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Adverse Events Associated With Novel Cancer Therapies

Grace Yin, MD, MPhil
C. Maya Tong, MD, FRCSC

Introduction

Advancements in novel anticancer therapeutics have enhanced the precision with which cancerous cells can be selectively identified and destroyed. Breakthroughs in adoptive cell therapy, checkpoint inhibitors, and anti-drug conjugates have been at the forefront of these advancements. The purpose of this review is to highlight the mechanisms of action underlying these novel anticancer therapeutics, provide an overview of their reported ocular adverse effects (AE), and where possible, provide a starting point for ocular AE prophylaxis and management.

Adoptive Cell Therapy (CAR T and TIL)

CAR T Therapy

Chimeric antigen receptor T-cell (CAR T) therapy is a novel therapeutic approach used to treat hematological malignancies, particularly those refractive to first-line therapies. Ongoing research is evaluating its utility within retinoblastoma, uveal melanoma, and neuromyelitis optica spectrum disorder.[1] First approved by the Food and Drug Administration (FDA) in 2017, CAR T therapy involves extracting T cells from the patient, then genetically engineering them to express chimeric antigen receptors specific for antigens on the surface of the malignant cells of interest. The engineered CAR T cells are clonally expanded and infused back into the patient's circulation, where they continue to expand and target cells expressing the chimeric antigen of interest. Despite its promise, CAR T therapy can be associated with serious ocular AEs, including conjunctivitis and keratitis, exudative retinal detachment, candida endophthalmitis, optic neuropathy, worsening ocular graft versus host disease, and acute retinal necrosis[1,2] **(Table 1)**. There have been case reports of intraocular recurrence of hematological malignancies following completion of CD19 CAR T therapy.[1] CAR T therapies can also be associated with life-threatening systemic complications induced by rapid immune activation, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[3] These syndromes can present with optic neuropathy, increased intracranial pressure with optic nerve edema, and intraocular inflammation.[1] The underlying mechanism of these AEs is hypothesized to be disruption of the blood-brain-barrier, causing immune cell invasion and neurotoxicity.[1] Due to a paucity of data, the outcomes of these AEs are limited to a few case reports that demonstrate variability in their treatment response and reversibility. Ongoing monitoring will be essential toward elucidating a more comprehensive pattern of ocular toxicities associated with CAR T therapies.

TIL Therapy

Tumour-infiltrating lymphocyte (TIL) therapy is another form of cell therapy showing promise for treating solid tumour malignancies. The process involves surgically excising a tumour sample from the patient, extracting TILs (primarily CD8+ cytotoxic T cells) that have already infiltrated the tumour, and then selecting the most potent TILs ex vivo for clonal expansion. Patients are preconditioned with lymphodepletion, and the expanded TILs are reinfused into the patient, where they circulate, infiltrate, and destroy cancer cells by recognizing tumour-associated antigens and neoantigens retained by the TIL. Although TIL therapy has not yet been approved for use by Health Canada, it was approved for use by the FDA in 2024 for treating unresectable or metastatic melanoma that has failed previous therapies. While early results show tremendous promise to induce early complete tumour regression and maintain remission up to 24 months after therapy, it has been associated with significant ocular autoimmune sequelae.[4]

Examples	Applications	Reported Ocular Toxicities	Reported Treatment/ Reversibility
CAR T Therapy			
Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Tescarta®) Brexucabtagene autoleucel (Tecartus®) Lisocabtagene maraleucel (Breyanzi®)	Acute lymphoblastic leukemia Non-Hodgkin lymphoma Mantle cell lymphoma Multiple myeloma Refractory hematological malignancies	Mydriasis Xerophthalmia Allergic conjunctivitis Retinal vein occlusion Vitreous hemorrhage Exudative retinal detachment Retinal hemorrhage Retinitis Blindness Ocular lymphoma Candida endophthalmitis Intraocular hematological relapse Worsening ocular graft versus host disease (persistent epithelial defects, symblepharon) Herpes zoster ophthalmicus Acute retinal necrosis Optic neuropathy Anisocoria Nystagmus Keratitis Conjunctivitis Visual field defect Diplopia Optic disc edema Metamorphopsia	Improvement with intravenous antiviral therapy (herpes zoster ophthalmicus, acute retinal necrosis) Aggressive lubrication, topical steroid, amniotic membrane corneal bandage contact lenses, topical cyclosporine, scleral lens for worsened ocular graft versus host disease patients with minimal improvements Improvement in cases of bilateral exudative retinal detachment with optic disc edema and intravitreal triamcinolone injections, bilateral orbital radiation
TIL Therapy			
Lifileucel (Amtagvi®)	Melanoma (unresectable, refractory, metastatic)	Ocular autoimmune sequelae Bilateral anterior uveitis Bilateral panuveitis Vogt-Koyanagi-Harada Bilateral cystoid macular edema	Persistently elevated proinflammatory cytokines in aqueous humor reported with cessation of treatment
Checkpoint Inhibitors			
Ipilimumab (Yervoy®) Nivolumab (Opdivo®) Pembrolizumab (Keytruda®) Atezolizumab (Tecentriq®) Avelumab (Bavencio®) Durvalumab (Imfinzi®)	Melanoma Renal cell carcinoma Small cell lung cancer Non-small cell lung cancer Colorectal cancer	Dry eye disease Uveitis Ocular myasthenia gravis Inflammatory orbitopathy Uveal effusion Optic neuritis Papillitis Vitritis Choroidopathy Ocular myositis Cerebellar ataxia with nystagmus Retinal vasculitis Vogt-Koyanagi-Harada-like syndrome Birdshot-like uveitis Corneal graft rejection Corneal perforation Fundus depigmentation Acute macular neuroretinopathy Extraocular muscle paresis Stevens-Johnsons syndrome Periorbital edema Glaucoma or elevated IOP	Consider suspension of treatment until normalization or improvement of ocular symptoms with moderate adverse effects Majority of inflammatory AEs improved with systemic corticosteroids, but rarely with observation alone Consider continuation of treatment if ocular adverse effect experienced is secondary to a paraneoplastic event

