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Approach to The Patient With Hypertensive Uveitis and Uveitic Glaucoma

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Introduction

Elevated intraocular pressure (IOP) and glaucomatous optic neuropathy are common complications in patients with uveitis. Ocular hypertension occurs in approximately 25% of uveitic patients.[1] In addition, retrospective observational studies have found that 31-77% of patients with ocular hypertension had converted to glaucomatous optic neuropathy over a 10 year period.[2,3] Ocular hypertension occurs in approximately 35% of children with uveitis, with secondary glaucoma occurring in 11-38%.[4,5] Many of these children will require surgical glaucoma interventions: 11.5% at 1 year after a diagnosis of ocular hypertension, increasing to 50% by 5 years.[6] In adults with non-infectious uveitis, the rate of surgical glaucoma interventions is between 20-40%.[7,8]

Mechanisms of Elevated Intraocular Pressure in Patients With Uveitis

To understand the mechanisms of elevated IOP in uveitis, it is helpful to categorize them into open angle and angle closure mechanisms. These mechanisms are illustrated in **Figure 1**.

History, Review of Systems, and The Uveitis Course Timeline

A closer look at the hypertensive uveitic patient's disease course and timeline will provide important clues about the etiology of the elevated IOP. If, upon initial assessment, the patient presents with active uveitis and elevated IOP, the etiology is either going to be a primary hypertensive uveitis, trabeculitis, or sequelae of untreated chronic uveitis, such as bombe, seclusio papillae, or ciliary body effusion with anteriorization of the lens-iris diaphragm. If, however, the patient's ocular hypertension was noted 2-3 weeks or more after the initiation of

