Gowri P, Visalakshi J (2016) Leptospiral Uveitis: Usefulness of Clinical Signs as Diagnostic Predictors. Ocul ImmunolInflamm..doi: 10.1080/09273948.2016.1217341*
22. *Rathinam SR. Ocular manifestations of leptospirosis. J Postgrad Med. 2005;51(3):189-194*
23. *Budihal SV, Perwez K (2014) Leptospirosis diagnosis: competancy of various labortory tests. J ClinDiagn Res doi: 10.7860/JCDR/2014/6593.3950*

Uveitis diagnosis at a glance- Part A

Amod Gupta

Uveitis diagnosis at a glance			
Primary site of inflammation	**Symptoms**	**Signs**	**Labs**
Anterior Chamber- infectious			
Fuchs' Uveitis	▪ Unilateral ▪ light scattering, photophobia; diminution in vision; ▪ floaters especially after cataract surgery	▪ Stellate KPs over entire endothelium; ▪ Iris atrophy with loss of iris crypts and pupil ruff; iris transillumination defects; ▪ No posterior synechiae; ▪ Unilateral cataract ▪ Vitreous opacities/ cells without CME ▪ Raised IOP +/- ▪ Amsler Sign-streak hyphema during cataract surgery	None
Viral AU-HSV/ VZV	▪ Unilateral+ ▪ Pain and redness	▪ Loss of corneal sensations ▪ Raised IOP ▪ Pigmented KPs ▪ Posterior synechiae ▪ Recurrent	▪ PCR for HSV/ VZV from Aqueous humour
CMV AU	▪ Unilateral ▪ pain and redness	**Acute** ▪ U/L, recurrent ▪ Very high IOP ▪ Low inflammation ▪ Few KPs ▪ Endothelitis with owl-eye KPs ▪ No vitritis ▪ No CME **Chronic** ▪ Low inflammation ▪ Mimics Fuchs' uveitis ▪ IOP not very high ▪ No synechiae	▪ PCR

Chikungunya virus anterior uveitis	▪ Insidious or abrupt onset of pain, redness unilateral or bilateral	▪ Flare ▪ Cells ▪ Synechiae+/- ▪ Iris atrophy ▪ Stellate KPs over the lower half of the cornea ▪ Raised IOP ▪ Mimics Fuchs uveitis	▪ CHIKV RNA RT-PCR in 1st week of fever ▪ Elisa for IgM after 1 week of fever
Zika virus anterior uveitis	▪ Red eyes (Nearly half of red eyes in Zika virus infection have anterior uveitis)	▪ Bilateral Conjunctival hyperemia ▪ anterior uveitis ▪ Flare ++ ▪ Cells <+ ▪ Fine KPs ▪ No synechiae ▪ Raised IOP	▪ RT-PCR for ZIK V from Aqueous ▪ Elisa for anti-ZIKV IgM abs
Ebola virus uveitis Half of the survivors	▪ Blurring of vision ▪ Pain ▪ Redness ▪ Photophobia ▪ Discharge	▪ Flare ▪ Cells ▪ KPs ▪ Posterior synechiae ▪ Vitritis, vitreous membranes ▪ CME ▪ ODE +/- ▪ Macula/retinal scars	▪ Highly infectious care in collecting samples with PPE kits ▪ RT-PCR for EBV from blood ▪ ELISA for IgM Abs
Anterior Chamber- Non-Infectious			
HLA B27 -associated AAU	▪ Abrupt onset with pain; ▪ the eye may be tender to light touch even before signs of inflammation are obvious	▪ Young M > W, ▪ recurrent, alternating, ▪ sudden onset, acute course, ▪ intense flare, cells, and fibrin. ▪ Synechiae break easily with cycloplegics. ▪ Leave behind a ring of pigment on the crystalline lens. ▪ CME occasionally	▪ HLA B 27 ▪ MRI SI joints ▪ ROS

JIA -associated uveitis	▪ Asymptomatic ▪ Insidious progressive visual loss ▪ Detected on screening of JIA	▪ CAU seen in 10-30%, 90% develop in < 4 years ▪ JIA-oligoarticular (< 4 joints); asymmetric ▪ Uveitis is silent in > 90% ▪ Bilateral BSK; flare and cells; posterior synechiae, Hypotony or raised IOP; Complicated cataract	▪ ANA ▪ if > 5 Joints -RF, Anti-CCP, ANA ▪ HLA B27 if Male, AAU ▪ USG/UBM
Screening guidelines JIA-associated uveitis **Slit-lamp exam**: Every 3 months if Oligoarthritis; onset ≤ 6 yrs.; ANA+ Every 6 months if Oligoarthritis; onset < 6 yrs.; ANA- Annual check if systemic onset			
TINU	▪ Sudden onset ▪ bilateral pain, redness, photophobia ▪ H/O drug intake or infection	▪ < 20 years; F>M ▪ Bilateral flare/cells/ fine KPs ▪ Vitreous cells ▪ FFA- Peripheral vascular leaks/ Optic disc leak/ CME ▪ Raised IOP in 50% ▪ Recurrent steroid withdrawal	▪ Urine β-2 microglobulin ▪ ESR ▪ S creatinine ▪ Low grade proteinuria ▪ Urine eosinophilia, pyuria, haematuria, glycosuria (Normogl ycemic) ▪ Renal biopsy- interstitial lymphocytes, plasma cells, and eosinophil infiltrates ▪ HLA-DQA1*01, HLA-DQB1*05, and HLA-DRB1*01

Sarcoidosis	▪ Insidious onset visual symptoms	▪ Mutton fat KPS ▪ Busacca nodules ▪ Berlin nodules in the angle of the AC ▪ Tent-like peripheral anterior synechiae ▪ Koeppe nodules at the pupillary border	▪ CECT chest ▪ Mx test ▪ Cytopathology of the hilar lymph nodes
Vitreous cavity			
Intermediate uveitis	▪ Floaters ▪ Diminution of vision	▪ Vitreous cells/ opacities ▪ String of pearls ▪ Pars plana exudates ▪ MS-associated intermediate uveitis- ▪ Look for optic disc pallor ▪ diplopia ▪ Vitritis with peripheral vascular sheathing,	Rule out Sarcoidosis/TB/ MS
Posterior Uveitis- Infectious			
Toxoplasma retinoch-oroiditis	▪ Sudden onset, painless blurring of vision	▪ Unilateral, mono-focal, necrotizing retinitis lesion with or without an adjacent pigmented scar ▪ Bilateral, multifocal, extensive in HIV+ ▪ intense vitritis over the lesion giving a headlamp in the fog appearance	▪ Goldmann -Witmer coefficient to measure local production of Ab-IgG/IgM; > 3X in aqueous than blood ▪ PCR from aqueous in HIV+ ▪ Negative serology rules out Toxo infection

Acute retinal necrosis	▪ Sudden onset, painless blurring of vision	▪ unilateral or bilateral, ▪ one or more wedge-shaped areas of retinal necrosis in the retinal periphery ▪ rapidly progressive circumferential and posterior spread ▪ variable vitreous reaction in immunocompetent > immunodeficient individuals. ▪ Retinal vascular (arterioles) occlusion or sheathing ▪ Extensive retinal atrophy with sieve-like retinal holes ▪ If >1 quad ARN, RD in ~40-50%	▪ PCR for VZV and HSV ▪ In HIV- patients, VZV >HSV
Progressive outer retinal necrosis	▪ Sudden painless loss of vision in HIV+ or organ transplant/ malignancy ▪ History of recent herpes zoster lesions/scars.	▪ No or minimal vitritis ▪ Multifocal deep retinal opacification ▪ sparing of retinal vessels (mud crack appearance) ▪ No retinal hemorrhages ▪ Early involvement of macula/optic disc	▪ PCR for VZV ▪ HIV testing
CMV retinitis	▪ Insidious painless blurring of vision ▪ HIV ▪ Non-HIV- Seek a history of Immunosuppressive therapy/ Organ transplant or connective tissue disorders	▪ Wedge-shaped hemorrhagic or granular areas of retinitis with indistinct borders ▪ slowly progressive ▪ perivenous sheathing, ▪ minimal or no vitritis. ▪ In non-HIV CMV, unilateral, vitritis, and retinal arterial occlusion, may present as ARN	▪ HIV ▪ PCR for CMV ▪ CD4 counts

Post-fever retinitis- Dengue	▪ Visual symptoms within 1-7 days of onset of fever ▪ Blurring of vision, photopsia, floaters ▪ Rash, myalgia, arthralgia	Ocular signs result from ischemic, inflammatory thrombocytopenic mechanisms ▪ Multifocal retinitis, Cotton-wool spots ▪ Optic neuropathy ▪ Maculopathy ▪ Foveolitis ▪ Vasculitis ▪ Retinal hemorrhages	▪ NS-1 antigen detection ▪ IgM antibodies ▪ RT-PCR ▪ Platelet counts ▪ CRP
Post-fever retinitis- Chikungunya	▪ H/O epidemic fever weeks to months before visual symptoms ▪ Arthralgias, myalgia, rash	▪ Multifocal chorioretintis ▪ Cotton wool spots ▪ Retinal hemorrhages ▪ Papillitis, neuroretinitis, optic neuropathy ▪ Vascular occlusion ▪ Exudative RD	▪ CHIKV RNA RT-PCR in 1st week of fever ▪ Elisa for IgM after 1 week of fever
Post-fever retinitis- West Nile	▪ H/O epidemic fever weeks to months before mild visual symptoms ▪ Asymptomatic in a majority ▪ Myalgia, rash ▪ Neurologic symptoms	▪ Bilateral Linear or scattered creamy deep-seated 200-500µ chorioretinal lesions. ▪ Healed lesions- atrophic scars ▪ Active lesions hyperfluorescent, healed lesions hypo in the center with a peripheral hyperfluorescent ring ▪ Best seen on ICG as hypo lesions ▪ Retinal vasculitis in the elderly ▪ Retinal hemorrhages ▪ Kyrieleis' periarterial plaques ▪ Optic disc edema, papillitis	▪ Serology for IgM /IgG WNV Abs ▪ PCR

Subacute Sclerosing panencephalitis (SSPE)	▪ Insidious onset ▪ History of cognitive decline, ▪ poor scholastic performance in school ▪ myoclonic jerks. ▪ The prognosis for life is extremely poor	▪ Young boys ▪ one or more areas of unilateral retinal opacification with full-thickness necrolysis ▪ spares Bruch's membrane and internal limiting membrane which shows billowing ▪ most rapid progression, no vitritis, heals rapidly in ~two weeks with atrophy of the necrotic retina and radiating ILM folds. ▪ other eye involved within 1-2 weeks of onset.	▪ Serology for Measles virus Abs from blood and CSF ▪ EEG for classical periodic spikes ▪ MRI-T2 weighted images show high-intensity signals in periventricular or subcortical areas in both cerebral hemispheres.
Syphilitic chorioretinitis	▪ Vision disturbance ▪ Photopsia ▪ Pain, redness ▪ Scotoma ▪ Mucocutaneous rash (palmer) ▪ Penile ulcer	▪ M > F ▪ Chorioretintis most common ▪ Acute syphilitic posterior placoid chorioretinopathy (ASPPC) ▪ > 1 yellow outer retinal lesion in the posterior pole > periphery ▪ FAF shows hyperautofluorescence ▪ OCT shows nodular excrescences overlying RPE, disruption of EZ, and preretinal hyperreflective dots ▪ Vitritis M>F ▪ Neuroretinitis ▪ Optic disc edema; optic perineuritis ▪ Retinal vasculitis	**Treponemal tests** ▪ IgG for syphilis ▪ Treponema pallidum hemagglutination test (TPHA); TPPA ▪ FTA-ABS ▪ Enzyme immunoassay* ▪ Chemiluminescence immunoassay* **Non-treponemal test** ▪ VDRL ▪ RPR ▪ CSF should be tested for syphilis ▪ HIV must be tested ▪ NB: VDRL and RPR are not interchangeable for measuring antibody titres. * Not known if their titres are reversed following treatment of syphilis

TB retinal periphlebitis	▪ Blurring vision ▪ Sudden loss of vision	▪ Segmental periphlebitis with exuberant perivenous exudates ▪ Vitritis ▪ retinal hemorrhages in the active stage ▪ pipestem sheathing in the healed stage ▪ with or without peripheral new vessels ▪ Perivascular active or healed retinochoroiditis lesions are almost pathognomonic of tuberculosis. ▪ may present as vitreous hemorrhage ▪ the other eye is likely to show evidence of healed retinal vasculitis.	▪ QuantiFERON gold TB test ▪ Tuberculin skin test ▪ CECT chest ▪ qPCR from ocular fluids
TB Choroidal granuloma	▪ Painless blurring of vision	▪ Single or few elevated choroidal granuloma/s in the posterior pole ▪ with or without associated retinal detachment. ▪ Variable-sized intraretinal hemorrhage is highly suggestive of TB etiology.	▪ QuantiFERON gold TB test ▪ Tuberculin skin test ▪ CECT chest ▪ qPCR

TB-Serpiginous like Choroiditis	Blurring of vision	▪ Young unilateral or bilateral, ▪ non-contiguous to optic disc multifocal plaque-like choroiditis lesions ▪ Lesions heal centrally and show active grey borders ▪ centrifugal expansion, ▪ variable vitritis. ▪ The foveal centre is preserved for a long time. ▪ Lesions heal with extensive pigmentary changes. ▪ Very often show paradoxical worsening of lesions on anti-tubercular therapy without ▪ concurrent use of full corticosteroids.	▪ QuantiFERON gold TB test ▪ Tuberculin skin test ▪ CECT chest ▪ qPCR
Posterior uveitis - Non-infectious			
Sarcoidosis	Visual disturbance Nearly 2/3rd patients present first with visual disturbances	▪ Bilateral Multifocal choroidal granulomas ▪ Candle wax nodular perivascular infiltrates ▪ Retinal arterial macroaneurysm ▪ Taches de bougie spots as yellowish streaks or white spots in the periphery	▪ Complete blood counts ▪ Blood urea nitrogen ▪ Creatine kinase ▪ CRP ▪ Urine for albuminuria/ hypercalciuria/ hematuria ▪ CECT chest ▪ Pulmonary function tests ▪ Biopsy from mediastinal or extrapulmonary lymph nodes/ skin/liver/kidney
Non-infectious organ-specific immune mediate posterior uveitis (White dot syndromes) are discussed in section B			

Panuveitis			
Behcet's syndrome	▪ 20% may present first with visual symptoms ▪ Recurrent aphthous and genital ulcers, ▪ erythema nodosum, ▪ pseudo-folliculitis or acneiform nodules.	▪ Mobile hypopyon ▪ transient retinal infiltrates, ▪ vitritis, retinal vasculitis, BRVO ▪ optic neuritis, optic atrophy ▪ CME ▪ Fern pattern dye leakage from all retinal vessel walls ▪ Flare meter and FFA leakage are the most sensitive tools to monitor ▪ The presence of choroiditis rules out Behcet's disease.	▪ HLA-B*5101
VKH disease	▪ Sudden blurring of vision ▪ dysacusis, headache, and stiffness of the neck may precede days before visual symptoms ▪ untreated/ incompletely treated patients may develop poliosis, vitiligo, and alopecia	▪ Young F>M ▪ Bilateral exudative RD ▪ Optic disc edema ▪ Vitreous cells ▪ Choroidal thickness on USG/OCT ▪ FFA during the acute uveitis phase shows delayed patchy choroidal filling followed by punctate hyperfluorescent dots and pooling of dye in subretinal space in late phases. ▪ ICG shows hypo lesions ▪ Granulomatous uveitis in chronic recurrent phase ▪ Peripheral and peripapillary nummular scars ▪ Sunset glow fundus in convalescent phase	▪ During the prodrome stage, pure tone audiometry ▪ CSF for lymphocytic pleocytosis ▪ HLA-DR 4/ HLA-DRB1*04

Sympathetic Ophthalmia	▪ Penetrating trauma or intraocular surgery preceding the onset of visual symptoms ▪ loss of accommodation is the earliest symptom ▪ Pain, redness and loss of vision	▪ Acute uveitis phase resembles VKH ▪ Exudative RD in the sympathizing eye, may have no anterior segment inflammation in the early stages ▪ Vitreous cells ▪ Yellow white peripheral lesions ▪ Optic disc edema ▪ Sunset glow fundus in the late recurrent phase of SO.	No tests

For further reading:

1. *Gupta, A., Bansal, R., Sharma, A., Kapil, A. (2023). Retinal and Choroidal Infections and Inflammation. In: Ophthalmic Signs in Practice of Medicine. Springer, Singapore. https://doi.org/10.1007/978-981-99-7923-3_10*
2. *Gupta, A., Bansal, R., Sharma, A., Kapil, A. (2023). Red Eyes—Conjunctivitis, Corneal Ulcers, Dry Eye Disease, and Acute Uveitis. In: Ophthalmic Signs in Practice of Medicine. Springer, Singapore. https://doi.org/10.1007/978-981-99-7923-3_17*
3. *Lee JH, Agarwal A, Mahendradas P, Lee CS, Gupta V, Pavesio CE, Agrawal R. Viral posterior uveitis. Surv Ophthalmol. 2017 Jul-Aug;62(4):404-445. doi: 10.1016/j.survophthal.2016.12.008. Epub 2016 Dec 22. PMID: 28012878; PMCID: PMC5654632.*
4. *Khairallah M, Abroug N, Smit D, Chee SP, Nabi W, Yeh S, Smith JR, Ksiaa I, Cunningham E. Systemic and Ocular Manifestations of Arboviral Infections: A Review. Ocul Immunol Inflamm. 2024 Mar 5:1-19. doi: 10.1080/09273948.2024.2320724. Epub ahead of print. PMID: 38441549.*
5. *Khairallah M, Kahloun R. Ocular manifestations of emerging infectious diseases. Curr Opin Ophthalmol. 2013 Nov;24(6):574-80. doi: 10.1097/ICU.0b013e3283654e09. PMID: 24030241.*
6. *More A, Singh J, Chandak N, Shetty SB, Sen A. Macular Necrotizing Retinitis as a Presenting Feature of Atypical Fulminant SSPE: A Case Report. Ocul Immunol Inflamm. 2023 May;31(4):856-860. doi: 10.1080/09273948.2022.2054824. Epub 2022 Apr 11. PMID: 35404754.*
7. *Barthwal S, Kaur N, Kaur R, Zaidi R, Randev S. Magnetic Resonance Imaging in Subacute Sclerosing Panencephalitis: Two Case Reports and Review of Literature. Cureus. 2021 Oct 31;13(10):e19161. doi: 10.7759/cureus.19161. PMID: 34873504; PMCID: PMC8631486.*
8. *Mirzania D, Zacks DN, Zhou Y, Huvard MJ. Clinical Characteristics and Visual Outcomes of Acute Syphilitic Posterior Placoid Chorioretinopathy. Ophthalmol Retina. 2023 Dec;7(12):1080-1086. doi: 10.1016/j.oret.2023.07.014. Epub 2023 Jul 19. PMID: 37479085.*
9. *Shields MK, Arantes TE, Lake SR, Belfort R Jr, Muccioli C, Nascimento H, de Pinho Queiroz R, Vasconcelos-Santos DV, Furtado JM, Smith JR. Influence of gender on clinical presentation, management practices and outcomes of ocular syphilis. Sci Rep. 2024 Jul 16;14(1):16390. doi: 10.1038/s41598-024-66412-3. PMID: 39013925; PMCID: PMC11252369.*

Uveitis diagnosis at a glance-Part B

Amod Gupta

Organ-specific (Ocular) immune-mediated inflammations (White dot syndromes)

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Disorder	Clinical characteristics	Imaging studies
MEWDS[1]	1. Young women > Men 2. Photopsia, blurring of vision 3. Unilateral 4. Optic disc edema 5. Macular granularity 6. Multifocal white lesions in paramacular and peripheral fundus 7. Spontaneous resolution in ~8 weeks	**FFA**: 1. Hyperfluorescent dots (<100 µ), in wreath configuration 2. OD staining 3. minimum staining of white dots **ICG**: Hypofluorescent dots in late frames **FAF**: Hyperautofluorescent **OCT**: Hyperreflective lesions centered on the ellipsoid zone protruding from RPE into outer nuclear layer **OCTA**: Flow voids in choriocapillaris All changes reversible on healing
APMPPE[2]	1. Young, preceding flu 2. Sudden loss of vision, photopsia, scotomas 3. Sequential bilateral creamy placoid lesions in outer retina 4. Lesions heal spontaneously with pigmentary changes	**FFA**: Initial hypofluorescent, late hyperfluorescence **ICG**: hypofluorescent throughout **FAF**: Hypoautofluorescent with a ring of hyperautofluorescence **OCT**: Hyperreflective material in the outer retina, disruption of EZ and IZ; SRF+ **OCTA**: Flow void in CC All changes reversible on healing except transmission defects on FFA

PIC[3]	1. Young, myopic women 2. Blurring, photopsia, 3. metamorphopsia 4. Discrete, 100-300µ multifocal outer retina and inner choroidal lesions in macula, heal with punched out atrophic scars 5. Subfoveal hemorrhage 6. Serous macular RD	**FFA**: 1. Hyperfluorescent in early and late frames. 2. Type 2 CNV 3. Hyperfluorescence in macula **ICG**: Hypofluorescent lesions throughout **FAF**: Hyperautofluorescence **OCT**: Hyperreflective lesions in inner choroid with conical RPE elevation, with intact BM, photoreceptors not visible in active lesions **OCTA**: CNV between RPE and neurosensory retina
IMFC[4] (MFC with panuveitis)	1. Young myopic women 2. Photopsia, scotomas 3. Unilateral/bilateral/sequential 4. Multifocal choroiditis lesions or scars 5. Vitreous cells 6. Recurrent, progressive 7. CNV	**FFA**: 1. Non-contributory in acute stage. 2. Some hyperfluorescent in late frames. 3. Transmission defects in scars. 4. Type 2 CNV **ICG**: Hypofluorescent lesions from 50-400 µ, most remain hypofluorescent in late frames **FAF**: Hyperautofluorescence **OCT**: 1. Hyperreflective material in the inner choroid elevating the RPE, with a rupture at the peak of BM/RPE and material extending into outer retina. 2. Disruption of EZ, IZ, and ELM 3. Increased light transmission through the lesion. **OCTA**: CC flow voids reversible in smaller lesions

AZOOR[4, 5]	1. Young to middle aged healthy women 2. Moving Photopsia-lightening in a thunderstorm, photophobia, scotoma, blind spot in temp field, visual field loss, night vision problems 3. Bilateral asymmetric disease 4. Peripapillary normal or subtle lesion; white demarcation line between normal and affected retina may be prominent but transient; trizonal lesions are diagnostic. 5. Bone spicule pigment and atrophy	**FFA**: Non-contributory in acute, window defect in late stage **ICG:** Non-contributory in acute, trizonal pattern **FAF**: Patch hyperautofluorescence, progressive, later hypoautofluorescence, hyperautofluorescent demarcation line; normal outside the demarcation line **OCT**: 1. Loss of EZ, thickening of outer plexiform layer and loss of outer nuclear layer; foveal centre may be spared for a long time 2. Loss of RPE in late stages
BCR[6,7]	1. Middle-aged, F>M, Caucasians 2. HLA-A29*02 in >95% 3. Blurring of vision or floaters both eyes 4. Creamy oval/streak lesions choroidal 500-1500 µ radial to optic disc 5. Vitritis 6. CME 7. Retinal vasculitis 8. ODE 9. Cellophane maculopathy	**FFA**: 1. Delayed A-V transit 2. Hypo lesions in the early and mild hyperfluorescence in late frames 3. Late OD staining 4. CME, retinal perivenous staining and leakage **ICG**: 1. Most sensitive tool 2. Hypofluorescent lesions corresponding to creamy lesions aligned with choroidal vessels. **FAF**: Linear hypoautofluorescence along retinal vessels **OCT**: 1. Disruption of ellipsoid zone, focal to generalized 2. Outer retinal atrophy **ERG**: Full field and mfERG shows delayed implicit time and decreased amplitude
AMN[8,9]	1. Young women 2. Unilateral or bilateral Paracentral scotomas after flu like illness, transient or permanent 3. Fundus shows multiple reddish brown, sharp petaloid lesions deep in the retina centered around foveal centre 4. >100 µ outer retinal changes are often permanent.	**NIR imaging**: Shows hyporeflective sharply defined lesions in the macula **FFA**: Normal **ICG**: Normal **FAF**: Normal **OCT**: Loss of ellipsoid zone/IZ and thinning of outer nuclear layer and OPL hyperreflectivity **OCTA:** flow deficit in deep capillary plexiform layer. Flow may reverse but OCT changes may not revert **VF**: paracentral scotoma

MEWDS, multiple evanescent white dot syndrome; FFA, fundus fluorescein angiography; ICG, indocyanine angiography; FAF, fundus autofluorescence; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; OD, optic disc; CC, choriocapillaris; PIC, punctate inner choroidopathy; RD, retinal detachment; CNV, choroidal neovascular membrane; IMFC, idiopathic multifocal choroidopathy; RPE, retinal pigment epithelium; BM, Bruch's membrane; EZ, ellipsoid zone; IZ, interdigitating zone; ELM, external limiting membrane; AZOOR, acute zonal occult outer retinopathy; BCR, birdshot chorioretinopathy, ERG , electroretinography; mfERG, multifocal ERG; AMN, Acute macular neuroretintis; NIR, near infrared; OPL, outer plexiform layer

References:

1. *Marsiglia M, Gallego-Pinazo R, Cunha de Souza E, Munk MR, Yu S, Mrejen S, Cunningham ET Jr, Lujan BJ, Goldberg NR, Albini TA, Gaudric A, Francais C, Rosen RB, Freund KB, Jampol LM, Yannuzzi LA. EXPANDED CLINICAL SPECTRUM OF MULTIPLE EVANESCENT WHITE DOT SYNDROME WITH MULTIMODAL IMAGING. Retina. 2016 Jan;36(1):64-74. doi: 10.1097/IAE.0000000000000685. PMID: 26166804.*
2. *Testi I, Vermeirsch S, Pavesio C. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE). J Ophthalmic Inflamm Infect. 2021 Nov 1;11(1):31. doi: 10.1186/s12348-021-00263-1. PMID: 34524577; PMCID: PMC8443720.*
3. *Ahnood D, Madhusudhan S, Tsaloumas MD, Waheed NK, Keane PA, Denniston AK. Punctate inner choroidopathy: A review. Surv Ophthalmol. 2017 Mar-Apr;62(2):113-126. doi: 10.1016/j.survophthal.2016.10.003. Epub 2016 Oct 15. PMID: 27751823.*
4. *Pichi F, Invernizzi A, Tucker WR, Munk MR. Optical coherence tomography diagnostic signs in posterior uveitis. Prog Retin Eye Res. 2020 Mar;75:100797. doi: 10.1016/j.preteyeres.2019.100797. Epub 2019 Sep 9. PMID: 31513851.*
5. *Mrejen S, Khan S, Gallego-Pinazo R, Jampol LM, Yannuzzi LA. Acute zonal occult outer retinopathy: a classification based on multimodal imaging. JAMA Ophthalmol. 2014 Sep;132(9):1089-98. doi: 10.1001/jamaophthalmol.2014.1683. PMID: 24945598.*
6. *Minos E, Barry RJ, Southworth S, Folkard A, Murray PI, Duker JS, Keane PA, Denniston AK. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. Orphanet J Rare Dis. 2016 May 12;11(1):61. doi: 10.1186/s13023-016-0429-8. PMID: 27175923; PMCID: PMC4866419.*
7. *Fogel-Levin M, Sadda SR, Rosenfeld PJ, Waheed N, Querques G, Freund BK, Sarraf D. Advanced retinal imaging and applications for clinical practice: A consensus review. Surv Ophthalmol. 2022 Sep-Oct;67(5):1373-1390. doi: 10.1016/j.survophthal.2022.02.004. Epub 2022 Feb 17. PMID: 35183611.*
8. *Yzer S, Freund KB, Engelbert M. Imaging in the diagnosis and management of acute macular neuroretinopathy. Int Ophthalmol Clin. 2012 Fall;52(4):269-73. doi: 10.1097/IIO.0b013e31826704a4. PMID: 22954950.*
9. *Fawzi AA, Pappuru RR, Sarraf D, Le PP, McCannel CA, Sobrin L, Goldstein DA, Honowitz S, Walsh AC, Sadda SR, Jampol LM, Eliott D. Acute macular neuroretinopathy: long-term insights revealed by multimodal imaging. Retina. 2012 Sep;32(8):1500-13. doi: 10.1097/IAE.0b013e318263d0c3. PMID: 22846801.*

Holistic Care of the Uveitis Patient: Relevant Concepts with Basis in Immunology

Mayur R. Moreker, Virender Singh Sangwan

Introduction:
The importance of self-management strategies in patients with uveitis cannot be over-emphasized and can be extrapolated from our rheumatology colleagues who have published the European Alliance of Associations for Rheumatology (EULAR) recommendations for non-pharmacological interventions to "optimise the well-being of patients with Rheumatoid Arthritis".[1]

Taking a leaf from our rheumatology colleagues, as described by Taylor PC et al., our aim in the practice of uveitis should be to attain "optimal health" and "wellness" for each patient beyond that which can be promised and achieved by pharmacotherapy alone.[2]

The Wellness Concept:
Before proceeding further, we need to define "Wellness"
Wellness is 'an active process through which people become aware of, and make choices toward, a more successful existence.' It is a multidimensional or holistic concept that includes lifestyle, environment, and mental and spiritual aspects.[3]
While this concept may sound appealing, there could be barriers to wholly integrating it into our uveitis practices. Does this concept include immunology?

We try to answer this question through the next few paragraphs of this short write-up.

Wellness practices include:[2]
1. Exercise
2. Optimised sleep
3. Optimised nutrition
4. Mindfulness and social connectedness
5. Positive emotions.

Exercise:
Some of the most frequent perceived barriers to exercise have been studied in patients with Rheumatoid Arthritis and include pain, fatigue, fear of damaging joints, and comorbidities. However, two important barriers are glaringly insufficient advice from healthcare providers and lack of time or support.[4] The role of doctors here is to be fitness role models themselves; as we have touched upon in a previous publication.[5]

You T et al. have described the possible immunological mechanisms of the beneficial effects of exercise, including stimulation of interleukin-6 release from skeletal muscle, increased angiogenesis and consequent reduction in hypoxia and inflammation; reduced endothelial cell production of adhesion molecules, stimulation of regeneration of these cells and reduced vascular wall inflammation; decreased expression of toll-like receptors and proinflammatory cytokine production in monocytes and increased regulatory T-cell production.[6]

Sleep:
The role of adequate sleep for maintaining well-being is known and need not be reiterated. Sleep deprivation reduces ATP production and modulates the lymphatic system so that there is a reduction in the clearance of cellular waste products. This leads to the accumulation of molecules like hyperphosphorylated tau and amyloid ß plaques, increasing cell apoptosis.

From an immunological standpoint, persistent sleep deprivation activates ß-adrenergic signalling, increasing inflammatory gene expression, proinflammatory cytokine production, monocyte production of signal transducer and activator of transcription proteins, which mediate inflammatory cytokine signalling. The sympathetic nervous system and hypothalamic–pituitary– adrenal axis is also involved in such inflammatory signalling.[7]

Nutrition:
The role of diet and the gut microbiome in the immunopathology of inflammatory eye disorders has been well described and can be accessed in our previous Uveitis Society (India) Newsletter on HLA B27 Uveitis by Patnaik G.[8]
But while emphasizing an increased intake of fruits, vegetables and water, and switching to low-calorie food, reducing intake of unhealthy and junk food, and explain the role of the gut microbiome, it is important that we doctors emphasize that these dietary changes are only complementary to the pharmacological therapy as is also reiterated by Taylor PC et. al.[2]

It may be pertinent to explain to our patients the concept of secondary prevention (pharmacotherapy during an attack of uveitis) vs. primary prevention (of future relapses by nutrition-related and other interventions) described in this article.

Mindfulness:
Mindfulness can be defined as 'the awareness that arises from paying attention, on purpose, in the present moment and non-judgmentally to the unfolding of experience moment by moment.' [9]

"Mindfulness-based stress reduction" is found to cause grey matter concentration in the left hippocampus of the brain, which has areas involved in learning and memory processes, emotion regulation, self-referential processing and perspective taking and thus, mindfulness activates brain regions that modulate or reduce the perception of pain in inflammatory diseases.[10]

Social connections:
Often, we find the calming effect that comes in a patient's demeanour, when he/she is informed that there are others in the clinic's waiting room with similar diseases and are "doing well" with regular treatment and follow-up. This is the effect of the concept of social connection and "the feeling of being in the same situation and feelings of inclusion",; which are essential for positive physical and mental health. [11]

Conversely, social isolation promotes immune dysfunction, including pro-inflammatory cytokine production, and increases inflammatory markers. Such isolation may exacerbate inflammatory symptoms in our patients. [12]

Positive Emotions:
Positive emotions (joy, contentment, happiness, love, optimism, serenity and amusement) contribute to mental and physical well-being. However, as doctors we often focus on reducing symptoms and thus automatically on negative emotions. Thus, there is a need to learn to be mindful and integrate "positive emotions" into our clinical workplaces in an attempt to go beyond the traditional clinical approach. More so, as studies have shown that positive emotions are also associated with lower circulating pro-inflammatory cytokine levels[13]

In our previous publication, we have emphasized the role of rational emotive behaviour therapy, which is a form of cognitive behaviour therapy in counselling patients with inflammatory eye diseases. [14]
A recent publication emphasizes the concept of Salutogenesis as a novel approach to prevention and management of ocular inflammatory diseases. [15]

To conclude, our aim in uveitis practice should be to attain "optimal health" and "wellness" for each patient beyond that which can be achieved by pharmacotherapy alone using the above tenets of wellness.

References:

1. *Nikiphorou E, Santos EJF, Marques A, et al. EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. Ann Rheum Dis 2021;2021:1278–85.*
2. *Taylor PC, Van de Laar M, Laster A, et al. Call for action: incorporating wellness practices into a holistic management plan for rheumatoid arthritis—going beyond treat to target. RMD Open 2021;7:e001959.*
3. *National Wellness Institute. The six dimensions of wellness. Available: Six Dimensions of Wellness - National Wellness Institute (Accessed on 15th September 2024)*
4. *Veldhuijzen van Zanten JJCS, Rouse PC, Hale ED, et al. Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: a review of the literature. Sports Med 2015;45:1401–12*
5. *Moreker MR; Tiwari NK. Doctors as physical fitness role models for the society – Is it the need of the hour?. Journal of Clinical Ophthalmology and Research 12(2):p 186-187, May–Aug 2024.*
6. *You T, Arsenis NC, Disanzo BL, et al. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. Sports Med 2013;43:243–56.*
7. *Irwin MR, Opp MR. Sleep health: reciprocal regulation of sleep and innate immunity. Neuropsychopharmacol Rev 2017;42:129–55.*
8. *Role of Microbiome in HLAB27 associated Uveitis. Available: indianuveitis.org/wp-content/uploads/2023/10/USI-Newsletter-HLA-B27-Sep-2023.pdf (Accessed on 15th September 2024)*
9. *Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. Clin Psychol Sci Prac 2003;10:144–56.*
10. *Zeidan F, Emerson NM, Farris SR, et al. Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia. J Neurosci 2015;35:15307–25.*
11. *My Health My Community. Social connection and health, 2019. Available: MHMC_SocialConnections_web.pdf (myhealthmycommunity.org) (Accessed on 15th September 2024)*
12. *Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci 2017;11:316.*
13. *Burgdorf J, Panksepp J. The neurobiology of positive emotions. Neurosci Biobehav Rev 2006;30:173–87.*
14. *Moreker MR, Moreker SR, Bhonsle MR, Bhonsle R. Counselling in Neuro-ophthalmic and Inflammatory Eye Disorders – A definite role for REBT. Bombay Hospital Journal. 59(3); 2017: 309-315.*
15. *Tan Yip Ming, C., Rojas-Carabali, W., Cifuentes-González, C., Agrawal, K., Grover, S., Anand, A., Agrawal, R. (2024). Beyond Pathology– Exploring Salutogenesis as a Novel Approach to Eye Inflammatory Disease Prevention and Management: A Perspective. Ocular Immunology and Inflammation, 1–9.*

Publications in Uveitis from India

Jyotirmay Biswas

INTRODUCTION

Publication is the gold standard for research communication in any branch of medicine, particularly in PUBMED-indexed journals. In recent years, uveitis specialists in India have published a significant number of high-quality papers in both national and international ophthalmic journals. These publications cover various aspects of uveitis specialists from India including epidemiology, etiology, pathogenesis, management and complication of uveitis.

This article will briefly highlight the key publications that contributed significantly in the understanding of uveitis, especially in India.

EPIDEMIOLOGY

Before 1990, there was limited publication on uveitis. Dr. D.K. Sen. from Delhi conducted some basic science studies in uveitis while Prof I.S. Jain from the Post-Graduate Institute of Ophthalmology and Medical Sciences and Research, Chandigarh published works on Fuchs uveitis, herpes zoster ophthalmicus, and human leukocyte antigen (HLA) in acute anterior uveitis[1].

In 1995, the first publication on the pattern of uveitis in India came from our group[2]. This was followed by a significant series of epidemiological uveitis studies conducted by Dr. Rathinam and her team at the uveitis clinic of Aravind Eye Hospital, Madurai[3]. Subsequently, several studies have been published from various parts of India.[4-7] These publications have contributed to understanding the pattern of uveitis across different parts of India.

ETIOLOGY

One of the landmark articles on the etiology of uveitis was provided by Prof. Amod Gupta and his colleagues from the Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh on the ocular signs predictive of tubercular uveitis[8] (274 citations) and classification of intraocular tuberculosis was published by Prof. Amod Gupta et al[9] (245 citations). The same group from PGIMER, Chandigarh led by Amod Gupta et al., also published new concepts in presumed serpiginous choroiditis of tubercular etiology[10]. We have published an article on a clincopathologic study of 5 cases of histopathologically proven tuberculosis, which demonstrated that direct invasion of tubercle bacilli into ocular structures causes uveitis[11].

In recent years, Dr. Soumyava Basu published new observations and future directions in the pathogenesis of ocular tuberculosis[12]. Outstanding work was done by Dr.Rathinam et al. and colleagues from Madurai, who described new entities in uveitis such as leptospira uveitis[13], trematode-induced uveitis[14], and uveitis due to West Nile uveitis[15].

Dr. Padmamalini and her group published findings on post-fever retinitis, particularly chikungunya uveitis[16].
In 1987, AIDS was first reported in India. In 1995, we reported two cases of ocular lesions in AIDS[17]. Subsequently, we reported 100 cases of ocular lesions in patients with HIV infection18 and 1,000 cases of ocular lesions in AIDS in India[18]. These articles by Indian authors were published in leading international ophthalmology journals.

INVESTIGATIONS

High-resolution computed tomography (HRCT) as well as polymerase chain reactions (PCR) are emerging investigative tools in uveitis. We reported on the role of HRCT chest in granulomatous uveitis[19] and patients with Eales disease[20] in India. From our institute and PGIMER Chandigarh, studies on the molecular biological study of vitreous, epiretinal membrane, enucleated specimens from Eales disease[21-24] patients and eyeball of acute retinal necrosis patient showed the histopathology and molecular biologic correlation in uveitis. These research publications have contributed to a new understanding of uveitis[25].
PCR has emerged as a new investigative tool for infectious uveitis, helping to elucidate the etiopathogenesis of various uveitic diseases. We published a series of 100 cases demonstrating the outcomes of real-time PCR in suspected cases of infectious uveitis[26.] Additionally, our publication on the correlation of quantitative PCR with clinical characteristics in patients with viral retinitis highlighted the importance of molecular biology in predicting and monitoring treatment response[27].