Examples	Applications	Reported Ocular Toxicities	Reported Treatment/ Reversibility
Antibody-Drug Conjugates Brentuximab vedotin (Adcetris®) Trastuzumab emtansine (Kadcyla®) Sacituzumab govitecan (Trodelvy®)	Acute lymphoblastic leukemia B-cell lymphoma Multiple lymphoma Hodgkin lymphoma Hairy cell lymphoma Breast cancer Cervical cancer Ovarian cancer Urothelial carcinoma Gastric cancer Non-small cell lung cancer Pleural mesothelioma Pancreatic adenocarcinoma	Foreign body sensation Blurred vision Dry eye disease Conjunctivitis Keratitis/keratopathy Xerophthalmia Cataract formation Ocular pain Photophobia Microcystic corneal disease Nyctalopia Purtscher-like retinopathy Retinal hemorrhage	Artificial tears and aggressive lubrication Topical ocular corticosteroids Consideration of vasoconstrictor drops prior to treatment initiation as prophylaxis Consideration of cooling eye pads during treatment infusion as prophylaxis
Molecularly Targeted Therapies Trametinib (Mekinist®) Cobimetinib (Cotellic®) Binimetinib (Mektovi®) Vemurafenib (Zelboraf®) Dabrafenib (Tafinlar®) Encorafenib (Braftovi®) Osimertinib (Tagrisso®) Neratinib (Nerlynx®) Cetuximab (Erbitux®) Alectinib (Alecensa®) Brigatinib (Alunbrig®)	Metastatic melanoma Leukemia Non-small cell lung cancer Breast cancer Ovarian cancer Colorectal cancer Renal cancer Esophageal cancer Mesothelioma Prostate cancer Glioblastoma Pancreatic cancer	MEK-associated retinopathy Retinal vein occlusion Periorbital edema Dyschromatopsia Glaucoma Eye pain Ocular inflammation (anterior uveitis) Epiphora Conjunctivitis Cataract development Tear film dysfunction/dry eye Central serous chorioretinopathy Blepharitis Trichomegaly Meibomitis Iridocyclitis Corneal epithelial lesions Corneal keratopathy Corneal ulcers Presbyopia Blurry vision Optic neuropathy Retinal hemorrhage Diplopia Macular edema Positive visual phenomena	The majority of long-term adverse events associated with MEK inhibitors had resolved without long-term consequences or interruption of therapy A minority of adverse events associated with BRAF inhibitors required short-term corticosteroids The incidence of ocular adverse events induced by EGFR inhibitors varied significantly with the agent of choice

Table 1. Range of reported ocular toxicities and their outcomes; *courtesy of Grace Yin, MD, MPhil and C. Maya Tong, MD, FRCSC*

Abbreviations: AEs: adverse events; **BRAF:** V-Raf murine sarcoma viral oncogene homolog B; **CAR-T Therapy:** Chimeric antigen receptor T-cell therapy; **CRS:** cytokine release syndrome; **EGFR:** Epidermal growth factor receptor; **IOP:** intraocular pressure; **MEK:** mitogen-activated protein kinase; **TIL Therapy:** Tumor-infiltrating lymphocyte therapy.

Early in the treatment course, TIL therapy has been associated with bilateral anterior uveitis.[5] Later in the treatment course, bilateral panuveitis with diffuse retinal pigment epithelium hypopigmentation concerning for Vogt-Koyanagi-Harada syndrome, and bilateral cystoid macular edema has been reported.[5] Even with cessation of treatment, persistently elevated proinflammatory cytokine levels have been demonstrated in the aqueous humour, suggesting strong ocular immune sequelae.[5] Given the novelty of TIL therapy and its recent introduction to the market in 2024, ongoing surveillance of its potential ocular AEs will be critical as more patients undergo TIL therapy.