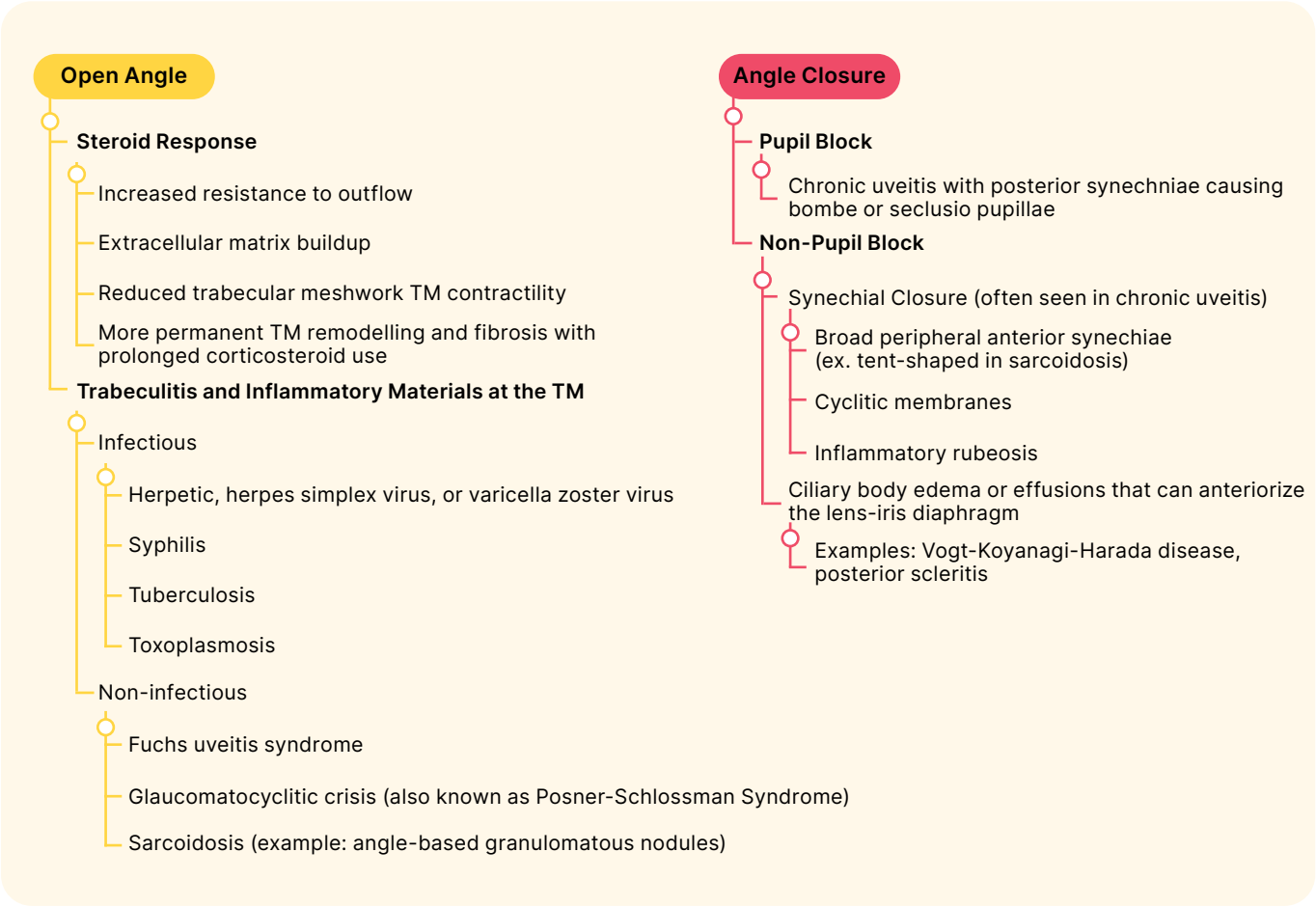

Figure 1. Mechanism of elevated intraocular pressure in uveitis.[8,9,21]; *courtesy of Carol Tadrous, MD, FRCSC*

corticosteroid therapy, the most likely cause is a steroid response.

Obtaining a thorough history of any patient presenting with uveitis will help achieve an appropriate diagnosis and strengthen pretest probabilities to acquire a more meaningful and focused workup. A helpful rubric for obtaining a history of presenting illness for uveitis includes:

- Past symptomatic episodes including experiences of reduced vision, redness, photophobia, eye pain, floaters, or photopsias
- Timeline of prior episodes with respect to onset, duration, and periods of remission
- Prior treatment employed, including dosing, efficacy, and taper schedule
- Current therapy

It is also essential to complete a full ocular history, which includes any history of steroid response or glaucoma. Additionally, it is important to obtain a detailed review of systems, such as social history and medical history as outlined in **Table 1**.

Clinical Examination Clues For The Diagnosis of Hypertensive Anterior Uveitis

For the patient with hypertensive anterior uveitis, several clues obtained on slit lamp examination are helpful in guiding the physician toward a more specific etiology.[9,10,11] These clues, focusing on keratic precipitates (KP) and iris morphology, are summarized in **Table 2**. Iris nodules can form at the pupillary margin (Koeppe) and tend to be involved in granulomatous disease, although smaller ones may be observed in acute non-granulomatous anterior uveitis. Nodules within iris stroma (Busacca) almost always occur in the context of granulomatous uveitis, while nodules at the angle (Berlin) are also observed in granulomatous disease. In cases of chronic anterior uveitis, fine pinpoint white iris crystals, thought to represent crystalline immunoglobulins (Russell bodies) from activated plasma cells, can be diffusely distributed. In chronic uveitis,

Relevant Medical History	Autoimmune disease Previous cancer Immune compromise Long-term immune modulatory therapy Exposure to tuberculosis	
Relevant Medication History	Examples: checkpoint inhibitors, immune modulatory therapy, antiviral therapy, anti-mycobacteria therapy, fluoroquinolones, bisphosphonates, sulfonamides, topical prostaglandin analogues, topical alpha-adrenergic agonists	
Family History	Autoimmune disease or demyelinating disease	
Social History	Occupation Smoking Sexual activity and exposure to sexually transmitted illness Illicit drug use Unstable housing Recent travel Country of birth and date of immigration with specific attention to endemic areas of tuberculosis (Africa, Southeast Asia, Western Pacific, Indigenous) Animal contact, farm work Driving status	
Review of Systems	Neurological	Headache Focal neurologic symptoms of weakness/paresthesias/numbness
	Musculoskeletal	Lower back pain/stiffness (time of day, onset after activity/inactivity)
	Ear, nose, throat	Sinus problems Nose bleeds Hearing loss Tinnitus
	Respiratory	Cough Difficulty breathing Shortness of breath Chest pain
	Gastrointestinal, genitourinary	Bloody stools or mucus in stool Bloody urine or dysuria
	Dermatological	Skin rashes/skin changes Oral/genital painful ulcers
	Constitutional symptoms	Fevers Weight loss Chills Fatigue or malaise

Table 1. Review of systems and history; *courtesy of Carol Tadrous, MD, FRCSC*

inflammatory neovascularization of the iris can sometimes be observed.