MANAGEMENT

In recent years, significant advancements in the management of uveitis have occurred. The role of intravitreal implants, such as Ozurdex as an oral steroid-sparing treatment for noninfectious intermediate uveitis has been published, evaluating its role in patients with persistent chronic cystoid macular edema and vitritis with intermediate uveitis[28.] A randomized trial conducted over three years across 15 centers in India using fluocinolone acetonide intravitreal implant in chronic noninfectious posterior uveitis was found to maintain visual acuity and reduce the rate of recurrences[29] at the end of six months. The role of Mycophenolate mofetil in controlling disease and preventing worsening in recalcitrant intermediate uveitis has also been published[30]. Dr. Rathinam et al.,compared the effectiveness of methotrexate and mycophenolate mofetil in controlling inflammation of noninfectious uveitis in a multicentre randomized clinical trial and found them to be equally effective[31]. Recently the same group reported on the use of first-line anti-metabolites as steroid-sparing treatments for uveitis in Vogt-Koyanagi-Harada disease[32].

Targeted therapy with biologics has proven effective in uveitis management. In 2020, the use of biologics was first reported in a series of 18 patients with noninfective refractory uveitis[33]. The role of adalimumab in noninfectious pediatric uveitis[34] and Bechet's uveitis[35] and HLA B-27 positive anterior uveitis[36] have been documented. JAK inhibitors such as Tofacitinib, are new molecule used in scleritis and uveitis. We reported the successful use of JAK inhibitors in two cases of scleritis and subsequently in a series of cases[37,38]. Secukinumab has been used for the first time in South India for managing the autoimmune[39]. In tubercular uveitis intravitreal anti-vascular endothelial growth factor and moxifloxacin injection have been successfully used for tubercular

granuloma, subretinal abscess, and tubercular choroiditis[40,41].
Cataract surgery in patients with uveitis presents significant challenges. Various studies provided guidelines for managing uveitic-related cataracts and post-operative care[42-44]. Diagnostic and therapeutic vitrectomy in uveitic cases, especially Microincision vitreous surgery (MIVS) has gained popularity due to its remarkable safety even in inflamed eyes[45].

BASIC RESEARCH

It is quite encouraging that many recent publications from Indian researchers have advised basic research in uveitis. These include studies on the use of proteomics uveitis as a biomarker for various specific diseases[46]. The proteomic profile of vitreous in tubercular uveitic patients has identified biomarkers that differentiate between tubercular and nontubercular uveitis[47.] Dr.Soumyavu Basu's group has published on the role of auto-reactive T cells in the immunopathogenesis of TB-associated uveitis[48]. They also investigated the interaction between mycobacteria and the host immune cells using an atypical mycobacterium zebrafish model of ocular tuberculosis[49]. This research demonstrated that antigen-specific intraocular cytokine responses can distinguish tubercular uveitis from undifferentiated uveitis in tuberculous-immunoreactive patients[50.]

CONCLUSION

As an emerging specialty, the Uveitis Society of India was formed in 1999 and now has more than 600 members. It is heartening to see that uveitis researchers across the country have published several clinical studies[51]. There is significant scope for more publications especially through collaborative studies from our country. One such collaborative study, the Collaborative Ocular Tuberculosis Study (COTS) led by Dr. Vishali Gupta and or Rupesh Agarwal on tuberculosis has enhanced our understanding of various aspects of tubercular uveitis. They published a series of articles from this study. More such studies on diseases like viral retinitis, viral uveitis, AZOOR, autoimmune retinopathy, vitreoretinal lymphoma, and such related diseases are needed to improve the evaluation and management of such conditions in our country.

REFERENCES

1. *Biswas J, Jadhav S, Eswaran BV. Evolution of researchin diagnosis and management of uveitis over four decades in India. Indian J Ophthalmol 2024;72:809-15.*
2. *Das D, Biswas J, Ganesh SK. Pattern of uveitis in a referral uveitis clinic in India. Indian J Ophthalmol 1995; 43:117-21.*
3. *Rathinam SR, Namperumalsamy P. Global variation and pattern changes in the epidemiology of uveitis Indian J Ophthalmol 2007; 55:173-83.*
4. *Sen DK, Sarin GS, Pal S, Sharma VK. Serum immunoglobulin levels in endogenous uveitis: Before and after therapy. Indian J Ophthalmol 1985; 33:167-70.*
5. *Venkatesh P, Gogia V, Shah B, Gupta S, Sagar P, Garg S. Patterns of uveitis at the Apex Institute for eye care in India: Results from a prospectively enrolled patient database (2011-2013). Int Ophthalmol 2016; 36:365-72.*
6. *Dogra M, Singh R, Agarwal A, Sharma A, Singh SR, Gautam N, et al.Epidemiology of uveitis in a tertiary-care referral institute in North India.Ocul Immunol Inflamm 2017;25:S46-53.*

7. *Borde P, Priyanka, Kumar K, Takkar B, Sharma B. Pattern of uveitis in a tertiary eye care center of central India: Results of a prospective patient database over two years. Indian J Ophthalmol 2020; 68:476-81.*
8. *Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. Am J Ophthalmol 2010; 149:562-70.*
9. *Gupta A, Sharma A, Bansal R, Sharma K. Classification of intraocular tuberculosis. Ocul Immunol Inflamm 2015; 23:7-13.*
10. *Gupta V, Gupta A, Arora S, Bambery P, Dogra MR, Agarwal A. Presumed tubercular serpiginous like choroiditis: Clinical presentations and management. Ophthalmology 2003; 110:1744-9.*
11. *Biswas J, Madhavan HN, Gopal L, Badrinath SS. Intraocular tuberculosis.Retina 1995;15:461-8.*
12. *Basu S, Elkington P, Rao NA. Pathogenesis of ocular tuberculosis: new observations and future directions.Tuberculosis. 2020 Sep 1; 124:101961.*
13. *Chu KM, Rathinam R, Namperumalsamy P, Dean D. Identification of Leptospira species in the pathogenesis of uveitis and determination of clinical ocular characteristics in south India. J Infect Dis 1998; 177:1314-21.*
14. *Rathinam SR, Usha KR, Rao NA. Presumed trematode-induced granulomatous anterior uveitis: A newly recognized cause of intraocular inflammation in children from south India. Am J Ophthalmol 2002; 133:773-9.*
15. *Sivakumar RR, Prajna L, Arya LK, Muraly P, Shukla J, Saxena D, et al. Molecular diagnosis and ocular imaging of West Nile virus retinitis and neuroretinitis. Ophthalmology 2013; 120:1820-6.*
16. *Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM, Babu RB,et al. Ocular manifestations associated with chikungunya. Ophthalmology 200; 115:287-91.*
17. *Biswas J, Madhavan HN, Badrinath SS. Ocular lesions in AIDS: A report of first two cases in India Indian J Ophthalmol 1995;43:69-72.*
18. *Biswas J, Madhavan HN, George AE, Kumarasamy N, Solomon S. Ocular lesions associated with HIV infection in India: A series of 100 consecutive patients evaluated at a referral center Am J Ophthalmol 2000;129:9-15.*
19. *Ganesh SK, Roopleen, Biswas J, Veena N. Role of high-resolution computerized tomography (HRCT) of the chest in granulomatous uveitis: A tertiary uveitis clinic experience from India. Ocul Immunol Inflamm2011; 19:51-7.*
20. *Kharel Sitaula R, Iyer V, Noronha V, Dutta Majumder P, Biswas J. Role of high-resolution computerized tomography chest in identifying tubercular etiology in patients diagnosed as Eales' disease. J Ophthalmic Inflamm Infect 2017; 7:4.*
21. *Biswas J, Therase L, Madhavan HN.Use of polymerase chain reaction in detection of Mycobacterium tuberculosis complex DNA from a vitreous sample of Eales' disease. British Journal of Ophthalmology. 1999 Aug 1; 83(8):994-.*
22. *22. Gupta A, Gupta V, Arora S, Dogra MR, Bambery P. PCR-positive tubercular retinal vasculitis: Clinical characteristics and management. Retina 2001; 21:435-44.*
23. *Madhavan HN, Therese KL, Gunisha P, Jayanthi U, Biswas J. Polymerase chain reaction for detection of Mycobacterium tuberculosis in the epiretinal membrane in Eales' disease Invest Ophthalmol Vis Sci 2000;41:822-5.*
24. *Shah A, Giridhar S, Patnaik G, Mhatre R, Das D, Janani MK, et al. Histopathological, immunohistochemical, and molecular biologic study of an enucleated specimen of a case of Eales' disease. J Ophthalmic Inflamm Infect 2021; 11:29.*

25. Chatterjee S, Nair N, Patnaik G, Madhuravasal Krishnan J, Das D, Biswas J.Histopathology and molecular biology study of an eyeball of a case of acute retinal necrosis. Ocul Immunol Inflamm 2022; 30:1471-4.
26. Kharel R, Janani MK, Madhavan HN, Biswas J. Outcome of polymerase chain reaction (PCR) analysis in 100 suspected cases of infectious uveitis. J Ophthal Inflamm Infect 2018; 8:1-8. Doi: 10.1186/s12348-017-0144-1.
27. Mohan S, Dhanurekha L, Janani MK, Biswas J. Correlation of quantitative polymerase chain reaction with clinical characteristics of patients with viral retinitis.Indian Journal of Ophthalmology. 2022 1; 70(6):2090-3.
28. Palla S, Biswas J, Nagesha CK. Efficacy of ozurdex implant in the treatment of noninfectious intermediate uveitis. Indian J Ophthalmol 2015; 63:767-70.
29. Biswas J, Tyagi M, Agarwal M. The 0.2-µg/day fluocinolone acetonide intravitreal implant in chronic noninfectious posterior uveitis: 3-year randomized trial in India. Ophthalmol Sci 2023; 4:100403.
30. Ali S, Kharel Sitaula R, Biswas J. Efficacy and safety of mycophenolate mofetil in the treatment of recalcitrant intermediate uveitis. Ocular Immunol Inflamm 2019; 27:851-7.
31. Rathinam SR, Babu M, Thundikandy R, Kanakath A, Nardone N, Esterberg E, Lee SM, Enanoria WT, Porco TC, Browne EN, Weinrib R A randomized clinical trial comparing methotrexate and mycophenolate mofetil for noninfectious uveitis. Ophthalmology. 2014 Oct 1; 121(10):1863-70.
32. Acharya NR, Rathinam SR, Thundikandy R, et al Outcomes in Patients with Vogt-Koyanagi-Harada Disease from the First-line Antimetabolites for Steroid-sparing Treatment Uveitis Trial.American Journal of Ophthalmology. 2024 Jun 22.
33. Sadhu S, Dutta Majumder P, Biswas J. Biological therapy in refractory cases of uveitis and scleritis: An analysis of 18 cases from a tertiary eye care center from South India. Indian J Ophthalmol 2020; 68:1929-33.
34. Khan N, Majumder PD, Janarthanan M, Biswas J. Efficacy of adalimumab in noninfectious pediatric uveitis: Analysis of 29 eyes from a tertiary eye care center in India. Indian Journal of Ophthalmology. 2024:10-4103.
35. Ramdoss J, Singh P, Ahmed AS, Biswas J. Clinical profile and management with immunosuppressants and biologics in Behcet's uveitis: A cohort of 25 patients from a tertiary eye care center in South India. Indian J Ophthalmol. 2023 ;71(5):1972-1976.
36. Lakra R, Shah A, Kaushik V, Biswas J, Dutta Majumder P. Use of Anti-Tumour Necrosis Factor-Alpha Agents in the Management of HLA-B-27-Associated Uveitis: The First Case Series from India. Ocul Immunol Inflamm. 2021 Feb 17;29(2):232-236.
37. Pyare R, Kaushik V, Dutta Majumder P, Biswas J. Tofacitinib in recalcitrant scleritis: First case report from India. Indian J Ophthalmol 2020; 68:1988-90.
38. Pyare R, Dutta Majumder P, Shah M, Kaushik V, Agarwal M, Biswas J. Tofacitinib in Scleritis: A Case Series. Ocul Immunol Inflamm. 2022 Sep 20:1-7.
39. Mahendradas P, Jain VK, Thomas S, Kawali A, Sanjay S, Shetty BK. Role of secukinumab in ankylosing spondylitis with tubercular uveitis. Indian J Ophthalmol. 2020;68(11):2569-2572.
40. Agarwal M, Gupta C, Mohan KV, Upadhyay PK, Dhawan A, Jha V. Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas. Ocul Immunol Inflamm. 2023;31(1):158-167.
41. Manoharan A, Mohan S, Raman R, Biswas J. Intravitreal anti-vascular endothelial growth factor and moxifloxacin for treatment of tubercular choroidal granuloma and subretinal abscess. Ocul Immunol Inflamm 2023; 13:1-5. doi:10.1080/09273948.2022.2159843.

42. Ganesh SK, Padmaja MS, Babu K, Biswas J. Cataract surgery in patients with Vogt-Koyanagi-Harada syndrome. J Cataract Refract Surg 2004; 30:95-100.
43. Ganesh SK, Sundaram PM, Biswas J, Babu K. Cataract surgery in sympathetic ophthalmia. J Cataract Refract Surg 2004; 30:2371-6.
44. Yangzes S, Seth NG, Singh R, Gupta PC, Jinagal J, Pandav SS, Gupta V, Gupta A, Ram J. Long-term outcomes of cataract surgery in children with uveitis. Indian Journal of Ophthalmology. 2019 Apr 1; 67(4):490-5.
45. Bansal R, Dogra M, Chawla R, Kumar A. Pars plana vitrectomy in uveitis in the era of micro-incision vitreous surgery. Indian J Ophthalmol 2020;68:1844-51.
46. Bansal R, Gupta A. Protein biomarkers in uveitis. Front Immunol 2020; 11:610428. Doi: 10.3389/fimmu. 2020.610428.
47. Bansal R, Khan MM, Dasari S, Verma I, Goodlett DR, Manes NP, et al. Proteomic profile of vitreous in patients with tubercular uveitis. Tuberculosis (Edinb) 2021; 126:102036. Doi: 10.1016/j.tube. 2020.102036.
48. Tagirasa R, Parmar S, Barik MR, Devadas S, Basu S. Autoreactive T cells in immunopathogenesis of TB-associated uveitis. Invest in Ophthalmol Vis Sci 2017; 58:5682-91.
49. Damera SK, Panigrahi RK, MitraS, Basu S. Role of extracellular mycobacteria in blood-retinal barrier invasion in a Zebrafish model of ocular TB. Pathogens 2021; 10:333.
50. Alam K, Sharma G, Forrester JV, Basu S. Antigen-Specific Intraocular Cytokine Responses Distinguish Ocular Tuberculosis From Undifferentiated Uveitis in Tuberculosis-Immunoreactive Patients. Am J Ophthalmol. 2023 ;246:31-41.
51. Agrawal R, Testi I, Mahajan S, et al The Collaborative Ocular Tuberculosis Study (COTS) Consensus (CON) Group Meeting Proceedings. Ocul Immunol Inflamm. 2020 30;28(sup1):85-95.

Role of Artificial Intelligence in Uveitis

Nitin Kumar Menia, Vishali Gupta

Artificial Intelligence (AI) or Machine Learning (ML) create machines capable of learning and making decisions independently. AI can learn from huge datasets and make decisions similar or superior to humans without fatigue. The availability of this technology in the public domain has opened new avenues for its application in various spheres of life. Recently, the integration of AI in medicine and healthcare has emerged as one of the most sought-after technological innovations. However, one of the first applications of AI in medicine dates back to the 1970s when a computer algorithm helped physicians prescribe appropriate antibiotics. Although AI is being used in all medical specialities, subspecialties like ophthalmology, radiology, pathology and dermatology, which are data-rich and image-based, are at the helm. In ophthalmology, AI has been instrumental in correctly diagnosing etiologies with precision and accuracy. AI helps diagnose diseases, suggest treatment options, predicting outcomes and prognosis.

Uveitis is an umbrella term for a subset of diseases presenting with ocular inflammation. It is one of the major causes of blindness worldwide. A major reason for vision loss in patients with uveitis is delayed or missed diagnosis, leading to persistent and recurrent disease. This can also be attributed to the limited availability of ophthalmologists practising uveitis, especially in resource-depleted settings. Uveitis is a highly specialised subspecialty in ophthalmology; the disease is complex, encompasses a wide range of presentations and may be difficult to tackle even for skilled uveitis experts. A wide range of etiologies may produce similar signs, symptoms and ocular presentations, making the diagnosis challenging. Sometimes, uveitis can present as rare, challenging presentations that do not fit the known patterns. If adequately trained, AI can help identify the patterns precisely and make appropriate decisions. Innovative technologies like ML can also address the unmet need for specialities to provide optimal care to uveitis patients. AI has capabilities like pattern recognition, assessment of multi-modal imaging, and prediction of treatment responses, which are of utmost importance in successfully managing uveitis patients. AI not only assists physicians in complex situations and suggests possible diagnoses, but it can also suggest treatment options and predict complications. However, challenges like the availability of annotated data and the validation of algorithmic models in real-world scenarios are still present. Herein, we briefly discuss the role of AI in uveitis and prospects.

AI helps in the augmentation of the diagnosis of Uveitis:

Diagnosis of uveitis can be challenging due to varied clinical presentations and etiologies. A missed diagnosis can lead to progression of disease, severe complications and impairment of vision. AI can suggest a possible diagnosis based on the interpretation

and analysis of patient data, clinical history, laboratory results, and imaging findings. The large language models (LLMs) have been trained on huge datasets and can interpret clinical histories and medical literature. The LLMs can play an important role in guiding the uveitis specialist in the institution of evidence-based therapies by rapidly summarising the information available in the literature in split seconds. The LLMs can also address the global disparity in the availability of uveitis specialists by providing genuine information about the disease. It can help the practitioners narrow down the correct diagnosis and institute specific therapy with exemplary efficacy. One of our global collaborative studies assessed the diagnostic accuracy of different AI chatbots (Chat GPT versions 3.5 and 4.0 and Glass 1.0) compared to human uveitis experts in diagnosing uveitic diseases. The study results showed that the AI chatbots could predict the uveitic entities based on specific inputs. Human experts, however, had higher diagnostic accuracy than the AI chatbots.[1] Moreover, the uveitis experts positively embraced integrating AI into clinical uveitis practice.

Another study by our group further highlighted that the diagnostic accuracy of AI chatbots could reach as high as 72% compared to human experts.[2,3] LLMs can further help in the education of the patients as well as practitioners who have not specialised in uveitis. This can guide the patient and the physician to follow a certain treatment plan before an expert uveitis specialist sees the patient. The application of AI in this domain is still in its infancy because of associated ethical issues and the reliability of the data used to develop such models. More AI tools are readily available in public, so more patients are expected to come to clinics with adequate knowledge about their symptomatology, possible diagnosis and treatment options. So, the physicians will have to update them about the latest information about various uveitic entities, maybe by making themselves more knowledgeable using the AI tools. However, the role of the human touch and physician is here to stay as the current AI models may not efficiently offer a detailed discussion about all the patient queries and fears.

Personalized and Precision Medicine using AI:

Uveitis is a heterogeneous complex of diseases with a spectrum of etiologies (infectious, autoimmune and non-infectious). The management of the disease may vary, involving the administration of antibiotics, antivirals, antifungal, antiparasitic agents and immunosuppressive therapy. The response to treatment can be variable, affecting the prognosis of the patients. So, most patients may require a tailored approach depending on the disease's cause and severity. AI can play a central role in the analysis of patient data and the institution of patient-specific therapy. The historical details of the patients can be analysed, specific patterns may be identified, and predictive models may be used to personalise therapy in uveitis. In this way, AI will lead to improved therapies and outcomes. Recently, more researchers have been looking into the intricacies of microbiome and uveitis. Significant research has also been done in the field of proteomics. These molecular markers can be of significant value in arriving at a specific diagnosis. AI can be harnessed to use datasets to add value to the diagnostic capabilities of these molecular technologies, improving precision in uveitis diagnosis. AI can also take care of data entries and other redundant activities, thus allowing

physicians to dedicate more time to their patients. It can also be used to follow-up the patients with uveitis. AI algorithms can analyze the treatment responses by reading the serial imaging, thus aiding in assessing the treatment response. LLMs can also play a central role in the research, identification of therapeutic targets and development of new drugs.

Multimodal Imaging and AI:
Multi-modal imaging (MMI) has evolved as a new norm in the imaging of uveitis. It encompasses acquiring multiple imaging modalities to image a section of the eye on a single platform. Imaging can play a central role in the documentation, diagnosis and follow-up of patients with uveitis. AI algorithms have been trained for automated interpretation and diagnosis of various uveitic entities on the assessment of multi-modal imaging. It also allows automated assessment and grading of image quality. AI can detect specific patterns of involvement of the retina or choroid, thus leading to early diagnosis, and can detect subtle changes in imaging, which human experts may otherwise miss. AI models have been used to quantify anterior and posterior segment inflammation.[4,5] These studies showed that AI was useful in quantifying uveitis, but there was significant scope for improving the algorithms.

Challenges: There have been certain reservations and challenges regarding using AI in uveitis. The various challenges include:
1. The **reliability of the training datasets** and the validation of models in real-world scenarios is a major challenge. Also, if the datasets are taken from one population, they may not perform well for others. Here comes the role of data universality and regulatory authorities. To develop universally applicable models, datasets from varied populations should be taken, and regulatory authorities should ensure that the data is of adequate quality, unbiased, diverse and ensure data privacy. In uveitis, obtaining large, high-quality datasets can be challenging due to the disease's heterogeneity and relatively low prevalence. Collaborative efforts across institutions and standardized data collection protocols are essential to overcome this limitation.
2. Although LLMs have been used in uveitis, they are rarely trained on the data specific for uveitis. Also, there may be associated ethical issues concerning the r**eliability of information** provided by these models.
3. **Grading of Images:** Images in patients with uveitis may not be gradable due to vitreous or anterior chamber haze. Posterior synechiae, limited pupillary dilation and complicated cataracts limit the acquisition of quality, gradable photographs for training and interpretation by models. This is a major challenge in the training of AI models. The MUST trial also found that many acquired images were ungradable due to media opacities. Developing models which can compensate for the quality of images and still provide good results is a challenge.[6]
4. **Training the end users:** As patients and physicians are the end users of AI technology, they should be appropriately trained. A dedicated team may be required who look into the efficient integration of AI in the existing hospital workflows. Introducing the new tools will not work if AI integration into clinical settings is not properly planned and tested.
5. **Real-world Integration of AI in Clinics** is still far from reality due to the technology's cost and the time to invest in developing models for such a complex disease.

Conclusions: Artificial intelligence (AI) is emerging as a transformative tool, promising to enhance the accuracy and efficiency of diagnosing and managing uveitis. AI systems can provide a more comprehensive assessment, reducing the reliance on individual expertise and minimizing diagnostic errors. AI-based tools must be more cost-effective and effective to be integrated into uveitis clinics. To conclude, AI in the field of uveitis is evolving, and there is a need to look into the possibility of developing algorithms which not only provide the diagnosis but also help to provide a holistic treatment and follow-up plan for patients with uveitis.

References:

1. *Rojas-Carabali W, Sen A, Agarwal A, et al. Chatbots Vs. Human Experts: Evaluating Diagnostic Performance of Chatbots in Uveitis and the Perspectives on AI Adoption in Ophthalmology. Ocul Immunol Inflamm. Published online October 13, 2023.*
2. *Rojas-Carabali W, Cifuentes-González C, Wei X, et al. Evaluating the Diagnostic Accuracy and Management Recommendations of ChatGPT in Uveitis. Ocul Immunol Inflamm. Published online September 18, 2023.*
3. *Rojas-Carabali W, Cifuentes-González C, Wei X, et al. Evaluating the Diagnostic Accuracy and Management Recommendations of ChatGPT in Uveitis. Ocul Immunol Inflamm. Published online September 18, 2023.*
4. *Sorkhabi MA, Potapenko IO, Ilginis T, Alberti M, Cabrerizo J. Assessment of Anterior Uveitis Through Anterior-Segment Optical Coherence Tomography and Artificial Intelligence-Based Image Analyses. Transl Vis Sci Technol. 2022;11(4):7.*
5. *Mhibik B, Kouadio D, Jung C, et al. AUTOMATED DETECTION OF VITRITIS USING ULTRAWIDE-FIELD FUNDUS PHOTOGRAPHS AND DEEP LEARNING. Retina. 2024;44(6):1034-1044.*
6. *Altaweel MM, Gangaputra SS, Thorne JE, et al. Morphological assessment of the retina in uveitis. J Ophthalmic Inflamm Infect. 2016;6(1):33.*

Role of Ocular Pathologists in Uveitis

Dipankar Das

Uveitis is a subspecialty of ophthalmology which deals with intraocular infections, inflammations and masquerade syndromes. In uveitis, apart from clinical and related ancillary investigations, pathological diagnosis plays a key role in the management of uveitis. Several dilemmas in uveitis need to be solved for the patients' care and benefit by using pathology, cytology and molecular diagnosis in ocular pathology laboratory. [1]

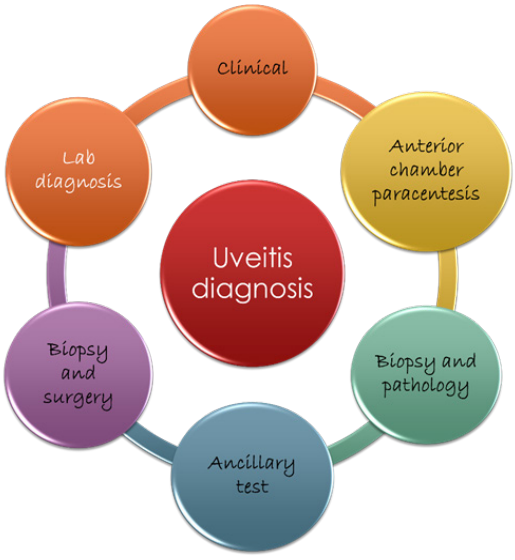


Figure showing clinical and various pathological modalities for diagnosis in uveitic patients.

Glimpse of Sri Sankaradeva Nethralaya, Guwahati. India ocular pathology laboratory.

Role of ocular pathologist in a tertiary care hospital is to confirm the clinical diagnosis and help in the management of the uveitic patients.
Biopsy procedures in uveitic clinic include anterior chamber paracentesis for cytology, vitreous tapping, fine needle aspiration biopsy/ cytology; biopsy of Iris, ciliary body, choroidal, retino-choroid and enucleated/eviscerated specimens. Anterior chamber aspiration is modest and innocuous method in rapid diagnosis of uveitis. Adequate aseptic precautions are taken during the procedure, and it is generally done in the out-patient department set up under local anaesthesia. For children, operation theatre setting may be required and carried out under general anaesthesia. Cytological aspiration can be carried out in anterior chamber for lens induced intraocular inflammation; various masquerades like retinoblastoma, leukaemia or other metastasis; parasitic diseases, sequestrated endophthalmitis and so on.[1]

Vitreous aspiration and diagnostic vitrectomy by vitreo-retina surgeon facilitates diagnosis of Infective posterior uveitis, intractable and non-responding posterior uveitis, suspected large cell lymphoma particularly in the elderly uveitic patients. A diagnostic vitrectomy when performed provides large number of fluid materials include diluted and undiluted specimens. Specimens can be tested for cytology, histopathology, polymerase chain reaction (PCR), immunohistochemistry (IHC), ELISA, flowcytometry etc. Special stains in uveitic pathology are also very important in determining for various pathological entities.[1]

Enucleated eyeball, eviscerated specimens can be diagnosed for various uveitic conditions and then IHCs and PCRs can be performed for various disease conditions.
Role of ocular pathologists are immense in research in uveitis where molecular pathology is one of the focused areas. Animal models' study in uveitis is an integral part in understanding the patho-physiology of disease process and ocular/ research pathologists can contribute in those understanding immensely. [2]

In conclusion, role of ocular pathologists in uveitis are enormous in routine diagnosis of ocular fluids, histopathology and molecular pathology diagnostics. Role of this subspecialty has tremendous scope in uveitic research.[2]

References:

1. Biswas J, Annamalai R, Krishnaraj V. Biopsy pathology in uveitis. Middle East Afr J Ophthalmol. 2001;18: 261-7
2. Bodaghi B, Rao N. Relevance of animal models to human uveitis. Ophthalmic Res. 2008;40: 200-2

Nomenclature and Classification of Uveitis

Rohit Modi, Shishir Narain
(Standardization of Uveitis Nomenclature Working group)

1. What was the aim of the SUN working group?
The aim of the Standardization of Uveitis Nomenclature (SUN) Working Group was to create a universally accepted set of definitions and criteria for the classification, diagnosis, and monitoring of uveitis

2. What was the major conclusion of the SUN working group?
The major conclusion of the SUN working group was the establishment of a standardized set of criteria and definitions for the classification, diagnosis, and assessment of uveitis. This consensus aimed to enhance the consistency and reproducibility of clinical and research practices in the field of uveitis.

3. Define in detail the anatomical classification of uveitis according to SUN criteria?
Anatomical classification of Uveitis is classified based on the primary site of inflammation within the uveal tract of the eye, which includes the iris, ciliary body, and choroid.

Here are the primary categories:
1. Anterior Uveitis:
- Primary site of inflammation: Anterior chamber.
- Includes: Iritis and iridocyclitis.

2. Intermediate Uveitis:
- Primary site of inflammation: Vitreous.
- Includes: Pars planitis, posterior cyclitis, and hyalitis.

3. Posterior Uveitis:
- Primary site of inflammation: Retina or choroid.
- Includes: Focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and retinal vasculitis.

4. Panuveitis:
- Primary site of inflammation: Inflammation in all segments of the eye (anterior chamber, vitreous, and retina/choroid)

4. How is anterior chamber inflammation classified?

The SUN Working Group classifies anterior chamber inflammation based on the number of cells. Observer can assess cells and flare in the anterior chamber using a slit lamp beam of 1 X 1 mm in height and width (in a dark room/dark adaptation)
The grading system is as follows:

Anterior Chamber Cells

- Grade 0: <1 cell
- Grade 0.5+: 1–5 cells
- Grade 1+: 6–15 cells
- Grade 2+: 16–25 cells
- Grade 3+: 26–50 cells
- Grade 4+: >50 cells

Anterior Chamber Flare

- Grade 0: None
- Grade 1+: Faint
- Grade 2+: Moderate (iris and lens details clear)
- Grade 3+: Marked (iris and lens details hazy)
- Grade 4+: Intense (fibrin or plastic aqueous)

This classification system provides a standardised method for assessing the severity of anterior chamber inflammation, aiding in the diagnosis, monitoring, and treatment of patients with uveitis.

5. Is there a difference between the terms "intermediate uveitis" and "pars planitis"?

Intermediate Uveitis

- Definition: Intermediate uveitis refers to inflammation primarily involving the vitreous body.
- Anatomical Location: Vitreous, peripheral retina, and pars plana.
- Clinical Features: Floaters, blurred vision, minimal pain, and redness.

Pars Planitis

- Definition: Pars planitis is a specific subset of intermediate uveitis.
- Anatomical Location: Inflammation specifically centred on the pars plana, often with snowbanking (white, inflammatory material) and/or snowballs (clumps of inflammatory cells) in the peripheral retina.
- Clinical Features: Same as intermediate uveitis, but with the characteristic findings of snowbanking or snowballs.
- In summary, pars planitis is a more specific diagnosis within the broader category of intermediate uveitis.

6. Describe the difference between acute, recurrent uveitis and chronic uveitis

The terms "acute," "recurrent," and "chronic" uveitis describe the course and duration of the disease. Here are the distinctions:

Acute Uveitis

- Definition: Acute uveitis is characterized by a sudden onset and limited duration.
- Course: Typically, the inflammation resolves within three months of treatment.
- Example: Anterior uveitis associated with HLA-B27.

Recurrent Uveitis

- Definition: Recurrent uveitis refers to repeated episodes of inflammation separated by periods of inactivity without treatment.
- Course: Each episode is typically acute, resolving within three months, but the inflammation recurs after varying intervals of inactivity.
- Example: Herpetic uveitis.

Chronic Uveitis

- Definition: Chronic uveitis is characterized by persistent inflammation.
- Course: The inflammation lasts for more than three months, and relapses occur within three months of discontinuing treatment.
- Example: Chronic anterior uveitis in juvenile idiopathic arthritis (JIA).

Summary of Key Differences

- Duration: Acute uveitis resolves within three months, while chronic uveitis persists for more than three months.
- Recurrence: Recurrent uveitis consists of repeated episodes of inflammation with periods of inactivity, whereas chronic uveitis involves continuous or frequently relapsing inflammation.
- Treatment Response: Chronic uveitis relapses within three months after stopping treatment, while acute uveitis typically does not.

7. How is “improvement” or “worsening” of uveitis activity described according to the SUN criteria? Explain with a simple example.

According to the SUN criteria, "improvement" or "worsening" of uveitis activity is described based on changes in the number of cells in the anterior chamber as observed through a slit-lamp examination.

Definitions:

- Improvement: A decrease of two or more steps in the level of anterior chamber cells or a decrease to grade 0.
- Worsening: An increase of two or more steps in the level of anterior chamber cells.

Example:
Imagine a patient with anterior uveitis being evaluated over time.
Initial Assessment:

- Anterior chamber cell grade: 3+ (26–50 cells)

Follow-Up Assessment:

- **Scenario 1: Improvement**
- After treatment, the patient's anterior chamber cell grade decreases to 1+ (6–15 cells).
- Interpretation: This is a two-step decrease (from 3+ to 1+), indicating an improvement in uveitis activity.
- **Scenario 2: Worsening**
- Later, the patient's anterior chamber cell grade increases to 4+ (>50 cells).
- Interpretation: This is a one-step increase from 3+ to 4+. For it to be considered worsening according to SUN criteria, it would need to increase by two or more steps. Therefore, another example would be if the grade increased from 1+ to 3+, which is a two-step increase and thus represents worsening.

Summary:

- Improvement: A two step decrease (eg cells 3+ to 1+)
- Worsening: A two step increase (eg cells 1+ to 3+)

This standardized approach helps in monitoring and managing the treatment of uveitis by providing clear criteria for evaluating changes in disease activity.

8. Is there a consensus for describing uveitis in "remission"

Yes, the SUN Working Group provides criteria for describing uveitis in "remission." According to the SUN classification:

Remission:

- Definition: Remission in uveitis is defined as the absence of inflammatory activity (grade 0 anterior chamber cells) for a period of at least three months after discontinuing all treatments for uveitis.

Criteria:

- No Inflammatory Activity: The patient must show grade 0 anterior chamber cells.
- No Treatment: The patient must not be receiving any systemic or local treatments for uveitis during the three-month period.

9. Was there a consensus on grading of vitreous inflammation?

Yes, the SUN Working Group established a consensus on the grading of vitreous inflammation. Although it was agreed that the presence of vitreous cells was an important clinical feature, no consensus could be reached on a standard grading system for vitreous cells. The NIH has proposed a system based on vitreous cells counts. The National Eye Institute system for grading vitreous haze was adopted with the proviso that the designation "trace" be recorded as 0.5+. The grading system is based on the visibility of the optic disc and retinal vessels through the vitreous haze during a clinical examination. This system helps in standardizing the assessment and communication of vitreous inflammation severity.

Vitreous Haze Grading:

The vitreous haze is graded on a scale from 0 to 4+, as follows:

- Grade 0: No vitreous haze.
- Grade 0.5+: Trace vitreous haze.
- Grade 1+: Slight blurring of the optic disc and retinal vessels.
- Grade 2+: Moderate blurring of the optic disc and retinal vessels.
- Grade 3+: Marked blurring of the optic disc and retinal vessels, but they are still visible.
- Grade 4+: Severe blurring, where the optic disc and retinal vessels are barely visible.

Laboratory Investigations- Targeted Approach

Anup Kelgaonkar, Mudit Tyagi

1. Is there a standard set of laboratory tests (basic tests) that are performed in all cases of uveitis?

There is not a one fixed set of laboratory tests to fits them all. However, few general tests like blood sugar levels, complete blood counts are necessary while erythrocyte sedimentation rate, C reactive protein levels and human immunodeficiency virus test can be done in all cases. It is also essential to rule out syphilis (treponemal test) and sarcoidosis in almost all phenotypes of uveitis.

2. What are the pros and cons of ordering "blanket testing" in uveitis?

"Blanket testing" is like carpet bombing sometimes it works but many a times it doesn't.

Cons:

i. Unnecessary economical burden to the patient.

ii. Limitations in a resource limited setting or country.

iii. Unrelated positive tests can create confusion for trainees and novices in uveitis. Example - Mantoux test positive in recurrent hypopyon anterior uveitis in patient with inflammatory back pain.

iv. Interpretation of incidental and accidental positivity is challenging especially when the pre-test probability is not known.

Pros:

i. Helpful in diagnoses of masquerades like syphilis.

ii. Diagnoses of a novel or unreported presentation of uveitis and in rare atypical phenotypes may need a blanket testing.

3. Explain in simple words - the term "targeted investigations"

History and a thorough clinical examination are often the cornerstones in diagnoses and management of uveitis.

Imagine a clinical scenario of 'ping pong' pattern of recurrent hypopyon anterior uveitis in a patient who has joint pains in the morning which get relieved on exercise or movement. One would investigate him/her for 'HLA B27 test by flowcytometry or PCR method' along with basic and routine tests.

So, 'targeted investigations' are the set of specific focussed investigations to either confirm or rule out differential diagnoses which are curated by a thorough history and complete comprehensive ocular and general examination of the patient.

4. Which radiological investigations are preferred as a part of uveitis evaluation? Explain in brief, why are they important.

Uveitis is often an ocular manifestation of a systemic disease and trying to identify the systemic either active or healed disease is an essential component of etiological diagnosis.

Few examples are:

i. Ocular Tuberculosis is often diagnosed with help of a known phenotype of uveitis along with immunoreactivity test (TST/IGRA) along with evidence of Tb in other sites like lungs, bones, gastrointestinal or lymphatic system. Hence, chest imaging (CT scan preferably, chest X-ray alternatively) and abdominal imaging helps detect lymphadenopathy or old lung affections due to Tb. Sarcoidosis the chest imaging is again of prime importance. Rarely a PET scan can identify an active focus of infection in TB or an MRI can help detect CNS tuberculoma.

ii. In seronegative spondyloarthropathies' – MRI or ultrasound help detect clinical or subclinical changes in the affected joints like sacroiliac joint.

iii. MR angiography can detect the changes in large arteries in systemic vasculitis affecting larger vessels like Takayasu arteritis.

5. Does endemicity of a disease dictate any specific test - explain with the concept of "pre-test" and "post-test" probabilities.

The endemicity of a disease affects the prevalence of disease and infection in the general population. The interpretation of a similar test in endemic and non-endemic test can differ due to the increased plausibility of the disease in general population.

Example:

the positivity cut-off value of Tuberculin skin test is set at above 15 mm induration in Tb non-endemic countries while it is set at 10 in TB endemic countries.

Pre-test probability is the likelihood of a disease before a diagnostic test, while post-test probability is the likelihood after the test results are received.

Example:

i. Pre-test probability: The pretest probability of Tuberculin skin test would be very high in a case of serpiginous like choroiditis wherein the likelihood of the disease is Tb being high while it would be low in the aforementioned scenario of hypopyon anterior uveitis.

ii. Post-test probability: a case of placoid chorioretinitis with features predictive of syphilis on OCT the post-test probability of a positive TPHA would be very high due to high specificity and low false rates of the test.

6. What is the significance for testing for syphilis in uveitis - which test is preferred over the another and under what circumstances?