Checkpoint Inhibitors

Checkpoint inhibitors are monoclonal antibodies that bind to specific T-cell receptors (programmed cell death protein 1 [PD-1], cytotoxic t-lymphocyte-associated protein 4 [CTLA-4], and programmed cell death ligand 1 ([PD-L1]) to override inhibition of T-cell activation by cancerous cells and reactivate programmed cell death signal pathways. This allows the patient's immune system to recognize and attack malignant cells more effectively. Checkpoint inhibitors have shown benefit in treating melanoma, renal cell carcinoma, lung cancer (small cell, and non-small cell), colorectal cancer, and more. Although ocular AEs are rare, approximately 15 toxicities have been reported in <1% of patients, with approximately 70% occurring within the first 2 months of starting treatment.[6] However, the degree of variability in toxicity is high and includes dry eye disease, uveitis, ocular myasthenia gravis, inflammatory orbitopathy, uveal effusion, optic neuritis, papillitis, vitritis, choroidopathy, ocular myositis, cerebellar ataxia with associated nystagmus, retinal vasculitis, Vogt-Koyanagi-Harada (VKH)-like syndrome, corneal graft rejection, and corneal perforation.[7] A key concern raised with checkpoint inhibitor therapy resides in the risk of unopposed immune reactivation with the potential to cause broad-spectrum toxicity to non-target systems such as the eye. It has been speculated that high-levels of PD-L1, PD-1, and CTLA-4 expressed within ocular tissues, including the retinal pigment epithelium, may provide an explanation for the mechanisms driving the ocular toxicities observed with checkpoint inhibitors.[8] Moderate ocular AEs may warrant suspending treatment until symptoms normalize or improve, with concurrent consideration for corticosteroids. For severe ocular reactions, both suspending therapy and initiating high-dose systemic corticosteroids are typically indicated. Notably, some ocular toxicities, particularly uveitis-like responses, have been observed to correlate with regression of tumour burden and are thus speculated to be a prognostic marker of therapeutic response.[7] Some ocular AEs observed with checkpoint inhibitor therapy may be confounded by the emergence of paraneoplastic events triggered by autoimmunity. As such, decisions regarding the discontinuation and re-introduction of checkpoint inhibitor therapies following severe ocular toxicities may require careful multidisciplinary risk-benefit discussions involving the ophthalmologist, the patient, and their oncologist. Further, in cancer patients presenting with uveitis-like symptoms, clinicians should consider ocular toxicities secondary to immune checkpoint inhibitor use, and exercise caution before considering such reactions to be solely inflammatory-driven.

Antibody-Drug Conjugates

Antibody-drug conjugates (ADC)s are typically comprised of an antibody (often IgG) covalently linked to a cytotoxic drug. The antibody component is specific for an intended antigen expressed by malignant cells. The ideal antigen target is exclusively or overly expressed on malignant cells of interest (e.g., human epidermal growth factor receptor 2 [HER2], epidermal growth factor receptor [EGFR], CD19, among others), and is internalized following antigen-antibody complex binding to facilitate an effective portal of entry for the linked cytotoxic drug. Thus, ADCs target tumour tissue while minimizing off target, or "bystander killing". ADCs have demonstrated greatest promise in treating acute lymphoblastic leukemia, multiple myeloma, and various lymphomas, including B-cell, Hodgkin, and hairy cell lymphoma subtypes, as well as breast cancers, cervical cancer, ovarian cancer, urothelial carcinoma, gastric cancer, and non-small cell lung cancer. The most commonly reported AEs associated with ADCs have involved the corneal surface, including dry eye symptoms, conjunctivitis, keratitis, xerophthalmia, cataract formation, ocular pain, night blindness, photophobia, and microcystic corneal disease.[9] Posterior-involving AEs including nyctalopia, retinal hemorrhage, and Purtscher-like retinopathy have also been reported.[10] It is speculated that the

mechanism by which ADCs cause ocular AEs may be secondary to uptake of ADCs by non-target cells (e.g., HER2 receptor expression on normal corneal epithelial cells), or through non-target uptake facilitated by endocytosis, and diffusion, among others.[10] Strategies for managing ADC-induced ocular AEs include artificial tears and lubrication, topical ocular corticosteroids, vasoconstrictor drops prior to infusions, and consideration for suspension, discontinuation, or dose-reduction of ADCs.[10] However, the effectiveness of each intervention is highly variable and ADC-specific. Due to limited available data, our ability to understand the precise rate and reversibility of identified ocular toxicities remains poorly understood.