Workup of Hypertensive Uveitis

There is no one-size-fits all diagnostic workup for the uveitis patient. It is paramount to tailor investigations to avoid false discoveries, patient anxiety, and undue costs to the healthcare system. Bayesian analysis is a helpful framework in this regard, which can help by using what you already know about the patient (demographics, history, review of systems, and exam findings) to inform your pretest probability in selecting

		Keratic precipitates (KP)	Iris transillumination defects and atrophy	Iris nodules and other findings
Autoimmune/ Autoinflammatory	**Fuchs Uveitis syndrome**	Fine Stellate Diffuse Some with inter connecting spindles Pigmented if chronic	Patchy scattered atrophy Depigmentation of anterior iris stroma, and can also lose posterior stroma Heterochromia	Iris sphincter function maintained Prominent iris vessels which may cross the trabecular meshwork
	Glaucomatocyclitic Crisis (Posner-Schlossman Syndrome)	Small-medium Round Discrete Predominantly inferior/near angle		
	Sarcoidosis	Medium-large Mutton-fat/ granulomatous appearing		
Infectious	**Cytomegalovirus**	Small Coin-shaped Linear Discrete		Iris sphincter function sometimes affected
	Herpes simplex virus, Varicella-zoster virus	Medium-large Granulomatous or non-granulomatous Arlt's triangle or diffuse	Sectoral or diffuse atrophy	Iris sphincter may be compromised
Masquerades	**Lymphoma**	Peculiar appearance Large branching Some with inter-KP dendritiform digitations Can have caked-on infiltrative appearance		
	Uveitis-Hyphema-glaucoma syndrome/ intraocular lens malposition		Transillumination defects (TID) along sulcus-placement of haptics	
	Bilateral Acute Iris Transillumination		Diffuse TID post-systemic or intraocular fluoroquinolone use	Fixed or mid-dilated pupil
	Pigment dispersion syndrome	Nil	Radial TIDs	

Table 2. Clues from slit lamp examination for the hypertensive anterior uveitis patient.[10,11,12]

and interpreting tests.[12] This framework aids in arriving at an accurate diagnosis, and thereby in administering the most appropriate treatment.

Nonetheless, it is recommended to order certain tests for every patient presenting with hypertensive and active uveitis. These tests include syphilis serology, angiotensin converting enzyme level, chest X-ray, and an anterior chamber (AC) tap sent for cytomegalovirus (CMV), Herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), and polymerase chain reaction (PCR) testing. Some studies have shown that obtaining an AC tap for viral PCR findings alters disease management in up to 37.7% of cases.[13]

Additional tests are guided by patient-specific factors and your clinical pretest probability. The following examples further illustrate this concept.

- A patient presenting with hypertensive uveitis and active KP, who shows a strong response to topical corticosteroid therapy but is also highly dependent on it, with a pattern of rebounding soon after tapering, raises suspicion for a viral etiology. If the initial AC tap results were negative, the next consideration would be to obtain viral serologies for their negative predictive value, to increase the yield with repeat confirmatory viral PCR testing.
- For a patient older than 50 years presenting with bilateral hypertensive uveitis, vitreous veils, and peculiar-appearing KPs, it would be appropriate to obtain an initial computed tomography of the chest, and magnetic resonance imaging of the brain and spine with gadolinium. This helps rule out conditions such as sarcoidosis and central nervous system lymphoma. Further testing may include an AC tap for MYD88 and diagnostic vitrectomy.
- A patient with granulomatous hypertensive uveitis in any anatomical segment, who was born in a region endemic for TB, is a healthcare worker, or has other risk factors (unstable housing, intravenous drug use, history of incarceration, prison work, or known TB contacts) would benefit from undergoing a TB skin or interferon-gamma release assay (IGRA) testing.

Fuchs Uveitis Syndrome (FUS) is under-diagnosed in the field of uveitis.[9,10] In 2021, the Standardization of Uveitis Nomenclature (SUN) Working Group published classification criteria for FUS, with high accuracy rates for its diagnosis. The key criteria include unilateral anterior uveitis (with or without vitritis), along with either heterochromia or unilateral diffuse iris atrophy with stellate KPs.[14] Exclusion criteria consist of endotheliitis, nodular or coin-shaped endothelial lesions, positive syphilis serology by treponemal testing, evidence of sarcoidosis, and positive aqueous tap for CMV, HSV, and VZV PCR.[15]

Ocular diagnostics such as optical coherence tomography of the optic nerve and macula, visual field testing, pachymetry, fundus autofluorescence, widefield retinal imaging, fluorescein angiography, and ultrasonography (B-scan and ultrasound biomicroscopy) should be utilized in the workup as appropriate.