Syphilis is the greatest masquerader in uveitis. In can manifest and mimic almost all known patterns of uveitis and lead to atypical and rare patterns.

i. For screening of syphilis – treponemal tests (TPHA, FTA-Abs) are preferred tests over the non-treponemal tests (VDRL, RPR)

ii. When syphilis is the prime suspicion or first differential diagnoses both one treponemal test and one non-treponemal tests like TPHA with VDRL are advised.

iii. In case of monitoring the disease resolution on treatment, falling titres of non-treponemal test like VDRL is used and a fourfold reduction in VDRL titres is one of the indicators of a clinical cure.

7. Under what set of circumstances is the sampling of ocular fluids advised?
Anterior chamber fluid and vitreous are the common ocular fluids to be sampled while subretinal biopsy/retinal and/or choroidal biopsies are done very rarely.

i. AC tap for PCR is commonly used in diagnoses and identification of viral uveitis like HSV, VZV and CMV.
ii. Vitreous sampling is commonly done in endogenous endophthalmitis including focal retinitis like fungal, nocardia, pneumococci, shigella, bacillus etc.
iii. Vitreous sampling for PCR can also be an adjuvant in diagnoses of Tuberculosis, Herpesviruses and Toxoplasmosis (or atypical Toxoplasmosis presenting like ARN)
iv. Subretinal/choroidal biopsy can be diagnostic in cases of primary vitreoretinal lymphoma.

8. In which cases does PCR testing benefit to a maximum extent, to the diagnosis of uveitis?
PCR of AC sample in persistent or non-resolving anterior uveitis can help differentiate between CMV, VZV or HSV uveitis; wherein either the treatment advised or their dosages would differ.
PCR sampling of vitreous in cases of Tuberculosis can be helpful in cases with atypical phenotype or incomplete features according to COTS criteria.
Toxoplasma retinitis can have atypical manifestations like multifocal retinitis, ARN like retinitis, punctate lesions wherein PCR of vitreous can be diagnostic.

Suggested further reading:

1. *Majumder, P. D., Sudharshan, S., & Biswas, J. (2013). Laboratory support in the diagnosis of uveitis. Indian journal of ophthalmology, 61(6), 269–276. https://doi.org/10.4103/0301-4738.114095*
2. *Hwang, D. K., Hung, J. H., Chang, Y. C., Chen, C. L., Chen, S. N., Cheng, C. K., Hwang, Y. S., Kuo, H. K., Li, A. F., Lin, C. J., Yang, C. H., Sheu, S. J., & Lin, C. P. (2022). Step-wise diagnostic approach for patients with uveitis - Experts consensus in Taiwan. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi, 55(4), 573–580. https://doi.org/10.1016/j.jmii.2022.02.003*
3. *Dutta Majumder, P., Mochizuki, M., González-López, J. J., Gonzales, J., Sharma, M., Sharma, K., & Biswas, J. (2023). Laboratory Investigations in Infectious Uveitis. Ocular Immunology and Inflammation, 31(7), 1405–1415. https://doi.org/10.1080/09273948.2022.2164728*
4. *Rathinam, S. R., & Babu, M. (2013). Algorithmic approach in the diagnosis of uveitis. Indian journal of ophthalmology, 61(6), 255–262. https://doi.org/10.4103/0301-4738.114092*
5. *Gupta, Vishali; Gupta, Amod. Ancillary investigations in uveitis. Indian Journal of Ophthalmology 61(6):p 263-268, June 2013. | DOI: 10.4103/0301-4738.114093*

Anterior Uveitis

Anindya Majumder, Sudha Ganesh

1. What is anterior uveitis - what symptoms does it present with?
Intraocular inflammation where the primary site of inflammation is the anterior chamber. The patient can present with redness, pain, intolerance to light, watering, dimness of vision, and rarely with halos around a light source (hypertensive uveitis).
The patient could be asymptomatic in the case of Fuchs disease/ children with JIA.

2. Enlist the characteristic clinical signs observed during the slit-lamp examination of a patient presenting with an acute episode of anterior uveitis.
- Circumciliary congestion
- Cilliary tenderness
- Keratic precipitates (KP): Endothelial dusting(NGU)/ Mutton Fat KPs(GU)
- Aqueous Flare
- Anterior chamber cells
- Hypopyon
- Muddy iris/iris atrophic patches /iris nodules /Koeppe /Busacca nodules/iris hole
- Pupillary response slow and poorly dilating pupil/festooned pupil
- Evolving posterior synechiae
- Low intraocular pressure/High IOP in case of hypertensive uveitis
- Anterior vitreous cells (Cyclitis)

3. Describe "keratic precipitates" and various types of keratic precipitates (KP)
Keratic precipitates (KP) are inflammatory cellular deposits on the corneal endothelium.
Mechanism of KP formation: The aqueous humor has a normal convection current due to the temperature gradient between a warmer iris and a relatively cooler cornea. During inflammation, this gradient increases which results in more rapid aqueous convection. The relatively higher molecular weight proteins, protein clumps along with inflammatory cells deposits on the endothelial surface by hydrostatic interaction and gravitation. This results in the formation of keratic precipitate (KP). These are inflammatory cells stuck on corneal endothelium based on hydrostatic interaction and gravitation.
In a hypothetical triangular fashion known as the Arlt triangle, KP are predominantly seen in the lower part of the cornea on the endothelial surface. These can be of fine variety as seen in nongranulomatous uveitis and mutton fat type as seen in granulomatous uveitis. Based on the morphology of the KP, uveitis has been classified into granulomatous and nongranulomatous entities.

4. How do differing types of keratic precipitates point towards different diagnoses?

i. Fine KPs: Seen in acute non granulomatous uveitis
ii. Mutton fat KPs: Seen in acute granulomatous uveitis
iii. Pigmented KPs: Seen in viral uveitis
iv. Crenated KPs: Chronic uveitis
v. Stellate KPs with diffuse distribution: Seen in Fuchs uveitis

5. Is there a role in assessing corneal sensations in anterior uveitis?

The herpetic infection causes a decreased corneal sensation

6. What is the correlation of varying intra-ocular pressure in anterior uveitis?

i An acute attack of uveitis generally presents with normal or borderline low IOP due to ciliary process malfunction secondary to inflammatory toxins
ii. High intraocular pressure is noted in hypertensive uveitis like viral uveitis, lens-induced uveitis, post-traumatic uveitis due to outflow obstruction as a result of trabeculitis, edema and clogging of trabecular meshwork due to lens protein and RBCs
iii. High IOP can also result from pupillary block, secondary glaucoma and steroid response

7. What are the key findings to be noted in chronic anterior uveitis?

i. Old KPs
ii. Band shaped keratopathy
iii. Iris nodules may be seen in both chronic and active uveitis
iv. Posterior synechiae/peripheral anterior synaechia (PAS)
v. Seclusio pupillae
vi. Occlusio pupillae
vii. Iris atrophy/sectoral or patchy /heterochromia
viii. Complicated cataract
ix. Hypotony

8. Discuss the available treatment options for managing anterior uveitis

i. Topical steroid
ii. Topical cycloplegic
iii. Topical NSAIDs
iv. Subtenon Steroid: In case of CME
v. Oral steroid: In case of severe disease not responding adequately to local steroid
vi. Immunosuppressive molecules: In case of uveitis with systemic collagen vascular disease like JIA, Ank spondylitis HLA B27 associated

9. What are the potential complications of untreated anterior uveitis?

i. Hypotony/secondary glaucoma
ii. Complicated cataract
iii. Pupillary membrane
iv. Cystoid macular edema
v. BSK formation
vi. Loss of Vision

10. What is the recommended treatment for Fuch's uveitis?

i. Aqueous biopsy to rule out viral etiology, especially if IOP is raised followed by anti-viral treatment if viral PCR is positive.
ii. Steroids have a controversial role. However, steroids may be required during symptomatic anterior chamber reaction.
iii. Topical cycloplegics have a limited role.
iv. IOP control may be required in case of concurrent glaucoma or steroid response
v. Cataract surgery is frequently required, where steroids again have a questionable role.

11. What are the "red flags" in anterior uveitis? Or Are there any critical identifiers for etiological diagnosis?

i. Hypopyon and its mobility/blood-tinged hypopyon /color of hypopyon
ii. Distribution of KPs (as in Fuchs)
iii. Iris atrophic patches /IOP raise as in viral AU
iv. MF KPS /Koeppe /Bussaca nodules indicate granulomatous etiology
v. Pseudohypopyon- in case of leukaemia in children
vi. Chronic hypotony
vii. Lens matter in AC as in POP AU (indicates lens-induced AU)
viii. PC Plaque in POP AU (possible P Acne)
ix. Sphincter tears / angle recession as in traumatic uveitis

12. What specific monitoring is advised while treating a patient for anterior uveitis?

Monitoring of anterior chamber reaction, resolution of KPs /iris nodules and IOP monitoring

13. How is anterior uveitis managed in patients with concurrent glaucoma?

i. Using a low potency topical steroid
ii. IOP monitoring and proper choice of anti-glaucoma
iii. Avoid prostaglandin analogues
iv. Avoiding posterior sub-tenon depot steroid injection
v. Anterior chamber tap PCR studies in cases of suspicious viral uveitis

References:

Babu, Kalpana; Konana, Vinaya Kumar; Ganesh, Sudha K; Patnaik, Gazal; Chan, Nicole S W; Chee, Soon-Phaik, Sobolewska, Bianka; Zierhut, Manfred. Viral anterior uveitis. Indian Journal of Ophthalmology 68(9): 1764-1773, September 2020. | DOI: 10.4103/ijo.IJO-928-20

Intermediate Uveitis

Vidya S Moos, Kalpana Babu

1. What are the salient features of intermediate uveitis according to SUN classification? How is disease activity monitored?

According to the Standardization of Uveitis Nomenclature (SUN) working group criteria, intermediate uveitis is defined as an intraocular inflammation involving the intermediate zone of the eye including the vitreous, peripheral retina and the ciliary body. The site of inflammation is the vitreous. It is characterised by presence of vitreous cells, vitreous membranes, snowball and snowbanking. Sometimes spill over anterior uveitis, cystoid macular edema, peripheral retinal vasculitis, peripheral chorioretinal scars, neovascularisation over the snowbanking and disc edema may be seen.

Disease activity is clinically monitored by the grading the vitreous haze(SUN). It can also be monitored objectively with imaging modalities such as wide field fluorescein angiography for retinal vascular and disc leakages and OCT for increase in macular thickness or presence of cystoid macular edema.

2. Can intermediate uveitis & pars planitis the same?

As per the SUN criteria, we label parsplanitis only when the aetiology of intermediate uveitis is not known ie idiopathic.

3. What are common etiologies of intermediate uveitis?

The table below gives the various etiologies of intermediate uveitis

Infectious	Non infectious	Masquerades
Tuberculosis Syphilis Toxocariasis(Young, U/L) Toxoplasmosis HTLV-1 Lyme disease EB virus Cat-scratch disease	Sarcoidosis Multiple sclerosis Idiopathic Rarely: ▪ Children with renal diseases ▪ TINU syndrome ▪ Mesangial glomerulonephritis ▪ ANCA associated vasculitis ▪ Post streptococcal uveitis ▪ Autoimmune lymphoprolierative syndrome ▪ Inflammatory bowel syndrome ▪ ▪Whipple's disease (Older)	Malignant ▪ Primary vitreoretinal lymphoma ▪ Metastasis Non Malignant ▪ Retinitis Pigmentosa ▪ Chronic Retinal Detachment ▪ Fuchs Heterochromic iridocyclitis ▪ Old Vitreous Haemorrhage ▪ Amyloidosis

4. Elaborate on the management of pediatric intermediate uveitis.

Management of paediatric intermediate uveitis involves ruling out infectious etiologies first through laboratory investigations and radiology. The goal of treatment is to control inflammation, improve vision, prevent sequelae such as glaucoma, cataract, cystoid macular edema, hypotony and amblyopia.

Oral steroids are the drug of choice for control of inflammation initially. If infection is the cause, treatment with appropriate antimicrobials is necessary. But if it is noninfectious, the inflammation is generally chronic and requires systemic immunomodulation.

Conventional DMARDs such as azathioprine, methotrexate, mycophenolate mofetil and cyclosporine are generally used.

However if inflammation continues to persist, worsen or if cystoid macular edema occurs, they may need to shifted to biologics. Adalimumab, tocilizumab and tofacitinib are commonly used especially with refractory cystoid macular edema.

Treatment should be done in conjunction with a pediatric rheumatologist monitoring closely for any side effects due to the drugs and adjusting the doses as per body weight.

Regular follow-up with comprehensive eye examinations and imaging studies, like OCT and FFA, are essential for monitoring the disease activity and adjusting treatment plans. Educating the parents about the chronic nature of uveitis and the importance of adherence to therapy is also a key component of successful management.

5. What significance does the presence of snow banking constitute for intermediate uveitis?

Snowbanks are exudates on the pars plana, when present are usually found inferiorly, but may also extend 360 degrees of the retinal periphery.

Snow banking is usually associated with the more severe form of the disease, and warrants aggressive therapy.

6. What is the role of ultrasound biomicroscopy in the management of intermediate uveitis

UBM provides high resolution images of ciliary body and helps in detecting pars plana membranes/cyclitic membrane, supraciliary effusion, blunted ciliary processes and ciliochoroidal detachment which are not visible during slit lamp or dilated fundus examination. Sometimes foreign-bodies like caterpillar hairs can be detected.

UBM is also generally done prior to a cataract surgery to assess the risk of ocular hypotony and need for any additional procedures at the time of cataract surgery.

7. Describe the potential complications of intermediate uveitis

Complications of chronic/ untreated intermediate uveitis include cataract, glaucoma, epiretinal membrane, cystoid macular edema, macular hole, foveal thinning, development of inflammatory choroidal neovascular membranes, retinoschisis, retinal cysts, retinal detachment, neovascularisation, Coats disease like picture, amblyopia, cyclitic membrane, ocular hypotony and pthisis bulbi

8. What are available treatment options for intermediate uveitis?

Once infection is ruled out, treatment options include:

- Corticosteroids: They are mainstay in the management of intermediate uveitis. This includes oral steroids (if bilateral and continued upto 3-4 months till the immunomodulation starts working), periocular and intravitreal steroids (if unilateral, systemic corticosteroids insufficient/contraindicated /unable to tolerate due to side effects, with significant macular edema/persistent vitreous membranes)

- Conventional Immunomodulators-most commonly used ones are Methotrexate, Mycophenolate mofetil, Azathioprine and Cyclosporine
- Biologics: used when there is no response/suboptimal response to immunomodulators and refractory cystoid macular edema. Commonly used biologics include TNF alpha blockers like Adalimumab/ Infliximab, IL-6 receptor inhibitors like tocilizumab and jannus kinase inhibitors like Tofacitinib

10. What is the role of corticosteroid implants in managing intermediate uveitis?
Intravitreal steroid implants play a significant role in cases where systemic therapy is insufficient, contraindicated or when there is significant macular edema /persistent inflammation. It delivers a sustained release of steroids into the vitreous cavity, providing anti inflammatory effects locally within the eye. Eg. Ozurdex, Iluvien

Further reading:

1. *Ozdal PC, Berker N, Tugal-Tutkun I. Pars Planitis: Epidemiology, Clinical Characteristics, Management and Visual Prognosis. J Ophthalmic Vis Res. 2015 Oct-Dec;10(4):469-80.*
2. *Saincher SS, Gottlieb C. Ozurdex (dexamethasone intravitreal implant) for the treatment of intermediate, posterior, and panuveitis: a systematic review of the current evidence. J Ophthalmic Inflamm Infect. 2020 Jan 10;10(1):1.*

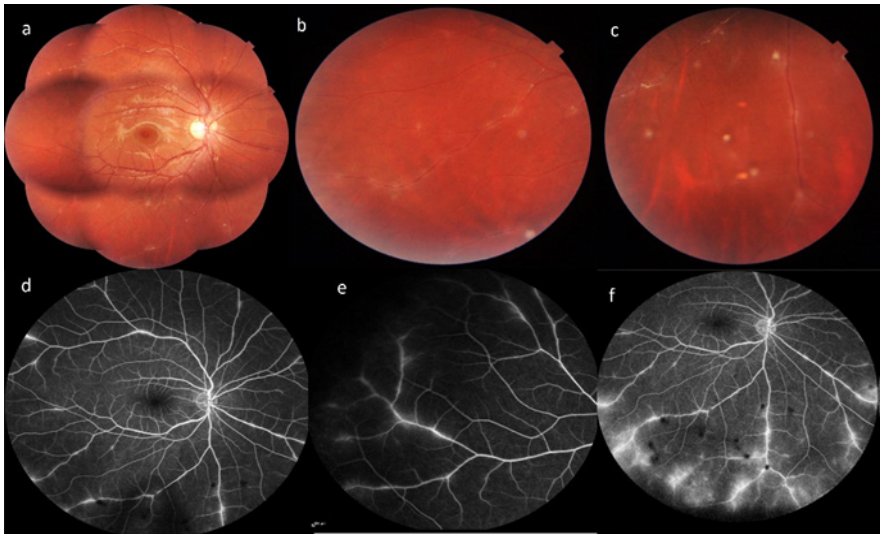


Fig 1. *a-c- colour fundus photo of a 30 year old male with intermediate uveitis showing retinal vascular cuffing(1b) and snowballs (1c). d-f: FFA of corresponding areas showing vascular leaks*

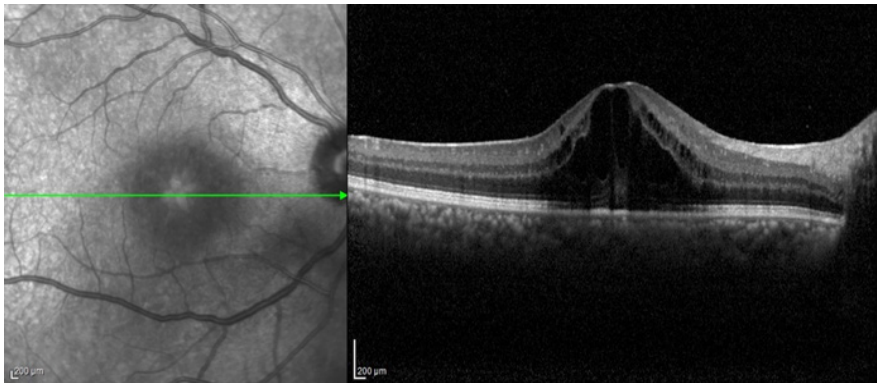


Fig 2*. OCT of a patient with intermediate uveitis showing cystoid macular edema*

Infectious Posterior Uveitis

Samendra Karkhur, Alok Sen

1. What are the key points to the diagnosis of infectious posterior uveitis?

1. yellow glow/absent glow
2. presence of retinitis ± arteriolar vasculitis.

2. What are the common differentials of infectious posterior uveitis?

1. endophthalmitis
2. toxoplasma retinochoroiditis
3. viral retinitis
4. syphilitic chorioretinitis
5. presumed ocular tuberculosis

3. Describe the clinical features of ocular toxoplasmosis

The classical presentation is of focal retinitis/retinochoroiditis adjacent to a punched-out pigmented chorioretinal scar, associated with a variable amount of vitritis and anterior segment inflammation.

Congenital transmission shows large atrophic chorio-retinal scar in macula (incidental finding).

4. Enumerate the various treatment options for ocular toxoplasmosis

1. Classic triple therapy: Pyrimethamine 200mg on day one followed by 50mg daily + Sulphadiazine 2g loading dose followed by 1g QID + predinisolone 0.5-1mg/kg daily for 4 to 6 weeks.

2. Septran DS (Sulphamethaxazole + Trimethoprim) + oral prednisolone is most commonly used in clinical practice.

3. Alternate therapy: Clindamycin 300mg QID + oral prednisolone. intravitreal Clindamycin (1g/0.1ml) + dexamethasone (400mg/0.1ml) weekly for two to four weeks is as effective as oral therapy.

4. In pregnancy,

First trimester	Spiramycin+ sulphadiazine
Second trimester	Spiramycin+ sulphadiazine+ pyrimethamine+ folinic acid
Third trimester	Spiramycin+ pyrimethamine+ folinic acid

Goh EJH, Putera I, La Distia Nora R, Mahendradas P, Biswas J, Chee SP, et al. Ocular Toxoplasmosis. Ocul Immunol Inflamm. 2023 Sep;31(7):1342–61.

5. Considering the clinical diagnosis of retinal necrosis, what would be the next step by step approach towards reaching a diagnosis (considering the location, extent & characteristic of retinal necrosis or retinitis)

Toxoplasma	ARN	CMV retinitis	Post-fever retinitis	Tubercular retinitis	Retinal infilteration in Behcets disease	SSPE
Dense vitritis, Solitary retinitis chorioretinal scar ±vasculitis	Tongue shaped retinitis in periphery extending circumferen -tially, ±arteriolitis, haemorrahges, ±retinal detachments. Immunoco mpetent host	Pizza pie appearance-large retinitis with few haemorrhages in mid-periphery± periphlebitis. Immuno-compromised host	Multi-focal retinitis lesion in Posterior pole/along arcades. Sparse haemo-rrhage, Sub-retinal fluid, hard exudates upon resolving	Neuro-retinitis, Tubercular retinal vasculitis.	Smaller lesions, multiple in number associated with vasculitis	B/L placoid retinitis in posterior pole, Rapid progression

6. What conditions demand the starting of systemic antivirals.

1. Acute retinal necrosis
2. progressive outer retinal necrosis
3. CMV retinitis

7. Give the doses of systemic antivirals and intravitreal antiviral injections.

Hoffman J. Overview of antiviral medications used in ophthalmology. Community Eye Health. 2020;33(108):85.

Drug	Route	Dose	Indication
Acyclovir	oral	Acyclovir 400 mg orally, five times a day for 10 weeks	HSV endothelitis
	oral	Acyclovir 800 mg orally, five times a day for 7 days	herpes zoster ophthalmicus
	intravenous	10mg/kg three times a day for 5-10 days	ARN, PORN
Valganciclovir	oral	Induction dose: 900 mg orally twice a day for 14-21 days, followed by maintenance dose 900 mg orally once a day until CD4 count normalises	CMV retinitis
Ganciclovir	intravenous	Induction dose: 5mg/kg/dose every 12 hours for 1-21 days followed by a maintenance dose of 5mg/kg once a day till CD4 count normalises	CMV retinitis
	intravitreal	2.5mg in 0.1 ml once a week	CMV retinitis
Valaciclovir	oral	2 g four times a day for 7–10 days, then oral valaciclovir 1 g three times a day for six weeks	CMV retinitis

8. Should steroids be given in infectious posterior uveitis? Is there any specific condition where steroids should be avoided? Enumerate the pros and cons of steroids in this condition.

Steroids can be used as an adjuvant to organism specific anti-microbial therapy in order to control the damage due to inflammation. It should be avoided in eyes with suspected fungal endophthalmitis or when the cause of infective uveitis is not known.

9. Why is syphilis called as a great masquerade in uveitis? What are its known morphological presentations?

Treponema Palladium is capable of infecting all the layers of the eye and can hence mimic a variety of intraocular inflammation.

i. Primary stage: chancres of the eyelids and/or conjunctiva

ii. Secondary-tertiary stage:

a. maculopapular rash involving eyelids
b. Blepharitis± Conjunctivitis
c. EpiscleritisScleritisKeratitis
d. Iridocyclitis ± iris nodules

Uveitis is the most common manifestation

A. Anterior uveitis:

- Unilateral
- Granulomatous or non-granulomatous
- Iris roseola (rare but specific for syphilis)
- Raised intraocular pressure

B. Posterior segment involvement:

- Dense vitritis
- Necrotising retinitis+ punctate retinal lesions
- Chorioretinitis (most common)
- Retinal vasculitis
- Acute posterior placoid chorioretinopathy (APPC) (most common overall)
- Syphilitic retinal necrosis
- Optic neuritis and consecutive optic atrophy
- Argyll Robertson pupil

Congenital syphilis:

Bilateral interstitial keratitis
Pigmentary retinitis
Syphilitic keratouveitis

Reference:
Koundanya VV, Tripathy K. Syphilis Ocular Manifestations. StatPearls Publishing; 2023

10. How is ocular syphilis treated?

Ocular syphilis is treated in line of CNS syphilis aqueous crystalline penicillin G, 3-4 million units IV QID for 2 weeks or

benzathine penicillin G, 2.4 million units IM weekly for 3 weeks.

(in patients with allergy to penicillin, IV ceftriaxone 1gm BD for 2 weeks can be used)

Corticosteroids (systemic and topical) to be used to reduce ocular inflammation but to be started after antibiotics.

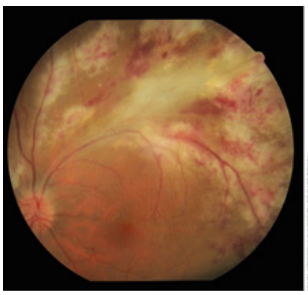
Reference:

Koundanya VV, Tripathy K. Syphilis Ocular Manifestations. StatPearls Publishing; 2023

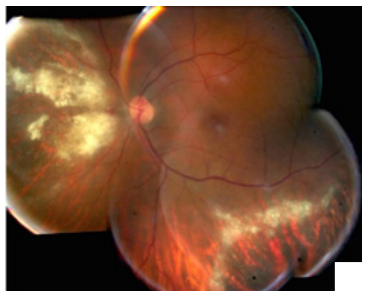
11. Describe the classical features of CMV retinitis.

It commonly occurs in three clinical forms:

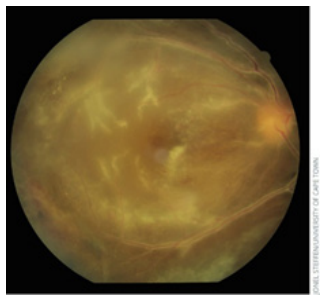
- Fulminant- "Pizza pie" appearance or/ "brush fire" appearance (dense white areas of retinitis and retinal necrosis with interspersed retinal hemorrhages extending along the vascular arcades
- Granular form- mild granular mid peripheral retinal opacification with few hemorrhages. Progresses slowly
- Frosted branch angiitis- least common, with perivascular exudates



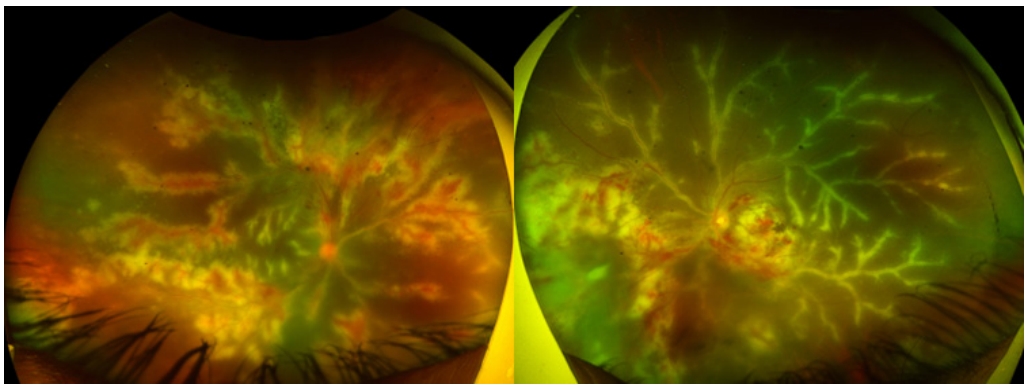
Fulminant CMV retinitis



Granular CMV retinitis



Frosted branch angiitis



Bilateral Frosted Branch Angiitis Pattern of vasculitis with ARN in a case of CMV Retinitis

12. What are various treatment protocols for CMV retinitis?

- Systemic anti CMV treatment

Intravitreal Ganciclovir treatment-

Weekly injections of 500-2000 microgram of ganciclovir

Drug	Dose	Side effect
Ganciclovir	Induction- IV 5 mg/kg 12 hourly X 14-21 days Maintenance- IV 5 mg/kg/day	Myelosuppression Liver dysfunction
Valganciclovir (treatment of choice)	Oral induction dose- 900 mg BD X 14-21 days Maintenance- 900 mg OD	Myelosuppression Renal toxicity
Foscarnet	Induction- IV 90 mg/kg BD X 14 days Maintenance- IV 90 mg/kg OD	Renal dysfunction Anemia, seizures
Cidofovir	Induction-IV 5 mg/kg weekly X 14 days Maintenance- IV 5 mg/kg every other week	Hypotony Anterior uveitis, nephrotoxicity

Reference:

Port AD, Orlin A, Kiss S, Patel S, D'Amico DJ, Gupta MP. Cytomegalovirus Retinitis: A Review. J Ocul Pharmacol Ther. 2017 May;33(4):224–34.

13. How essential is laboratory testing for the diagnosis of infectious posterior uveitis?

Essential in diagnostic confirmation of infectious posterior uveitic entity but require further interpretations in the context of test-specific/ patient-specific testing parameters. Careful correlation between clinical picture and laboratory investigations needed.

14. Does the presentation of infectious posterior uveitis differ in immunocompromised versus immunocompetent patients?

Yes, the presentation can be more fulminant and resistant requiring prolonged treatment due to risk of recurrences, e.g. ocular toxoplasmosis may present with multifocal lesion or fulminant ARN in immunocompromised patient. Also, one has to remember that Infection with multiple organisms may be seen in immunocompromised patients.

15. How is Bartonella-associated posterior uveitis diagnosed and treated?

1. Diagnosis:

History of exposure to cats (biting/ scratching)
Ocular inflammation not attributed to other causes
Visual field testing shows Centro caecal scotoma
OCT shows subretinal fluid and retinal thickening
Fundus fluorescein angiography shows optic nerve leakage and vessel occlusion
ELISA and indirect immunofluorescence assay (IFA) >1:64 titre
Polymerase chain reaction
Biopsy with warthin starry staining identifies bacteria

2. Management of Bordetella induced uveitis:

Doxycycline 100mg BD for 2-4 weeks
In immunocompromised patients, doxycycline to be continued for months or till clinical improvement.
Children <12 years of age to be treated with erythromycin.
Systemic corticosteroids to reduce ocular inflammation.

Reference:

Kalogeropoulos C, Koumpoulis I, Mentis A, Pappa C, Zafeiropoulos P, Aspiotis M. Bartonella and intraocular inflammation: a series of cases and review of literature. Clin Ophthalmol. 2011;5:817–29.

Non-infectious Posterior Uveitis

Dr. Rashi Taori Sawal, Rohan Chawla

1. Do infectious and non-infectious posterior uveitis have any clinical features in common?

Yes. Uveitis due to some infectious agents may have a distinct phenotypic presentation, however there is an overlap of many clinical features between infectious and non-infectious uveitis. This is why it is all the more important to correctly identify an infectious uveitis early based on the entire clinical setting including history, examination, ocular and systemic investigations so as to initiate appropriate anti-infective therapy early in the course of the disease.

2. What are the key points towards diagnosis of non-infectious posterior uveitis?

Infectious	Non infectious
▪ Any retinitis or retinochoroiditis ▪ Dense vitritis (≥ Grade 3) ▪ Choroiditis – paucifocal, irregular margins ▪ Chorioretinits ▪ (Unilateral) ▪ Contiguous involvement of adjacent anatomical structures	▪ Known clinical pattern – Vogt Koyanagi Harada disease, sarcoidosis, White Dot Syndromes ▪ Multifocal, well-defined choroidal lesions ▪ Known systemic disease (e.g. sarcoidosis, Behcets) ▪ (Bilateral)

First step in diagnosis is to differentiate between infectious and non infectious posterior uveitis and rule out infectious causes. It often requires a thorough clinical evaluation, including detailed history, examination findings, imaging studies, and sometimes specific laboratory tests.

Factors favouring infectious vs non infectious posterior uveitis:

Clinical history of fever, rash, systemic infection anywhere in the body, specific history of systemic active tuberculosis or syphilis, immunosuppression, use of intravenous medication may indicate infectious uveitis.

Apart from these, recognising particular clinical pattern of various entities whether infectious or non infectious is of paramount importance.

3. Give a broad categorisation of the morphological manifestations of non-infectious posterior uveitis.

A. Vitritis

Idiopathic Intermediate uveitis, Sarcoidosis, Primary vitreoretinal lymphoma, Multiple sclerosis, Behcets

B. Retinal Vasculitis

Veins	Arteries	Capillaries
Sarcoidosis	SLE	Relapsing Polychondritis
Behcets	Behcets	Behcets
Multiple Sclerosis	Granulomatosis with polyangitis	Crohns disease
Idiopathic retinal vasculitis		

C. Choroiditis or White dot syndromes

Choriocapillaritis with discrete lesions	MEWDS, MFC, PIC
Choriocapillaritis with larger lesions	APMPPE, SC, Relentless Placoid chorioretinitis
Choroidal stromal diseases	Primary: VKH, SO, Birdshot Secondary : Sarcoidosis
Predominantly retinal/retinal pigment epithelial diseases	AZOOR, AMN, ARPE, SFU

D. Retinitis

Behcets, sarcoidosis, SLE, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis.

E. Posterior Scleritis

Associated conditions: Rheumatoid arthritis, Granulomatosis with polyangitis, Polyarteritis nodosa, Crohn's disease, Ulcerative colitis, Gout, Relapsing Polychondritis, Sarcoidosis, Behcets, IgA nephropathy, SLE, etc.

4. What are the common etiologies of Non-Infectious Posterior Uveitis

Common etiologies:

Etiology	Key Features
Sarcoidosis	Granulomatous inflammation, lung and skin involvement, bilateral hilar lymphadenopathy.
VKH	Multisystem autoimmune disorder with uveitis, meningitis, and vitiligo, bilateral serous retinal detachments, sunset glow fundus
Behcets	Recurrent oral and genital ulcers, retinal vasculitis with haemorrhages, white eyed mobile hypopyon.

Uncommon white dot syndromes

White dot syndrome	Key features
Multiple evanescent white dot syndrome:	Multifocal grey-white spots with foveal granularity, 'wreath-like' hyperfluorescence on FA, hyper-reflective lesions on OCT from RPE to ellipsoid/outer nuclear layer, and absent/ minimal anterior chamber/vitreous inflammation
Acute posterior multifocal placoid pigment epitheliopathy:	Paucifocal/multifocal plaque-like lesions with early hypofluorescence and late hyperfluorescence on FA.
Multifocal choroiditis with panuveitis:	Multifocal round-to-oval lesions more than 125 microns, with punched-out atrophic scars or active lesions with minimal vitreous inflammation (possible posterior and/or peripheral involvement).
Punctate inner choroidopathy:	Multifocal punctate choroidal lesions less than 250 microns, posterior pole involvement, and absent anterior chamber/ vitreous inflammation
Birdshot Chorioretinopathy:	'Birdshot' lesions (multifocal cream-yellow round/oval lesions in the peripapillary area), absent/ minimal anterior chamber or vitreous inflammation, positive HLA A29 testing, and multifocal hypofluorescent spots on ICGA.

5. What are the Key Diagnostic Tools for Evaluating Non-Infectious Posterior Uveitis

Diagnostic Tools:

1. Fundus Photography

▪ To document and monitor retinal and choroidal lesions, assess vitreous activity, detect vasculitis.

Ultra wide field fundus imaging :

1) In small pupil(posterior synechiae),

2) In occlusive retinal vasculitis for FFA guided laser photocoagulation, detect peripheral vascular leakage,

3) Assessment of vitritis, peculiar pattern of vitritis along vitreous fibrils in vitreoretinal lymphoma. 4) Paradoxical worsening in SLC

2. Optical Coherence Tomography (OCT):

▪ Detection of posterior vitreous cells, vitreomacular surface abnormalities, detect changes and damage to retinochoroidal architecture, detection and monitoring of macular oedema, quantitative follow-up of choroidal thickness and structural changes, secondary complications like CNV, distinguishing predominant retinal involvement (retinitis) from choroidal involvement (choroiditis), detecting choroidal granulomas.

3. Optical Coherence Tomography Angiography(OCT-A):

▪ Detecting inflammatory CNV, retinal capillary hypoperfusion & perifoveal capillary changes in retinal vasculitis, choriocapillaris hypoperfusion in APMPPE,VKH,SC

4. Fluorescein Angiography (FA):

▪ Detect vascular leakage in vasculitis and as a marker of activity in intermediate uveitis, detect macular ischemia, cystoid macular edema,inflammatory CNVM, patterns of fluorescence in determining structures involved and response to treatment, detecting CNP areas and secondary NVE formation.

5. Indocyanine Green Angiography (ICG)

▪ Imaging of choroidal circulation, choroidal inflammation and nonperfusion and identifying and monitoring of choroidal granulomas

6. Fundus Autofluorescence

▪ Measure of health and function of RPE, useful in knowing the extent of disease and serves as marker of disease activity eg hyperAF in serpigenous like choroiditis, trizonal pattern in AZOOR,etc

7 Ultrasound (B-scan):

▪ Assess vitreous involvement and choroidal thickening, especially with media opacities, to know about presence of subtenon fluid in posterior scleritis.

8. Laboratory Tests:

▪ Infection Exclusion: TB screening (PPD, IGRA), syphilis serology (TPHA,VDRL).

▪ Specific other tests : ACE levels, chest X-ray/CT for sarcoidosis, HLA typing (e.g., HLA-A29 for birdshot). ▪ In specific situations- HIV antibodies, Blood culture, Toxo IgG,IgM levels,serology for rare infectious agents like lymes disease, rickettsia, bartonella if clinical suspicion high.

If clinical suspicion high and/or lack of response to standard treatment more invasive tests like PCR for HSV, HZV, CMV, Toxo, TB, Bacteria/Fungi may be considered.

6. What are the Treatment Options for Non-Infectious Posterior Uveitis

Treatment Options:

1. Corticosteroids:

- Systemic Steroids: Oral prednisone (1 mg/kg/day) with tapering.
- Local Steroids: Periocular injections (e.g., triamcinolone acetonide), intravitreal implants (e.g., dexamethasone implant).

2. Immunomodulatory Agents:

- Methotrexate: 7.5-25 mg/week, dose adjusted based on response.
- Azathioprine: 1-3 mg/kg/day for steroid-sparing.
- Mycophenolate Mofetil: 1-3 g/day
- Cyclosporine: 3-5 mg/kg/day, effective in refractory cases.

3. Biological Agents:

- TNF Inhibitors: Adalimumab (40 mg every other week), Infliximab (5-10 mg/kg at intervals).
- Interleukin Inhibitors: Tocilizumab for resistant cases.
- Anti-CD20 Monoclonal Antibodies: Rituximab in refractory cases.

4. Adjunctive Therapies:

- Anti-VEGF Agents: Bevacizumab or ranibizumab for inflammatory CNVM
- Laser Therapy: Panretinal photocoagulation for neovascularization.

Therapeutic drug category	Class	Drug
Corticosteroids	Periocular steroids Intravitreal steroids Systemic Steroids	Triamcinolone Dexamethasone Ozurdex (dexamethasone) Retisert (fluocinolone acetonide 0.59mg) Iluvien (fluocinolone acetonide 0.19mg) Yutiq(fluocinolone 0.18mg) Prednisolone
Immunomodulator therapy	T cell inhibitors	Cyclosporine A, Tacrolimus
	Anti metabolites	Azathioprine, Mycophenolate mofetil Methotrexate
	Alkylating agents	Cyclophosphamide, Chlorambucil
	Calcineurin inhibitors	Voclosporin
Biologic response modifiers	TNF alpha inhibitors	Infliximab, Adalimumab, Etanercept
	IL-1 inhibitor	Anakinra, Rilonacept, Canakinumab, Gevokizumab
	IL-2 inhibitor	Daclizumab
	IL-17 inhibitor	Secukinumab
	IL-6 inhibitor	Tocilizumab Sarilumab
	IL~12/23 inhibitor	Ustekinumab
	Interferons	IFN alpha and beta

	ACTH analogue	
	Protein kinase C inhibitors	Sotrastaurin
	JAK-1 inhibitor	Filgotinib, Tofacitinib
	Phosphodiesterase-4 inhibitor	Apremilast
Ocular gene therapy		Adeno associated virus(AAV), Lentivirus

7. What are the indications for using Immunosuppressive Agents in Non-Infectious Posterior Uveitis

Indications:

1. Steroid-Sparing:

▪ To reduce long-term corticosteroid side effects (e.g., osteoporosis, hypertension, diabetes,etc)

2. Refractory Cases:

▪ When inflammation is uncontrolled with corticosteroids alone especially on tapering steroids or in severe presentations.