Molecularly Targeted Therapies

MEK Inhibitors, BRAF Inhibitors

Molecularly targeted therapies encompass both monoclonal antibodies (mABs) and small molecule kinase inhibitors (SMKIs). Broadly, mABs exert their effects through inhibition of growth factor receptor signalling, while SMKIs suppress key protein kinases involved in the propagation of cancer cells. Among these, mitogen-activated protein kinase (MEK) inhibitors and V-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitors are two prominent classes, with promising effectiveness in treating metastatic melanomas, solid organ tumours, and some leukemias. BRAF inhibitors act by inhibiting cellular proliferation regulated by the Ras/Raf/MEK/ERK pathway, whereas MEK inhibitors target MEK1 and MEK2, which are critical components of this cascade. When used in combination, these inhibitors exert a synergistic effect. However, MEK inhibitors have been frequently implicated in the development of MEK-associated retinopathy (MEKAR). MEKAR primarily affects the outer retinal layers in a dose-response fashion and have been reported to be observed in up to 100% of patients receiving MEK-inhibitor therapy.[11] MEKAR is characterized by multifocal symmetrical central serous chorioretinopathy-like changes involving the fovea in the absence of altered choroidal thickness.[11] Additional cases of retinal vein occlusion, periorbital edema, dyschromatopsia, glaucoma, eye pain, ocular inflammation (especially anterior uveitis), epiphora, conjunctivitis, cataract development, and tear film dysfunction have been reported.[11] A recent review of MEK-inhibitor toxicities found that the majority of ocular AEs were resolved without long-term consequence or the need to interrupt therapy. Moreover, the overall incidence of serious, vision-threatening ocular AEs was found to be low. Patients may benefit from a baseline retinal examination before initiating treatment. Compared to MEK inhibitors, BRAF inhibitors have been more commonly associated with uveitis, dry eye, and central serous chorioretinopathy.[12,13] The majority of BRAF inhibitor toxicities were successfully managed without requiring discontinuation of therapy, and a minority required short-term corticosteroid treatment for resolution.[14]

Epidermal Growth Factor Receptor Inhibitors and Anaplastic Lymphoma Kinase Inhibitors

Epidermal growth factor receptor (EGFR) inhibitors are mABs that target the EGFR tyrosine kinase receptor to inhibit its phosphorylation and thereby prevent its subsequent ability to act as a docking site for key signalling molecules important for cellular proliferation. EGFR inhibitors have demonstrated clinical utility across a broad range of malignant solid tumours, including non-small cell lung cancer, breast and ovarian cancers, colorectal, renal, esophageal, mesothelioma, prostate, glioblastoma, and pancreatic cancers. Most reported ocular AEs involve the anterior segment and include blepharitis, trichomegaly, meibomitis, dysfunctional tear film, iridocyclitis, corneal epithelial lesions, cortex keratopathy, and corneal ulcers.[15,16] However, the incidence of these ocular AEs may differ significantly, with some agents being reported to have a low incidence rate (e.g., osimertinib at 0.5%) and others have shown a very high incidence of occurrence (e.g., ABT-414 has shown a 100% incidence of vortex keratopathy)[16] However, partial or complete recovery has been achieved with treatment discontinuation and/or treatment with topical steroids.[16]

Anaplastic lymphoma kinase (ALK) inhibitors function by targeting the ability of their corresponding receptor tyrosine kinase to autophosphorylate, thereby preventing activation of subsequent signal pathways involved in cellular proliferation. These agents have been shown to have excellent utility in treating non-small cell lung cancer and ALK-positive malignancy. Ocular AEs reported in association with ALK inhibitors include presbyopia, blurry vision, optic neuropathy, retinal hemorrhage, diplopia, macular edema, cataract

formation, and visual disturbances.[17,18] The majority of ocular AEs have not required discontinuation of therapy and have improved with conservative or medical management.

Summary and Future Directions

Oncology and cancer therapeutics represent a fast-growing area of research focused on precision medicine approaches such as small molecule inhibitors, therapeutic cancer vaccines, and T-cell receptor-based strategies. Although the eye is traditionally considered to be "immune privileged", this protection is not absolute. Patients on novel chemotherapeutic agents may benefit from timely access to care with ophthalmologists as an active part of the oncology care team to support co-management of treatment decisions when serious AEs occur. The rapid advancements in cancer therapeutics and the renewed hope that they offer to patients with malignancies is nevertheless exciting. The pace of innovation may re-shape the landscape of oncology, ocular immunity, and the boundaries of immune privilege.