Management of Uveitis In The Hypertensive Uveitic Patient

Appropriate treatment of the uveitic component of hypertensive uveitis requires identifying the diagnostic category into which it falls: FUS, autoimmune/autoinflammatory/idiopathic, and infectious.

FUS is one of the most over-treated conditions in uveitic patients. Topical steroids are at times liberally used but they are often futile or unnecessary.[9] Moreover, as glaucoma is the leading cause of vision loss in FUS patients, with 55-73% requiring surgical intervention, corticosteroid therapy may be counterproductive in worsening glaucomatous disease.[15] As such, topical steroids should be generally reserved for cases with dense KP accumulation, true significant AC cell and flare (beyond 0.5+ cells), and/or symptomatic lens deposits.[9] Steroids are also indicated during the perioperative phase of intraocular surgery.[9] Patients with low-grade AC inflammation may be closely observed without treatment.

For patients with an autoimmune, autoinflammatory, or idiopathic underlying etiology, a short course of topical, regional, or systemic corticosteroid therapy is appropriate. However, approximately 30% of patients will require escalation to immunomodulatory therapy (IMT) due to frequent recurrences, inadequate control on safe corticosteroid levels, or the need for steroid sparing treatment.[8,16] In most cases, an antimetabolite is the first-line therapy, followed by, or in addition to, a biologic such as an anti-tumour-necrosis factor monoclonal antibody. If the uveitic etiology is associated with a systemic disease, such as sarcoidosis, a multidisciplinary approach with the patient's internists is paramount.

For infectious hypertensive uveitis secondary to conditions such as syphilis, tuberculosis, or toxoplasmosis, systemic treatment of the underlying condition is required, often in conjunction with an infectious disease specialist.

For viral hypertensive anterior uveitis, it is useful to ascertain whether the virus involved is CMV or HSV/VZV. The TITAN-1 and TITAN-2 Consensus Reports on the Treatment of Viral Anterior Uveitis have been recently published, featuring consensus summary points agreed upon by >75% of international uveitis experts from 20-21 countries.[17,18] For HSV and VZV anterior uveitis, key concepts from the TITAN-1 report include:[18]

- topical corticosteroids should only be administered under antiviral coverage
- valacyclovir is often the most used agent for ease of dosing
- periocular or systemic corticosteroids have no role in this treatment
- topical beta-blockers are the first-line agents for treating associated ocular hypertension
- management of first episodes includes frequent prednisolone acetate 1% every 2-3 hours to 4 times daily for a 1-2 week induction period, followed by a slow taper over 3-12 months Oral valacyclovir is prescribed at 1 g twice or thrice daily for HSV and thrice daily for VZV for 10-14 days, followed by 500 mg twice or thrice daily for 3-12 months
- for recurrent or chronic disease, restart induction dosing with a slower taper and a longer maintenance period

For CMV anterior uveitis, key concepts from the TITAN-2 report include:[19]

- use of topical ganciclovir 0.15%
- valganciclovir is the oral agent of choice; however, only 50% of uveitis specialists in the TITAN-2 report started this agent if the patient course was prolonged, severe, or atypical
- if using valgancyclovir, it is important to obtain complete blood counts, creatinine, and liver function testing 2 to 4 times per year
- prednisolone acetate 1% should be used at least 4 times daily for 1-2 weeks with a slow taper depending on clinical response for up to 12 months
- topical beta-blockers are the first-line agents of choice for treating associated ocular hypertension
- for chronic uveitis or >2 episodes in 1 year, long-term therapy is indicated

Treating CMV significantly lowers recurrence rates of anterior uveitis as well as glaucoma surgery rates. The percentage of patients requiring glaucoma surgical intervention had reduced from approximately 60% to 36% with valgancyclovir and 18% with topical ganciclovir.[19]

Management of Ocular Hypertension and Glaucoma In The Hypertensive Uveitic Patient

Treatment pearls for managing elevated IOP and glaucoma in the hypertensive uveitis patient can be categorized by medical management, laser therapy, and surgical interventions.