3. Chronic or Severe Inflammation:

▪ For prolonged treatment to prevent relapses in conditions like Behçet's, birdshot, or VKH.

Power of Association for giving immunosuppressants	**Diseases**
Strong	Behcet disease Sympathetic ophthalmia Vogt-Koyanagi-Harada syndrome Rheumatoid necrotizing scleritis Granulomatosis with polyangiitis Relapsing polychondritis with scleritis Juvenile idiopathic arthritis
Relative	Intermediate uveitis Retinal vasculitis
Questionable	Intermediate uveitis in children Sarcoid-associated uveitis not adequately responsive to steroid

Drug	**Dose**	**Indications**	**Adverse Effects**
Azathioprine	2-3 mg/kg/day	VKH, Sympathetic ophthalmia	Gastrointestinal upset, Cytopenia, Hepatitis
Methotrexate	15 mg/weekly	JIA, Behcet's disease, Sarcoidosis	Hepatitis, Cytopenia
Mycophenolate mofetil	1 gm BID	JIA, Intermediate uveitis	Diarrhea, Cytopenia
Cyclophosphamide	2 mg/kg/day	VKH, Granulomatosis with polyangiitis	Cytopenia, Bladder toxicity, Alopecia
Chlorambucil	0.1 mg/kg/day	Adamantiades-Behcet's disease, Sympathetic Ophthalmia	Cytopenia
Cyclosporine	2-5 mg/kg BID	Behcet's disease	Hypertension, Nephrotoxicity, Hirsutism
Tacrolimus	2-3 mg BID	Behcet's disease	Nephrotoxicity, Neurotoxicity

8. Which Biological Agents are commonly used in managing Non-Infectious Posterior Uveitis?

Biological Agents:

1. Adalimumab: Less immunogenic as compared to infliximab, used in JIA associated uveitis.

2. Infliximab:

▪ TNF inhibitor, used for severe refractory cases, especially in Behçet's disease

3. Tocilizumab:

▪ IL-6 inhibitor, used for uveitis resistant to TNF inhibitors, effective in JIA-associated uveitis.

4. Rituximab:

▪ Anti-CD20 monoclonal antibody, used in refractory cases with suspected B-cell involvement.

Generic Names	Specific Targets	Route	Dosage	Description
TNF- Inhibitors				
Adalimumab	TNF-α	SC Intra-vitreal	Initial dose of 80 mg followed by 40 mg in subsequent weeks 0.03mL (1.5 mg) at baseline, 8 and 12 weeks, then once a month	Allergic reactions, headache, malignancy, thrombolytic events, congestive heart failure, reactivation of TB
Infliximab	TNF-α	IV Intra-vitreal	3-5 mg/kg at baseline, 2nd and 6th weeks, and every 4-8 weeks thereafter 1 mg/0.05 ml 6 weeks apart	Headache, abdominal pain, rash, pneumonia, urinary tract infection, reactivation of TB
Etanercept	TNF-α and TNF-β	SC	0.4 mg/kg twice a week	Rashes, diarrhea, infection
Golimumab	TNF-α	SC	50 mg per month	ANA positivity, development of infections
Certolizumab	TNF-α	SC	400 mg every week	Nausea, infections
Anti-Interleukin Therapy				
Anakinra	IL-1 receptor	SC	100 mg/day	Headache, vomiting Antibody development, allergic reactions, fever, nasopharyngitis
Abatacept	T cells (CTLA-4)	IV	0.5-1g at loading, 1.25g SQ weekly in RA 0.1g to max of 1 g IV at baseline. 2nd & 6th	Headache, nausea, nasopharyngitis, infections

Rituximab	B cells (CD20)	IV Intra-vitreal	375 mg/m² at 4 week intervals or 1,000 g/ infusion 2 weeks apart third dose interval is variable according to the disease severity 1mg/0.1ml monthly	Cardiovascular, fatigue, pruritus, nausea, bronchospasm, antibody development, infections
Interferons	No specific target	SC	3-6 million units daily with slow taper	Headache, fever, flu-like syndrome, myelosuppression, neuropsychiatric issues, elevated liver enzymes, endocrine disorders, thrombocytopenia
Fusion Protein of CTLA-4				
Canakinumab	IL-1β	IV, SC	150 mg for 6 weeks	Headache, vertigo, obesity, diarrhea, abdominal pain, hyperuricemia, respiratory issues
Gevokizumab	IL-1β	IV, SC	60 mg every	Infections, hypersensitivity
Tocilizumab	IL-6R	IV	Initially 4 mg/kg once at every 4 weeks	Increased serum cholesterol, alanine aminotransferase levels, injection site reaction
Secukinumab	IL-17	IV	3 mg/kg every 2 weeks	Headache, infections, gastrointestinal complications hypercholesterolemia
Ustekinumab	Anti-IL-12 and IL-23	SC	45 mg at 0 weeks and 4 weeks, then every 12 weeks	ANA positivity, infections nasopharyngitis
Alemtuzumab	Anti-CD52	IV	30 mg, 3 times a week for 12 months	Headache, skin rashes, nausea, urinary tract, lymphocytopenia, thyroid disease, infusion related reaction, fever, nasopharyngitis

9. What care should be taken while recommending use of Immunosuppressive Agents and Biological Agents in treating Non-Infectious Posterior Uveitis

Care Considerations:

1. Monitoring:

▪ Regular blood tests for side effects (liver function test, renal function test, CBC & TLC).

▪ Regular imaging (OCT, FFA, ICGA) to assess treatment response and detect complications.

2. Infection Risk:

▪ Screen for latent infections (TB, hepatitis) before therapy initiation.

▪ Prophylactic measures and vaccinations as per patient's history and risk

For TNF alpha inhibitors - Also rule out multiple sclerosis

3. Patient Education:

▪ Inform patients about potential side effects and risks (infections, malignancies).

▪ Careful family planning -Avoiding certain drugs like methotrexate & switching to safer alternative like azathioprine;

▪ Do not consume alcohol while on methotrexate.

▪ Emphasize adherence to treatment and the importance of regular follow-ups and repeated blood tests.

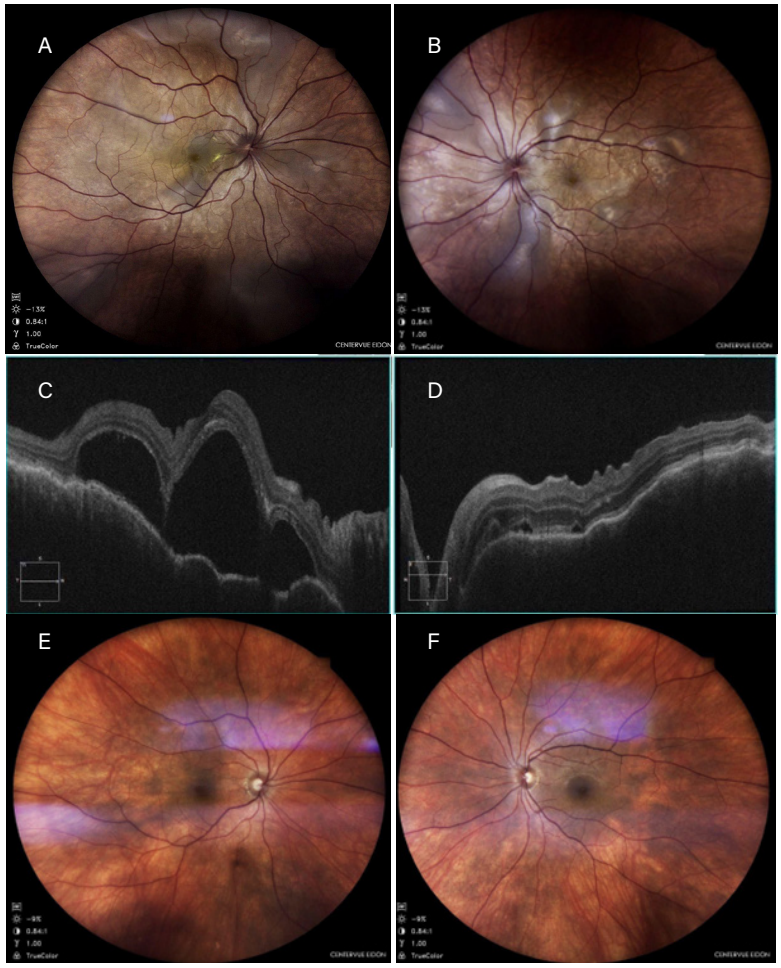


Figure: *Vogt Koyanagi Harada disease(A & B) TrueColor Fundus photographs(Eidon, iCare) showing optic disc hyperemia with blurred margins, deep yellowish lesions & multifocal exudative retinal detachments in both eyes during acute uveitic phase of disease (C & D) Corresponding Spectral domain optical coherence tomography scans (Cirrus HD-OCT, Carl Zeiss) demonstrate subretinal fluid with RPE undulations and thickened choroid.*

(E & F) Sunset glow fundus in convalescent phase of disease.

Suggested reading:-

Pathogenesis and current therapies for non-infectious uveitis
Clin Exp Med. 2023 Aug;23(4):1089-1106.
Doi: 10.1007/s10238-022-00954-6. Epub 2022 Nov 24.

Scleritis

Samyak Mulkutkar, Somasheila Murthy

1. Enumerate the clinical features that distinguish scleritis from episcleritis
Episcleritis:
Episcleritis presents with nil to mild pain/discomfort and a bright-red eye. Salmon pink" area is noted due to congestion of the superficial episcleral plexus. "Blanching" or disappearance of the congestion on application of 5 or 10% phenylephrine eye drops is a pathognomic feature.
In nodular episcleritis, mobility of the nodule is easily noted over the deeper layers.

Scleritis: The pain associated with scleritis is severe, insidious or "dull boring" type localised to the sclera and referred to the temple or the jaw, disturbing their night sleep. Ocular examination shows a voilaceous hue in one or more quadrants or an elevated & congested scleral nodule.
The necrotising variety of scleritis is painful with areas of severe scleral congestion alongside areas of vascular drop-out that lead to scleral necrosis. Scleromalacia perforans, a rare disorder, is the presence of necrotising scleritis without overt inflammation and without severe pain. This leads to areas of scleral melt and exposure of the underlying uveal tissue.
Patients with recurrent scleritis will show a gradual thinning of the sclera with each attack, leading to a "greyish-blue" hue due to showing of the underlying uveal tissue. Asymptomatic patients with an old history of scleritis may also show this feature, suggesting the tell-tale of an old scleritis.

Table 1: The major clinical differences between epi-scleritis and scleritis

	Episcleritis	**Scleritis**
PAIN	Mild or no discomfort	Severe, dull boring pain, sleep affected
APPEARANCE	**Salmon pink**	**Voilaecious**
10% phenylephrine	Blanching	Persistence of congestion
Nodule	nodules can be moved	nodules are not mobile, fixed to sclera
Corneal involvement	None	cornea can be affected
Course	Acute, spontaneous resolution - 3 weeks	Acute/slow onset, not resolve, treat
Signs	Conjunctival & superficial episcleral plexuses	Deep episcleral plexus
Types	Simple, nodular	Sectoral, diffuse, nodular, necrotising
Outcomes	No residual signs	Scleral and/or corneal thinning, perforations & other complications

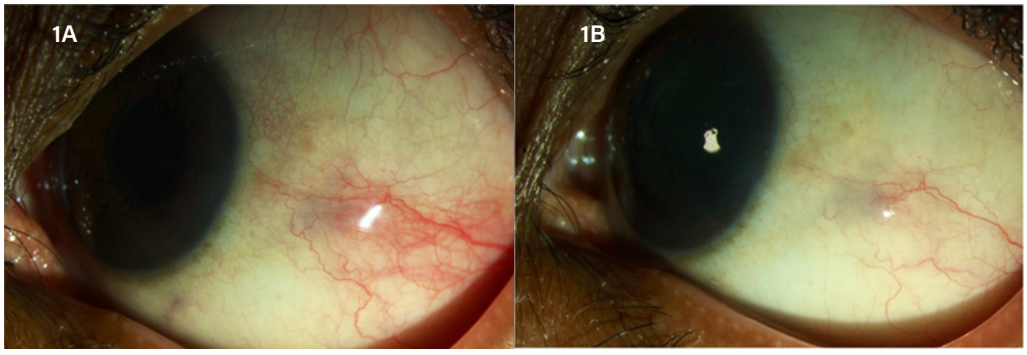


Figure 1. Episcleritis

1A Episcleritis before application of topical phenylephrine (5%)

1B Blanching of episcleritis after application of topical phenylephrine (5%)

2. How does scleritis affect the adjacent ocular structures?

Anterior scleritis can involve the adjacent cornea in the form of peripheral corneal infiltrates, small whitish lesions, thinning and ulcerationAnterior uveitis and vitritis can be occasionally noted.

Posterior scleritis can have associated choroiditis, choroidal granulomas, exudative retinal detachment, uveal effusion and optic nerve involvement causing disc edema.

3. Describe the various clinical subtypes of scleritis.

Scleritis is broadly divided into anterior and posterior scleritis depending on the anatomical involvement.

The easily identifiable anterior scleritis is further divided into diffuse, nodular and necrotising scleritis. The diffuse anterior scleritis variety has a significant scleral edema with congestion of the scleral vessels and ill-defined margins. This involvement may be extensive or may be localised to a certain area of the sclera (sectoral involvement)

Scleral inflammation in the form of a single or multiple, non-mobile, edematous, congested, elevated, smooth nodular appearance is called nodular scleritis.

Necrotising scleritis presents with areas of severe congestion alongside avascular areas that may lead scleral necrosis. Necrotising scleritis without inflammation or pain is called scleromalacia perforans.

Though posterior scleritis may also be classified as diffuse, nodular and necrotising, such a differentiation is not easy and requires ultrasonography or fluorescein angiography for detailed evaluation.

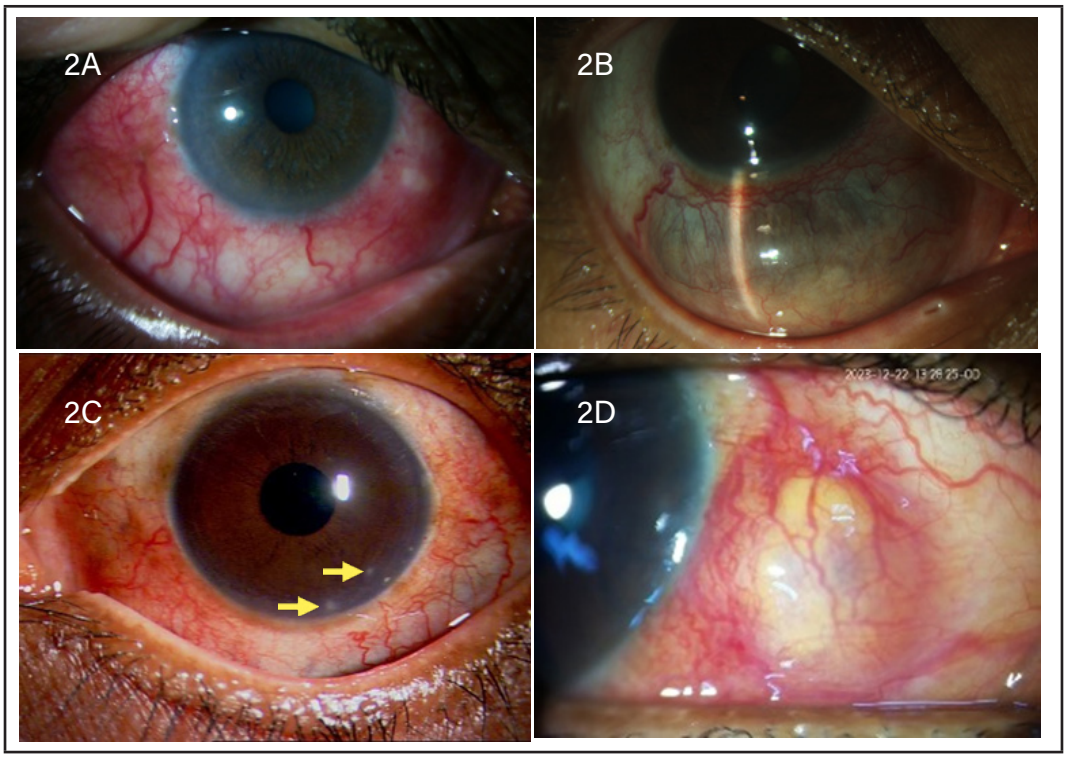


Figure 2. Scleritis
2A Diffuse scleritis
2B Necrotising scleritis (chronic) with staphylomatous changes
2C Scleritis with inferior peripheral corneal infiltrates (yellow arrows) in a case of relapsing polychondritis
2D Nodular infectious scleritis

4. What are the common systemic associations of scleritis?

Systemic disease association is noted in about 15% of patients.

i. Immune mediated diseases:

a. Rheumatoid arthritis (RA) is the commonest

b. Granulomatosis with polyangitis (GPA)

c. Ankylosing spondylosis, seronegative spondyloarthropathies, juvenile idiopathic arthritis

d. relapsing polychondritis

e. systemic lupus erythematosus (SLE),

f. Rare conditions: giant cell arteritis, Takayasu's disease, polyarteritis nodosa

ii. Infectious diseases:

About 5-10 % of anterior scleritis are secondary to infections such as viruses (herpes simplex, herpes zoster), bacteria (pseudomonas, various mycobacteria, tuberculosis, syphilis) and fungi.

iii. Surgically induced necrotizing scleritis S developing within a month of ocular surgery

iv. Paraneoplpastic syndromes and metabolic causes such as gout, masquerades are less commonly associated with scleritis.

5. What is the pathophysiology of necrotising scleritis and its clinical implications?

Biopsy of tissues with necrotising scleritis have shown vasculitis with fibrinoid necrosis and high numbers of neutrophil invasion in the vessel wall. All types of T cells and macrophages have been seen in these tissues. These findings suggest immune-complex-mediated vasculitis in necrotising scleritis.

There is also a role of proteolytic enzymes called as matrix metallo-proteinases (MMP-3, MMP-9) and the tissue-inhibitors of matrix metallo-proteinases (TMMP-1) leading to the destruction of the sclera and cornea.

Due to the recent understanding of the immune-pathogenesis of scleritis, a number of potential targets have been identified for action by biological agents for the treatment of scleritis. Commonly used amongst these are the TNF-alpha inhibitors group of drugs and anti CD-20 class of drugs.

6. What is the typical treatment approach for a patient of episcleritis?

Episcleritis are usually asymptomatic without any pain or with minimal discomfort. They may even resolve spontaneously.

If treated, they respond well to topical NSAIDs or topical lower potency steroids. Rarely, recurrent episcleritis or those with larger areas of involvement they may require stronger potency steroid eye drops.

Asymptomatic episcleritis that resolves well with minimal treatment, does not warrant any systemic investigations other than a detailed history of trauma, systemic issues such as joint pains or any other pre-resisting conditions.

Recurrent episcleritis or episcleritis evolving to a scleritis-type presentation or episcleritis presenting along with a new-onset systemic presentation would warrant detailed systemic laboratory investigations and a treatment approach based on scleritis.

7. What is the recommended treatment approach for a patient of scleritis?

Depending upon the severity of scleritis, both non-steroidal anti-inflammatory drugs such as oral indomethacin (NSAIDs) and systemic steroids are utilized.

It is essential to exclude an infectious etiology of scleritis, especially when high dose systemic steroids are used.

Preliminary laboratory investigations include CBC, ESR, CRP, Mantoux test, chest X-ray, TPHA and urine analysis, and these tests are directed towards fitness for therapy.

Tests to look for etiology include RA factor, c-ANCA, p-ANCA, HLA B-27, ANA or depending upon relevant clinical or systemic signs.

A detailed systemic evaluation of all patients of scleritis by an internist or a rheumatologist is strongly recommended to exclude underlying systemic conditions.

Non-infectious scleritis presenting with significant scleral inflammation & pain usually require systemic steroids.

Bilateral scleritis and posterior scleritis also qualify for the usage of systemic steroids.

Diffuse scleritis or nodular scleritis usually respond well to high dose oral steroids (1mg/kg body weight dose) in a tapering fashion.

Severe painful necrotising scleritis and impending perforation due to severe scleral inflammation may require administration of intravenous pulse steroids to initially control inflammation and before shifting to high dose oral steroids.

Recurrent scleritis may require repeated doses of systemic steroids.

Such cases will require systemic immunosuppression to benefit from its steroid sparing effect. Systemic immunosuppression is also indicated in presence of a concurrent underlying systemic disease associated with scleritis.

Intravenous cyclophosphamide and biological agents are reserved for the most severe varieties of scleritis and those with associated life-threatening systemic inflammation.

8. How can infectious scleritis be differentiated from non-infectious scleritis?

Infectious scleritis constitute about 5-10% of all cases of scleritis, mostly in the elderly population and have poor visual outcomes. It is important to exclude infectious from non-infectious or idiopathic causes of scleritis because their treatments tend to be diametrically opposite.

A wide variety of agents such as bacteria (commonly pseudomonas aeruginosa), fungi, nocardia, mycobacterial infections and the herpes viruses can lead to infectious scleritis.

Taking a detailed history of trauma (especially with organic matter), a variety of ocular surgeries such as pterygium excision, cataract surgery, glaucoma surgeries (with topical Mitomycin C), retinal surgeries (scleral buckling, vitrectomies, secondary IOL implantation) and excision of anterior segment neoplasms is important.

Such a history may need not necessarily be recent occurrence and can date back months or years.

Pertinent history of concurrent ocular or systemic medications, hospitalisation, systemic interventions, systemic immune suppression such as HIV or chemotherapy should also be enquired into.

Presence of a bare or an exposed sclera, excessive use of cautery, poor contact lens hygiene or non-healing epithelial defects may all contribute towards infectious scleritis.

Symptomatology of infectious scleritis, such as red eye, varying ocular pain and conjunctival hyperaemia will present similarly to that of non-infective scleritis.

Clinical signs such as scleral necrosis, unifocal or multiple scleral abscesses, purulent discharge, presence of a calcified plaque at the base of scleral ulcers, corneal ulcers & infective-looking infiltrates, disproportionate anterior chamber inflammation, foreign-body type granulomas, rarely endophthalmitis and other such atypical presentations of scleritis should raise a red flag towards infectious aetiology.

At times, clinical features may overlap between infectious & non-infectious scleritis without a definitive clue. In such cases, a progressive indolent scleral necrosis with suppuration not responding to conventional anti-inflammatory treatment may point towards infectious cause.

9. What are the indications for the use of systemic corticosteroids in the management of scleritis?

Non-infectious scleritis presenting with significant scleral inflammation & pain usually require systemic steroids. Bilateral scleritis and posterior scleritis also qualify for the usage of systemic steroids.

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Severe painful necrotising scleritis and impending perforation due to severe scleral inflammation may require administration of intravenous pulse steroids to initially control inflammation and before shifting to high dose oral steroids.

10. What is the role of immunosuppressive agents in treating scleritis?

Recurrent scleritis may require repeated doses of systemic steroids.

Such cases will require systemic immunosuppression to benefit from its steroid sparing effect.

Systemic immunosuppression is also indicated in presence of a concurrent underlying systemic disease associated with scleritis.

Intravenous cyclophosphamide and biological agents are reserved for the most severe varieties of scleritis and those with associated life-threatening systemic inflammation.

11. What are the potential complications of untreated or inadequately treated scleritis?

Inadequately treated scleritis or recurrent scleritis, leads to chronic thinning of the sclera giving a greyish-blue hue from the underlying uveal tissue.

Severe scleral inflammation, untreated scleritis and necrotising scleritis can cause thinning of the scleral tissue, scleral melt and eventually leading to perforation of the globe eventually leading to the loss of vision.

12. When are surgical options recommended in scleritis?

Medical management is the mainstay of therapy in scleritis. Surgical interventions such as scleral biopsy and scleral patch grafts in cases of scleritis are reserved for complications of scleritis. It is pertinent to note that scleritis is a clinical diagnosis and a scleral biopsy is not indicated routinely as it can increase the risk of perforations and complications of the disease.

A few indications are outlined below:

i. scleral biopsy to differentiate infectious from non-infectious scleritis in cases not responding to conventional treatment regimens. And rarely, to rule out a malignancy in such cases.

ii a diagnostic biopsy to obtain a definitive diagnosis of the organism - in cases of suspected infectious scleritis not responding to conventional antimicrobial regimens

iii. to de-bulk inflammatory residue to allow better penetration of ocular and/or systemic medication

iv. to diagnose/treat a suspected foreign body granuloma mimicking nodular scleritis

v. scleral patch grafts to preserve the integrity of the globe.

vi. rehabilitative procedures such as cataract surgery in chronic cases of scleritis are only indicated if the affected eye is stable from inflammation for at least 3 months while on treatment. History of old scleritis/scleral inflammation not presently on treatment may also need careful pre-op evaluation prior to any ocular surgeries.

All such cases require additional peri-operative oral steroids starting three to five days prior to surgery followed by close monitoring post operatively with slow tapering of oral steroids.

Cataract Surgery in Uveitis and Scleritis- Tips and Tricks

Arshee Ahmed, S Balamurugan

1. How to prioritise cataract surgery in uveitis?
Cataracts are responsible for up to 40% of all cases of visual loss among patients with uveitis and cataract surgeries are the most commonly done surgeries in uveitis patients.

2. What are the recommendations for advising cataract surgery in patients with uveitis?
Cataract surgery is recommended when:
a) there is a drop in best corrected visual acuity due to presence of complicated cataract
b) presence of lenticular opacities which hinder evaluation of the posterior segment
Consensus amongst uveitis experts is that the underlying uveitis should be well-controlled for a period of at least 3 months prior to the surgery.
Although in eyes with severe panuveitis like Behcet's disease, sympathetic ophthalmia (SO), Vogt-Koyanagi-Harada disease (VKH) it may be prudent to wait longer (even up to 6 months) prior to planning cataract surgery.

3. Describe in detail the peri-operative management strategies to control inflammation for a patient with uveitis undergoing cataract surgery.
Pre-op planning is important to ensure a good outcome in uveitic cataracts.
a. Preop evaluation : Refer Tables 1 and 2
b. Indications for surgery : as above in Q2
c. Timing of surgery: A quiet eye with at least 3 months of interval between the last uveitic episode and the timing of cataract surgery is important.
d. Control of uveitis

Perioperative measures include
a. hiking up dosage of oral steroids: 0.5-1 mg/kg body weight starting 3 days prior to planned surgery
b. pulse intravenous methylprednisolone (IVMP) doses: 3 days of IVMP 1 gm per day in adults
c. immunosuppressive drugs: can be continued at an optimal dosage and/ or biologics
d. periocular steroids can be administered for those patients who have oral steroid intolerance via posterior subtenon's route.
e. topical NSAIDs like nepafenac, flurbiprofen etc can be started to prevent macular edema post-surgery
f. Need of additional surgeries:
i. Patients with secondary glaucoma need adequate control of intraocular pressure (IOP) medically. Or glaucoma filtration surgeries may be planned along with the cataract surgery.

ii. Patients with hypotony – discussed later
iii. Patients with tractional retinal detachments or macular holes may require concomitant vitreoretinal (VR) procedures.

Counselling
Uveitic cataracts are unlike age-related cataracts and surgery is usually technically demanding. Possibility of post operative complications and need of regular follow ups should be discussed with the patients.

4. What are the common postoperative complications in uveitis patients after cataract surgery?
Early and Late complications:
Early: severe anterior fibrinous uveitis, cystoid macular edema (CME), glaucoma, recurrence of uveitis
Late: capsular phimosis, posterior capsular opacification (PCO), intraocular lens (IOL) deposits, IOL decentration, optic capture, posterior synechiae, pupillary membranes, bag weakness and drop resulting in IOL dislocation, hypotony

5. Is there a definitive role for topical NSAIDs in such cases?
Yes, topical nsaids can be added pre-operatively to prevent CME rather than treat pre-operative uveitic macular edema.

6. Describe the necessary modifications in the surgical techniques for cataract surgery in patients with scleritis.
In patients with scleritis, areas of scleral thinning should be avoided to make any incisions. Hence, clear corneal incisions are preferred. These also prevent the possibility of post operative scleral melts. It is also important to assess pre-op astigmatism due to scleral thinning.

7. How does the presence of uveitis affect the choice of intraocular lens (IOL) in cataract surgery?
a. Hydrophobic or hydrophilic acrylic IOLs are the preferred IOLs as they are biocompatible.
b. Silicon IOLs are avoided if there is a possibility of requiring VR surgery with silicon oil in the future. For example in eyes post ARN.
c. Plate haptic IOLs to be avoided as future Nd:YAG capsulotomy may cause the IOL to dislocate posteriorly
d. Multifocal/ diffractive IOLs are not preferred in uveitic eyes due to presence of irregular pupils, possibility of IOL decentration post-operatively which can lead to glare and haloes. Also, as uveitic eyes may have pre-existing retinal changes, there is a higher possibility of losing contrast sensitivity post MFIOL implantation.

8. How does post operative management of cataract surgery in a patient of uveitis different from that of a normal cataract surgery?
Post-operative management in uveitic cataracts involves close monitoring.
a. Aggressive topical therapy with steroids like prednisolone acetate and mydriatic agents like homatropine is required.
b. Topical non-steroidal anti-inflammatory agents like nepafenac can be added to reduce chances of post-operative CME.
c. Oral steroids are usually started 3 days prior to surgery in a quiet eye and then slowly tapered post-operatively based on degree of inflammation.

d. If patient is on immunosuppressive or biologic therapy, it should be continued post-operatively as well as per the maintenance dosage.
e. Intraocular steroid injections like dexamethasone implants or intravitreal triamcinolone acetonide (IVTA) may be used in case of severe post-op inflammation or CME.
f. Postoperative glaucoma should be addressed with use of appropriate anti-glaucoma medication (important to avoid prostaglandin analogues in uveitic eyes). Recalcitrant cases may need glaucoma-filtration surgery.

9. What is the list of uveitis conditions that need special care before planning cataract surgery?
a. JIA associated uveitis- It is of utmost importance to attain a quiet eye prior to surgery as children tend to have severe post-operative inflammation post-surgery. Perioperative control of inflammation with possible need of intravenous methylprednisolone prior to surgery may be advisable. Continuing optimal dosage of oral steroids and immunosuppressive drugs like methotrexate is important to attain good outcome post-surgery.
b. Infectious conditions like viral anterior uveitis, acute retinal necrosis, toxoplasmosis may need additional anti-infective agent cover prior to surgery along with oral corticosteroid cover.
c. Chronic panuveitis like VKH, SO, Behcet's disease, sarcoidosis etc need adequate immunesuppression prior to planning cataract surgery along with hiking up of oral steroids to at least 1 mg/kg body weight 3 days prior to planned surgery.
d. Fuch's heterochromic iridocyclitis (FHI) is a low-grade inflammation which doesn't need aggressive pre-op or post-op anti-inflammatory therapy
e. Glaucoma -eyes with h/o steroid induced or angle closure glaucoma need adequate control of IOP prior to surgery. Uveitic eyes with medically uncontrolled glaucoma may require combined surgery.

10. When do you plan cataract surgery by posterior segment approach?
Pars plana approach to cataract surgery in uveitic eyes can be opted for in the following circumstances
a. Cases where there is pre-existing zonular weakness, lens subluxation, vitreous prolapse in anterior chamber (AC)
b. Cases where additional VR procedures are warranted for associated retinal detachment
c. Pre-existing hypotony due to cyclitic membranes or in cases with extensive retrolental membranes
d. Pediatric uveitic cataracts
e. Cases with silicon oil and significant posterior capsular opacification
f. >270 degrees peripheral anterior synechaiae (PAS)

11. Do we have evidence to use multifocal IOL s in uveitis?
Multifocal/ diffractive IOLs are not preferred in uveitic eyes due to presence of irregular pupils, possibility of IOL decentration post-operatively which can lead to glare and haloes, pre-existing poor macular function which would preclude a good visual outcome. Also, MFIOLs are known to cause drop in contrast sensitivity.
So their use in eyes with an already compromised visual function (uveitic eyes may have pre-existing retinal changes, macular edema, choroidal neovascular membranes (CNVM), scarring) is not recommended.

12. Are toric IOLs safe in uveitis?
Toric IOLs require a perfectly centred capsulorrhexis and a stable zonule- bag complex to prevent decentrations post-operatively.
Uveitic eyes may preclude a good anatomical outcome due to possibility of zonular weakness and resultant IOL decentration.

13. When is surgical peripheral iridotomy indicated in uveitic cataract surgery?
in cases with angle closure glaucoma due to presence of extensive PAS and in cases where severe or recurrent post-op anterior segment inflammation is expected to prevent pupillary block, eg. JIA associated uveitis.

14. Are there any specific anti-infective prophylaxis needed before cataract surgery?
Yes, conditions like toxoplasmosis, viral anterior uveitis, post ARN eyes require concomitant anti-infective prophylaxis to prevent re-activation of uveitis. Drugs like tab trimethoprim-sulfamethoxazole, valacylcovir etc can be re-started prior to surgery along with oral corticosteroids and continued post-operatively based on inflammatory response post-surgery.

15. Are there any cases of uveitis cases, IOL implantation is contraindicated?
Intraoperative posterior capsular rent with vitreous loss, extensive zonular weakness, JIA associated uveitis in children under 4 years of age

16. What are the predictors of visual outcome in a uveitic cataract?
Management of uveitis cataracts is challenging as many pre-existing issues may limit a good outcome.
A quiet eye with no macular issues like cystoid macular edema or CNVM or scarring at macula would portend a favorable prognosis.
Poor predictors - pre-existing corneal scarring, band-shaped keratopathy, extensive PAS or angle closure glaucoma, RAPD, optic nerve atrophy, secondary glaucoma, chronic CME, CNVM, tractional retinal detachment, hypotony.

17. What are the intraoperative do's and don'ts in operating a uveitic cataract?
a. Phacoemulsification is the procedure of choice in uveitic eyes. However, SICS may be done in cases with dense corneal opacities, very hard cataracts or low endothelial counts.
b. Intra-operative challenges include shallow and irregular AC, peripheral anterior synechiae, posterior synechiae, thin atrophic iris prone to tears, difficult capsulorrhexis due to presence of posterior synechiae, thin posterior capsule prone to pc rents.
c. Corneal issues - Band-shaped keratopathy should be addressed before surgery to attain a clear cornea.
d. Pupillary issues- Pharmacological agents can be used to dilate the pupil in cases where there are no synechiae or pupillary membranes. Intracameral use of balanced salt solution with adrenaline (1:1000 0.5 mL adrenaline in 500 mL). Use of viscoadaptive viscoelastics can maintain the pupil shape due to its high molecular weight. In cases with bound-down pupil, adequate exposure of the cataract is done by synechiolysis, pupillary membrane removal and stretching the iris with hooks. Gentle and precise use of instruments is necessary as the iris is very fragile in such eyes and is prone to tearing and bleeding.

e. Rhexis and Bag issues – Trypan blue can be used for staining the anterior capsule for better visualisation. A larger capsulorrhexis is usually preferred due to the risk of postoperative capulsar phimosis.
f. Phacoemulsification - The phaco machine parameters can be varied depending on the density of the cataract and the zonular integrity. It is important to do a good posterior capsular polishing to avoid early PCO formation.
g. IOL placement- It is imperative to do an in-the-bag placement of the IOL to prevent chronic ciliary body irritation and resultant inflammation.
h. Adjuncts – Subconjunctival steroids can be administered at the end of surgery to prevent severe post-op inflammation.
i. IVTA is not routinely used in all cases of uveitic cataract. It can be used in non-steroid responder eyes with documented prior history of CME. It can also be used in patients who have steroid intolerance.

18. BSK with uveitic cataract: How do you manage differently?
EDTA chelation- 2 % ethylenediaminetetraacetic acid (EDTA) can be used for BSK removal prior to planning cataract surgery to improve intra-op visualisation and prevent intra-op complications.

19. Glaucoma in uveitic cataract: How do you manage differently?
Adequate control of IOP is attempted with maximal medical therapy (MMT) prior to surgery. However, in case with extensive PAS formation, or high IOP in spite of MMT, surgical management of glaucoma may be required.
Glaucoma surgeries can be combined with cataract surgery.

20. Hypotony in uveitic cataract: How do you approach differently?
a. An IOP <7-8 mm Hg in an uveitic eye is usually considered to be low.
b. Hypotony in eyes with uveitis can be due to the chronic uveitis leading to ciliary body (CB) damage, post filtering surgery, post chronic retinal detachment (RD) or RD surgery. Portends a poor visual prognosis.
c. Higher incidence in childhood onset uveitis
d. Presence of anatomical sequelae like angle closure, peripheral anterior synechiae, posterior synechiae, pseudophakia, aphakia etc are associated with higher odds of hypotony.
e. Pre-op investigations like ultrasound biomicroscopy (UBM) can assess the anatomical integrity of the ciliary body and ciliary processes and look for signs like blunting and shortening or total absence which indicate poor prognosis.
f. Additional steps like- pre-operative hiking up of oral steroids, intensive topical steroids, injection PST, intravitreal steroids, pars plana vitrectomy (PPV) + membrane removal, intraocular oil or gas injections can be attempted to manage hypotony.

