INTRODUCTION
In 1813, Joseph Beer first reported the association of uveitis and glaucoma, describing it as arthritic iritis followed by glaucoma and blindness. In 1891, Priesley Smith proposed the first modern classification of uveitic glaucoma. In 1906, Fuchs described heterochromic uveitis and in 1948, Posner and Schlossman described glaucomatocyclitic crisis.1-3

The form of ocular inflammation that most frequently produces intraocular pressure (IOP) elevation is iridocyclitis.4 When glaucoma is associated with other types of ocular inflammation, there is usually secondary involvement of the anterior uvea. While dealing with uveitis and refractory glaucoma, we should also keep in mind serious intraocular diseases like endophthalmitis, tumors, secondary reactions to intraocular foreign body, etc.

Uveitic glaucoma is a challenging problem, both from the diagnostic and the therapeutic point. About 25% of patients with uveitis develop increased IOP at some time in the natural course of disease. Uveitis of varying etiologies can be associated with glaucoma and a tailored approach is required for identification of the infectious/noninfectious pathology. This review article highlights the pathogenesis, clinical features, investigations and management of this complex disease with a focus on specific uveitis entities associated with glaucoma.

Pathogenesis
The pathogenesis is multifactorial and application of its understanding helps in the better management of patients. The mechanisms by which uveitis leads to elevated IOP are numerous and poorly understood. In general, iridocyclitis affects both aqueous production and resistance to aqueous outflow, with subsequent change in IOP representing a balance between the two. There is no predilection for race, sex or age.

1. Aqueous production: Under normal circumstances, aqueous production has little effect on the level of IOP due to the ability to regulate outflow facility. However, in uveitis, the perfusion rate of the trabeculum becomes impaired due to an underproduction of the aqueous by the inflamed ciliary body. This suboptimal perfusion of the trabeculum contributes to the elevated outflow resistance. This concept is supported by data7 that a trabecular perfusion rate less than 1 μl/min may have a deleterious effect on the trabecular function. In some cases like the Posner Schlossman syndrome, there may be an increased aqueous production.

2. Role of aqueous humor proteins: In uveitis, with the breakdown of blood aqueous barrier, protein influx into the anterior chamber is the first clinically visible intraocular inflammatory event, seen as flare on slit-lamp examination. The type of proteins found depends on the extent of the barrier breakdown. With severe inflammation, larger proteins like globulins enter the anterior chamber.8 These proteins influence the IOP either directly or indirectly. Immediate effects are due to aqueous sludging which compromises the aqueous outflow. Proteins also have an adhesive effect, causing posterior iridolenticular synechiae or peripheral anterior synechiae. The risk for synechiae formation can be evaluated by laser flare photometry (<30 photons/ms, the risk for synechia formation is low).

3. Role of inflammatory cells: Following the protein influx, occurs the influx of inflammatory and immunocompetent cells into the anterior chamber. Cellular infiltration affects the IOP directly more than the protein influx. Cells infiltrate the trabecular meshwork and Schlemm’s canal, which together with cellular and other debris cause
a mechanical blockage to the aqueous outflow. This debris in the angle can also cause formation of peripheral anterior synechiae leading to a secondary pressure rise. Development of inflammatory nodules at the iris base can also lead to formation of anterior synechiae. Because of the presence of particular combinations of cells and macrophages in granulomatous uveitis, the risk of IOP rise is greater in these types of uveitis. Other secondary effects of cells on IOP may be due to the liberation of cytokines (transforming growth factor β1 and β2),9 chemokines, autacoids, angiotensin converting enzymes,10 interleukin 1, interleukin 6, tumor necrosis factor and others.11,12

4. Role of arachidonic acid metabolites (autacoids): Prostaglandin E2 produced early in inflammation has a pressure raising effect but long-term effects of different prostaglandins on IOP in uveitis is not known.

5. Direct inflammatory involvement of the outflow pathways: In rare cases, especially herpetic uveitis and Posner Schlossman syndrome, there may be direct inflammation of the trabecular meshwork, causing edema and impaired aqueous outflow.