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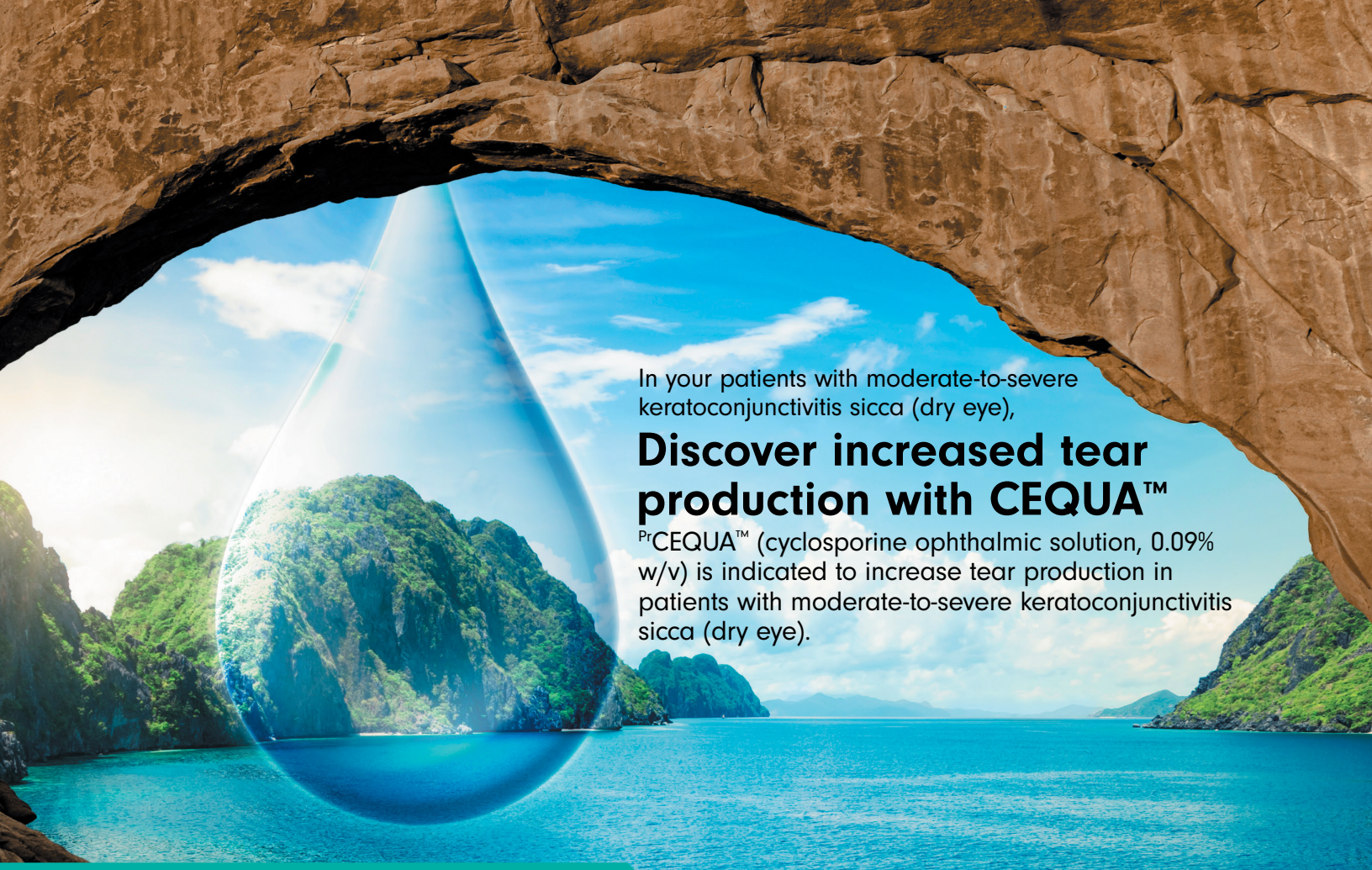

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Integrating Virtual Reality Visual Perimetry Into Clinical Practice: A Review of Devices, Applications, and Limitations

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Introduction

Visual field testing has long been a cornerstone of glaucoma diagnosis, monitoring, and management. The evolution of perimetry, from the early Tangent screen formalized by Julius Hirschberg in the 1870s to modern standard automated perimetry (SAP) such as the Humphrey Visual Field Analyzer (HFA), has aimed to improve accuracy and accessibility. In the 1940s and 1950s, the Goldmann perimeter and Tübingen perimeter were developed, with the Goldmann retaining a limited but important role in specific clinical scenarios.[1] The Tübingen perimeter is now rarely used. By the 1980s, automated perimetry had become the standard, leveraging computational advances to reduce human involvement while preserving the spatial testing strategies introduced by earlier kinetic methods. Devices such as the Humphrey and Octopus perimeters became widely adopted and remain in clinical use today. Among these, the HFA is widely regarded as the gold standard for automated visual field testing.

Although the HFA is the gold standard for automated perimetry, it has well-known limitations. The device is expensive, requires substantial physical space, and requires a trained technician to operate. Importantly, many patients find the test uncomfortable or frustrating and often dread the experience. It is rare to encounter a patient who enjoys visual field testing, and poor tolerance can lead to unreliable results.[2–5] Nevertheless, perimetry remains a cornerstone of glaucoma care, offering functional insights not captured by structural imaging alone. Improving patient compliance and enhancing the test experience are therefore critical.

It is also well established that any factor impairing concentration can compromise the accuracy of the visual field results.[6] Many patients find the test mentally fatiguing, frustrating, and time-consuming, with few describing the experience positively. Common complaints include the prolonged duration, unpredictable endpoints, and the sense of being pushed to the limits of their visual capacity, often evoking a sense of failure. Physical discomforts are also common, including neck strain, difficulty maintaining posture, and suboptimal seating, despite manufacturer's efforts to improve ergonomics.