Table 1: Pre-op investigations prior to planning surgery in uveitic eyes:

Investigation	Indications	Look for
Pupillary exam	To assess optic nerve function	RAPD
PAM	To assess macular function	
USG	Media opacities precluding view of the posterior segment	Media opacities, disc cupping, retinal status, choroidal thickening
UBM	Cases with chronic uveitis, hypotony	Status of ciliary body, ciliary processes, any effusions, cyclitic membranes and CB traction etc
OCT	Assess macular integrity	Macular edema, scarring, choroidal neovascular membranes, epiretinal membranes (ERM), holes
FFA	All cases of posterior uveitis and retinal vasculitis	Signs of disease activity like disc leak, macular leak, capillary leak, areas of capillary non-perfusion (CNP), status of foveal avascular zone

Table 2: Pre-operative structural signs to look for:

Anterior Segment	Posterior Segment
Scleral thinning	Vitreous debris
Band shaped keratopathy	Macular edema
Peripheral anterior synechiae	Retinal ischemia
Posterior synechiae	CNVM
Atrophic iris	Retinal detachment
Inflammatory membrane across pupil	Chorioretinal atrophic patches
Rubeosis iridis	Optic disc cupping, pallor
Shallow AC	

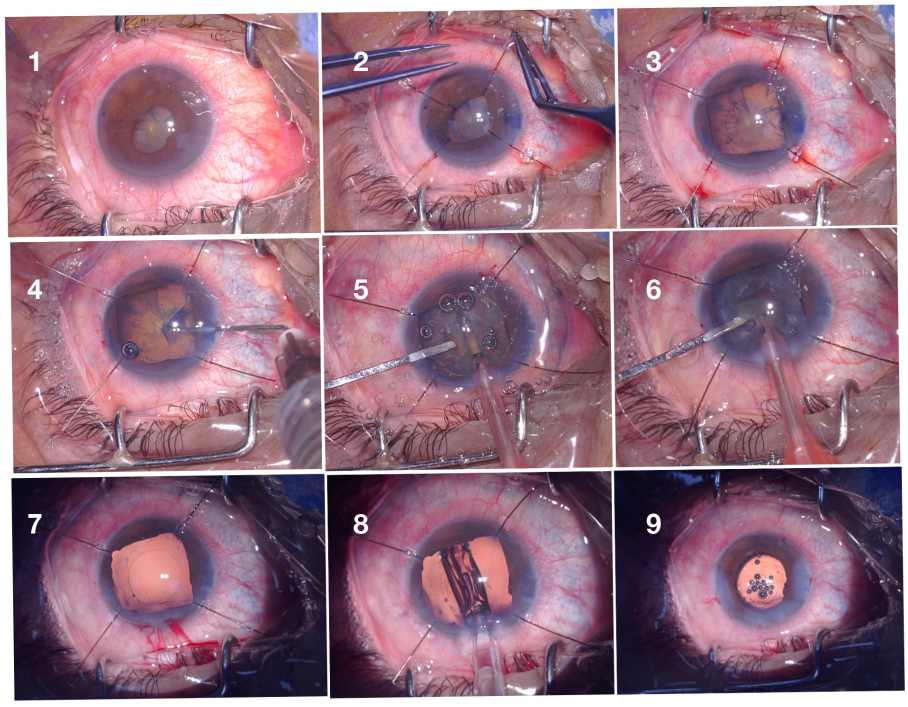


Fig 1: *Intraoperative image of a 44 year old female with intermediate uveitis showing a uveitic cataract with posterior synechiae*

Fig 2: *Flexible iris hooks being inserted through small limbal ports. Capsule has been stained with trypan blue.*

Fig 3: *Good exposure of lens achieved with all iris hooks in place.*

Fig 4: *Adequate size capsulorrhexis being done with cystitome.*

Fig 5: *Phacoemulsification being done through a clear corneal incision.*

Fig 6: *in-the-bag phacoemulsification with removal of last nuclear fragment.*

Fig 7: *retro-illumination view showing a clear bag after good cortical aspiration and posterior capsule polishing.*

Fig 8: *foldable single-piece hydrophilic acrylic IOL being inserted into the bag.*

Fig 9*: well-centred IOL in the capsular bag at the end of surgery.*

References:

1. *Agarwal R, Murthy S, Ganesh SK, Chee SP et al. Cataract surgery in uveitis. Int J Inflam. 2012;2012:548453. doi: 10.1155/2012/548453. Epub 2012 Feb 8. PMID: 22518338; PMCID: PMC3299394*
2. *M. A. Elgohary, P. J. McCluskey, H. M. A. Towler et al., "Outcome of phacoemulsification in patients with uveitis," British Journal of Ophthalmology, vol. 91, no. 7, pp. 916–921, 2007*
3. *Sen HN, Drye LT, Goldstein DA, Larson TA et al for the Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group (2012) Hypotony in Patients with Uveitis: The Multicenter Uveitis Steroid Treatment (MUST) Trial, Ocular Immunology and Inflammation, 20:2, 104-112*
4. *Leung TG, Lindsley K, Kuo IC.Types of intraocular lenses for cataract surgery in eyes with uveitis (Review). Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD007284.*

Immunosuppressive Therapy (IMT) in Uveitis

Sharanya Abraham, Parthopratim Dutta Majumder

1. What are IMTs and explain their mechanism of action in brief.

The suppression of aberrant immune responses in presumed autoimmune or autoinflammatory uveitis is the assumed action of prescribed systemic immunosuppression. However, these drugs also have antimicrobial effects.

2. What are the criteria for initiating immunosuppressive therapy in uveitis patients?

Systemic immunosuppression has become routine in the management of chronic sight-threatening uveitis, once intraocular infection has been excluded by standard investigations that include microscopy and culture, polymerase chain reaction assessment and serology.

- As corticosteroid-sparing therapy when substantial toxicity is expected at the dose required
- For inflammation that is recalcitrant to corticosteroids
- For the management of specific diseases expected to have limited response to corticosteroids alone

3. What basic evaluation should be done before immunosuppressive therapy in uveitis?

All the infective causes of uveitis must first be ruled out. A baseline evaluation of total and differential blood counts, platelet count and liver function tests along with screening of viral markers should be done. A more specific evaluation may be done depending on the choice of IMT for a specific condition and patient.

4. What should the uveitis specialist look for every time while he/she clinically evaluates a patient on IMTs/biologicals?

While clinically reviewing a patient on IMT or biologic agents, it is important to look for resolution of the disease as well as reactivation of the same inflammatory process or development of new inflammatory or infectious lesions.

Systemically, side effect profiling and blood evaluation may be done and when required a rheumatologist review may be sought.

5. What counselling should a patient of uveitis receive during the process of initiation of IMTs?

A detailed counselling of the indication for starting IMT/ biologic agents in addition to oral steroid or alone should be done with the patient and attender. In children, consent must be taken from the parent. The side effect profile, drug safety and risks versus

benefits should be explained. The need for monitoring with blood tests and regular follow-up must be emphasised. Self-medication should be discouraged and the patient and attender should be reassured that doses may need to be reduced or a medication may need to be stopped if adverse side effects develop while on treatment.

6. What care should you advise your uveitis patient who is being treated on IMTs?

Depending on the IMT the patient is on, they may be advised about side effects and monitoring as follows:

Antimetabolites

Antimetabolites antagonize or compete with a metabolite, which is essential for nucleotide synthesis, leading to impaired cell division and proliferation.

a. Azathioprine

Side effects may include nausea, vomiting, and diarrhoea. Mild elevation of hepatic enzymes may also be observed in less than 2% of patients. The most serious and common side effect is myelosuppression, which is dose-dependent, reversible, and varies highly among individual patients. Low-dose azathioprine therapy (1–2 mg/kg/day) has been reported to cause leukopenia and thrombocytopenia in patients who were already suffering from chronic renal failure.

Thiopurine methyltransferase (TPMT) is the main enzyme responsible for inactivating toxic products of azathioprine metabolism. Patients with homozygous deficiency of this enzyme have no enzyme activity and ideally should not be given the drug. Patients with heterozygous deficiency have 50% of enzyme activity and have been shown to respond well and tolerate half a standard dose. Patients with homozygous deficiency of TPMT may develop life threatening neutropenic sepsis. Ideally, TPMT enzyme testing should be done before starting the patient on Azathioprine. However, in India due to the cost of testing it is not routinely performed.

Monitoring: Complete blood counts and liver function tests to be monitored every 4–6 weeks.

b. Methotrexate

The most common gastrointestinal intestinal side effects are nausea, vomiting and abdominal pain. More serious potential side effects include hepatotoxicity, bone marrow suppression, and interstitial pneumonia, which presents as cough or dyspnoea. A small proportion of patients may develop hepatic cirrhosis. Alopecia and rash may occur less commonly. Patients must also be counselled about the teratogenic potential of methotrexate and its contraindications in pregnancy. In addition, patients must abstain from alcohol consumption while taking methotrexate.

Monitoring: At the time of initiation of therapy, complete blood counts, hepatitis B surface antigen, and hepatitis C antibody should be done. Complete blood counts and liver function tests should be repeated every 1–2 months.

c. Mycophenolate mofetil

Like Azathioprine and Methotrexate, the most common side effects are gastrointestinal. Leukopenia, lymphocytopenia, and elevation of liver enzymes have also been reported infrequently.

Monitoring: Patients should be monitored with complete blood counts weekly for 4 weeks, then twice monthly for 2 months, thereafter monthly. Liver function tests need to be done every 3 months.

Alkylating agents

These agents act by alkylating DNA, leading to cross-linking, inhibition of DNA synthesis, and cell death. Alkylating agents induce remission but are not prescribed as first-line therapy due to toxicity.

a. Cyclophosphamide

The most common adverse event is dose-dependent bone marrow suppression. When the leukocyte counts are less than 2500–3500 cells/mL, the drug may have to be discontinued. Another serious complication is hemorrhagic cystitis and increased risk of bladder cancer. While on medication, patients should be advised good hydration. The risk of hemorrhagic cystitis is lower with intermittent intravenous pulse therapy. Cyclophosphamide can cause ovarian suppression, testicular atrophy, azoospermia, alopecia, nausea, and vomiting. Other side effects are granulocytopenia, lymphopenia, and opportunistic infections.

Monitoring: complete blood count, urinalysis weekly initially and when dosing is stable, at least every 4 weeks.

b. Chlorambucil

Bone marrow suppression, opportunistic infections, permanent sterility in men, and amenorrhea in women are the most common side effects.

Monitoring: Complete blood count weekly initially followed by monthly monitoring.

T-Cell Inhibitors

They inhibit replication and activation of T-cell lymphocytes by inhibiting a phosphatase known as calcineurin, which dephosphorylates the nuclear factor of activated T-cells, which is a transcription factor regulating IL-2 production.

a. Cyclosporine

Nephrotoxicity is the most serious adverse effect noted with cyclosporine especially at higher doses. Cyclosporine can also cause hepatotoxicity, gingival hyperplasia, myalgia, tremors, paresthesia, hypomagnesemia, and hirsutism.

Monitoring: Blood pressure should be checked monthly for the initial 3 months and then every 3 months. Serum creatinine should be checked every 2 weeks initially and then monthly once the dosage has stabilized.

b. Tacrolimus

In addition to nephrotoxicity, it can cause significant neurotoxicity including tremor, headache, trouble sleeping and paresthesia. Gastrointestinal symptoms, hyperglycemia, hypertension and hypomagnesemia have also been reported.

Monitoring: Blood pressure, weekly liver function tests, blood urea nitrogen, creatinine, electrolytes including calcium, magnesium, phosphate, cholesterol and triglycerides levels also need to be monitored.

Biologics

This newer group of drugs are therapeutic proteins designed to block the activity of biologically active molecules. These are specifically targeted therapies with reduced side effects but an increased risk of unmasking of latent tuberculosis with anti- TNF agents and lack of vaccine response for 6–12 months with B-cell blockade.

a. Infliximab and Adalimumab

TNF-α inhibitors are contraindicated in multiple sclerosis. Infections such as tuberculosis, HIV, syphilis, hepatitis B virus, hepatitis C virus, and toxoplasma must be ruled out before initiating therapy. Common side effects include hypersensitivity

while more serious side effects include infections, hematologic reactions, malignancies, and myocardial infarctions.

Monitoring: Patients on TNF-α inhibitors require regular blood evaluations including complete blood count, liver function tests, blood urea nitrogen, and serum creatinine levels every 6 to12 weeks.

b. Tofacitinib

JAK-inhibitors may have adverse effects such as infections, reduction in CD4 + T cell count, elevation of cholesterol levels, headache, slight reversible increases in serum creatinine levels, increased risk of herpes zoster, major cardiovascular events and thrombosis.

7. What is the step-ladder approach to treat uveitis with IMTs? How often should you recommend changing the dosages and/or changing medicines?

IMTs may be started along with oral steroid/ following intravenous pulse steroid or a month later depending on the uveitic entity, aggressiveness of lesion, chance of reactivation of infection and macular status. In sight threatening non-infectious conditions like VKH, Behcets disease and JIA, IMT may be started at onset. The dose may be regulated based on response and maintenance after reducing or stopping steroid. Ideally, a time period of 3 months may be considered before changing medicines.

8. How long do various IMTs take to have optimal action on ocular inflammation?

6 months can be given to have a significant effect on resolution of ocular inflammation.

9. Can some IMTs be given for quick action to control severe ocular inflammation?

Intravenous administration of biologics and intravitreal methotrexate 400 αg/0.1 mL may be used with better bioavailability for a faster response.

10. Why does a patient on methotrexate need folate supplementation?

Methotrexate is a folic acid analog and an inhibitor of dihydrofolate reductase, the enzyme responsible for converting dihydrofolate to tetrahydrofolate, thereby inhibiting de-novo purine synthesis. As such, methotrexate inhibits rapidly dividing cells, such as leukocytes, producing an anti-inflammatory effect. Folic acid supplementation at 1–5 mg/day or 5 mg twice a week should be given concurrently to maintain adequate folate stores and to reduce toxicity.

11. What standard laboratory monitoring is required for a patient while on IMTs?

Monitoring mentioned in question 6

12. How often should IMTs be continued for uveitis?

IMTs are especially useful in children, where the aim is to get the child off steroid within 3 months. Conventional synthetic disease-modifying agents (csDMARDs) such as alkylating agents, antimetabolites, calcineurin inhibitors and biological

DMARDs (bDMARDs) are tried early in them with successful visual and systemic outcomes. bDMARDs take about 3-5 months to act and retreatment may be required at 6-12 months. The majority of studies suggest that a minimum of 2–3 years of

steroid-free remission of uveitis should precede any attempt at reducing the dose of csDMARDs and bDMARDs and deciding on their tapering.

13. How should treatment be titrated while planning pregnancy for a patient of uveitis, stable on IMTs.

Pregnancy presents a challenge in the management of uveitis. Although uveitis may be well controlled at the start of pregnancy, pregnancy and immunosuppression can interfere with fetal well-being resulting in abnormalities or prematurity-related issues. During the first trimester in pregnancy, uveitis can flare up while in the second and third trimester, inflammation can reduce on its own because of the increase in intrinsic hormones. Due to ethical issues, there are no randomized control trials of drug safety in pregnancy with active uveitis. Irrespective of their clinical uveitic activity, all patients on immunosuppressants should be advised and counselled regarding family planning.

14. What are the options/choices for treating a pregnant patient with active uveitis?

It is recommended that the rheumatologists and obstetricians along with the treating ophthalmologists discuss with patients the risk of disease progression and the risk to the fetus. It is also important to have a detailed ultrasound between 12 and 16 weeks of pregnancy to detect anomalies. In isolated uniocular disease, it may be safer to use local acting periocular or intraocular steroids, which reduce the systemic side effect of the drugs.

15. Which IMTs are safe and recommended to be used in pregnancy?

The drugs which have been shown to be safe in pregnancy are steroids (low dose), hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, and TNF-blockers like infliximab, adalimumab, and certolizumab. However, a placental transfer of these drugs is known to exist. Infliximab can be limited to the first trimester, adalimumab to the second trimester, and certolizumab to the third trimester since it has a low placental transfer.

The drugs which are not advised to be taken when planning a pregnancy are methotrexate, mycophenolate, cyclophosphamide, and leflunomide.

Children in whom the mothers have been exposed to TNF-blockers should not be administered live-attenuated vaccines until 7 months of age. Other biologicals like rituximab and tocilizumab have limited data and are preferably avoided in pregnancy. Methotrexate, mycophenolate and cyclophosphamide should be avoided in both men and women at least 3–6 months before planning a pregnancy.

16. What is the role of intra-vitreal injection of IMTs?

Intravitreal Methotrexate 400 µg/0.1 mL has been used primarily in the treatment of intraocular lymphoma but may also be used in other posterior or panuveitis.

It induces immunosuppression through the inhibition of leukocyte differentiation and has been found to be well tolerated and an effective corticosteroid-sparing agent.

Biologics in Uveitis

Vijay Pratap Singh Tomar, Amit Khosla

Uveitis is a potentially blinding disease due to frequent recurrences that may damage the delicate ocular anatomy and physiology with each active episode. Based on etiology it can be broadly classified into infectious uveitis (IU) and non-infectious uveitis (NIU). NIU are considered mostly auto-immune in nature and require suppression of both inflammatory and immunological component.

The management approach to a patient with chronic non-infectious is always challenging. Use of corticosteroids was first advocated by Gordon in 1956 for the successful management of uveitis. Later in the 1960s 6-mercaptopurine and methotrexate were used in the treatment of recalcitrant non-infectious uveitis. In 1994, CM-T412 was the first biologic used in the management of chronic non-infectious uveitis and etanercept was the first tumor necrosis factor alpha (TNF α) inhibitor prescribed for the management of juvenile idiopathic arthritis associated uveitis in children.

Biologics:

Biologics are therapeutic proteins which are designed to block the activity of biologically active molecules and thus controls the inflammation without causing generalised damage. Most biologics are monoclonal antibodies directed against one specific cytokine, one specific type of inflammatory cell, or one specific cell surface receptor and thus selectively inhibit some specific part of immune system to prevent inflammation induced anatomical and functional damage to eye without generalised suppression of immune system.

Monoclonal antibodies:

These are basically an antibody produced by a single clone of cells or cell lines and consisting of identical antibody molecules. Based on the origin and method of synthesis, mAb can be further divided into-

- **i.** Murine mAb ("–omab"): generally used to rodents like rats and mice
- **ii.** Chimeric mAb ("–ximab"): prepared by combining genetic material from mice with genetic material from human beings.
- **iii.** Humanized mAb ("–zumab"): Humanized antibodies made in a similar way to chimeric antibodies but contains higher (90-95%) human genetic materials.
- **iv.** Human mAb ("-umab"): produced by first transferring human immunoglobulin genes into murine genome.
- **v.** Fusion proteins: They are Fc based fusion proteins composed of immunoglobulin Fc domain directly linked to another proteinaceous molecule of interest. The suffix "-cept" is usually used to denote such proteins. E.g. Etanercept

Biosimilar:

It is a "biological product highly similar to the approved innovator product, with no clinically meaningful differences in safety, purity, and potency hence they are cheaper and widely available.

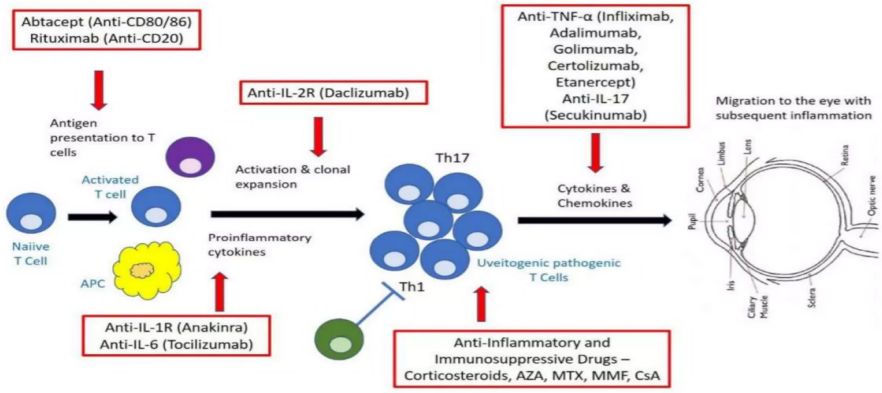
Based on the target receptor, biologics can be classified into following categories:

Tumor necrosis factor alpha (TNF α) inhibitors: Adalimumab, Cetrolizumab Etanercept, Infliximab, Golimumab

i. Interleukin inhibitors: Tocilizumab
ii. B-cell inhibitors: Rituximab
iii. Fusion protein of CTLA-4: Abatacept

Small molecule drugs:

Janus kinase inhibitors (JAK inhibitors or jakinibs) are often confused as biologics since both can have targeted effects in the body but they are different from biologics as they are made from chemicals and have a simple structure which is well defined, making them easier to copy for generic version.



CRITICAL CHECKPOINTS IN DISEASE PATHOGENESIS
TARGETS FOR IMMUNOTHERAPY

Courtesy: Trivedi A, Katelaris C. The use of biologic agents in the management of uveitis. Intern Med J. 2019;49(11):1352-1363

Biologics available in India:

Tumor necrosis factor inhibitor	B cell inhibitors	Interleukins inhibitor
Adalimumab[a]	Rituximab[b]	Tocilizumab[c]
Infliximab[b]		
Golimumab[c]		

a:biosimilar drug, b: original and biosimilar drug, c: original drug

Indications:

Biologics are commonly used in systemic diseases like rheumatoid arthritis, systemic lupus erythmatosus, granulomatosis with polyangitis (Wegner's), psoriatic arthritis, ankylosing spondylitis, Crohn's disease, lymphoma, sarcoidosis, and Behcet's disease.

Since this group of drugs are helpful in achieving the complete remission in systemic diseases, they are also used in all chronic/ recalcitrant non-infectious anterior, intermediate, posterior and panuveitis, scleritis, and idiopathic orbital inflammatory disease cases which are not responding to conventional treatment.

Adalimumab, infliximab, rituximab, golimumab and tocilizumab is available in India but the cost and adverse effects of therapy are the major issues associated with them.

Drug	Indications
TNF inhibitors	Recalcitrant non-infectious anterior, intermediate uveitis, posterior uveitis, panuveitis
Interleukin inhibitors	Systemic Vasculitis, chronic macular oedema
B cell inhibitors	Scleritis, Idiopathic orbital inflammatory disease and optic neuropathies

Adalimumab is a fully humanised monoclonal antibody directed against TNF- α and it was approved in 2016 by FDA for the management of chronic recalcitrant non-infectious anterior, intermediate, posterior and panuveitis cases. Since it is human monoclonal antibody, the risk of allergic reactions and loss of efficacy are low. The advantage of adalimumab over other biologics is that it is administered subcutaneously. Recent studies have supported the use of adalimumab in sarcoidosis-related uveitis, VKH syndrome and birdshot chorioretinopathy.

Like adalimumab, golimumab is also a fully humanized monoclonal antibody with slmost similar safety profile and is used in JIA associated uveitis, ankylosing spondylitis associated uveitis and Behcet's disease refractory to TNF-α inhibitors.

Infliximab is a chimeric monoclonal antibody and can be used as first line therapy for selected diseases such as Behcet's disease or in cases of moderate to severe idiopathic retinal vasculitis and optic disc inflammation or as third-line therapy in uveitis refractory to corticosteroids and conventional DMARDs.

Tocilizumab (STOP study) has shown promising results in the management of non-infectious uveitis with regard to minimizing the corticosteroids dosage, reducing vitreous haze score (≥ 2 steps), and improving visual acuity with a relatively benign safety profile.

Rituximab is a chimeric monoclonal antibody directed against the activation of B- cell production and is useful in the management of scleritis and non-infectious uveitis refractory to other drugs.

Etanercept is not recommended in uveitis as it's not very effective in attaining the remission of the disease and the prevention of recurrences.

Laboratory investigations to be done prior to starting BRMs:

1. Complete blood count
2. Erythrocytic sedimentation rate (ESR)
3. C-reactive protein
4. Mantoux test
5. QuantiFERON TB gold test
6. HRCT chest (better tool to pick up latent TB than chest X-ray)
7. VDRL, TPHA
8. Urine analysis: routine , microscopy
9. Liver function test
10. ELISA for HIV1,2
11. Hepatitis B surface antigen
12. Anti-hepatitis B antibody
13. Anti-hepatitis C antibody

A complete systemic evaluation by a general physician is a must to rule out any congestive heart failure, demyelinating diseases, malignancies, and infections prior to start the biologics. Haematological analysis, liver function test and renal function test should be done at every 3 monthly intervals while patient is on treatment.

Duration of treatment:

There is no consensus on the optimum time to stop and tapering schedule of the biologics but majority of the studies suggest that a minimum of 2-5 years of steroid free remission of uveitis should precede any attempt to reduce the dose or to stop them.

Common adverse effects:

1. Hypersensitivity reaction
2. Systemic infection
3. Flaring up of latent systemic infection
4. Reactivation of TB
5. Reactivation of hepatitis B
6. Blood disorders: Neutropenia, thrombocytopenia
7. Hepatotoxicity
8. Drug induced lupus
9. Demylinating disease

Patients on anti-TNFα therapy should be up-to-date for pneumococcal, influenza, and hepatitis B vaccines. Live virus vaccines are contraindicated in patients who are on anti-TNF therapy.

Children whose mothers have been exposed to TNF blockers should not be vaccinated with live attenuated vaccine until 7 month of age.

Safety in pregnancy:

TNF blockers like adalimumab, infliximab, and certolozumab are considered safe during pregnancy. There is, however, a placental transfer of these drugs occur. Infliximab can be limited to first trimester, adalimumab to the second trimester and certolizumab to the third trimester since it has a low placental transfer.

Other biologics like rituximab and tocilizumab have very limited data so they should be avoided in pregnancy. It's advisable to discuss with the patient regarding the risk of disease and risk to the foetus.

It's better to avoid pregnancy till 5 months after stopping the last dose of biologics.

Conclusion:

Biologics are thus potent medications and very useful when convention therapy has failed or poorly has been poorly tolerated, or to treat concomitant uveitis and systemic inflammation. They are limited in their use at this point of time because of the cost involved but they are the future of uveitis management.

References:

1. *Agrawal H, Doan H, Pham B, Khosla A et al. Systemic immunosuppressive therapies for uveitis in developing countries. Indian J Ophthalmol2020;68:1852-62*
2. *Priyanka, Biswas J. Biologicals in uveitis. J Clin Ophthalmol Res 2017; 5:3-10*

Intravitreal Injections in Uveitis

Dhaivat Shah, Manisha Agarwal

1. Enumerate intravitreal antibiotics used for infectious uveitis and their dosages.

ANTI-BACTERIAL	Vancomycin	1.0mg/ 0.1mL
	Ceftazidime	2.25mg/0.1mL
	Amikacin	0.4mg/0.1mL
	Gentamycin	0.1mg/0.1mL
	Moxifloxacin	0.5mg/0.1mL
ANTI-FUNGAL	Amphotericin B	0.05mg/0.1mL
	Voriconazole	0.1mg/0.1mL
ANTI-VIRAL	Ganciclovir	2mg/0.05mL
	Foscarnet	2.4mg/0.1mL
ANTI-PROTOZOAL	Clindamycin	1mg/0.1mL

2. What is the role of anti-vegf agents in uveitis?
Which anti-vegfs have been safely used in uveitis?

Role of Anti-VEGF Agents in Uveitis
i. Reduction of Macular Edema
ii. Control of Neovascularization
iii. Adjunctive local therapy in tubercular granulomas

Anti-VEGF Agents Used in uveitis
i. Bevacizumab (Avastin)
ii. Ranibizumab (Accentrix/Biosimilars)
iii. Aflibercept (Eylea)

3. Describe the doses & regimens of various intravitreal antivirals in treating cytomegalovirus (CMV) retinitis in uveitis patients.
Below are the doses and regimens for commonly used intravitreal antiviral agents:
i. Ganciclovir
A. Dose: 2 mg/0.05 mL
B. Regimen: Administered twice weekly until retinitis is controlled, followed by maintenance doses typically once a week.

ii. Foscarnet
A. Dose: 2.4 mg/0.1 mL
B. Regimen: Administered twice weekly until retinitis is controlled, with maintenance dose as once a week.

iii. Cidofovir
A. Dose: 20 µg/0.1 mL
B. Regimen: Given every other week until control is achieved followed by maintenance dose as necessary.
C. Cidofovir is less commonly used due to potential side effects, including anterior uveitis and hypotony.

4. What are the broader indications for using intravitreal steroids in uveitis?
Intravitreal steroids are used in uveitis for early management of inflammation specially in vision threatening uveitis.
The following are the broader indications for their use:
i. Macula threatening non-infectious uveitis
ii. Chronic non-Infectious Uveitis
iii. Macular Edema
iv. Vitritis
v. Post-Surgical Inflammation
vi. Combination Therapy with Immunosuppressive Agents

5. How would you choose intravitreal steroids formulation in uveitis?
Several factors are considered for choosing an appropriate intravitreal steroid formulation in uveitis: uveitis subtype, the location of inflammation, the severity of the disease, patient-specific factors, and potential side effects.

The following is the guide to help in making this decision:
i. Type of Uveitis
A. Anterior uveitis: Typically managed with topical or periocular steroids.
B. Intermediate, Posterior, or Panuveitis: Intravitreal steroids are more commonly used to avoid systemic complications.

ii. Severity and chronicity
A. Acute Inflammation: May benefit from a short-acting steroid like triamcinolone.
B. Chronic or Recurrent Inflammation: Long-acting implants (e.g., dexamethasone or fluocinolone) are preferred for sustained release and prolonged control.

iii. Location of inflammation
A. Macular edema: intravitreal steroids are effective in reducing macular edema secondary to uveitis.
B. Vitritis: intravitreal steroids help in early reduction of the inflammation

iv. Patient-specific actors
A. Glaucoma: Avoid or carefully monitor in patients with a history of glaucoma due to the risk of elevated intraocular pressure.
B. Cataract: Consider the risk of cataract formation, especially in phakic patients.
C. Previous Treatment Responses
D. Evaluate the patient's response to previous treatments, including efficacy and side effects, to guide future therapy choices.

6. What are risks and benefits of peri-ocular steroids?

Benefits:

i. Targeted delivery: Peri-ocular injections deliver high concentrations of steroids directly to the site of inflammation, enhancing efficacy.

ii. Reduced systemic side effects: Compared to systemic steroids, peri-ocular steroids minimize systemic exposure and related side effects.

iii. Effective for chronic conditions: Useful for managing chronic inflammation in intermediate, posterior, or panuveitis.

iv. Decreased frequency of administration: Longer duration of action than topical steroids, leading to fewer administrations.

Risks:

i. Elevated intraocular pressure: Risk of steroid-induced glaucoma, requiring regular monitoring.

ii. Cataract formation: Increased risk of posterior subcapsular cataract, especially with repeated injections.

iii. Infection: Potential risk of injection site infection or endophthalmitis

iv. Pain and discomfort: Discomfort during and after the injection though often transient.

v. Local complications: Risk of orbital fat atrophy, ptosis or hemorrhage

7. What are the off-label indications for using intravitreal steroids/intravitreal injections in uveitis?

The indications for Intravitreal steroids (off-label use) in uveitis are:

i. Refractory macular edema: Persistent macular edema secondary to uveitis not responding to conventional therapy.

ii. Recalcitrant vitritis: Persistent or severe vitritis requiring direct intraocular anti-inflammatory effect.

iii. Post-Surgical inflammation: Severe inflammation following ocular surgeries such as cataract or vitrectomy in uveitis patients.

iv. Combination therapy: Used in conjunction with systemic immunosuppressants for enhanced control of severe uveitis or vision threatening uveitis.

v. Prophylaxis in high-risk patients: Prophylactic use in patients with a history of severe recurrent uveitis to prevent flare-ups.

8. What are the contraindications for using intravitreal steroids in uveitis?

Absolute contraindications:

i. Active ocular or periocular infection: Risk of exacerbating infections particularly viral infections like herpes simplex.

ii. Hypersensitivity to steroid compounds: Known allergy to the steroid formulation being used.

Relative contraindications:

i. Glaucoma: Caution in patients with a history of glaucoma or ocular hypertension as steroids may elevate intraocular pressure.

ii. Advanced cataracts: Patients with significant cataracts may experience progression of lens opacity.

iii. Recent ocular surgery: Increased risk of infection in eyes that have recently undergone a surgery due to local immunosuppression.

iv. Systemic conditions: uncontrolled diabetes may increase the risk of infection and endophthalmitis and high blood pressure or recent history of coronary artery disease may increase the risk of stroke after anti-VEGF injection.
v. Ocular surface disease: Pre-existing conditions like severe dry eye or significant ocular surface inflammation can be exacerbated by intravitreal steroids

9. What standard precautions are taken before and after intravitreal injections?
Before Injections:
i. Patient consent and education: An informed consent is mandatory before an intravitreal injection explaining the procedure, potential benefits and side effects.
ii. Review medical history: for drug allergies and any contraindications such as active ocular infection, glaucoma.
iii. Aseptic technique: Ensure a sterile environment to minimize the risk of infection and give intravitreal injections in operation theatre set up under strict aseptic precautions
a. Preparation: Clean the periocular skin and eyelids with povidone-iodine.
b. Sterile instruments: Use sterile gloves, drapes, and instruments.
iv. Topical anesthesia: apply topical anesthetic drops prior to the injection
v. Antiseptic application: Apply povidone-iodine to the conjunctival sac to further reduce the risk of infection
vi. Pre-injection assessment: Evaluate intraocular pressure (IOP) and perform a brief slit-lamp examination.

After Injections:
i. Immediate post-procedure care:
a. Apply an antibiotic drop to the eye to reduce the risk of infection.
b. Gently patch the eye if necessary.

ii. Patient instructions:
a. Inform the patient to monitor for any signs of infection, increased pain, vision changes, or severe redness.
b. Provide guidance on activity restrictions and follow-up appointments.
iii. Follow-up:
a. Schedule a follow-up visit to assess the injection site, intraocular pressure, and overall response to treatment.
b. Regularly monitor for potential complications such as endophthalmitis, retinal detachment, or elevated IOP.

10. What are the side effects of intravitreal corticosteroid injections?
Common Side Effects:
i. Increased intraocular pressure (IOP): Steroids can cause a rise in IOP, potentially leading to glaucoma. Requires regular monitoring and management with IOP-lowering medications.
ii. Cataract formation: Particularly posterior subcapsular cataracts, which may progress and require surgical intervention.
iii. Ocular discomfort: Mild pain or discomfort at the injection site, usually transient.

Less Common but serious side effects:
i. Infection (Endophthalmitis): rare but a serious complication. Patients should be advised to report symptoms such as severe pain, redness, or vision loss immediately.
ii. Retinal detachment: may occur secondary to the injection process or induction of

posterior vitreous detachment after the intravitreal injection. Symptoms include a sudden increase in floaters, flashes of light or a black shadow in the field of vision.
iii. Vitreous hemorrhage: bleeding in the vitreous cavity causing vision loss or floaters.
iv. Uveitis: Inflammation of the uveal tract can be triggered or exacerbated.
v. Hypotony: abnormally low intraocular pressure causing decrease in vision.

Rare Side Effects:
i. Ocular surface disease: Prolonged use may exacerbate dry eye or other ocular surface conditions.
ii. Ptosis: Drooping of the upper eyelid due to the injection.
iii. Orbital fat atrophy: Localized loss of orbital fat leading to cosmetic changes.

References

1. *Sallam AB, Kirkland KA, Barry R, Soliman MK, Ali TK, Lightman S. A Review of Antimicrobial Therapy for Infectious Uveitis of the Posterior Segment. Med Hypothesis Discov Innov Ophthalmol. 2018 Winter;7(4):140-155. PMID: 30505865; PMCID: PMC6229674.*
2. *Sugita S. Intravitreal anti-inflammatory treatment for uveitis. Br J Ophthalmol. 2007 Feb;91(2):135-6. doi: 10.1136/bjo.2006.105601. PMID: 17244658; PMCID: PMC1857624.*
3. *Modugno, R.L., Testi, I. & Pavesio, C. Intraocular therapy in noninfectious uveitis. J Ophthal Inflamm Infect 11, 37 (2021). https://doi.org/10.1186/s12348-021-00267-x*
4. *Sudharshan S, Ganesh SK, Biswas J. Current approach in the diagnosis and management of posterior uveitis. Indian J Ophthalmol. 2010 Jan-Feb;58(1):29-43. doi: 10.4103/0301-4738.58470. PMID: 20029144; PMCID: PMC2841371.*

HIV and Uveitis

Bhuvan Eshwaran, Amitabh Kumar

1. Features of HIV retinopathy:

i. Retinopathy in HIV/AIDS can be due to Virus per se or can be due to opportunistic infections. Microangiopathy is the most common ocular manifestation in HIV retinopathy and is associated with low CD4 counts. This is due to the virus per se. Clinical findings include cotton wool spots with or without intraretinal hemorrhages and microvascular changes like microaneurysms and telangiectasia. Patients remain relatively asymptomatic till posterior pole is involved. A subset of patients are noted to have loss of nerve fiber layer which manifests clinically as decreased contrast sensitivity, abnormal color vision and visual field loss. (Fig 1.)

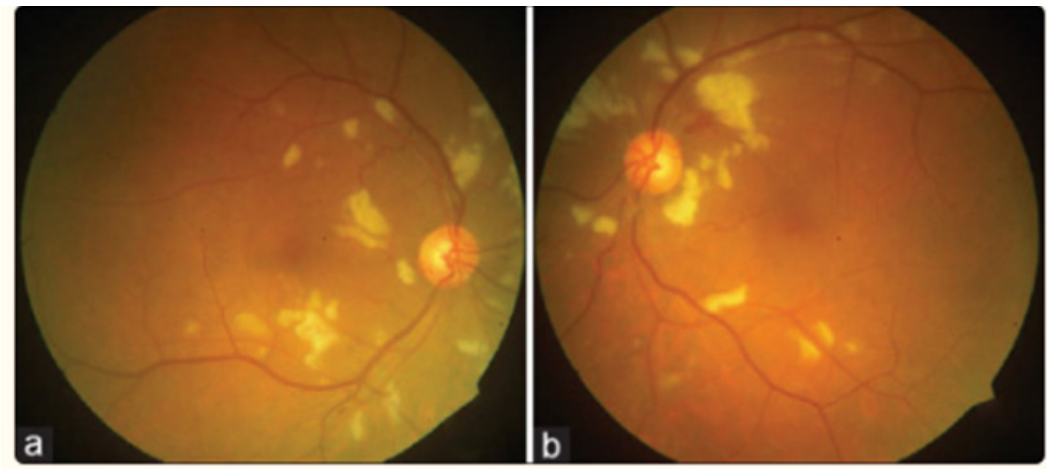
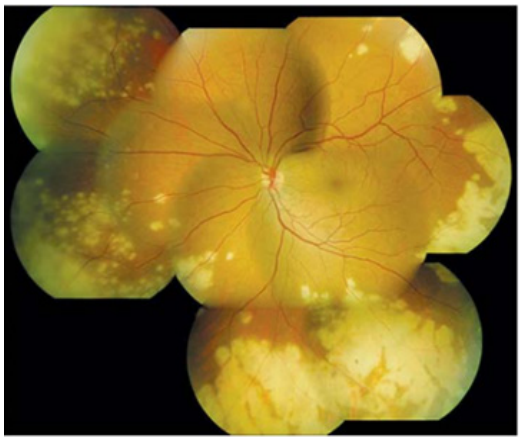


Fig 1: *HIV microangiopathy with cotton wool spots*

ii. Retinal whitening and hemorrhages are characteristics of necrotizing retinitis, which are due to opportunistic infections. The lesions are usually multifocal and progress rapidly. There are two clinical forms: Acute retinal necrosis(ARN) and Progressive outer retinal necrosis(PORN). ARN is characterized by peripheral retinal necrosis with vasculitis and significant vitritis. Multifocal, deep retinal infiltrates with minimal vitritis characterize PORN. Retinitis can have associated secondary vascular occlusions. (Fig 2.)



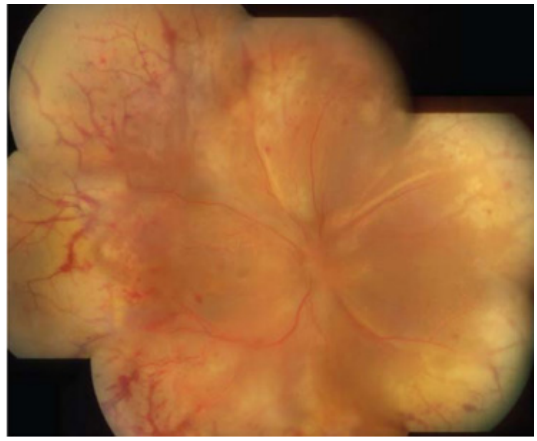
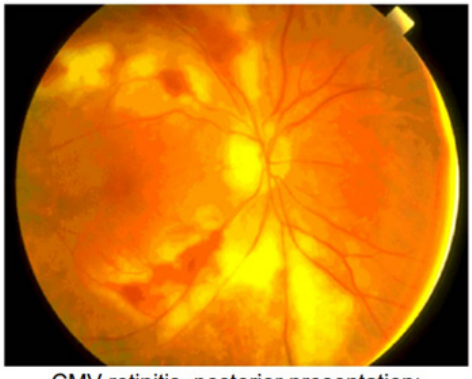


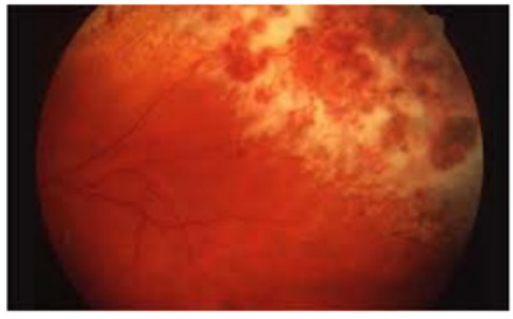
Fig 2: *Acute Retinal Necrosis (ARN)* *Progressive outer retinal necrosis (PORN)*

iii. CMV retinitis is the commonest ocular opportunistic infection. There are three clinical types:1. Classic type - cottage cheese with ketchup retinopathy which is seen as confluent areas of retinal necrosis with hemorrhages in the posterior pole. 2. Granular type – which is characterized by granular peripheral retinal lesions with little or no haemorrhages. 3.Frosted branch angiitis type- which is characterized by diffuse vascular sheathing. (Fig 3.)