Prostaglandin analogues (PGA) have been reported to induce intraocular inflammation and uveitis is often cited as a contraindication. However, a recent meta-analysis found the incidence of uveitis with PGA used to be low, at 0.22%.[20] Despite these findings, I prefer to use a topical beta-blocker or carbonic anhydrase inhibitor as my first-line treatment in patients with uveitis requiring IOP reduction. Pilocarpine can break down the blood-aqueous-barrier, and as this barrier is already compromised in uveitic patients, this agent is best avoided. One should not forget that patients may have an idiosyncratic granulomatous anterior uveitis with the use of brimonidine, and that discontinuing this drug may resolve their uveitic episode.

If a patient with active uveitis requires intensive corticosteroid therapy and has elevated IOP from a steroid response, the corticosteroid therapy should not be compromised or reduced to manage the elevated IOP. Instead, better alternatives include glaucoma surgery to allow for continued corticosteroid use or the initiation of systemic IMT in cases of non-infectious uveitis.[10] Of note, most IMT require 6-8 weeks for full effect.[8]

Laser therapy for ocular hypertension (OHT) and glaucoma includes selective laser trabeculoplasty (SLT), laser peripheral iridotomy (LPI), and diode cyclodestructive procedures. Each of these treatments has specific considerations for the patient with uveitis. There have been limited and conflicting retrospective case series reporting on the association of SLT with flares of uveitis. This is typically not a modality I use to treat the patient with active or severe uveitis, but I will use it judiciously for patients with remote, controlled, and quiescent uveitis. Diode cyclodestructive laser therapy is best avoided for the uveitic patient,

as it is known to induce intraocular inflammation and carries a rare but serious risk of phthisis. LPI should be approached with extreme caution in this patient population, especially in the setting of a partially secluded pupil as it can induce bombe via a path of least resistance and can worsen inflammation.[10,21] If an LPI is needed, large or multiple iridotomies are preferable.[10,21] A surgical peripheral iridectomy with goniosynechiolysis can be an even better option in more acute cases.[10,21]

Multiple case series have demonstrated good outcomes for glaucoma surgery in uveitic patients, particularly with procedures such as gonioscopy-assisted transluminal trabeculotomy (GATT) and valved glaucoma drainage devices.[22] It is advisable to pursue glaucoma surgical interventions that have lower rates of postoperative hypotony, fibrosis, and encapsulation, as these adverse effects can be compounded by active or inadequately controlled uveitis and potential ciliary body shutdown.[8,21] Clinical hypotony, arguably the most dreaded complication for the glaucoma surgeon, carries an increased risk of suprachoroidal hemorrhage, anterior chamber flattening with iridocorneal, corneal-tube or corneal-lenticular touch (at times irreversibly damaging corneal endothelial cells), and other structural sequelae up to and including phthisis. The glaucoma surgeon must be ready to insufflate the chamber, administer aggressive corticosteroid therapy, and may also need to pursue a revision (for example, intraluminal stenting with a polypropylene suture for glaucoma drainage devices).

To set the patient up for surgical success, it is ideal for uveitis to be quiescent for at least 3 months; however, this is not always possible if IOP is uncontrolled on maximally tolerated medical therapy. Key perioperative strategies to mitigate the risk of surgical failure and postoperative complications include burst dosing of topical/systemic corticosteroids with a slow taper in cases of non-infectious uveitis, and a course of relevant antimicrobials (antiviral, antibacterial, anti-parasitic) often 1-2 weeks preoperatively and 4 weeks postoperatively in infectious cases. Patients requiring IMT should be induced prior to surgery and maintained on treatment during the perioperative period. Additionally, there should be a low threshold for administering local corticosteroid therapy (i.e., posterior subTenon triamcinolone or intravitreal dexamethasone) in high-risk uveitis patients, such as those with severe panuveitis, retinal vasculitis or a history of uveitic macular edema. This therapy can be delivered either at the time of surgery or during the acute postoperative period.

Conclusion

Diagnosing and treating patients presenting with both uveitis and ocular hypertension or glaucoma requires a thorough history, review of systems, and an individualized and meaningful workup. Appropriate therapy should be initiated, often in close collaboration with multidisciplinary teams, to address both IOP and uveitis. There is an intricate interplay between IOP and uveitis, with a clinical course fraught with peaks and valleys, including lability of IOP and recurrences of uveitis. Careful attention to the patient's unique course and thoughtful preparation while undertaking interventions can improve short- and long-term visual outcomes.

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Financial Disclosures

C.T.: Advisory Board: AbbVie

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