These challenges carry tangible clinical implications. When patients find visual field testing extremely unpleasant, they may even avoid coming for appointments altogether. This behaviour may be far more detrimental than poor adherence to treatment.[7] If perimetry itself becomes a barrier to care, clinicians must weigh its diagnostic value against its potential to undermine patient engagement and continuity of care.

For those reasons, there is a clear need for technology that is more patient-friendly—this is where virtual reality perimetry (VRP) offers promising potential. VRP is a novel approach that leverages virtual reality (VR) technology environments, typically accessed through lightweight, head-mounted displays. In the context of perimetry, this technology allows for visual field testing to be performed in a more natural, ergonomic position, often without the need for a dedicated dark room or large stationary equipment. As a result, VRP enhances patient comfort, portability, and accessibility. **Table 1**

Category	Advantage	Explanation
Physical Accessibility	Accommodates patients with limited mobility	VR headsets offer flexible positioning, making them ideal for those with neck stiffness, back pain, or those who are bedridden.
	Suitable for a range of body sizes	Patients who fall outside the size range recommended by standard perimeters (smaller or larger) can undergo testing more comfortably.
	Portability	Unlike conventional perimeters, VR systems are compact and portable, enabling testing in various settings.
Patient Comfort	Improved comfort and tolerance	Greater ergonomic flexibility (eliminating the need for a chinrest or rigid posture) helps reduce fatigue.
	Reduced claustrophobia	Head-mounted systems feel less enclosing than bowl perimeters.
	Enhanced patient experience	The immersive nature of VR may reduce anxiety and improve cooperation, particularly in anxious patients.
Clinical Usability	Tolerable in movement disorders	Head-tracking adjusts for tremors or involuntary movements, minimizing artifacts.
	Reduced rim artifact	Eliminates visual interference caused by the perimeter lens rim which can interfere with testing, especially when patients move or have deep-set eyes.
	Potential for home monitoring	Some VR platforms are being developed and tested for home use, which could allow for more frequent disease monitoring.
Technical and Language Features	Multilingual support	Some platforms have automated instructions in multiple languages (up to 25 on some platforms).
	Alternative visual backgrounds	Patients report that light-on-dark backgrounds are easier to interpret and cause less visual strain.
Operational and Cost Benefits	Cost-effectiveness	VRP systems are significantly less expensive to purchase and maintain. They also eliminate the need for large, table-based infrastructure.
	Enhanced patient engagement	The novelty effect may initially increase cooperation and reduce anxiety associated with testing.

Table 1. Advantages of VRP testing compared to SAP[2-4,8-13]; *courtesy of Abdullah Al-Ani, MD, PhD, Derek Waldner, MD, PhD, and Andrew Crichton, MD, FRCSC*

Abbreviations: VR: virtual reality; **VRP:** virtual reality perimetry.

highlights the advantages associated with VRP compared to SAP.

Physical Limitations

One of the main physical limitations that can affect SAP is patient positioning.[2,3] For example, patients with significant neck stiffness or kyphosis may have difficulties with placing their chin on the chinrest due to a forward head tilt, making it difficult for them to complete an HFA test. **Figure 1** shows a patient with a very stiff neck, making it nearly impossible to complete an HFA test. Another common scenario involves patients who are unable to sit up, such

as bedridden patients, where the upright position is simply not feasible. VRP offers a particularly helpful alternative, especially during hospital consultations. Additionally, patients who are either too large to fit comfortably in the perimeter chair or too small to reach the chinrest often cannot be tested accurately or comfortably with traditional automated perimetry.