CMV retinitis, posterior presentation:
Crumbled cheese and ketchup

Fig 3



CMV retinitis, peripheral presentation: ***Brushfire***

iv. Retinochoroidal and choroidal lesions can be due toopportunistic infections like Toxoplasmosis, Cryptococcosis or Pneumocystis. Ocular tuberculosis or syphilis also have variable presentation when associated with HIV.

References

- *Sudharshan, Sridharan et al. "Ocular lesions in 1,000 consecutive HIV-positive patients in India: a long-term study." Journal of ophthalmic inflammation and infection vol. 3,1 2. 3 Jan. 2013, doi:10.1186/1869-5760-3-2.*
- *Moraes HV. Ocular manifestations of HIV/AIDS. Curr Opin Ophthalmol. 2002 Dec;13(6):397-403.*
- *Robinson MR, Ross ML, Whitcup SM. Ocular manifestations of HIV infection. Curr Opin Ophthalmol. 1999 Dec;10(6):431-7.*
- *Cunningham ET, Margolis TP. Ocular manifestations of HIV infection. N Engl J Med. 1998 Jul 23;339(4):236-44.*
- *Jabs DA, Drye L, Van Natta ML, Thorne JE, Holland GN; Studies of the Ocular Complications of AIDS Research Group. Incidence and long-term outcomes of the human immunodeficiency virus neuroretinal disorder in patients with AIDS.Ophthalmology. 2015.*

2. List the opportunist infections in HIV:

A. The following is the list of ocular opportunistic infections:

1. Herpes Zoster Ophthalmicus (HZO)
2. Viral Keratitis- HSV1/2, VZV or CMV
3. CMV Retinitis
4. Other Viral Retinitis- ARN/PORN
5. Ocular Toxoplasmosis
6. Ocular Tuberculosis
7. Ocular Syphilis
8. Ocular Cryptococcosis
9. Ocular Pneumocystis1

B. The following is the list of systemic opportunistic infections:

CD4 count	**Oppurtunistic infection**
All CD4+ count	Mycobacterium tuberculosis
CD4+ count less than 250 cells/mm^3	Coccidioidomycosis
CD4+ count < 200 cells/mm^3	Pneumocystis jirovecii pneumonia Mucocutaneous candidiasis
CD4+ count < 150 cells/mm^3	Histoplasma capsulatum
CD4+ count < 100 cells/mm^3	Cryptococcus neoformans Cryptosporidiosis Herpes simplex viruses (HSV) Microsporidiosis
CD4+ count < 50 cells/mm^3	Cytomegalovirus Mycobacterium avium complex (MAC) Toxoplasma gondii Bartonellosis
Coexisting infections with HIV Syphilis Human papillomavirus infection Hepatitis B virus infection Hepatitis C virus infection	

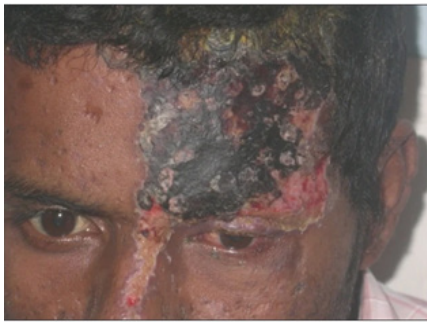
References

WHO HIV/AIDS fact sheet. Geneva: World Health Organization; 2019. Available from: https://wwwwhoint/en/news-room/fact-sheets/detail/hiv-aids . Last cited on 2019 Jul 11.
https://www.ncbi.nlm.nih.gov/books/NBK539787

3. Uveitis manifestations: Immune-competent Vs Immune-suppressed:

Clinical picture of any disease becomes atypical and aggravated in immune-compromised conditions. The lesions can be at atypical sites. The degree of inflammation depends on the CD4 level and immune status of the patient. For example, a toxoplasma lesion in an immunocompetent person is at posterior pole and is usually a single lesion. In an HIV positive patient, the lesions can be multiple and in periphery (atypical). Sometimes there can also be CNS lesions related to the same. Hence the patient needs to be questioned for neurological symptoms. The amount of inflammation is variable depending on the immune status and CD4 count of the patient.

4. Approaching the eyes of HIV patients in the uveitis clinic:



Do both ocular and external examination.

i. External examination gives clues - herpes zoster ophthalmicus (HZO)

ii. Dysphagia- esophagitis- associated with CMV retinitis

Performing a complete Eye examination is a must.

Anterior segment:

i. Keratoconjunctivitis sicca

ii. Iridocyclitis

iii. Uveitis without any lesions- in HAART naive patients or in nonresponders (on long term treatment and persistently low CD4 count) or

iv. Immune recovery Uveitis (on HAART / higher CD4 count/low viral load)

PCR from aqueous aspirate for HSV, VZV, CMV, MTB, and toxoplasma- can help confirm/rule out other infections. Real-time PCR indicates the actual number of viral copies and can help us in assessing the efficacy of the treatment.

Treatment:

Topical steroids/ NSAIDS to control the inflammation, with cycloplegics.

If there is any opportunistic infection, anti-microbials are added to the anti-inflammatory therapy.

Reference:

Selvaraj JR, Sudharshan S, Therese LK, Janani MK, Selvamuthu P, Rewri P, Biswas J. Real-time polymerase chain reaction for diagnosis and management of HIV-induced uveitis. Indian J Ophthalmol. 2018 Nov;66(11):1634-1636. doi: 10.4103/ijo.IJO_509_18. PMID: 30355888; PMCID: PMC6213659.

Posterior Segment:

Lesions directly due to HIV (like retinopathy) are already discussed above.

Lesions due to opportunistic infection are listed as follows:

Herpes zoster ophthalmicus

The risk of developing HZO is 6.6 times higher in HIV infected individuals than in the general population.

Treatment :

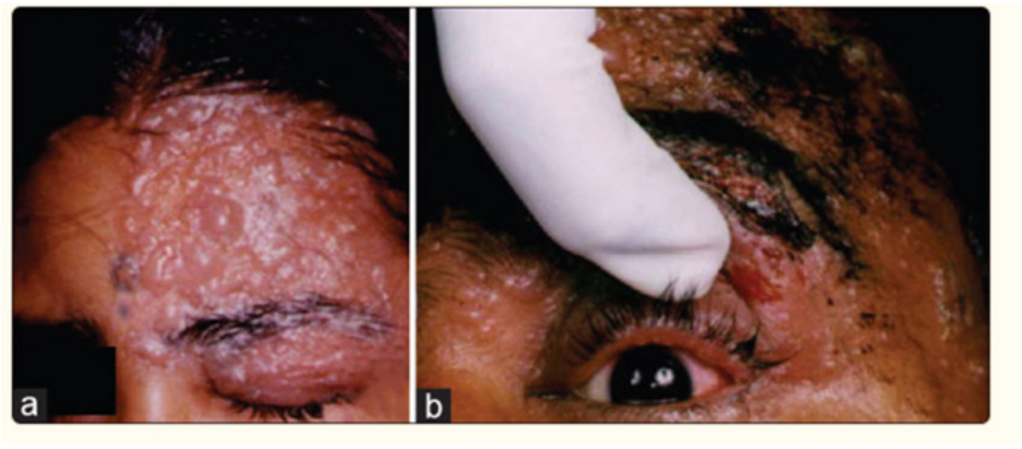
Oral Acyclovir 800 mg five times a day

or

Oral Valacyclovir 1 gram thrice daily (for 3 to 6 weeks)

Reference:

1. *Jeng BH, Holland GN, Lowder CY, Deegan WF, 3rd, Raizman MB, Meisler DM. Anterior segment and external ocular disorders associated with human immunodeficiency virus disease. Surv Ophthalmol. 2007;52:329–68.*
2. *Johnson JL, Amzat R, Martin N. Herpes Zoster ophthalmicus. Prim Care. 2015;42:285–303*



(a) External photograph of a HIV positive patient with herpes zoster ophthalmicus (HZO) showing the vesiculo bullous rash along the trigeminal nerve distribution V1, V2 segments, (b) note the necrotic skin lesions and ocular involvement

Viral Keratitis/ Sclero-keratitis:

Can be due to Varicella -Zoster virus (VZV), Herpes Simplex 2 virus (HSV), and Cytomegalovirus (CMV).

Treatment:

Topical and systemic antivirals.

For VZV and HSV - Acyclovir eye ointment five times daily.

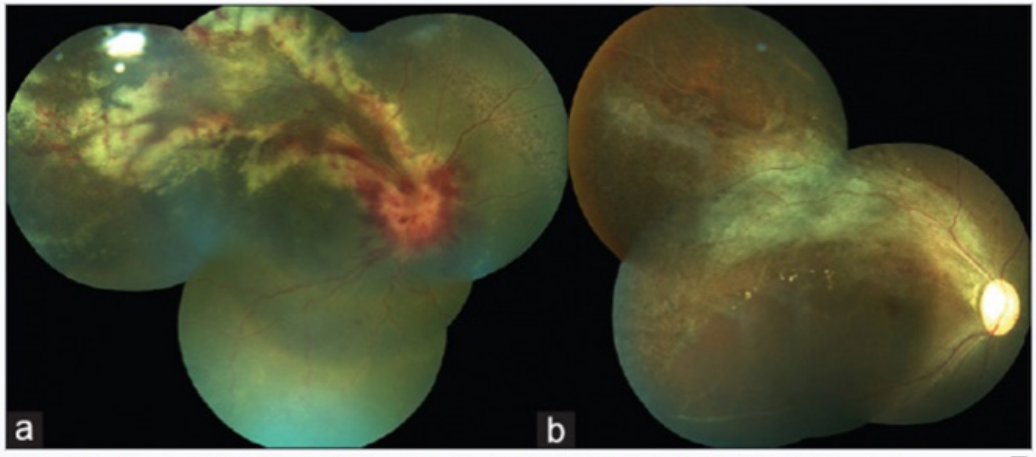
For CMV- Ganciclovir gel 0.15% five times daily (until healing occurs) followed by three times daily for 7 days.

For VZV and HSV – Acyclovir (800 mg five times a day) or Valacyclovir (1 gram thrice daily for 3 to 6 weeks)

For CMV-Valganciclovir 900 mg twice daily

Low dose topical steroids may be cautiously given in select cases reduce surface/ stromal inflammation. In recurrent cases, long term oral antiviral prophylaxis is recommended.

CMV retinitis:



Active(a) and healed (b) CMV retinitis From Tripathy K, Mittal K, Venkatesh P, Bakhshi S, Chawla R. Treatment of unilateral zone I cytomegalovirus retinitis in acute lymphoblastic leukemia with oral valganciclovir and intravitreal ganciclovir. Oman J Ophthalmol [serial online] 2017 [cited 2018 Dec 2];10:250-2. Available from: http://www.ojoonline.org/text.asp?2017/10/3/250/215997

Treatment:

Induction dose:

IV Ganciclovir: 5 mg/kg twice daily for 14-21 days

or

Oral Valganciclovir – 900 mg twice daily

Maintenance dose:

IV Ganciclovir – 5 mg/kg/day to continue

or

Oral Valganciclovir – 900 mg once daily to continue

Intravitreal Ganciclovir: Induction - 2 mg/0.1 mL – twice weekly

maintenance - 2 mg/0.1 mL weekly

Reference:

1. *Stewart MW. Optimal management of cytomegalovirus retinitis in patients with AIDS. Clin Ophthalmol. 2010 Apr 26;4:285-99. doi: 10.2147/opth.s6700. PMID: 20463796; PMCID: PMC2861935.*
2. *Sudharshan S, Nair N, Curi A, Banker A, Kempen JH. Human immunodeficiency virus and intraocular inflammation in the era of highly active anti retroviral therapy - An update. Indian J Ophthalmol. 2020 Sep;68(9):1787-1798. doi: 10.4103/ijo.IJO_1248_20. PMID: 32823395; PMCID: PMC7690468.*

ARN/PORN:

Treatment:

Induction dose:

Intravenous Acyclovir: -500 mg 8th hourly for 2 to 3 weeks

(10-13mg/kg every 8 hours or 1500mg/m2/day intravenously)

Maintenance dose:

Oral Acyclovir- 800 mg 5 times daily (15 mg/kg in three divided doses) for 6 weeks to 3 months.

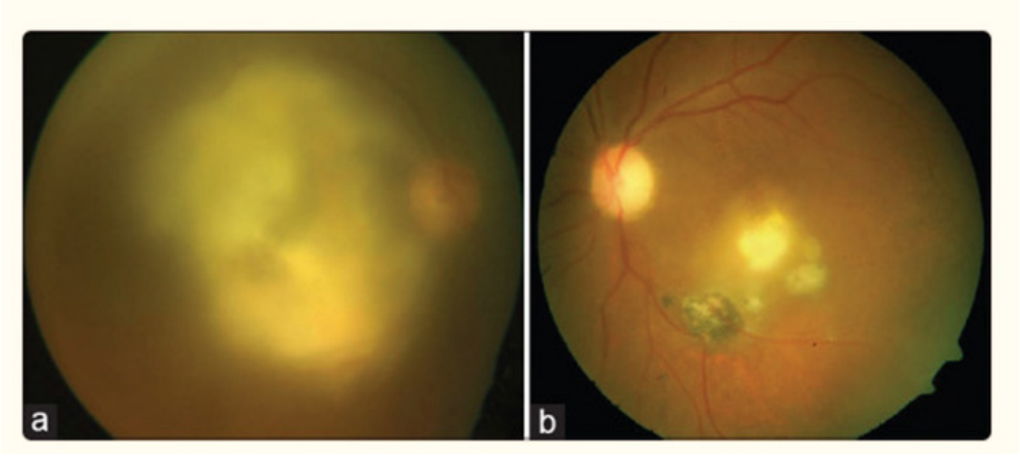
Or

Oral Valacyclovir: 1 gram three times daily

There is very high risk of developing retinal breaks and detachment. Hence, need for close follow up is advised. In case of detachment, vitreoretinal surgery is done under steroid + anti-viral cover.

Ocular Toxoplasmosis:

Atypical toxoplasmosis in HIV infected individuals can present as focal, multifocal, or diffuse necrotizing retinitis type with indistinct borders with or without hemorrhages. They can mimic CMV retinitis. Diagnosis is confirmed based on raised serumanti-toxoplasma IgM and IgG titers.PCR method seems more efficient in immunocompromised individuals with atypical retinitis



(a) Color fundus photograph of the right eye in a HIV positive patient showing intense vitritis with necrotizing retinochoroiditis at the posterior pole; (b) Color fundus photograph of the left eye in another HIV positive patient, showing an active toxoplasma lesion adjacent to a retino-choroidal scar

Treatment:

Pyrimethamine- 200 mg on the first day, followed by 75-100 mg daily

Sulfadiazine- 1-1.5 g four times daily, and

Folinic acid-10-50 mg daily

With/or (in sulpha allergy)

Oral Clindamycin-300 mg 4 times a day for 6 weeks.

Oral steroids are used to reduce the inflammation.

Intravitreal clindamycin is helpful as an adjunct to systemic therapy.

Reference:

Verma L, Thulasidas M, Gupta A. Intravitreal Clindamycin as First-Line Therapy for Toxoplasmic Retinochoroiditis: A Case Series. Clin Ophthalmol. 2020 Dec 7;14:4279-4285.

Ocular Tuberculosis:

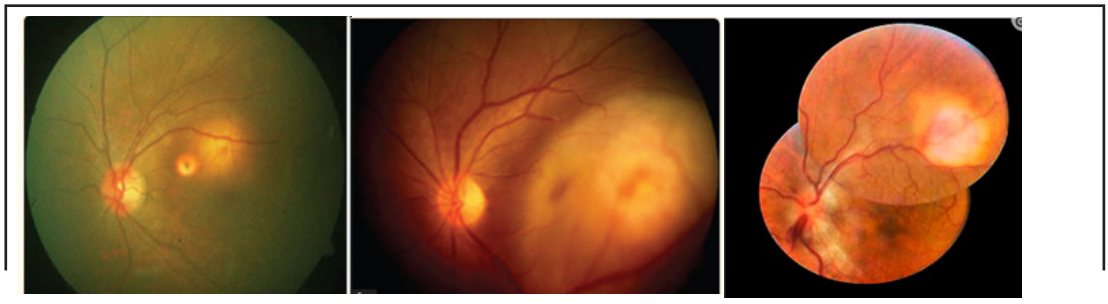
Ocular TB may be seen as part of disseminated systemic disease and may be a clue to diagnose a miliary disease. Usually, they are found as asymptomatic choroidal tubercles. Paradoxical worsening of tubercular infection following the initiation of HAART due to the improvement of the host's immune response to mycobacterial antigens is common and can have devastating complications. Systemic antitubercular therapy (ATT) is the treatment of choice along with HAART.

Treatment:

ATT along with oral steroids

New ATT regimen- $2H_7\ R_7\ Z_7\ E_7 + 4H_7\ R_7\ E_7$

(H=Isoniazid, R=Rifampicin, Z=Pyrazinamide, E=Ethambutol)



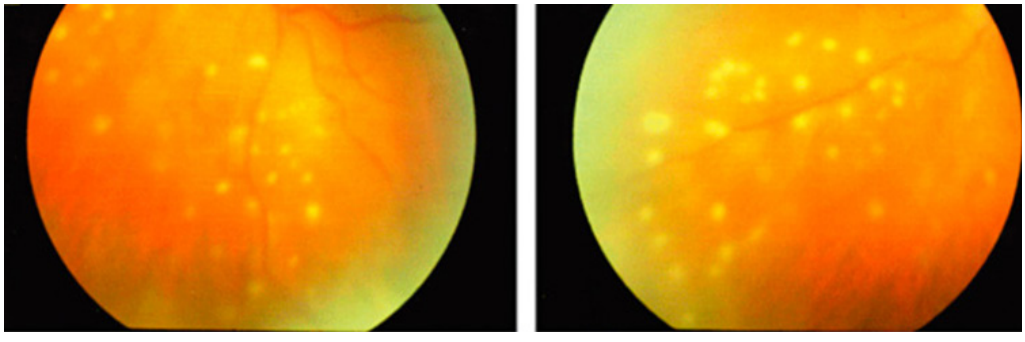
Choroidal tubercle *Sub retinal abscess* *Choroidal granuloma*

References:

Sudharshan S, Kaleemunnisha S, Banu AA, Shrikrishna S, George AE, Babu BR, et al. Ocular lesions in 1,000 consecutive HIV-positive patients in India: A long-term study. J Ophthalmic Inflamm Infect. 2013;3:2.

Babu RB, Sudharshan S, Kumarasamy N, Therese L, Biswas J. Ocular tuberculosis in acquired immunodeficiency syndrome. Am J Ophthalmol. 2006;142:413–8.

Ocular Syphilis: As the name of "the great imitator" the clinical findings of syphilitic uveitis are highly diverse and nonspecific. Any segment or disease stage may be associated with syphilitic uveitis and hence diagnosis is challenging. Panuveitis or posterior uveitis is the most common manifestation of syphilitic uveitis. It can also present as bilateral chorioretinitis.



Syphilitic panuveitis with punctate inner retinitis

Treatment: Aqueous crystalline penicillin G: 18-24 million units/day, administered as 3-4 million units IV every 4 hours or continuous infusion for 10-14 days, along with oral steroids to control the inflammation.

Other Choroiditis:

Pneumocystis carinii choroiditis

Deep orange lesions are characteristic.

Sulfamethoxazole and Trimethoprim is the treatment of choice.

(SMX- 50 -75 mg/kg/day+ TMP 10-15mg/kg/day)

Cryptococcus neoformans choroiditis - associated with meningitis.

Combination therapy of flucytosine and amphotericin B is the treatment of choice for cryptococcal meningitis.

An alternative regimen of fluconazole and flucytosine is used.[Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day) + flucytosine (100 mg/kg/day orally) for 2 weeks]

Reference:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9962278

5. What are the differences in the management approach between infectious and non-infectious uveitis in HIV-infected individuals

Infectious Uveitis is always the first to be suspected in case of HIV patients. Non infectious Uveitis is usually that of exclusion. Clinical picture of an infectious etiology is confirmed serologically because of atypical presentation.

Steroids are used with caution, after clearance from infectious disease specialist.

6. How does immune deficiency in HIV/AIDS patients affect the response to uveitis treatment?

The amount and duration of antibiotics required for treating a disease; the amount of inflammation that occurs secondary to infection and the amount of anti-inflammatory therapy required to treat- are all affected by the immune status of the patient.

For instance, a patient with high viral load and low CD4 count is expected to harbour plenty of opportunistic infections without much inflammation. So they require prolonged antibiotic with minimal anti-inflammatory therapy. Whereas, a patient with relatively less viral load and a high CD4 count with an infection will require less antibiotic and a relatively more anti-inflammatory treatment. And a patient with low viral load but a persistently low CD4 count will need prolonged antibiotic prophylaxis to prevent infection.

Treatment of uveitis is more challenging in patients with HIV disease than in immunocompetent patients. Every attempt should be made to encourage the use of HAART to promote immune reconstitution and to minimise the risk of HIV related complications. Any identified infections or neoplasms should be treated with specific antimicrobial or antineoplastic therapy, and drugs associated with uveitis should be discontinued, if possible, and replaced with alternative medications.

Finally, inflammatory complications such as heavy vitritis, cytoid macular oedema, or posterior synechiae should be treated with corticosteroids, often in conjunction with a cycloplegic/ mydriatic agent.

While this sort of systematic approach to the management of uveitis in HIV positive patients can be time consuming, and requires a close working relationship between the ophthalmologist, the patient, and the patient's primary medical doctor, such coordinated efforts are often successful at restoring and maintaining good vision.

Reference:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1723394/pdf/v084p00233.pdf

7. Is there a benefit of interdisciplinary collaboration between infectious disease specialists and ophthalmologists for HIV-infected patients with uveitis?

Yes. Since multiple systems are involved and the treatment is different in an immunosuppressed patient, a multidisciplinary approach is mandatory.

Reference:

https://www.ncbi.nlm.nih.gov/books/NBK554533.

8. What laboratory investigations are additionally required in diagnosis and management of uveitis in HIV-infected patients? (CD4 counts etc.)

1. CD4 count
2. Viral load
3. Treponemal and non-treponemal tests
4. Hepatitis B and C titres

9. Explain the role of immune reconstitution inflammatory syndrome (IRIS) contribute to uveitis in HIV-infected patients?

IRIS/IRU worsens the ocular inflammation. In view of this, the anti-inflammatory therapy needs to be stepped up.

The prevalence of immune reconstitution inflammatory syndrome (IRIS) from global research is unavailable but approximately 10–32% of patients with AIDS who received ART experienced IRIS. IRU (immune recovery uveitis) is one of the most common ocular manifestations of IRIS. It is defined as any new inflammation in an eye with controlled CMV retinitis or other ocular infections, not attributable to an alternative cause, following substantial recovery of immunity.

Currently, IRU has become an important cause of vision loss in patients with HIV who received ART. Hence, timing of ART is also important in treatment of the patient.

With the widespread availability of HAART, IRIS is to be watched for in any patient undergoing simultaneous treatment for HIV and tuberculosis.

Recommendation on timing of ART in HIV-TB Coinfection (WHO-Guidelines)[70]

Adults	TB treatment to be initiated first, followed by ART as soon as possible within the first 8 weeks (anytime between 2 weeks to 2 months) of ATT. CD4 counts <50 cells/μL-(HIV- TB patients with profound immunosuppression)- ART within the first two weeks of initiating TB treatment due to a higher risk of death.
Children	ART should be started in any child with active TB disease as soon as possible and within 8 weeks following the initiation of ATT, regardless of the CD4 cell count and clinical stage

Reference:

Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;58:1308–11.

10. What role does HAART (Highly Active Antiretroviral Therapy) play in the management of uveitis in HIV-infected individuals?

The HAART treatment basically targets all stages of the virus and virus infected cells throughout the body. Hence, IRIS and IRU are side effects that all patients experience at different scales, depending on the viral load and CD4 count of the person at the initiation of treatment. Hence HAART treatment increases the chances and need for anti-inflammatory treatment in patients to reduce the amount of damage in the vital tissues in the body.

The duration of antibiotics required to treat a condition and need for long term prophylaxis also depends on effectiveness of HAART therapy.

Reference:

https://www.ncbi.nlm.nih.gov/books/NBK554533/

Tuberculous Uveitis

Reesha Jithesh, Reema Bansal

1. What is Intraocular tuberculosis?

Intraocular tuberculosis is a well described form of extra-pulmonary tuberculosis that presents in the form of uveitis. While it is predominantly seen in the tuberculosis-endemic regions, it is now being increasingly recognised by uveitis specialists in tuberculosis non-endemic countries as well.

The term 'Ocular TB' is further classified as 'TB uveitis' when the inflammation is intraocular in location, and 'TB scleritis' when the inflammation involves the sclera.[1]

2. Is there any standardisation of terms used to describe the manifestations of tuberculous uveitis?

Based on the Standardisation of Nomenclature for Ocular Tuberculosis - the Collaborative Ocular Tuberculosis Study (COTS) Workshop, ocular tuberculosis (OTB) is a broad term used to define uveitis attributable to tuberculosis by the treating ophthalmologist based on positive immunological tests and radiological tests (and not necessarily a confirmed test such as histopathology or polymerase chain reaction).[1]

This standardisation of nomenclature for ocular tuberculosis is aimed at preventing ambiguity in communication amongst ophthalmologists and creating increased awareness regarding ocular tuberculosis.

a. Tubercular anterior uveitis (TAU) - if the inflammation is limited to the anterior segment (SUN classification - primary site of the inflammation is the anterior chamber, iris and ciliary body)

b. Tubercular intermediate uveitis (TIU) - for inflammation is limited to the vitreous as the primary site (pars plana area, posterior ciliary body and hyalitis as per SUN classification

c. Tubercular posterior uveitis (TPU) - if the inflammation is involving the retina and/or choroid (posterior uveitis as per SUN classification)

i. Serpiginous-like choroiditis (TB SLC) - Single/multiple discreet yellowish-white fuzzy choroidal lesions and slightly raised edges that show wave-like progression with an active serpiginous-like edge with central healing
ii. Tubercular multifocal choroiditis (TMC) - Multifocal choroiditis lesions with a phenotype similar to idiopathic multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and other phenotypes that do not resemble TB SLC
iii. Tubercles: single/multiple, small (≤ 0.5 disc diameter), discreet greyish-white lesions with a central core and surrounding rim of inflammation typically in a patient with miliary disease
iv. Tubercular focal choroiditis (TFC) - Unifocal choroiditis lesions that does not resemble TB SLC

v. Tuberculoma - Single/multiple yellowish subretinal lesion with indistinct borders and surrounding exudative fluid, along with oval/round lesion in the choroidal stroma. This would include Tubercular subretinal abscess (severe form with exudation, rapid necrosis and tissue destruction, and overlying retinal hemorrhages).

d. Tubercular retinal vasculitis (TRV) - If the patient has isolated retinal vasculitis (either periphlebitis and/or arteritis) with/ without occlusive disease

e. Tubercular Panuveitis (TBP) - If the inflammation is involving the anterior chamber, vitreous, and retina/choroid, (determined as panuveitis by the SUN working group)

f. Tubercular scleritis (TBS) - If the inflammation is involving the sclera and the disease is attributable to tuberculosis

3. What are clinical signs predictive of tubercular uveitis?

The presence of following clinical signs (in the presence of anterior chamber cells or vitreous cells) are high predictive of tubercular uveitis.[2]

a. Broad-based posterior synechiae

b. Multifocal serpiginoid choroiditis

c. Retinal perivasculitis with or without discrete choroiditis/scars

d. Choroidal granuloma (single or multifocal)

4. Elaborate on the basic workup (clinical and laboratory) for patients suspected with TB uveitis

Active uveitis patients suspected of having tuberculous etiology should undergo a detailed history including past incidence of TB, contact with active TB patients, systemic history suggestive of TB, history of immunosuppression or immune compromised states, past and present history of any other coexisting systemic diseases, workplace history, past and present country of residence amongst others.

Suspected TB uveitis patients are advised to undergo a TST (tuberculin skin test or Mantoux test) or IGRA (interferon-gamma release assay) to find immunological evidence of TB exposure, accompanied by radiological tests such X-Ray chest or CT-chest to find radiological evidence of TB.

If any of the above history and/or tests are positive, he/she should also undergo a detailed clinical evaluation by an internist.

Any evidences in the above steps will demand a detailed workup towards the etiological diagnosis.

It is pertinent to note that all other infectious/non-infectious causes of uveitis in the above group of patients have been ruled out by clinical or laboratory evidence.

5. Elaborate the procedure and interpretation of tuberculin skin test (TST) according to demography

a. Procedure: 1cc tuberculin syringe with a 27 Ga short bevel 1/4-1/2 inch needle is used to raise an intradermal wheal of 6-10 mm in diameter with the volume of 0.1ml of 5 TU of PPD tuberculin over the forearm 2-4 inches below the elbow joint.[3]

b. Reading: After 48 to 72 hours, presence of any induration (hard, dense, raised formation) is recorded in millimetres at its widest dimension over the skin at the point of injection. Erythema (redness) of the skin is not measured.

c. Interpretation[3]
   i. Induration ≥5 mm is considered positive in patients with HIV infection, organ transplants, immunosuppressed patients, close contacts of active TB patients and those showing fibrotic changes (or healed TB lesions) on chest radiography.
   ii. Induration ≥10 mm is considered positive in patients residing in TB endemic areas, laboratory workers or those working in high risk congregate settings (health care workers etc.), children ≤ 5 years and infants, children, adolescents exposed to adults in high risk categories, and those with high risk conditions (diabetes, advanced kidney disease, leukaemia etc.)
   iii. Induration ≥15 mm is considered to be positive in all patients with no known risk factors for TB.
   iv. Overwhelming TB illness, Hodgkin's disease, sarcoidosis, uremia, aging, corticosteroid use, and viral illness including HIV infection may be associated with false-negative reactions
   v. Measurement of 0 mm or below the defined cut-off point for above each category is considered negative
   vi. A positive Mantoux test indicates exposure to the TB bacilli (mycobacterium tuberculosis) but does not necessarily confirm active TB disease

d. Clinical correlation: The interpretation of TST in patients of uveitis should be done in the context of presence or absence of clinical signs predictive of TB uveitis, correlation with history, pertinent clinical examination and other diagnosis tests.

6. When should one order the interferon-gamma release assays (IGRA) for uveitis?

IGRA is a more specific marker of MTB exposure, not affected by prior BCG vaccine and nontuberculous mycobacteria.

Considering the cost issues related to IGRA, it may not be the first choice in all patients, when TST is available.

It is usually ordered when TST results are not available, or when one wants to further confirm the diagnosis when TST is negative but the clinical picture is highly suggestive of TBU.[4]

7. What is the difference in the interpretation of TST vs IGRA?

PPD skin test has a low positive predictive value and a high false negative rate in the absence of systemic disease, whereas IGRAs, although more specific, have a high false positive rate.

Thus, in the absence of clinical findings suggestive of TBU, physicians should not rely on positive IGRA as indication of disease diagnosis.

IGRA has a low pre-test probability in cases with low clinical suspicion, and the possibility of a latent TB in a patient with ocular inflammation not related to TB must be considered, especially in regions of the world where TB is endemic.

PPD skin test may be positive in patients immunized with Bacillus Calmette-Guerin (BCG) vaccination and in case of atypical mycobacteria.[5,22]

8. What are the essential clinical differences between classic serpiginous choroiditis and serpiginous-like choroiditis?

The essential clinical differences between classic serpiginous choroiditis and serpiginous-like choroiditis are tabulated below.[6,7]

	Serpiginous choroiditis (SC)	**Serpiginous-like choroiditis (SLC)**
Region specific	Though no geographical predilection, SC is more seen in Caucasian population	Populations endemic to tuberculosis
Etiology	Autoimmune	Presumed tubercular etiology (immune reaction to TB antigens)
Typical feature	Begins in the peripapillary region and spreads centrifugally in an ameboid pattern	Variable presentations: a) Most common: Non-contiguous multifocal lesions, progressing in a wave-like serpiginoid pattern b) Disseminated plaque-like choroiditis with ameboidal spread c) Mixed pattern (a combination of the above)
Laterality	Predominantly bilateral	Both unilateral and unilateral presentations described
Age	4th & 5th decade in Caucasians, rarely in younger ages	Predominantly in the younger age group
AC & vitreous	Less anterior segment or vitreous inflammation	Anterior segment and vitreous inflammation described
Treatment	Corticosteroids and immunesuppression	Corticosteroids, ATT after corroborative diagnosis of TB
Response to treatment	relentlessly progressive with multiple exacerbations, recurrences at the edge of the lesions	Milder variety as compared to SC, responds well to ATT and corticosteroids
Visual acuity	Foveal involvement	Fovea sparing, good final visual acuity
Long term Sequel	High incidence of secondary CNVM	Less incidence of secondary CNVM

9. How do chest radiography and CT scans support the diagnosis of TBU? Which one of them are a preferred choice?

Most cases of active TB-uveitis do not have symptomatic or manifest TB.

However, there is a high likelihood of latent TB in these patients.

CT-chest is superior to chest radiography in the diagnosis of latent TB and other etiologies such as sarcoidosis.

Apart from highly diagnostic radiologic features of TB on CT-chest such as centrilobular nodules, tree-in-bud appearance and cavities, it is also a sensitive modality for the diagnosis of mediastinal lymphadenopathy.

Since isolated TB-lymphadenitis in an asymptomatic patient is prevalent in countries with a high burden of TB, lymph node aspiration can offer a diagnostic opportunity towards TB or sarcoidosis.[8]

Patients with clinical features of granulomatous uveitis, intermediate, posterior or panuveitis, suggesting either TB or sarcoidosis and a positive or negative TST or IGRA test, in a TB-endemic country are likely to benefit from a CT-scan targeted towards a diagnostic etiology.

As a rule of thumb, all other causes of infectious/non-infectious uveitis are ruled out by clinical or laboratory evidence before ordering a CT-chest.

Results from COTS-1 showed that among 702 patients affected by OTB with documented radiological results, 26.9% had radiologic features suggestive of inactive TB on chest X-ray, and 68.6% had positive findings on chest CT. [9]

10. How do you classify intraocular tuberculosis?

The following table simplifies the classification of intraocular tuberculosis (IOTB)[10]

	Clinical diagnostic group	Case definition criteria
1	**Confirmed IOTB** (Both 1 & 2 should be fulfilled)	1) Atleast one clinical sign suggestive of IOTB 2) Microbiological confirmation of Mycobacterium tuberculosis (MTB) from ocular fluids/tissues
2	**Probable IOTB** (1,2 & 3 together to be fulfilled)	1) Atleast one clinical sign suggestive of IOTB (other etiologies excluded) 2) Evidence of chest x-ray consistent with TB infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites 3) At least one of the following: 1) Documented exposure to TB 2) Immunological evidence TB infection
3	**Possible IOTB** (1, 2, and 3 together) (or 1 and 4)	1) At least one clinical sign suggestive of IOTB (and other etiologies excluded) 2) Chest x-ray not consistent with TB infection and no clinical evidence of extraocular TB 3) At least one of the following: 1) Documented exposure to TB 2) Immunological evidence TB infection 4) Evidence of chest x-ray consistent with TB infection or clinical evidence of extraocular TB but none of the characteristics given in 3)

11. What are the recommendations for starting of anti-tubercular (ATT) therapy in patients of TB-uveitis?

The diagnosis of TBU is essentially presumptive based on local epidemiologic factors, specific ocular phenotype (read "clinical signs predictive of ocular tuberculosis"), corroborating immunologic tests (TST and/or IGRA or both) and radiologic tests to detect latent TB. While direct tissue diagnosis of mycobacterium tuberculosis in ocular samples is rare, the PCR method used for ocular samples has a low sensitivity value for diagnosis of TB.

Usually, the decision to start ATT in cases of TB-uveitis is made by the treating ophthalmologist in coordination with pulmonologists and infectious-disease physicians while adhering to local treatment protocols.

The Collaborative Ocular Tuberculosis Study (COTS) has published international consensus guidelines and algorithms towards initiation of anti-tubercular therapy (ATT) in TB choroiditis in COTS-Report 1 and in other forms of TB uveitis in COTS-Report 2.[9,11]

In accordance with COTS-1, ATT can be initiated in cases of tubercular choroiditis, if any of the immunologic tests (TST or IGRA) are positive along with radiologic features suggestive of TB.[9]

ATT can be initiated in specific ocular phenotypes such as tubercular serpiginous-like choroiditis and tuberculoma, provided one of the immunologic tests (TST or IGRA) are positive and even though radiologic features suggestive of TB are negative.

Based on COTS-2 recommendations, ATT can be initiated in patients with recurrent TB-anterior uveitis, TU-intermediate uveitis, TU-retinal vasculitis, TB-panuveitis based on TB endemicity and if any one of the immunologic tests (TST or IGRA) are positive along with radiological evidence of past TB infection.[11]

Concomitant use of corticosteroids reduce the inflammation associated with TBU. They are particularly helpful in treating active serpiginous-like choroiditis with macular involvement. The dose and duration of oral corticosteroids are individualised and are titrated according to presence and recurrences of ocular inflammation.

12. How does anti-tuberculosis treatment (ATT) affect the management of tuberculous uveitis?

Patients treated with ATT along with systemic corticosteroids showed to have a decreased risk of developing recurrences of uveitis by approximately two-thirds, as compared to treatment with corticosteroids alone.[12]

ATT also reduces the recurrences of TB choroiditis by almost 75%.[13]

Evidence indicates efficacy of ATT in reducing the rate of disease recurrences in patients with TBU treated with ATT. A meta-analysis from 28 studies evaluated the effect of ATT on the ocular outcome of 1,917 patients. The results showed that 84% of patients treated with ATT did not experience recurrences of inflammation during the follow-up.[14]

13 What are the common side effects of ATT that clinicians should monitor in patients with TBU?

Ocular side-effects: Paradoxical worsening or the localized Jarisch–Herxheimer-like reaction can occur in patients treated with ATT or with both ATT and systemic corticosteroids, due to severe inflammatory response. Stepping up of oral corticosteroids are helpful in this setting.

Systemic side-effects: Other known complications of ATT are hepatotoxicity, skin rash, gastrointestinal side effects, optic neuropathy, and angioedema. Hence ATT should preferably be given under supervision of an internist.

14. Is there an indication for using immunomodulatory therapy in TBU?

Immunomodulatory therapy in TBU is indicated as a second line therapy in cases which show poor control of inflammation with systemic corticosteroids and ATT. It is also indicated in patients who develop paradoxical worsening after starting ATT, or those who show relentless progression of inflammation despite aggressive systemic therapy, or those who develop recurrences.

Patients intolerant to systemic steroids are also candidates for immunosuppressive therapy.[7,15,16]

15. Can intravitreal steroids be used to treat TBU?

Intravitreal dexamethasone implant has been successfully used in the management of TBU as a rescue therapy to induce rapid remission and at times for paradoxical worsening.[17-20]

Patients with systemic steroid intolerance, those having presence of concomitant systemic diseases where systemic corticosteroids are contraindicated or those with unilateral TBU are also potential candidates for intravitreal dexamethasone implants.

It can be also used to treat associated cystoid macular edema.