6. Secondary drug-induced impairment of outflow pathways (steroid induced): Corticosteroids given through any route can increase IOP in predisposed patients. Such steroid responders are about 5% of the population, more common in glaucoma, diabetes and myopia.13-15 Corticosteroids raise the IOP by altering the trabecular meshwork matrix, causing a decrease of aqueous outflow.16 Genes cytochrome P4501B1, CYP1B1 and mutations in the gene encoding the trabecular inducible glucocorticoid response protein (TIGR/MYOC) have also been implicated.17-19 IOP rises after about 2 weeks or later and returns to normal after discontinuation of the drug. Children less than 10 years are more susceptible.

Twenty-eight percent occurrence of elevated IOP in patients receiving an injection of intravitreal triamcinolone (IVTA) 4 mg for the treatment of cystoid macular edema in uveitis has been reported.20 In another study,21 of the 43 eyes that received a single 4 mg IVTA injection with at least 12 weeks of follow-up, 48.8% showed an increase of IOP ≥5 mm Hg and 27.9% had an IOP increase of ≥10 mm Hg. Patients with baseline IOP ≥15 mm Hg had a higher tendency for IOP rise.22 Based on these results, it is imperative to closely monitor the patients receiving IVTA, more importantly those with high baseline IOP which is common in uveitis. In most cases, glaucoma usually results from a combination of several factors and it can be severe enough to resist all medical therapy.

**Classification of Uveitic Hypertension and Glaucoma**

Uveitic glaucoma can be classified according to the morphological changes of the iridocorneal angle.

**Angle Closure Glaucoma**

a. **Posterior iridolenticular synechiae and pupillary block:** When there are 360° posterior synechiae or when there is a complete inflammatory pupillary membrane, aqueous flow toward the anterior chamber is interrupted leading to pupillary block, iris bombe and subsequent acute angle closure glaucoma.

Uveitis associated with juvenile chronic arthritis and with HLA-B27 antigen have a high tendency to form posterior synechiae. Granulomatous uveitis, especially tuberculosis and sarcoidosis have a tendency to form synechiae slowly and progressively. In such cases, apart from the proteins, cellular infiltration also form synechiae and they do so even in presence of low flare values.

b. **Peripheral anterior synechiae:** These can lead to progressive sectoral inflammatory angle closure. Partial closure may also cause sufficient impairment to the aqueous outflow to cause a rise in IOP because the remaining open angle may be blocked by inflammatory debris. PAS are more frequently seen with granulomatous uveitis and are the result of cellular infiltration which collects in the angle and causes adhesions between peripheral iris and trabeculum and are sign of remnants of previous angle closure attacks. In chronic uveitis, there may be neovascularization of the angle leading to secondary angle closure.

c. **Forward rotation of the ciliary body:** This may be due to supraciliary and suprachoroidal effusion caused by hyperacute inflammation. It is more commonly seen in Vogt Koyanagi Harada syndrome resulting in the induced myopia. It may rarely lead to angle closure glaucoma with pupillary block.

**Open Angle Glaucoma**

a. **Mechanical blockage of the outflow pathways:** In uveitis, the aqueous is saturated with proteins, inflammatory cells and cellular debris which are filtered by the trabecular meshwork but get trapped by the juxtaacanicular meshwork and impair the normal aqueous outflow. The particles can progressively pass into Schlemm’s canal or can be resorbed by trabecular endothelial cell phagocytosis. This leads to transient rise in IOP unless the inflammation is ongoing or recurrent.

b. **Damage to the outflow pathways by chronic inflammation:** In chronic or recurrent uveitis, there will
be permanent damage to the trabeculum leading to a permanent rise in pressure.

c. *Trabeculitis*: Occasionally, there may be associated inflammation of the trabecular meshwork itself which in chronic cases may lead to scar formation.

d. *Steroid-induced impairment of outflow pathways*: The increased IOP in uveitis may be due to the inflammation or there may be an added component to the IOP rise caused by the steroids used for management. Hence, steroids which have a minimal effect on IOP should be used in such responders. In case of ongoing active inflammation, they should be continued as per the need and the IOP should be controlled appropriately. After the inflammation is controlled, one can taper off the steroids but keeping in mind that the steroid-induced changes in the trabeculum will take at least 2 weeks to regress.