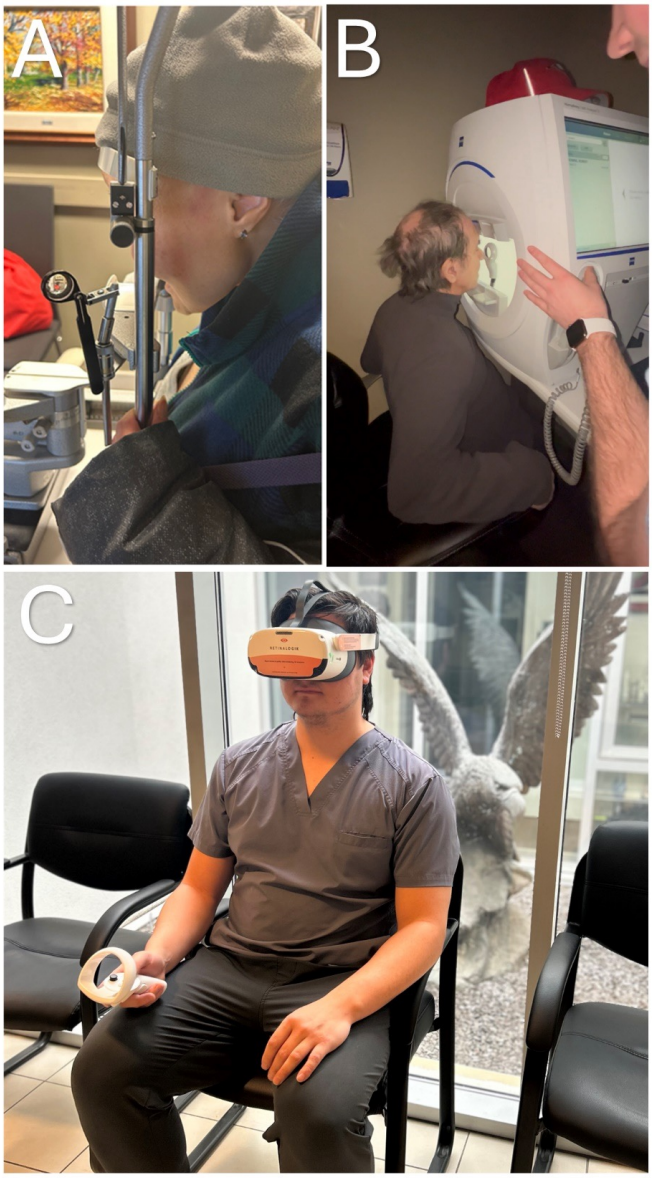

Figure 1. Comparison of patient positioning challenges in standard automated perimetry (SAP) versus virtual reality perimetry; *courtesy of Abdullah Al-Ani, MD, PhD, Derek Waldner, MD, PhD, and Andrew Crichton, MD, FRCSC*

A) A patient with significant neck stiffness is unable to achieve alignment at the chinrest due to a downward head posture. **B)** A patient with ankylosing spondylitis experiences great difficulty bending at the hips to position appropriately for SAP. **C)** A participant using a virtual reality headset is able to undergo visual field testing in a relaxed and more comfortable posture.

Beyond these extreme examples of physical limitations, there are broader comfort issues that affect many patients.[2,4] Back pain, hip stiffness, and general difficulty maintaining posture can make prolonged sitting uncomfortable. As mentioned earlier, anything that reduces comfort can affect concentration and, hence, compromise test accuracy. One of the advantages of VR-based perimetry is that it allows the test to be conducted in whichever position is most comfortable for the patient.

Movement Disorders

Movement disorders represent a separate but important challenge. In patients with conditions such as tremor or dystonia, constant head movements can lead to test artifacts, interruptions, and inaccuracies when using traditional perimetry. In contrast, with a VR headset, the display moves with the patient's head, reducing the impact of involuntary motion on test quality.

Rim Artifact

A common issue encountered with the HFA is the "rim artifact," which occurs when a patient unintentionally pulls back from the machine during testing, which brings the rim of the trial lens into the field of vision.[14] This can produce artificial peripheral defects that may be mistaken for pathology. Although lid artifacts can still occur, regardless of the device used, eliminating the rim artifact helps in confirming whether a defect is genuine. **Figure 2** shows examples of rim artifact.

Claustrophobia

Feelings of claustrophobia are a commonly reported concern among patients who undergo SAP testing. Some individuals describe the experience as feeling enclosed or trapped within the traditional bowl perimeter. In our glaucoma clinic, patients who have undergone VRP testing report feeling less confined and note a greater sense of space and comfort during the test.

Multilingual Support

Many VRP platforms offer multilingual support, enabling the test instructions to be delivered in multiple languages. This feature reduces reliance on interpreters and may improve patient understanding in diverse clinical settings. Devices such as the Retinalogik, VisuALL, and Vivid Vision Perimeter offer user-friendly