16. How are recurrences of tubercular uveitis managed?

Common approaches to recurrences of tubercular uveitis are:

a. Compliance to treatment
b. Assessing the adequacy of dosage and duration of corticosteroids for control of inflammation - if a repeat regimen of corticosteroids is necessary for adequate control of inflammation. Also check for paradoxical worsening.
c. Assess the need for steroid sparing treatment - if repeated regimens of corticosteroids are required
d. Adequacy of ATT - regarding both the regimen and dosage
e. Need for repeat ATT - similar regimen or change in regimen. Also evaluate if any resistance to conventional ATT is present.
f. Diagnostic sampling of ocular fluids in case of diagnostic dilemma and poor response to treatment

References

1. *Agrawal R, Agarwal A, Jabs DA, Kee A, Testi I, Mahajan S, McCluskey PJ, Gupta A, Palestine A, Denniston A, Banker A, Invernizzi A, Fonollosa A, Sharma A, Kumar A, Curi A, Okada A, Schlaen A, Heiligenhaus A, Kumar A, Gurbaxani A, Bodaghi B, Islam Shah B, Lowder C, Tappeiner C, Muccioli C, Vasconcelos-Santos DV, Goldstein D, Behra D, Das D, Makhoul D, Baglivo E, Denisova E, Miserocchi E, Carreno E, Asyari F, Pichi F, Sen HN, Uy H, Nascimento H, Tugal-Tutkun I, Arevalo JF, Davis J, Thorne J, Hisae Yamamoto J, Smith J, Garweg JG, Biswas J, Babu K, Aggarwal K, Cimino L, Kuffova L, Agarwal M, Zierhut M, Agarwal M, De Smet M, Tognon MS, Errera MH, Munk M, Westcott M, Soheilian M, Accorinti M, Khairallah M, Nguyen M, Kon OM, Mahendradas P, Yang P, Neri P, Ozdal P, Amer R, Lee R, Distia Nora R, Chhabra R, Belfort R, Mehta S, Shoughy S, Luthra S, Mohamed SO, Chee SP, Basu S, Teoh S, Ganesh S, Barisani-Asenbauer T, Guex-Crosier Y, Ozyazgan Y, Akova Y, Habot-Wilner Z, Kempen J, Nguyen QD, Pavesio C, Gupta V; Collaborative Ocular Tuberculosis Study (COTS) Group. Standardization of Nomenclature for Ocular Tuberculosis - Results of Collaborative Ocular Tuberculosis Study (COTS) Workshop. Ocul Immunol Inflamm. 2020 Sep 30;28(sup1):74-84.*

2. *Gupta A, Bansal R, Gupta V, Sharma A, Bambery P. Ocular signs predictive of tubercular uveitis. Am J Ophthalmol. 2010 Apr;149(4):562-70. doi: 10.1016/j.ajo.2009.11.020. Epub 2010 Feb 10. PMID: 20149341*

3. *Tuberculin skin test - https://www.cdc.gov/tb/*

4. *M A, El-Asrar A, Abouammoh M, Al-Mezaine HS. Tuberculous uveitis. Middle East Afr J Ophthalmol. 2009 Oct;16(4):188-201.*

5. *Agrawal R,Testi I, Bodaghi B.et al.Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study consensus guidelines on the management of tubercular uveitis–report 2: guidelines for initiating antitubercular therapy in anterior uveitis, intermediate uveitis, panuveitis, and retinal vasculitis.Ophthalmology. 2021; 128: 277-287*

6. *Gupta V, Agarwal A, Gupta A, Bambery P, Narang S. Clinical characteristics of serpiginous choroidopathy in North India. Am J Ophthalmol. 2002 Jul;134(1):47-56. doi: 10.1016/s0002-9394(02)01501-5. PMID: 12095807.*

7. *Bansal R, Gupta A, Gupta V, Dogra MR, Sharma A, Bambery P. Tubercular serpiginous-like choroiditis presenting as multifocal serpiginoid choroiditis. Ophthalmology. 2012 Nov;119(11):2334-42. doi: 10.1016/j.ophtha.2012.05.034. Epub 2012 Aug 11. PMID: 22892153.*

8. *Bansal, R., Gupta, A., Agarwal, R., Dogra, M., Bhutani, G., Gupta, V., _ Behera, D. (2018). Role of CT Chest and Cytology in Differentiating Tuberculosis from Presumed Sarcoidosis in Uveitis. Ocular Immunology and Inflammation, 27(7), 1041–1048. https://doi.org/10.1080/09273948.2018.1425460*

9. *Agrawal R, Testi I, Mahajan S, Yuen YS, Agarwal A, Kon OM, Barisani-Asenbauer T, Kempen JH, Gupta A, Jabs DA, Smith JR, Nguyen QD, Pavesio C, Gupta V; Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis-Report 1: Guidelines for Initiating Antitubercular Therapy in Tubercular Choroiditis. Ophthalmology. 2021 Feb;128(2):266-276.*

10. *Gupta A, Sharma A, Bansal R, Sharma K. Classification of intraocular tuberculosis. Ocul Immunol Inflamm. 2015 Feb;23(1):7-13. doi: 10.3109/09273948.2014.967358. Epub 2014 Oct 14. PMID: 25314361.*

11. *Agrawal R, Testi I, Bodaghi B, Barisani-Asenbauer T, McCluskey P, Agarwal A, Kempen JH, Gupta A, Smith JR, de Smet MD, Yuen YS, Mahajan S, Kon OM, Nguyen QD, Pavesio C, Gupta V; Collaborative Ocular Tuberculosis Study Consensus Group. Collaborative Ocular Tuberculosis Study Consensus Guidelines on the Management of Tubercular Uveitis-Report 2: Guidelines for Initiating Antitubercular Therapy in Anterior Uveitis, Intermediate Uveitis, Panuveitis, and Retinal Vasculitis. Ophthalmology. 2021 Feb;128(2):277-287. doi: 10.1016/j.ophtha.2020.06.052. Epub 2020 Jun 27. PMID: 32603726.*

12. *Bansal R, Gupta A, Gupta V, Dogra MR, Bambery P, Arora SK. Role of anti-tubercular therapy in uveitis with latent/manifest tuberculosis. Am J Ophthalmol. 2008 Nov;146(5):772-9. doi: 10.1016/j.ajo.2008.06.011. Epub 2008 Aug 16. PMID: 18708180.*

13. *Agrawal R, Gunasekeran DV, Grant R, Agarwal A, Kon OM, Nguyen QD, Pavesio C, Gupta V; Collaborative Ocular Tuberculosis Study (COTS)–1 Study Group. Clinical Features and Outcomes of Patients With Tubercular Uveitis Treated With Antitubercular Therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1. JAMA Ophthalmol. 2017 Dec 1;135(12):1318-1327. doi: 10.1001/jamaophthalmol.2017.4485. Erratum in: JAMA Ophthalmol. 2019 Feb 1;137(2):233. doi: 10.1001/jamaophthalmol.2017.6239. PMID: 29075752; PMCID: PMC6583556.*

14. *Kee AR, Gonzalez-Lopez JJ, Al-Hity A, Gupta B, Lee CS, Gunasekeran DV, et al. Anti-tubercular therapy for intraocular tuberculosis: A systematic review and meta-analysis. Surv Ophthalmol 2016;61:628-53.*

15. *Bigdon E, Steinhorst NA, Weissleder S, Durchkiv V, Stübiger N. Treatment in Latent Tuberculosis Uveitis-Is Immunosuppression Effective or Is Conventional 3- or 4-Drug Antituberculosis Therapy Mandatory? J Clin Med. 2022 Apr 26;11(9):2419.*

16. *Dutta Majumder P, Biswas J, Gupta A. Enigma of serpiginous choroiditis. Indian J Ophthalmol. 2019 Mar;67(3):325-333. doi: 10.4103/ijo.IJO_822_18. PMID: 30777946; PMCID: PMC6407399.*

17. *AgarwalA,HandaS,AggarwalK,SharmaM,SinghR,SharmaA, et al. The role of dexamethasone implant in the management of tubercular uveitis. Ocul Immunol Inflamm 2018;26:884-92.*

18. *Jain L, Panda KG, Basu S. Clinical outcomes of adjunctive sustained-release intravitreal dexamethasone implants in tuberculosis-associated multifocal serpigenoid choroiditis. Ocul Immunol Inflamm 2018;26:877-83.*

19. *HasanreisogluM,GulpinarIkizG,AktasZ,OzdekS.Intravitreal dexa- methasone implant as an option for anti-inflammatory therapy of tuberculosis uveitis. Int Ophthalmol 2019;39:485-90.*

20. *Fonollosa A, Valsero S, Artaraz J, Ruiz-Arruza I. Dexamethasone intravitreal implants in the management of tubercular multifocal serpiginoid choroiditis. J Ophthalmic Inflamm Infect 2016;6:31.*

21. *Testi, Ilaria; Agrawal, Rupesh; Mehta, Salil; Basu, Soumvaya; Nguyen, Quan; Pavesio, Carlos; Gupta, Vishali. Ocular tuberculosis: Where are we today? Indian Journal of Ophthalmology 68(9): p 1808-1817, September 2020. | DOI: 10.4103/ijo.IJO_1451_20.*

22. *Rahman S, Irfan M, Siddiqui MAR. Role of interferon gamma release assay in the diagnosis and management of Mycobacterium tuberculosis-associated uveitis: a review. BMJ Open Ophthalmol. 2021 May 12;6(1):e000663. doi: 10.1136/bmjophth-2020-000663. PMID: 34046524; PMCID: PMC8118067.*

Pediatric Uveitis: Juvenile Idiopathic Arthritis (JIA)

Aditya Patil, Padmamalini Mahendradas

1. What are the most common types of uveitis seen in pediatric patients?

Idiopathic uveitis is the most common etiology in children. Amongst infectious uveitis, tuberculosis is the most common etiology in children in India, whereas toxoplasmosis is the commonest presentation in the west. JIA is the most common systemic disease associated with uveitis in children. Other uveitic entities commonly seen in children include- idiopathic anterior uveitis, idiopathic retinal vasculitis, intermediate uveitis, traumatic uveitis, parasitic uveitis, Behcets disease, Blau syndrome, Tubulointerstitial nephritis and uveitis (TINU) syndrome, uveitis associated with Kawasaki disease, ocular toxocariasis, congenital syphilis, VKH disease, sarcoidosis and masquerade syndromes arising from retinoblastoma and leukemia. Trematode associated uveitis is seen in some parts of India while seasonal hyperacute panuveitis (SHAPU) is seen in Nepal and Zika virus associated uveitis is seen in Brazil and some Caribbean countries.

2. How does the clinical presentation of uveitis differ in children compared to adults?

Unlike in adults, uveitis in children is often asymptomatic and tends to become chronic and recurrent, resulting in a larger number of patients experiencing complications like posterior synechiae, cataract, elevated intraocular pressure or glaucoma and band shaped keratopathy at their first presentation to the ophthalmologist.

3. What are the challenges to diagnose, monitor and treat uveitis in children compared to adults?

Diagnosis of pediatric uveitis is uniquely challenging as it is difficult to elicit a clear history from children, many of whom may be pre-verbal or find it difficult to convey when or how the disease occurred. Smaller children are often afraid of the doctor making it all the more challenging to perform a thorough ocular examination. Examination under anasthesia is frequently required to examine and monitor these patients. These challenges lead to a delay in diagnosis and loss to follow up. Treatment is also complicated with poor compliance, adverse effects with systemic treatment like steroid response and growth retardation, and higher rate of complications. Likelihood of amblyopia is a unique concern for children under the age of 10, resulting in more visual morbidity from uveitis than in adults. Children also tend to have chronic, smouldering inflammation which requires early initiation of long-term systemic immunomodulation to prevent irreversible damage to ocular structures.

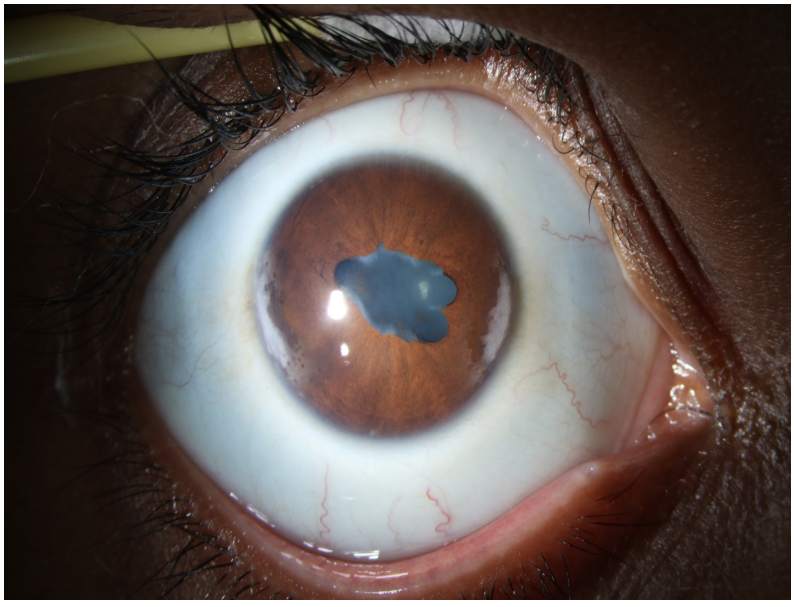
4. What are the characteristic features of JIA-associated uveitis?

Most common presentation of JIA-associated uveitis (JAIU) is a chronic non-granulomatous "white-eye" anterior uveitis which is often initially asymptomatic. JAIU usually occurs bilaterally, simultaneously or one eye after the other in a few months. There is mild to moderate anterior chamber reaction with presence of posterior synechiae, band-shaped keratopathy or cataract at the initial presentation. Granulomatous keratic precipitates may be rarely seen. Posterior segment manifestation may occur in the form of retinal vasculitis. Acute anterior uveitis with a painful red eye may occur in enthesitis-related arthritis patients who also test positive for HLA B27. Refer to figure below.

ILAR Category	ANA	JIA onset and duration	Screening Guidelines
OA, RF- PA, PsA, UA	ANA +	<7 years, ≤4 years	3 monthly
OA, RF- PA, PsA, UA	ANA -	<7 years, ≤4 years	6-12 monthly
OA, RF- PA, PsA, UA	ANA+	≥7 years, >4 years	6-12 monthly
ERA, RF+ PA, SA	ANA+/-	any	6-12 monthly

5. What are the recommended screening guidelines for uveitis in children with JIA?

First ocular examination is recommended immediately at the time of diagnosis of JIA. Then, as per the American College of Rheumatology/Arthritis Foundation 2019 criteria, following are the recommended guidelines.



12 year old female with unilateral JIA uveitis on MTX therapy.
The image shows a white eye with band shaped keratopathy and posterior synechiae.

Abbreviations: ANA, antinuclear antibodies; OA, Oligoarthritis; RF, Rheumatoid factor; PA, Polyarthritis; PsA, Psoriatic arthritis; UA, Undifferentiated arthritis; ERA, Enthesitis-related arthritis; SA, Systemic arthritis; ILAR, International League of Associations for Rheumatology.

6. What is the typical line of treatment for JIA-associated uveitis?

The goal of treatment in JIAU is to achieve zero cells (as per SUN grading) in the anterior chamber in both the eyes and maintain a corticosteroid-free remission.

- Treatment is initiated with topical corticosteroids tailored to the severity of inflammation. Cycloplegic agents are recommended for both acute and chronic anterior uveitis to prevent posterior synechiae and alleviate pain and photophobia. There is no consensus regarding the cycloplegic agent of choice or its frequency. Prolonged and excessive use of topical steroids can lead to adverse effects like elevated IOP and cataract.
- Short-term high-dose oral corticosteroids can be used to tide over severe inflammation as a rescue therapy.
- Peribulbar corticosteroids are not a standard treatment in these patients as they are associated with complications.
- For maintenance, corticosteroid-sparing DMARDs like methotrexate (MTX) with folic acid supplementation are used. If there are adverse effects with MTX like gastrointestinal side effects, elevated liver enzymes, rashes, mouth ulcers or hair loss, it can be substituted with mycophenolate mofetil or azathioprine.
- If there is insufficient response to MTX, treatment can be stepped up with humanized monoclonal antibodies that inhibit cytokine signalling pathways, including inhibitors of TNF-alpha and IL-6.
- Adalimumab is the first-line anti-TNF agent of choice for moderate-to-severe JIAU. Infliximab is the second choice and can be switched to in cases which don't respond to adalimumab.
- Combination therapy of adalimumab + MTX is recommended for better control of inflammation and to prevent formation of antibodies to adalimumab.
- Testing for anti-adalimumab antibodies should be considered if there are inflammatory relapses under adalimumab therapy.
- In cases where TNF inhibitors have failed due to anti-drug antibodies, IL-6 inhibitor Tocilizumab has been shown to be effective. For chronic uveitis, Janus kinase (JAK) inhibitors, abatacept (anti-CTLA4) and rituximab (anti-CD20) therapy have been effectively used in JIAU.

7. Which is the commonly used DMARD for the treatment of JIA-associated uveitis?

Methotrexate is the first-line agent of choice among corticosteroid-sparing DMARDs for JIAU if corticosteroid therapy fails or when poor prognostic factors are present.

8. What is the role of biological agents in treating JIA-associated uveitis?

Monoclonal TNF inhibitors are employed as second-line agents for JAIU if methotrexate therapy is insufficient. In the SYCAMORE trial, adalimumab in combination with methotrexate showed lower treatment failure rates compared to placebo with methotrexate. Infliximab and golimumab are effective alternatives to adalimumab. Etanercept is not recommended in JIAU as it may paradoxically worsen uveitis in JIA patients in whom it has worked for arthritis.

9. How are children with uveitis monitored while treating their uveitis? How often should they be followed up on treatment?

Thorough ocular examination to look for anterior chamber and vitreous inflammation is required at each visit. Visual acuity and intraocular pressure should be monitored and the development of adverse prognostic factors like band-shaped keratopathy, cataract, cystoid macular edema, amblyopia, glaucoma or hypotony should be looked for. Fundus fluorescein angiography may be necessary to grade the extent of retinal vasculitis in some cases, which has been recently reported.

Follow-up schedule has to be individualized to the patient- depending on the clinical presentation, disease severity, and response to treatment or presence of associated complications. However, all patients require frequent follow up till the inflammation resolves completely.

10. How is band-shaped keratopathy diagnosed and treated?

Band-shaped keratopathy is characterized by deposition of calcium hydroxyapatite in the corneal epithelial basement membrane and the anterior surface of Bowman's layer. Slit lamp examination will show the presence of a gray-white horizontal band with fine dusty deposits across the cornea from 9 o'clock to 3 o'clock, with a distinct lucent zone between the band and the limbus. Lucent holes may be present within the band keratopathy, which represent corneal nerves penetrating through Bowman's layer. Medical treatment is with topical tear substitutes to alleviate the foreign-body sensation and irritation. Surgical debridement involves scraping the band with a blade under topical anesthesia and EDTA chelation with a sponge soaked in 3% EDTA. EDTA is applied every three minutes until satisfactory removal of calcium deposits. EDTA can be toxic to the corneal surface therefore thorough irrigation after the procedure is recommended.

11. What are the recommendations and precautions for cataract surgery in children with uveitis?

Cataract extraction is necessary in children with uveitis if it causes significant visual loss, to prevent amblyopia and allow adequate monitoring of posterior segment inflammation. However, IOL implantation in JIAU is controversial and has been associated with a high rate of complications such as posterior synechiae, retrolental/ cyclitic membranes, CME, secondary glaucoma, hypotony, and phthisis bulbi. Visual axis opacification following cataract surgery is another complication as there is exuberant inflammatory response following surgery in children. If cataract surgery with IOL implantation is to be undertaken, an inflammation-free period of 3-6 months without corticosteroid therapy is recommended. Hydrophobic monofocal acrylic IOLs with in-the-bag implantation and posterior capsulotomy with anterior vitrectomy is recommended. Inflammation should be aggressively controlled with immunomodulation and pre-op and post-op systemic steroid therapy.

12. How can interdisciplinary care between rheumatologists and ophthalmologists benefit children with JIA-associated uveitis?

Children diagnosed with JIA should be referred to the ophthalmologist to screen for uveitis at regular intervals. Similarly, children presenting with non-infectious uveitis should be referred to the rheumatologist for assessment of joint involvement, as uveitis may precede arthritis in some cases. The severity of ocular and joint involvement is not found to be correlated, hence there is a need for liaison between rheumatologists and ophthalmologists. Early initiation of systemic immunomodulation under the care of a rheumatologist will help to prevent long-term systemic and ocular morbidity.

Recommended reading:

1. *van Meerwijk C, Kuiper J, van Straalen J, Ayuso VK, Wennink R, Haasnoot AM, Kouwenberg C, de Boer J. Uveitis Associated with Juvenile Idiopathic Arthritis. Ocul Immunol Inflamm. 2023 Dec;31(10):1906-1914.*
2. *Chen WD, Wu CH, Wu PY, Lin CP, Ou LS, Hwang DK, Sheu SJ, Chiang WY, Chang YC, Lin CJ, Chan WC, Fang YF, Chien-Chieh Huang J, Kao TE, Chiu FY, Hsia NY, Hwang YS. Taiwan ocular inflammation society consensus recommendations for the management of juvenile idiopathic arthritis-associated uveitis. J Formos Med Assoc. 2024 Feb 28:S0929-6646(24)00110-4.*
3. *Mahendradas P, Mishra SB, Mangla R, Sanjay S, Kawali A, Shetty R, Dharmanand B. Reactivation of juvenile idiopathic arthritis associated uveitis with posterior segment manifestations following anti-SARS-CoV-2 vaccination. J Ophthalmic Inflamm Infect. 2022 Apr 27;12(1):15.*
4. *M Bani Khalaf I, Jain H, Vora NM, Ul Ain N, Murtaza F, Ram MD, Nankani A, Motwani J. A clearer vision: insights into juvenile idiopathic arthritis-associated uveitis. Proc (Bayl Univ Med Cent). 2024 Feb 8;37(2):303-311.*
5. *Mooss VS, Babu K. Clinical profile and treatment outcomes in pediatric uveitis - A series from South India. Indian J Ophthalmol. 2024 Jul 1;72(Suppl 4):S584-S591.*
6. *Kumar P, Gupta A, Bansal R, Suri D, Gupta V, Gupta A, Singh S. Chronic Uveitis in Children. Indian J Pediatr. 2022 Apr;89(4):358-363.*

Masquerades in Uveitis - Focus on Lymphoma

Abhilasha Baharani, Minija C K

1. What do masquerades mean?

The term masquerade originates from the Latin word 'masca', which means mask.Uveitis masquerade syndromes (UMS) were defined by Nussenblatt and associates as a group of ocular disorders that present as apparent intraocular inflammatory processes, but are, in fact, non inflammatory in nature(1).

Masquerade syndromes can be neoplastic or Non neoplastic (infectious or non infectious)

2. When does one suspect a masquerade?

It is often suspected when uveitis occurs in very young patients or patients over the age of 60 years.

Non-response to anti-inflammatory therapy

(Though vitreoretinal lymphomas may show response to corticosteroids in the initial stages)

3. Which clinical features point towards a masquerade, rather than uveitis?

a. Older patients presenting with their first episode of "uveitis"

b. Initial response to corticosteroids with subsequent resistance

c. Any patient with uveitis and a history of carcinoma (particularly breast or lung) or hematologic malignancy.

d. Poor visual acuity at presentation as compared to uveitis

e. White hypopyon

f. Floaters or gradual painless reduction of vision in one or both eyes with absent ocular redness, pain or photophobia.

g. Visual acuity well preserved, seemingly out of proportion compared to the degree of vitreous haze

h. Though macular edema is uncommon, the tumour may incite a secondary inflammatory response resulting in exudation and angiogenesis.

4. What are the common differential diagnoses that should be considered when evaluating a patient for possible masquerade syndrome?

i. Intraocular lymphoma

ii. Leukaemia

iii. Intraocular foreign body

iv. Retinitis Pigmentosa

v. Retinal Detachment

vi. Juvenile Xanthogranuloma

5. How can imaging studies (e.g., MRI, PET-CT) be utilised to identify systemic involvement in patients with suspected masquerades?

Imaging studies such as MRI and PET-CT play crucial roles in diagnosing systemic involvement in patients with suspected masquerades.

MRI is highly effective for assessing soft tissues, making it useful for identifying systemic involvement in conditions like lymphoma, sarcoidosis, or metastatic disease.

PET-CT combines metabolic and anatomical imaging. PET scans show areas of increased metabolic activity by highlighting areas that absorb the radiotracer, often glucose. This can help in identifying areas of active disease or malignancy that may not be visible on a CT or MRI alone.

6. What are the various clinical signs of significance seen in primary intraocular lymphoma?

Primary Intraocular lymphoma (PIOL) is the most common among malignancy masquerading as Uveitis. Sites of ocular involvement can include the vitreous, retina, subretinal pigment epithelium (sub-RPE), and any combination thereof.

The most common presenting symptoms are decreased vision and floaters.

Examination reveals a variable degree of vitritis and anterior chamber cells.

In the anterior chamber few cells and keratic precipitates may occur

Lymphoma cells in the anterior chamber may give rise to a pseudo-hypopyon or to deposits on the cornea.

Exudates in the vitreous (pseudovitritis), often in the form of clumps or sheets, or sometimes may mimic the snowballs as seen in intermediate uveitis.

Posterior uveitis is the most common form of uveitis with which PIOL masquerades. Early in the course of the disease subretinal or sub RPE tumor cells may resemble drusen. Creamy yellow subretinal or deep outer retinal lesions are common. Such lesions may be unifocal, multifocal, or diffuse, with multifocal being the most common.

Characteristic “leopard spot” like pigmentary change overlying a subretinal lesion may be seen.

7. Are there any specific clues on optical coherence tomography (OCT) to suggest the presence of intraocular lymphoma?

i. Focal or diffuse RPE elevation, confluent RPE detachment, focal or diffuse RPE thickening

ii. Hyper-reflective vitelliform-like lesions in the subretinal space

iii. Band-like hyper-reflective subretinal infiltration

iv. pre-retinal deposits and

v. Fuzzy outer retinal borders are some of the OCT features suggesting the diagnosis of intraocular lymphoma.

8. What are the precautions to be taken while performing a vitreous biopsy for a case of suspected masquerade? What specific investigations should be the vitreous sample sent for?

Pars plana vitrectomy is preferred over fine-needle aspiration of vitreous.

It has the advantage of clearing the vitreous debris, maximizing sample collection and access to the subretinal space.

The following precautions may improve the diagnostic yield:

i. Any corticosteroids should be discontinued at least 2 weeks prior to biopsy.

ii. Vitrectomy under air allows collection of undiluted vitreous sample.

iii. Using large bore cutters and low cut rate during vitrectomy is preferred as it reduces shearing of fragile lymphoma cells.

iv. Lymphoma cells undergo morphological degeneration within an hour. Hence the sample should be sent to the laboratory at the earliest.

v. Fixation of the sample in HOPE (HEPES-glutamic acid buffer mediated Organic solvent Protection Effect) solution may improve the yield.

The vitreous sample can be sent for the following investigations (as tabulated below)

Test	**Analysis**
Cytology	H&E, Giemsa, Diff-Quik
Immunohistochemistry and Flow Cytometry	CD19, CD20, CD22, CD79a BCL6, CD10 Ki-67 Rarely T-cell markers
Cytokine analysis	IL-10:IL-6 ratio >1.0 Aqueous IL-10 level
Polymerase chain reaction	B- and T-cell receptor clonality B-cell lymphoma 2 (BCL2) translocation Myeloid differentiation primary response 88 (MYD88) L265P mutation

9. What are the various treatment options for primary intraocular lymphoma?

Once the diagnosis of vitreoretinal lymphoma has been made, it is important to confirm that there is only ocular involvement. In the absence of systemic involvement, the question arises as to whether one eye or both eyes are involved. If there is unilateral involvement, then local therapy should be considered.

A. Local treatment:

The goal of local treatment is to induce intraocular remission and improve vision without systemic toxicity. Intravitreal methotrexate is used at a dose of 0.4mg/0.1ml.

The induction dose is twice a week for 4 weeks followed by a predetermined number of injections for a total of 25 injections over 1 year or driven by clinical response.

Intravitreal rituximab at a dose of 1mg/0.1ml alone or combined with intravitreal methotrexate is an alternative.

B. Systemic treatment

Intravitreal therapy with systemic chemotherapy achieves satisfactory prognosis.

Current evidence supports combined intravitreal and chemotherapy as the first-line treatment.

If possible, the combination of radiotherapy further decreases the recurrence rate and death rate during follow-up.

Other more aggressive treatments showed limited efficacy in studies and were not recommended.

10. What are the potential complications of misdiagnosing intraocular lymphoma as chronic uveitis?

In a recent cohort of 1906 patients presenting with ocular inflammatory disease in a tertiary referral centre over a 7 year period, 6% were ultimately diagnosed with a non-inflammatory aetiology, with a third of these patients found to have a neoplastic or paraneoplastic cause. Misdiagnosing intraocular lymphoma as chronic uveitis can lead to several potential complications, some of which can significantly impact the patient's health and vision.

Here are a few key issues that might arise:

a. Delayed Treatment: Delay in diagnosis can lead to the progression of the lymphoma and potentially worsen the prognosis.

b. Disease Progression: Intraocular lymphoma can be aggressive and may spread to other parts of the eye or even the CNS if not treated appropriately. A misdiagnosis can result in the progression of the disease, which may lead to more severe complications and reduced treatment options.

c. Vision Loss: Both uveitis and lymphoma can cause vision problems, but intraocular lymphoma may cause more significant vision loss if not treated early.

d. Inappropriate Medication Side Effects: Treatment for chronic uveitis often involves corticosteroids, which can have significant side effects, such as increased intraocular pressure, cataract formation, and systemic complications. Using these medications inappropriately for intraocular lymphoma could exacerbate these side effects and may not address the underlying problem.

e. Complications from Incorrect Diagnosis: Misdiagnosis can lead to unnecessary treatments or interventions. For instance, if the patient undergoes procedures intended for uveitis, such as certain intravitreal injections or surgeries, these might be ineffective or even harmful if the underlying issue is lymphoma.

f. Psychological Impact: Being incorrectly diagnosed can also have psychological effects on the patient, causing anxiety, confusion, and stress. The uncertainty and prolonged treatment without improvement can significantly affect a patient's quality of life.

g. Impact on Overall Management: Intraocular lymphoma may be part of a systemic lymphoma process. Misdiagnosing it as uveitis could delay the diagnosis of a systemic malignancy, which might impact overall management and treatment of a potentially lethal condition.

Suggested reading:

1. *Majumder, P. D., Khetan, V., & Biswas, J. (2024). Masquerade Syndrome: A Review of Uveitic Imposters. Asia-Pacific Journal of Ophthalmology, 100054.*
2. *Lin, M. L., & Hall, A. J. (2024). Uveitis masquerade syndromes: An approach to diagnosis. Clinical & Experimental Ophthalmology, 52(1), 91-105.*
3. *Takhar, J., Doan, T., & Gonzales, J. A. (2021). Vitreoretinal lymphoma: a literature review and introduction of a new diagnostic method. The Asia-Pacific Journal of Ophthalmology, 10(1), 93-98.*
4. *El Zein, L., Smith, W. M., White, L. J., Hodge, D. O., Olsen, T. W., Pulido, J. S., & Dalvin, L. A. (2024). Optical coherence tomography features in vitreoretinal lymphoma compared with non-infectious uveitis. BMC ophthalmology, 24(1), 255.*
5. *Heiferman, M. J., Yu, M. D., & Mruthyunjaya, P. (2022). Update in molecular testing for intraocular lymphoma. Cancers, 14(19), 4546.*
6. *Soussain, C., Malaise, D., & Cassoux, N. (2021). Primary vitreoretinal lymphoma: a diagnostic and management challenge. Blood, The Journal of the American Society of Hematology, 138(17), 1519-1534.*
7. *Zhao, X. Y., Cheng, T. T., Meng, L. H., Zhang, W. F., & Chen, Y. X. (2022). Clinical features, diagnosis, management and prognosis of primary intraocular lymphoma. Frontiers in Oncology, 12, 808511.*
8. *Menean, M., Giuffrè, C., Cicinelli, M. V., Marchese, A., Modorati, G., Bandello, F., & Miserocchi, E. (2023). A comprehensive overview of diagnosis, imaging and treatment of vitreoretinal lymphoma. European Journal of Ophthalmology, 11206721231211931.*
9. *Touhami, S., Audo, I., Terrada, C., Gaudric, A., LeHoang, P., Touitou, V., & Bodaghi, B. (2019). Neoplasia and intraocular inflammation: from masquerade syndromes to immunotherapy-induced uveitis. Progress in Retinal and Eye Research, 72, 100761.*

Post Fever Retinitis

Gazal Patnaik, Ankush Kawali

1. What causes of fever can lead to post-fever retinitis?
Post fever retinitis (PFR) has been linked to community outbreaks and epidemics like rickettsiosis, dengue, typhoid, chikungunya and west Nile virus fever.

2. What are the common visual symptoms reported by patients with post-fever retinitis?
The most common presenting ocular symptoms is painless diminution of vision. Few patients may present with pain, when associated with acute iridocyclitis. Patients can have visual field defects due to large retinitis lesions even after the resolution and due to involvement of the optic nerve.

3. Elaborate the pathophysiology of post-fever retinitis.
The exact pathophysiology for the development of post-fever retinitis has not been established.
However, various proposed theories exist explaining the varied ocular manifestations.
i. Direct invasion of the infective agent –The infective agents can directly invade the retinal tissues, especially if the patient is presenting within few days to 2 weeks of the febrile episode. This hypothesis is supported by cases of endophthalmitis and panophthalmitis specifically. However, histopathological as well as molecular biologic evidences (like polymerase chain reaction) did not support the hypothesis thoroughly.

ii. Autoimmunity –Hypersensitivity reaction to the antigens released by the dead organism. A homology has been found between retinal S – antigen (and/or inter and microbial peptides like heat shock protein (HSP). This homology leads to a molecular mimicry causing inflammatory response. The clinical evidence comes from various ocular features starting from the onset being 2 to 6 weeks of the febrile illness and ocular manifestations in the form of vitritis, retinitis,, neuroretinitis and optic neuritis.

iii. Angiotrophism –The infective agents can directly invade the retinal vascular endothelial cells causing occlusive capillaritis which may manifestant in the form of cotton-wool spot like retinitis, iridocyclitis, vitritis and neuroretinitis.

4. What are the various fundus findings in post-fever retinitis?
PFR can manifest in various forms. It can be focal or multifocal. Most commonly seen in the posterior pole, however can occur peripherally as well. The retinitis lesion usually affects the inner retinal layers without signs of necrosis. It is usually associated with retinal haemorrhages and retinal edema as well as sub retinal fluid leading to visual deterioration. Macular star or macular fan and occasionally sub retinal precipitates can be seen during resolving phase.
Rarely, these are associated with neovascularization, vascular sheathing (arteriolitis / kyrieleis-like) and optic neuritis.

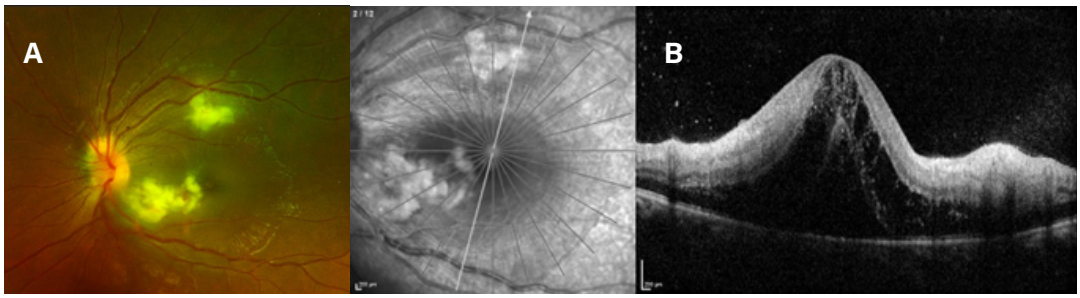


Figure: post fever retinitis
A - Fundus photo showing cotton wool spot-like retinitis lesions with macular edema.
B - OCT showing vitritis, hyper-reflectivity of inner retinal layers at the site of the retinitis lesions. Intra-retinal fluid in the outer nuclear layer and sub retinal fluid.

5. How does the clinical presentation of post-fever retinitis differ between patients with different underlying fevers?

The common infective agents causing PFR usually have a similar retinal affection. They primarily differ with the underlying systemic features. There is lack of a comparative study of morphological presentation of this condition between various reported causes of the fever. Very few studies have confirmed the diagnosis of the fever in their reports. No significant difference was found in the ocular presentation, although "dengue maculopathy" like condition has not been described for the macular changes due to other etiologies.

6. Is there a role of optical coherence tomography (OCT) in diagnosing post-fever retinitis?

OCT plays a pivotal role in the diagnosis and management of post-fever retinitis. Affection of inner retina with hyperreflectivity and back shadowing is quite characteristic of post-fever retinitis, as compared to other retinitis secondary to herpetic retinitis, toxoplasma retinitis or measles retinitis. In the later infection, OCT scan passing through the retinitis lesions may showa full thickness involvement of the retinal tissues with necrosis or loss of tissue, whereas in post-fever retinitis necrosis of the retinal layers is typically absent.
OCT helps in prognosticating the visual outcome as well as monitor the response to the treatment. It quantitatively monitors the resolution of vitritis, macular edema and the retinitis patch.

7. What is the treatment of post-fever retinitis?

Oral doxycycline 100mg BD for 3-4 weeks along with topical steroids and/or non-steroidal anti-inflammatory agents can achieve resolution in most of the cases.
In case of associated optic neuritis, clinically evident vasculitis, persisting significant vitritis, or persisting macular edema, systemic corticosteroids can be added.
Spontaneous resolution has also been observed, however, the resolution can be delayed without treatment.
Other antibiotics like azithromycin and ciprofloxacin can also be used but the efficacy is suboptimal.
Role of intravitreal anti-vascular endothelial growth factors (VEGF) has also been investigated for cases with macular edema.
No superiority has been observed as compared to oral and topical treatment.
In cases of vitreous haemorrhages secondary to inflammatory neovascularization anti-VEGFs can be used.
Rarely persistent vitreous haemorrhages and tractional retinal detachment may require surgical interventions.

8. How can corticosteroid therapy be beneficial in managing post-fever retinitis?
Systemic corticosteroids may help decreasing macular edema, vitritis and anterior uveitis.
In rare occasions when PFR is associated with optic neuritis or clinically evident vasculitis or persisting significant vitritis, systemic corticosteroids would be essential to manage the inflammation.

9. What is the typical time frame for the onset of retinitis following a febrile illness?
The onset of ocular symptoms due to PFR may range from 5 days – 6 weeks of the febrile episode. On average the latent period is 20 days.

10. How can post-fever retinitis be differentiated from other causes of infectious retinitis?
Non-granulomatous uveitis with "Cotton Wool Spot- like" retinitis, frequently associated with macular edema and neurosensory detachment is the hallmark of PFR. OCT scan passing through the retinitis lesions does not show necrosis during the course of the disease.
In contrast, most of the infectious retinitis lesions are necrotizing in nature (Eg. Herpetic and Toxoplasma retinitis, Measles retinitis). The OCT scan passing through the retinitis lesion may help differentiating necrotizing retinitis from non-necrotizing.
Rare occurrence of retinitis in tubercular uveitis is generally associated with choroiditis or exudative vasculitis, which could be absent in PFR.
Dramatic response to doxycycline may also help differentiating PFR from other infectious retinitis. Last but not the least, PFR which is also known as Epidemic retinitis has association with community outbreaks which may not be a case in other infectious retinitis.

11. How can blood tests and serology assist in the diagnosis of post-fever retinitis?
Post-fever retinitis (PFR) is also known as Epidemic retinitis (ER) which indicates that the fever is due to contemporary epidemics in the community, reportedly due to rickettsia, dengue, chikungunya, west Nile virus, and typhoid.
Serological test directed to identify these causes would help understanding the nature of the ongoing epidemic(s), alert healthcare authorities in that community and to further study the differences in the clinical presentation of ER due to various reported etiologies.
Baseline uveitis blood work-up including HIV and TPHA would rule out respective causes for the retinitis.