**Evaluation**

**History**

- A uveitis-oriented history has to be taken with a detailed history regarding the treatment regimens followed will be helpful.
- **Complaints**: Blurred vision—it may be due to glaucoma, uveitis or complications associated with uveitis.
  - *Ocular pain*: Pain is a frequent finding in acute iridocyclitis. Some patients with markedly elevated IOP often have severe eye pain associated with corneal edema.
  - *Brow ache*: Ocular pain associated with elevated IOP often is referred to the brow on the affected side.
  - *Ocular disturbances*: Photophobia and colored halos may be associated with acute iridocyclitis and corneal edema respectively.

**Clinical Assessment**

- *Visual function*: Decrease in vision is usually due to the uveitis rather than the glaucoma.
- *Slit-lamp examination*: It is important to establish the type of inflammatory reaction in the anterior chamber and anterior vitreous though the picture may be modified by the ongoing treatment.
  - Signs of granulomatous uveitis like mutton fat keratic precipitates and Koepe’s nodules indicate that the glaucoma is probably due to the inflammation and will warrant extensive and prolonged steroid treatment along with pressure lowering agents.
  - Stellate micro-mutton fat keratic precipitates, heterochromy, vitritis, unilaterality point toward Fuch’s heterochromic uveitis and the glaucoma will have to be treated independently from uveitis which usually does not need any intervention.
  - Presence of iris atrophy suggests herpetic uveitis indicating that the raised IOP will respond to steroid treatment itself.
  - Presence of mutton fat keratic precipitates (Fig. 1) at the periphery of the endothelium or in the angle, in a patient with IOP spikes and pain strongly suggests Posner Schlossman syndrome.
- *IOP measurement*: It should be measured over a 24 hours period and/or more frequently as there wide swings of IOP changes and an occasional measurement may lead to a missed diagnosis.
- *Gonioscopy*: It will detect the status of the angle, the presence of peripheral anterior synechiae, the extent of angle closure and angle neovascularization.
  - In Fuch’s heterochromic uveitis, prominent angle vessels may be seen.
  - Indentation gonioscopy may help to differentiate between appositional and synechial closure.
- *Fundus*: It will help to determine the type of uveitis and also help to evaluate the extent of glaucomatous damage at the disk and in the nerve fiber layer.
- *Laser flare photometry*: It helps to detect slight flare changes that cannot be appreciated by the human eye. It indicates, before the clinical changes occur, whether the inflammation is active and might be a contributing factor to the raised IOP.
- *UBM*: It gives information on the status of the angle and the morphology of the ciliary body. In patients with chronic uveitis and raised IOP, UBM often shows an atrophic ciliary body. This affects the management plan because there will be a high-risk of phthisis after glaucoma surgery.
- *Laboratory and other investigations*: They may help to establish the type and degree of uveitis.
Management

- Prompt identification of the cause of the uveitis and its appropriate management is important.
- Treatment of the inflammation and its complications – control of inflammation is beneficial in minimizing the adverse consequences of uveitis including elevated IOP. This is mainly achieved by introducing or adjusting the steroid therapy.

It is advisable to avoid periocular injections of depot steroids at this time because of their long-lasting effect and inability to be withdrawn in case of a pressure rise.

More recently, with a better understanding of ocular immunology, there has been a trend toward use of immunomodulators which reduce the systemic and local side effects of steroids.

In cases of acute and active inflammation, cycloplegia should also be achieved.

Neovascular angle closure generally occurs as a result of retinal ischemia and must be treated with retinal photocoagulation to induce regression of the new vessels in the angle.