12. What is the role of antiviral therapy in managing post-fever retinitis?
Anti-viral agents (specifically anti-herpetic agents) have no role in the treatment of Post-fever retinitis. The role of other anti-viral agents has not been studied.

13. What are the key differences between post-fever retinitis and autoimmune retinopathy?

As the words suggests, PFR is "retinitis" and developes after an episode of fever whereas autoimmune retinopathy (AIR) is "retinopathy."

Clinically appreciated yellowish-white retinitis lesions are NOT seen in AIR.

PFR affects the inner retinal layers, whereas AIR affects the outer retinal layers. AIR usually starts near the optic disc, whereas PFR could be focal or multifocal in the posterior pole region.

AIR is an immune – mediated response to an unidentified stimulus, which could be an unknown viral antigen as well. On the other hand, PFR is due to a systemic infection acquired during community outbreaks as mentioned previously.

PFR is an acute and non-recurrent uveitis whereas AIR is a chronic condition.

Anterior segment involvement is common in PFR and rare in AIR.

"Cotton wool spot-like" lesions are the hallmark of PFR. In AIR outer retina is affected.

Macular edema with neuro-sensory layer detachment is common in PFR and rare or absent in AIR.

PFR responds to oral doxycycline therapy with or without steroids whereas AIR needs long term steroids and immunosuppression.

14. Application of newer imaging technology in PFR?

The mainstay and essential imaging for PFR is SD-OCT scan as mentioned above.

FFA may reveal vasculitic component of the disease and highlight rare occurrence of inflammatory neovascularization without significant capillary non-perfusion areas.

Considering FFA as an invasive investigation, recent advancements has been made with non – invasive tool of OCTA (OCT – angiography).

Changes in the superficial (SCP) and deep capillary plexus (DCP) with capillary rarefaction and irregularity of larger vessels in the SCP has been observed. The DCP had more capillary rarefaction as compared to the SCP. The foveal avascular zone (FAZ) was altered with an irregular perifoveal network.

Role of ICG has not been investigated in detail for PFR.

15. Post fever retinitis: Summary Box

Post-fever retinitis (PFR) or Epidemic retinitis (ER) is linked to contemporary epidemics or outbreaks in the community, reportedly due to rickettsia, dengue, chikungunya, west Nile virus, and typhoid. However, the exact cause of the fever is often unknown.

Non-granulomatous uveitis with "Cotton Wool Spot- like" retinitis, frequently associated with macular edema and neurosensory detachment is the hallmark of post-fever retinitis (PFR).

Macular star or fan as well as subretinal precipitates can be seen during resolving stage of the disease. OCT has a key role in diagnosing and monitoring treatment.

Oral doxycycline with or without corticosteroids can achieve successful outcomes within a month.

Despite the aggressive presentation, the visual prognosis is generally good but the quality of vision may suffer due to long-lasting scotomas.

The following table help distinguish between the common etiological agents of PFR.

Organism	Systemic features	Retinal manifestation	Laboratory findings	Ancillary Imaging	Management
Rickettsia	Fever, Maculo-papular rash	Retinal vein engorgement, retinal haemorrhages, macular edema, cotton wool spot-like retinitis, vitritis, disc edema/ hyperemia, arteriolitis (kyrieleis like)	WFT, ELISA, Indirect immunofluo rescence assay (IFA) (gold standard), thrombocyto-penia	early hypofluorescence with late hyperfluo rescence in the areas of retinitis Vascular leakage on FFA. Inner retinal thickening with backshadowing on OCT	Doxycycline, azithromycin, ciprofloxacin (except in Rocky Mountain Spotted Fever), systemic corticosteroids
Chikun-gunya	Sudden fever with chills, arthralgia, malaise, lower back ache & myalgia	Cotton woold spot like Retinitis with vitritis, disc hyperaemia,and retinal vasculitis	ELISA, PCR, CD 4 T - lympho-cytosis	FFA – early hypofluo rescence with late hyperfluo rescence in the areas of retinitis, vascular leaks with or without capillary non-perfusion. OCT – inner retinal layer hyperreflectivity with after - shadowing	Doxycycline, with topical and systemic corticosteroids
West Nile virus	Sudden fever with chills, arthralgia, malaise, Neuro-logical involvement	Cotton wool spot like Retinitis with vitritis, disc hyperaemia, and retinal vasculitis	ELISA, LAMP assay, PCR	FFA – early hypofluorescence with late hyperfluo rescence in the areas of retinitis, vascular leaks with or without capillary non-perfusion. OCT – inner retinal layer hyperreflectivity with after - shadowing	topical and systemic corticosteroids
Dengue	Flu – like illness, abdominal discomfort, high grade fever, musculoskeletal pain, skin rash	Retinal vasculitis, foveolitis, optic disc hyperemia and retinitis, acute macular neuro-retinopathy (AMN)	NS I antigen assays (within the first week of illness), Dengue serology, Real-Time (RT)-PCR assay	FFA - non-ischemic venular occlusion, vasculitis, and leakage, OCT - neurosensory retinal detachment, outer neurosensory retina-RPE thickening at the fovea (foveolitis)	Intravenous immunoglobulins systemic corticosteroids
Typhoid	Fever, loose motion	Retinitis, stellate maculopathy, vasculitis, and neurosensory detachment	Blood culture, WIDAL serological test, PCR assay	FFA, OCT – features of retinitis and neurosensory detachment (similar to other PFR)	Ciprofloxacin, Azithromycin, Doxycycline and systemic corticosteroids

References:

1. *Kawali A, Mahendradas P, Mohan A, Mallavarapu M, Shetty B. Epidemic Retinitis. Ocul Immunol Inflamm. 2019;27(4):571-577.*
2. *Kawali A, Srinivasan S, Mohan A, Bavaharan B, Mahendradas P, Shetty B. Epidemic Retinitis with Macular Edema -Treatment Outcome with and without Steroids [published online ahead of print, 2020 Jan 21]. Ocul Immunol Inflamm. 2020;1–5. doi:10.1080/09273948.2019.1704792*
3. *Kawali A, Srinivasan S, Mahendradas P, Shetty B. Epidemic retinitis and community outbreaks. Indian J Ophthalmol 2020;68:1916-9.*
4. *Kawali AA, Mohan A, Mehta R, Mahendradas P, Srinivasan S, Shetty B. Anti-vascular endothelial growth factor in the treatment of macular edema in epidemic retinitis. Indian J Ophthalmol 2020;68:1912-5*
5. *Kawali A, Mahendradas P, Sanjay S, Mohan A, Shetty B. Epidemic Retinitis with Positive or Negative Weil Felix Test - a Comparative Study and Outcome with Doxycycline. Ocul Immunol Inflamm. 2021 May 18:1-6. doi: 10.1080/09273948.2021.1909072*
6. *Mahendradas P, Kawali A, Luthra S, Srinivasan S, Curi AL, Maheswari S, Ksiaa I, Khairallah M. Post-fever retinitis - Newer concepts. Indian J Ophthalmol. 2020 Sep;68(9):1775-1786*
7. *Sundar M D, Chawla R, Balaji A, Garg I, Kalathil R, Hasan N, Vikas SJ, Kumar A. Clinical features, optical coherence tomography findings and treatment outcomes of post-fever retinitis. Ther Adv Ophthalmol. 2020 Dec 18;12:2515841420979111*
8. *Sanjay, S., Gadde, S.G.K., Agrawal, S. et al. Optical coherence tomography angiography (OCTA) of retinal vasculature in patients with post fever retinitis: a qualitative and quantitative analysis. Sci Rep 11, 17647 (2021)*

Infectious and Endogenous Endophthalmitis

Navneet Mehrotra, Alay Banker

1. Which are the most common pathogens responsible for acute postoperative endophthalmitis?

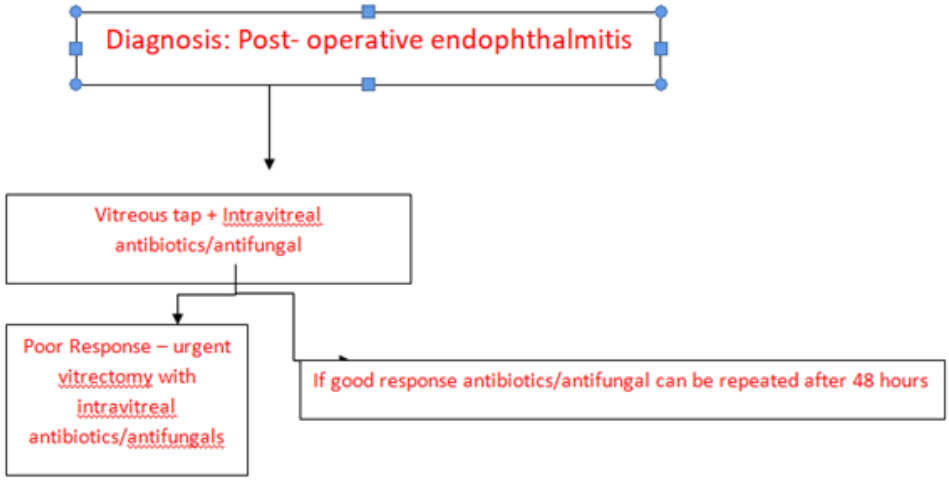
In most studies,Gram-positive, coagulase-negative staphylococci are the most common. Other common organisms are other Gram-positive cocci such as Staphylococcus aureus, Streptococcus and Enterococcus species,gram negative bacteria, like Klebsiella pneumonia, Pseudomonas aeruginosa and Enterobacter species. Candida albicans is the commonest fungal infection. In India, Gram negative and fungal infections are the commonest.

2. What are clinical signs distinguishing post-operative endophthalmitis from TASS (toxic anterior segment syndrome)

TASS signs include-

1. Rapid onset (within 12-24 hours, often with limbus-to-limbus corneal edema)
2. Relative less angry looking eye with less of congestion and no or white hypopyon
3. Absent vitreous inflammation
4. Response to steroid
5. Iris damage
6. Decreased intraocular pressure during initial period with raised intraocular pressure later due to trabecular meshwork damage
7. Lack of bacterial or fungal growth from cultures of intraocular taps

3. What should be the real-world step by step approach, once the clinical diagnosis of post operative endophthalmitis is made?



Vision should not be a criteria for management of endophthalmitis.

4. Are there any clinically differentiating features between bacterial and fungal endophthalmitis?

Bacterial endophthalmitis usually presents acutely, often within days of an inciting event such as cataract surgery. Fungal endophthalmitis typically has a subacute presentation with symptoms worsening over days to weeks. Patients with bacterial endophthalmitis are more symptomatic (pain and redness) than in fungal endophthalmitis. The intraocular inflammation in fungal endophthalmitis tends to occur in "clumps" within the aqueous and/or vitreous while intraocular inflammation is typically diffuse in bacterial endophthalmitis. Bacterial endophthalmitis has yellow hypopyon with high grade anterior chamber and vitreous involvement whereas fungal infection is relatively quiet eye with white hypopyon and vitreous opacities occuring late.

5. What are the pointers towards endogenous endophthalmitis?

Endogenous endophthalmitis results from hematogenous spread of microorganisms secondary to underlying systemic pathology like diabetes, immunosuppression, renal pathology,intravenous fluid infusion or placement of stents or tubes for any systemic surgery. There is absence of history of eye surgery but positive history of infection somewhere in the body. It typically involves more of posterior segment of the eye.

6. Describe the standard of care approach towards the diagnosis of endogenous endophthalmitis?

Suspected cases should undergo imaging like ultrasound B scan, aqueous and vitreous tap for culture and sensitivity, blood culture, vitreous biopsy, or polymerase chain reaction whenever indicated for rapid diagnosis. Once the blood culture results are available, systemic antibiotics/antifungals to be initiated. Severe ocular infection warrants the addition of intravitreal injections. Non-resolving cases with rapid progression require pars plana vitrectomy.

7. What are the indications for pars plana vitrectomy in managing endophthalmitis?

The following are broad indications for vitrectomy in endophthalmitis:

i. For patients with endophthalmitis presenting with poor visual acuity (Hand movements or PL/PR)

ii. Severe vitreous opacities (vitritis) confirmed on ultrasound or no red reflex.

iii. Non-Resolving vitritis after intravitreal antibiotics.

iv. Residual vireous opacities.

v. Chronic Endophthalmitis

vi. Endophthalmitis due to P. acne

8. What are the pros and cons of corticosteroids in treating a patient of endophthalmitis?

Corticosteroids help to modulate host immune response due to infection and helps to minimize damage due to this response. It has been beneficial in bacterial endophthalmitis. But they may interfere with the body's defenses against fungal infection, decrease the effectiveness of antifungal drugs and worsen the disease. So systemic steroids are contraindicated in fungal infections.

9. What are universally proven measures to reduce the incidence of postoperative endophthalmitis?

i. Primary Prevention: Managing the general good health and controlling the blood sugar levels for diabetics.

ii. Preoperative Regimens: Lid scrubs directed at the base of the lashes. Preoperative topical antibiotic regimens are often instituted.

iii. Perioperative Regimens: Proper sterile preparation of the surgical site. Instillation of povidone-iodine 5% onto the ocular surface at least 3-5 minutes prior to surgery. Sterile preparation of the skin surrounding the surgical eye with povidone-iodine 10%. Meticulous draping of the lids and eyelashes.

iv. Surgical Regimens: Proper construction of the incisions. Wound leak should be prevented. The injection of intracameral antibiotics reduces the occurrence of endophthalmitis.

v. Postoperative Regimens: Postoperative topical antibiotic regimens to reduce the bacterial burden during the time of healing of wounds. Maintain proper hygiene.

10. Is there any role of systemic antibiotics in treatment of endophthalmitis?

Intraocular penetration of systemic drugs is ordinarily limited by the blood-retina barrier and the blood-aqueous barrier. Role of systemic antibiotics in exogenous endophthalmitis is not well proven. But these can be supplemented in patients with endogenous endophthalmitis.

Oral voriconazole or fluconazole can be effective in fungal endophthalmitis due to good ocular penetration.

11. What criteria should be used for assessment while monitoring the course of treatment in a case of endophthalmitis?

i. Improvement of visual acuity

ii. Clearing of corneal haze and edema,

iii. Decrease in pain

iv. Resolution of anterior chamber reaction

v. Resolution of hypopyon and exudates.

vi. Decrease in the amount of vitritis or vitreous cells.

vii. Improvement of media opacities.

viii. Reduction in circumcorneal congestion and lid edema

ix. Resolution of disc and macular edema.

x. Decrease exudates on B-scan

Ocular Imaging in Uveitis

Richa Pyare, Aniruddha Agarwal

1. Which typical imaging techniques are useful for clinical diagnosis and management of uveitis?

- **Anterior uveitis**:
  - Essential: Only clinical examination.
  - Good to have: Slit lamp photo to document and monitor inflammation on follow up

- **Intermediate Uveitis**:
  - Essential: Clinical examination,
  - Good to have: Optical coherence tomography (OCT), Fundus fluorescein angiography (FFA). Ultrasound biomicroscopy is helpful to assess the ciliary body structures.

- **Posterior uveitis**:
  - Essential: OCT, colour fundus photo and autofluorescence (FAF).
  - Good to have: FFA and indocyanine green angiography (ICG), en face OCT
  - Great to have: Optical coherence tomography angiography (OCTA)

2. What are the various benefits of imaging in uveitis?

Imaging serves the following purposes in the management of uveitis:

Documentation: Uveitis is a chronic disease that often necessitates years of follow-up. The benefits of maintaining an objective record of the ocular condition from the initial visit and throughout subsequent follow-ups are clear. Such documentation is invaluable not only for monitoring disease progression but also for patient education, counselling, and prognostication.

Diagnosis: While clinical examination is the cornerstone of diagnosing uveitis, imaging plays a crucial role in providing a more comprehensive view. Imaging can reveal biomarkers and characteristic features that may be pathognomonic for specific disease entities, thereby enhancing diagnostic accuracy.

Therapeutic Response Monitoring: Resolution of signs of active inflammation can be monitored on imaging, these signs may precede clinical signs of resolution and provide an objective basis of step up or step of therapy as required.

3. How is fluorescein angiography (FFA) still relevant to the practice of uveitis? Explain with an example.

Fundus fluorescein angiography stands out from other diagnostic methods for uveitis due to its dynamic imaging capabilities. FFA is very relevant to uveitis because no other imaging modality can provide a dynamic visualization of the retinal vascular perfusion and leakage.

Diagnosis: In **retinal vasculitis**, FFA may be required to confirm active inflammation, especially in cases of partially treated/ resolved cases, or in cases where there have been multiple episodes of vasculitis. In vasculitis, staining and leaking of vessel walls is a sensitive indicator of active inflammation. FFA can be used to characterise the diagnosis of vasculitis, for example in Behçet's disease, the vasculitis is occlusive and typically involves veins, it also shows a typical ferning pattern due to capillaritis.

Exudative Neurosensory Retinal Detachment (NSD): FFA is indispensable to diagnose Vogt-Koyanagi-Harada (VKH) disease/ sympathetic ophthalmia (SO) and to differentiate it from multifocal central serous retinopathy (CSR). Acute VKH and SO may be diagnosed on FFA by the typical FFA features of multiple pin point leaks, often described as starry sky pattern, with late pooling of dye in areas of NSD. In the chronic stage of VKH, instead of the starry sky pattern, FFA shows multifocal areas of early hypofluorescence and late hyperfluorescence suggestive of choroidal granulomas. Optic disc leakage on FFA in VKH can be the sole inflammatory marker, specially early on, that can distinguish it from CSR.

Prognostication: The absence of the typical starry sky pattern of multifocal pinpoint leak on FFA is a poor prognostic factor, predicting development of chronic VKH.

4. How does indocyanine green angiography (ICGA) compare with FFA in uveitis - in what specific conditions would you prefer one over the other?

FFA and ICGA are complementary modalities of imaging in uveitis. ICGA is the gold standard of diagnosing and following up patients with choroidal inflammation. ICGA allows for direct visualisation of the choroidal vasculature and the disease process underlying choroidal inflammation.

Classification of choroiditis: It can be used to classify all choroidal inflammatory conditions into primary inflammatory choriocapillaropathies (PICCPs) in which hypocyanescent regions correspond to areas of choriocapillaris non perfusion, example disease entities classified as white dot syndrome like multiple evanescent white dot syndrome (MEWDS) and stromal choroiditis (primary stromal example: VKH, secondary stromal example: sarcoidosis), in which hypocyanescent regions represent space occupying granulomas.

PICCPs: Among the PICCPs, which can be difficult to classify clinically, ICGA can clearly delineate active choroiditis lesions as irregular, confluent areas of hypofluorescence, before they become clinically apparent. Moreover, ICGA can accurately delineate the extent of the inflammation, with clinical examination and FFA both underestimating the number and extent of lesions involved.

Stromal choroiditis: In conditions such as Birdshot retinopathy, ICGA demonstrates diagnostic hypofluorescent dark dots (HDDs) which are even sized round-oval dark areas over midperipheral fundus. In most clinical scenarios requiring angiography, whether choroiditis, retinal vasculitis or retinochoroiditis, FFA can be used to diagnose and manage the inflammation. ICGA reveals lesions earlier, in greater numbers, and more extensive in area than FFA and clinical examination. For instance, in cases of VKH with asymmetric and staggered presentation, one eye may show multiple pockets of SRF while the other appears normal. In such cases, ICGA can identify areas of HDDs in the apparently normal fellow eye, confirming the diagnosis of bilateral VKH.

5. Describe the utility of fundus auto-fluorescence (FAF) in the diagnosis and monitoring of posterior uveitis

In **choroiditis**, autofluorescence imaging is particularly informative. Active lesions appear hyper-autofluorescent, while inactive lesions are hypo-autofluorescent. The healing pattern in choroiditis typically progresses from the center to the periphery, characterized by a hyper-autofluorescent center surrounded by hypo-autofluorescent borders. Finally a completely inactive lesion will be uniformly hypo-autofluorescent. Patients of Acute zonal occult outer retinopathy (AZOOR), FAF shows a diagnostic trizonal pattern with central hypo-autofluorescence around the disc, surrounded by hyper-autofluorescent, active, spreading edge and finally and finally a third zone with normal autofluorescence of the fundus.

6. Elaborate how various aspects of optical coherence tomography (OCT) can be useful in uveitis.

OCT is possibly the most relevant, useful and dynamic imaging modality we have available today.

Diagnosis: In any case of suspected inflammation, OCT can be used to: first confirm the primary structure that is inflamed; next, assess contiguous areas of inflammation and associated typical biomarkers described in the literature; determine the choroidal thickness using enhanced depth imaging (EDI) OCT or swept-source (SS) OCT; confirm the presence or absence of associated inflammatory macular edema; and document the integrity of the outer retinal bands.

In case of primary **vitritis**, the vitreous cavity shows hyperreflective dots without any fundus lesions.

Retinitis shows up as hyperreflectivity of the retinal layers, with possible contiguous vitreous hyperreflective dots, such as seen in toxoplasma retinochoroiditis. Toxoplasma retinochoroiditis lesions also typically show pre-retinal hyperreflective oval deposits on OCT. In cases of confluent syphilitic retinitis, OCT can show pre/ inner retinal dots. Placoid syphilitic retinitis shows disrupted EZ junction, and granular hyperreflectivity of the RPE without elevation, which heals completely on appropriate antibiotic treatment. Behçet's disease shows transient retinal infiltrates which manifest on OCT as hyperreflective, focal thickening of inner retinal layers with back shadowing. Clinically these lesions appear to heal completely, but on OCT frequently show inner retinal thinning. It is also relevant to note that there is no choroidal thickening or RPE involvement noted on OCT in Behçet's disease.

Choroiditis lesions appear as round, hyporeflective, well demarcated lesions contained within the choroidal stroma, with *increased* signal transmission underneath it, which means underlying structures can be better visualised. These can be further characterised and their etiology can be determined. Granulomas involving the full thickness of the choroid, more superficial in location, with associated outer retinal hyperreflectivity and subretinal fluid (contact sign) is more likely to be tuberculous in origin, while smaller, deeper, more numerous granulomas with partial thickness involvement are characteristic of sarcoid granulomas. VKH and SO present with gross thickening of choroidal layers, with subsequent RPE undulations, subretinal hyperreflective dots, pockets of neurosensory detachment and bacillary layer detachment. OCT may also help differentiate VKH from CSR by documenting the presence of pigment epithelial detachment (PED) that points towards a diagnosis of CSR. On follow up, after appropriate management, choroidal thinning is noted and this can be used to monitor for treatment response. Choroidal thickening can be used as a marker of recurrence in chronic VKH where sunset glow has set in and NSD may not be noted even in active posterior inflammation.

7. Enumerate the typical clinical conditions wherein OCT-Angiography (OCT-A) has proven useful in the diagnosis and treatment of uveitis.

- Inflammatory CNVM: The most clinically relevant role of OCT-A in uveitis is in the diagnosis and management of inflammatory CNVM. Especially in cases with multiple healed scars of choroiditis/ chorioretinitis, the clinical presentation and fundus fluorescein angiography may both be unable to differentiate between re-activation/ fresh lesion and inflammatory CNVM. An important caveat is to be cautious in excluding projection artifacts, especially in areas of chorioretinal atrophy, and to avoid confusing the appearance of large choroidal vessels with a neovascular network. This can be done by meticulously examining the OCTA scans layer by layer.
- White dot syndromes: In cases of MEWDS, OCTA en face scans through the choriocapillaris layer show normal choriocapillaris flow with no vessel dilation, contrasting with findings on ICGA. This either suggests MEWDS may is a result of a reversible RPE disorder, leading to hypofluorescence on ICGA while maintaining normal choriocapillaris flow on OCTA. Alternatively, it could indicate that OCTA is not yet sensitive enough to detect subtle choriocapillaris non-perfusion. In contrast, in APMPPE the findings of ICGA and OCTA are consistent and colocalised, with OCTA showing flow voids at the level of choriocapillaris.
- Retinal Vasculitis: In cases of Behçet's, OCTA can be used to delineate the macular perfusion and the foveal avascular zone changes with more precision than FFA, where these microvascular changes may be obscured by significant leakage.

8. What is the role of B-scan ultrasonography in evaluating uveitis and its associated complications?

The role of B-scan can be divided into 2 broad scenarios:

- No view of vitreous cavity and fundus:
  USG B-scan is needed in almost every case with dense secondary cataracts, synechiae, or dense vitritis precluding the view of the posterior segment. B-scan helps to image the vitreous, look for signs suggestive of vitreous inflammation such as dot and clump echoes of low- moderate echogenicity, retinochoroidal-scleral (RCS) complex thickness.
- Vitreous and fundus visible:
  Posterior scleritis: To look for the pathognomonic T-sign in cases of posterior scleritis.
  In case EDI OCT is not available, it can be used to monitor RCS thickening in cases of VKH and SO.

9. Is wide-field imaging a must for managing uveitis?

Widefield imaging refers to the ability to image in a single retinal image, centred on the fovea, beyond the posterior pole but posterior to the vortex vein ampullae in all the four quadrants. Ultrawide field imaging refers to imaging modalities able to capture in a single frame, centred on the fovea, portions of the retina anterior to the vortex veins ampullae. One of the most clinically relevant advantages of widefield imaging is its ability to visualize the retinal periphery even in non-dilating pupils. However, it is not essential for diagnosis or management of uveitis.

10. What are imaging biomarkers in uveitis?

A biomarker is a reliable and measurable indicator of either normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Although many signs may be described in a particular disease process and imaging modality, they need to be validated by data as consistent markers of disease diagnosis, activity, or response to be considered biomarkers.

A few examples of imaging biomarkers in uveitis:

- RPE undulations with choroidal thickening on OCT in VKH
- Anterior segment OCT can be used to measure AC cells as an objective marker of anterior inflammation
- Use of ICGA to measure and follow up inflammatory CNVM
- OCTA is used to measure areas of choriocapillaris hypoperfusion in APMPPE and to document the recovery of perfusion as the inflammation resolves
- And, of course the measurement of central macular thickness (CMT) to measure severity of inflammatory macular edema (ME)

11. How can multimodal imaging be employed to assess uveitis comprehensively?

By leveraging the different advantages of different imaging modalities, uveitic entities can be diagnosed and managed more efficiently. A common example is uveitic macular edema, where there may be a macular leak on FFA without corresponding cystoid spaces on OCT, and vice versa. Similarly FAF can be used to visualise more choroiditis lesions than can be detected clinically or on colour fundus photograph and can be used to monitor response to treatment.

Ultimately imaging modalities are tools in our armamentarium which need to be used appropriately and always correlated with the clinical context of the patient.

Aqueous and Vitreous Biopsy in Uveitis

Himadri Chaudhary, Saurabh Luthra

1. Under what set of circumstances is the sampling of ocular fluids (aqueous or vitreous) advised?

Sampling of ocular fluids is done to diagnose patients with uveitis of uncertain etiology, especially:

i. Uveitis unresponsive to empirical treatment,
ii. atypical clinical presentation (reported in approximately 8% of uveitis cases),
iii. inconclusive non-invasive laboratory work-up and systemic medical evaluation,
iv. acute, sight-threatening condition,
v. to differentiate inflammatory from infectious process, and
vi. for prognostication and planning of intervention and management.

2. Are there any specific "dos and don'ts" regarding the sampling of ocular fluids for laboratory analysis?

AC tap can be performed using a 30-gauge needle mounted on a tuberculin syringe under topical anasthesia and aseptic precautions. It can be done on the slit lamp, or under an operating microscope, but lens injury is minimized when performed with the patient in supine position.

Vitreous specimen can be obtained by vitreous tap or vitreous biopsy, however, tap has the risk of retinal detachment due to vitreous traction.

After obtaining the sample, it must be transported to the laboratory immediately.

3. What are the best practices for preserving and transporting biopsy samples to ensure accurate diagnostic testing?

The sample is taken in a syringe and the needle is bent prior to capping. As the cells in the biopsy specimen are fragile and prone to rapid degradation, the sample should be be transported to the microbiology lab promptly. Efficient coordination and collaboration with dedicated microbiologist and cytopathologist are critical for achieving maximal positive yield in biopsy specimens.

4. What are the risks and potential complications associated with aqueous and vitreous sampling?

AC Tap : Risk of lens touch leading to cataract, iris injury, iris incarceration, hyphema, corneal infection, corneal abscess, endophthalmitis.

Vitreous biopsy : False negative results, needle track seeding, retinal detachment, vitreous hemorrhage, endophthalmitis.

5. What are the types of vitreous biopsy - what is the preferred choice of vitreous biopsy?

Vitreous can be obtained via fine needle aspiration biopsy (FNAB) or pars plana vitrectomy (PPV). The latter may be single port or a 3 port PPV.

a. For **FNAB,** a needle (attached to a syringe) is inserted through pars plana for sampling.

Though it is easier to perform, but due to difficulty in getting sufficient sample and the inherent risk of vitreoretinal traction related complications, this method is not recommended for vitreous biopsy.

However, it is an option for subretinal, sub-retinal pigment epithelium (RPE) or choroidal biopsy.

b. **3 port PPV** is the preferred choice to obtain safely adequate amount of vitreous sample.

Initially, undiluted vitreous sample is collected for culture, Polymerase Chain Reaction (PCR) and Immunohistochemistry (IHC).

Prior to turning on the infusion port, cutting is started with a 25-gauge / 27-gauge MicroIncision Vitrectomy Surgery (MIVS) cutter and sample is obtained through a broken aspiration line using an inline 3-way stopcock and tubing attached to a syringe.

After aspirating approximately 1.5 ml of undiluted sample, infusion is turned on and diluted sample is then obtained for cytology, culture, and flow cytometry.

Alternatively, air can also be used to restore the volume of the globe by switching on Air-Fluid Exchange once the undiluted sample has been collected.

Apart from improving diagnostic yield, PPV also has added advantages:

i. reduces microbial load, removes malignant cells and inflammatory cells and products responsible for inciting inflammation,
ii. improves fundus visualization,
iii. enhances penetration of intraocular drugs, and
iv. improves visual acuity.

6. What should you choose - aqueous or vitreous sampling? (Please elaborate with one or more than one typical clinical examples)

Vitreous Biopsy

Microbiological evaluation in cases of Infectious Uveitis to determine causative organism

Endophthalmitis: Organism and antibiotic sensitivity

For fastidious and slow growing organisms such as p. Acnes/Fungi, culture plates should be kept for a longer period of 2 weeks to 1 month.

AC Tap

HSV/HZV uveitis, CMV retinitis, Toxoplasma retinochoroiditis, PCR testing

PCR is very helpful in detecting extremely small loads of microbes by virtue of amplification of specific region of DNA to obtain multiple copies.

7. What are the most common pathogens identified in aqueous and/ or vitreous biopsies for infectious uveitis?

HSV/HZV uveitis, CMV retinitis, Toxoplasma retinochoroiditis

Staphylococcus, Sreptococcus species

8. In which cases is PCR testing of maximum benefit in the diagnosis of uveitis?

PCR is best suited for diagnosing viral infections, however, may it be used to diagnose protozoa (Toxoplasma gondii), fungi (Candida, Aspergillus), bacteria(Staphylococcus, Streptococcus, Mycobacterium)

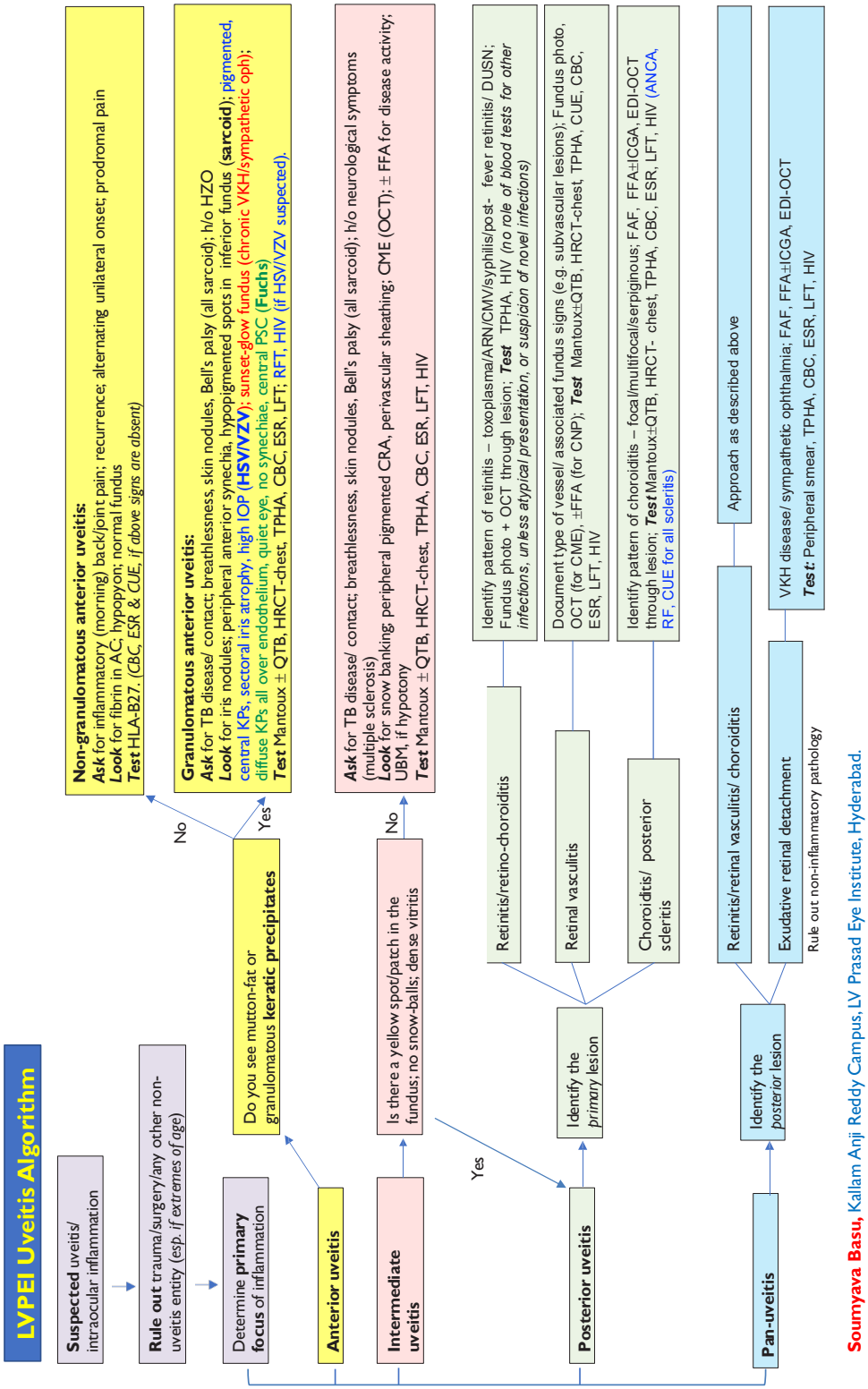
9. What are the other advanced diagnostic techniques that aqueous and vitreous biopsies can be subjected to?

1. Microbiology, culture, MADI-TOF-MS
2. PCR, nested PCR, RT-PCR
3. Cytopathological Analysis
4. Cytokine Analysis
5. Flow Cytometry
6. Immunohistochemistry (IHC)
7. Gene Rearrangement study, Metagenomic sequencing

Disclaimer: This algorithm is intended primarily for adult-onset uveitis (>16 years age) in a general ophthalmology practice. It does not aim to be a comprehensive account of uveitis.

Abbreviations: **CBC**: complete blood count; **ESR**: erythrocyte sedimentation rate; **CUE**: complete urine examination; **TB**: tuberculosis; **HZO**: herpes zoster ophthalmicus; **HSV**: herpes simplex virus; **VZV**: varicella zoster virus; **KP**: keratic precipitates; **QTB**: QuantiFERON TB Gold; **HRCT**: high resolution computed tomography; **TPHA**: treponema pallidium hemagglutination assay; **RFT**: renal function test; **CRA**: chorioretinal atrophy; **CME**: cystoid macular edema; **OCT**: optical coherence tomography; **FFA**: fluorescein angiography; **UBM**: ultrasound biomicroscopy; **ARN**: acute retinal necrosis; **CMV**: cytomegalovirus; **DUSN**: diffuse unilateral subacute neuroretinitis; **CNP**: capillary non-perfusion; **ICGA**: indocyanine green angiography; **VKH**: Vogt Koyanagi Harada; **ANCA**: anti-nuclear cytoplasmic antibody; **RF**: rheumatoid factor

Algorithm



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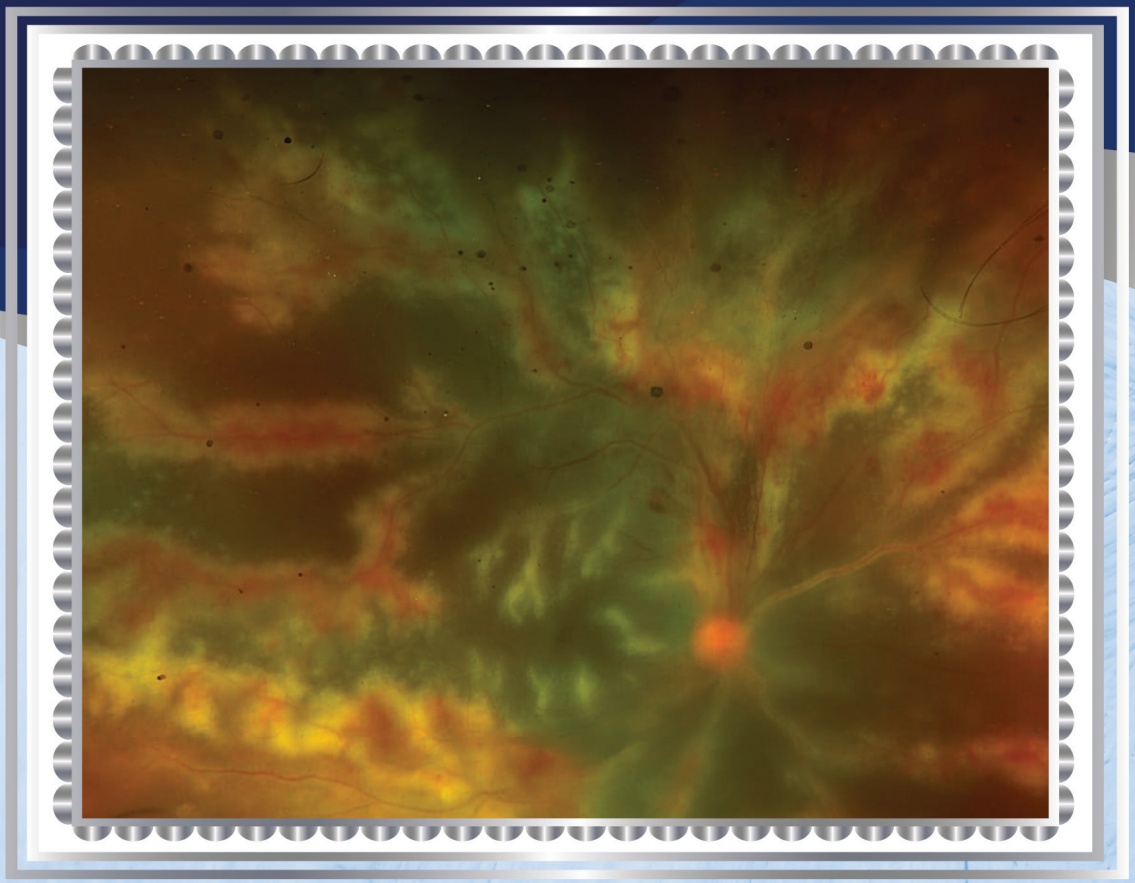

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