- Antiglaucoma therapy: In uveitis, control of the inflammatory component alone frequently leads to normalization of the IOP.

If the IOP is very high or not responding to the anti-inflammatory treatment, its needs to be managed specifically.

It is important to set a target IOP for each patient.

If the raised IOP poses an immediate threat to the optic nerve or if there are anatomic risk factors, more urgent and aggressive measures are needed.

**Medical:** Several drugs are now available but the choice is mainly empirical and the result of trial and error:

1. **β-blockers:** These are generally the first choice and usually they suffice because the mechanisms causing IOP rise are transient and controlled by anti-inflammatory treatment. The drugs used are:

Timolol (nonselective β-blocker) 0.5% twice a day.

Cardiac and pulmonary contraindications have to be kept in mind.

Betaxolol 0.5% iridocyclitis (cardio-selective β₁-blocker).

Metipranolol should be avoided in uveitis as it may cause granulomatous. The preservative used, the pH of the preparation and increased oxidative reaction in bottle sterilization by γ-radiation are the possible causative factors.

2. **Carbonic anhydrase inhibitors:** These are used as second choice. Topical 2% dorzolamide is given 3 times as monotherapy and 2 times if given as an adjunct.

Fixed dose combination of 5% timolol and 2% dorzolamide can also be used.

Dorzolamide has been shown to inhibit corneal endothelial anhydrase as well which may compromise corneal hydration control especially in cases of corneal decompensation. Topical dorzolamide should hence be used with caution in cases of compromised corneal endothelial function.

Topical brinzolamide can also be used as an alternative. In case if cystoid macular edema, oral acetazolamide with potassium supplement can be given up to 500 mg twice daily.

3. **Adrenergic agonists:** These are epinephrine (α and β agonist); propine (prodrug of epinephrine); apraclonidine (α₂-agonist); 0.2% brimonidine (α₂-agonist).

Brimonidine effectively reduces IOP otherwise not controlled with maximal medical therapy.

Byles et al reported granulomatous anterior uveitis in four patients 11 to 15 months after initiation of the drug though the uveitis resolved rapidly after cessation of treatment and with initiation of steroids.

4. **Hyperosmotic agents:** They are used when the IOP has to be lowered rapidly.

The most commonly used is 20% mannitol, given intravenously at the rate of 60 drops per minute over a 30 minutes period.

5. **Miotics:** They best avoided in uveitic glaucoma as they promote posterior synechiae formation and pupillary membranes, worsen ocular discomfort by aggravating ciliary spasm and tend to increase the inflammation by enhancing the blood-aqueous barrier disruption.

They also antagonize the hypotensive compensatory mechanism of uveoscleral outflow present during intraocular inflammation. In synechial closure, they are generally ineffective considering their mechanism of action of increasing trabecular outflow.

6. **Prostaglandin analogs:** They do not initiate the inflammation of uveitis but amplify the inflammation that has already been elicited by different stimuli. So these drugs should be avoided in the treatment of uveitic glaucoma. In eyes with acute fibrinous anterior uveitis and impending pupillary block with or without peripheral anterior synechiae, intracameral tissue plasminogen activator (6.25 to 12.5 μg) can avoid the need for further laser or surgical intervention.

**Laser therapy:** It can be done when maximal-tolerated glaucoma medications do not control IOP. In secondary angle closure glaucoma due to posterior synechiae, laser iridotomy is often needed.
The pre- and postlaser anti-inflammatory treatments usually have to be aggressive.

With severe inflammation, the risk of iridotomy closure is high often requiring repeated laser treatments and occasionally a surgical iridectomy.

Laser trabeculoplasty should not be done in open angle uveitic glaucoma as the angle structures are usually already inflamed. Added laser-induced inflammation at the trabeculum will decrease or stop the aqueous outflow.

Surgical: It is resorted to when medical therapy fails. As with laser procedures, filtering surgery may aggravate the inflammation, stimulating fibroblast proliferation and leading to increased surgical failure.

The eye should be quiet for at least about 3 months before surgery and intensive steroid therapy should be given before, during and after the surgery.

To improve the success of trabeculectomy in uveitic glaucoma, use of antimetabolites like 5-fluorouracil or mitomycin C has been advocated.

Ceballos et al in a study on uveitic glaucoma treated with trabeculectomy with mitomycin C or 5-fluorouracil, reported complete or qualified success of 78% at 1 year and 62% at 2 years.

The combination of postoperative inflammation and shallow anterior chamber can lead to the formation of PAS, which may lead to a failing filter and cataract formation. Therefore, prolonged periods of postoperative shallowing of the anterior chamber should be avoided.

Recently, nonpenetrating surgery may be a better option as it avoids the opening of anterior chamber or performing an iridectomy and thereby reduces the risk of increased postoperative inflammation.

But when significant anterior synechiae are present, obstruction of the trabecular meshwork precludes the use of this procedure. Since these, procedures do not involve the removal of Descemet’s membrane, a barrier remains between the anterior chamber and the subconjunctival space. This prevents aqueous filtration and thus reduces the risk of hypotony which can be difficult in uveitic patients.

Goniosurgery has also been discussed as an alternative in the surgical management of pediatric uveitic glaucoma.

When standard filtering surgery does not succeed because of repeated bleb fibrosis, valvu lar drainage devices can be considered which have been proven to be at least as safe and effective as trabeculectomy with mitomycin C.

Yet till date the best surgical procedure for management of uveitic glaucoma has yet to be determined.

Cycloablation procedures: These can be considered in those who cannot undergo or are not fit for filtering surgery.

Cyclocryocoagulation is usually successful but has a high-risk of postoperative phthisis bulbi.

Nd:YAG cycloablation is efficient but they induce intraocular inflammation which needs to be treated with high-dose topical steroids.

Treatment with diode laser is easier and induces less intraocular inflammation.

For both surgical and laser procedures, anti-inflammatory therapy should be tailored according to the type and severity of uveitis. Topical steroids should be given hourly for the first few postoperative days. Oral or intravenous steroids can be given in selected cases. Despite a functioning bleb, if there is an IOP rise postoperatively, steroid responsiveness should be suspected.

Specific Uveitis Entities often Associated with Glaucoma

All uveitis entities can be associated with IOP elevation occasionally:

Granulomatous uveitis: Because of the particular type of cellular infiltrate present, these have higher tendency to induce IOP changes. These include sarcoidosis, toxoplasmosis, tuberculosis, Vogt Koyanagi Harada syndrome, sympathetic ophthalmia, syphilis, leprosy. Westfall et al reported the prevalence of elevated IOP in active retinochoroiditis secondary to toxoplasmosis to be as high as 38%. In sarcoïdosis, chronic uveitis and associated glaucoma are poor prognostic signs. Almost all the pathogenic mechanisms for development of glaucoma in a case of glaucoma can be found in sarcoïdosis.

Herpetic uveitis: It causes IOP elevation because of the granulomatous character of the inflammation and trabeculitis. In addition to the granulomatous signs, there may be iris atrophy and posterior pole involvement in form of necrotizing retinitis. The entities often associated with IOP elevation are herpes simplex disciform keratouveitis, varicella zoster disciform keratouveitis, herpes simplex uveitis, varicella zoster uveitis, necrotizing herpetic retinopathies.

Fuch’s heterochromic uveitis: It is associated with glaucoma in about 1/4 cases (13-59%). The glaucoma typically persists after the uveitis has subsided since, it is not directly related to the inflammation. Anti-inflammatory intervention has little effect on the inflammation and no effect on IOP. The glaucoma is primary open angle type and is to be treated independently. It is not known whether the vessels in the angle contribute to the rise in IOP or reflect morphological changes.

Posner Schlossman syndrome (Glaucomatocyclitic crisis): There are episodes of markedly elevated IOP associated
with mutton fat precipitates, some of which can be seen in the angle. The IOP is typically elevated in the range of 40 to 60 mm Hg and coincides with the duration of the uveitis. One study found that patients with 10 years or more of disease have 2.8 times higher risk of developing disk and field damage. The crisis lasts from several days to several weeks. Involvement is unilateral and the inflammatory involvement is mild compared to the high IOP. Both pressure reducing therapy and anti-inflammatory drops are needed.

**Lens-induced uveitis—pacoanaphylactic:** There is a ruptured lens capsule and consequent granulomatous foreign body reaction. Glaucoma is common and is due to obstruction of the outflow pathways by inflammatory cells and lens debris. It can be diagnosed by the presence of ruptured lens and lens material in the anterior chamber. Treatment consists of surgical removal of the lens and the matter. Glaucoma is managed medically and usually improves after the lens removal.

**Phacolytic:** It occurs in hypermature cataracts and is thought to be a reaction to leaking lens proteins. It is classically associated with glaucoma and is characterized by marked anterior chamber inflammation with pronounced flare and numerous large phagocytic cells containing lens material. The condition invariably resolves after lens extraction.

**Lens particle:** In hypermature cataracts with ruptured capsule, the lens material leaks out. This material itself blocks the trabecular meshwork and causes a rise in IOP. Treatment consists of removal of the lens and the material from the anterior chamber.

**Uveitis glaucoma hyphema:** Pseudophakics may develop this syndrome because of irritation of the ciliary body by misplaced haptics. Medical treatment of glaucoma and the uveitis should be attempted first. When it fails, the IOL may need to be explanted. The glaucoma may, however, be irreversible.

**Behcet’s disease:** In a retrospective study, 47% eyes showed chronic posterior uveitis and 10% of these patients developed secondary glaucoma, including steroid or inflammation induced, open angle glaucoma, angle closure glaucoma or neovascular glaucoma.

**Juvenile rheumatoid arthritis:** Uveitis in this disease is the most common form of childhood uveitis (14-22%) Foster et al found that uveitic glaucoma or elevated IOP occurred in 42% patients at intervals ranging from 0.6 to 58 years after the onset of ocular disease. In another study, 44 out of 426 children diagnosed with JRA who were followed for a mean of 4.5 years, 104 children (24.4%) developed uveitis and glaucomatous optic nerve damage occurred in 8%. Treatment is typically difficult with only a partial response to steroids. Antiglaucoma surgery is occasionally needed although reported results are poor. Moreover, the condition is usually bilateral and the eyes are generally quiet. The cause is unknown but the patients may eventually develop some other form of uveitis. Response to steroids is good but occasionally pressure reducing drugs may be required temporarily. Recurrence is common.

**Epidemic dropsy:** There are no signs of anterior segment inflammation. Aqueous shows elevated levels of PGE2 levels, histamine activity and total protein levels suggesting hypersecretion as the mechanism of the raised IOP.

**Scleritis:** In a study, the prevalence of glaucoma was 11.6 and 13% and in another study, raised IOP was seen in 18.7% with rheumatoid scleritis and 12% with nonrheumatoid scleritis. In most cases, the glaucoma is associated with anterior scleritis and is due to trabecular damage, overlying corneoscleral inflammation, peripheral anterior synechiae, steroid-induced neovascularization and elevated episcleral venous pressure. Posterior scleritis causes a secondary angle closure. Glaucoma is uncommon in episcleritis.

**Infectious diseases:** They may cause an iridocyclitis with the occasional association of glaucoma. These include congenital rubella, syphilis, Hansen disease (more typically low IOP), disseminated meningococcemia, hemorrhagic fever with renal syndrome, AIDS bilateral (acute angle closure due to choroidal effusion and forward rotation of the ciliary body which responds well to medical treatment).

**Retinitis and choroiditis:** Inflammation, though posterior, may have an added anterior uveitic component leading to raised IOP or may cause angle closure by posterior pushing effect.

### REFERENCES