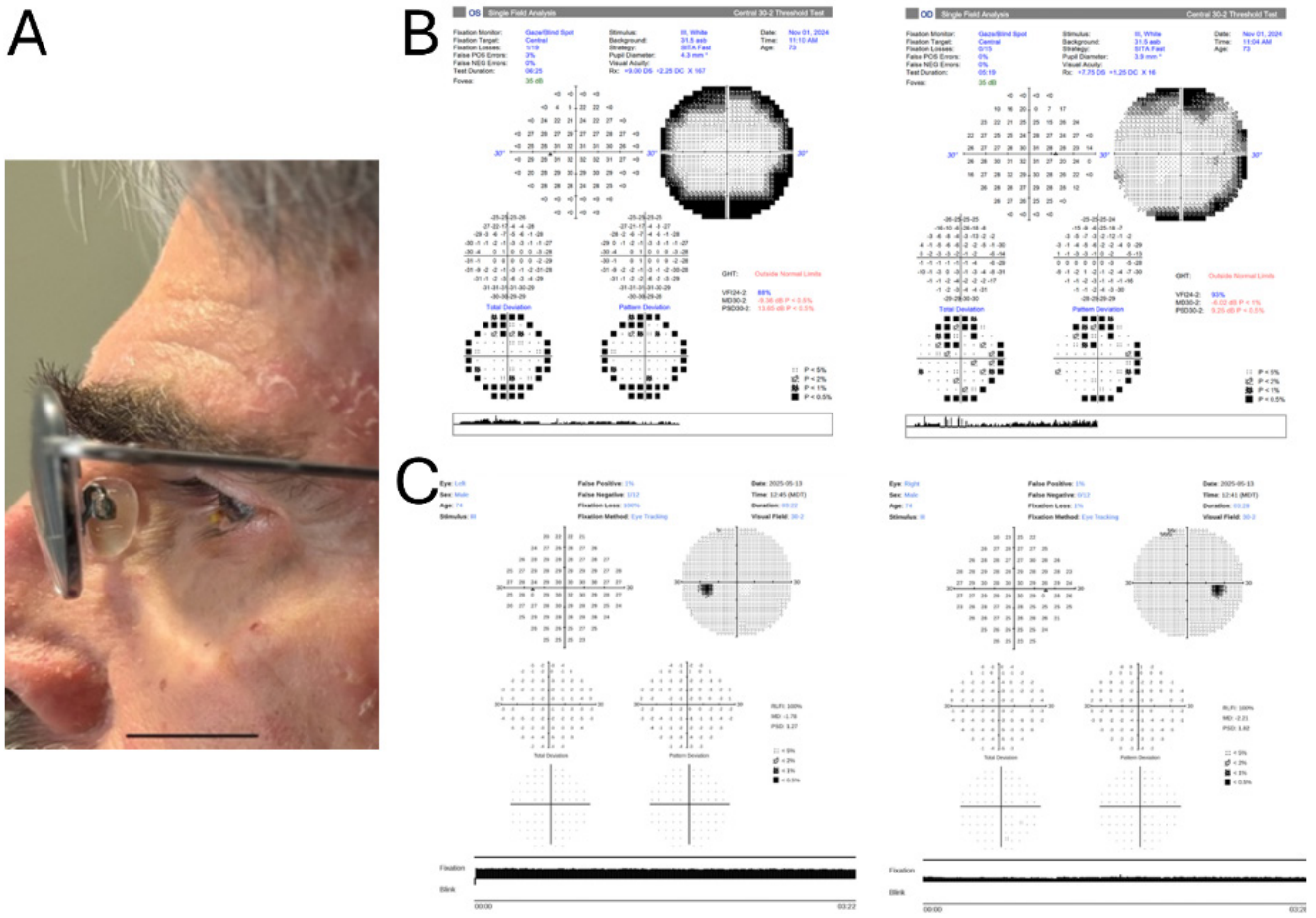

Figure 2. Illustration of rim artifact in standard automated perimetry and its elimination with virtual reality perimetry (VRP); *courtesy of Abdullah Al-Ani, MD, PhD, Derek Waldner, MD, PhD, and Andrew Crichton, MD, FRCSC*

A) Patient with deep-set eyes, anatomically predisposed to rim artifact due to the location of the trial lens. **B)** Visual field results from HFA 30-2 threshold testing showing a classic rim artifact, appearing as a dense peripheral field loss. **C)** The same patient underwent visual field testing using a VRP device, with no evidence of rim artifact.

interfaces that can be configured to support multiple languages, up to 25 in some cases.[5,13]

Background and Visual Environment

SAP typically uses white-on-white stimuli, which is the most validated and widely used method for detecting and monitoring visual field defects. However, VR perimetry platforms allow for flexibility in backgrounds and stimulus colours. Alternative combinations, such as blue-on-yellow or red-on-white, have been shown to improve sensitivity in detecting certain types of visual field defects in specific clinical scenarios.[15-17] In our clinical practice, many patients express a preference for a bright stimulus on a dark background, reporting less visual fatigue.

Novelty

One interesting factor reported by patients is the novelty of the VR experience. Many patients may find the VRP testing more engaging simply because it is different from the routine of traditional methods. While this could be a novelty effect rather than a sustained preference, our initial experience suggests that VRP testing is generally more well-received by patients. Whether this patient preference persists over time remains to be determined.

Cost

The cost difference between VR-based perimetry and conventional devices is considerable.[2] A VR unit may cost between $10,000 and $20,000 CAD if purchased outright, with some platforms offering an annual subscription model. In contrast,

the total cost of a new HFA, including five years of annual maintenance, software upgrades, calibration, and certification, can range from $45,000 to $55,000 CAD. This cost gap, along with the option for yearly subscription-based access, significantly lowers the barrier to adoption, particularly for smaller clinics and low-resource settings.

Patient and Staff Comments

Feedback from both patients and staff has been overwhelmingly positive. Patients report increased comfort, ease of use, a preference for dark background displays, and the availability of multiple language options. Reminders and voice prompts during the test are also frequently appreciated by patients. Staff have also reported favourably on the adoption of this technology, particularly regarding the ease of setup, reduced patient resistance, and improved workflow efficiency. These points are further explored in **Table 2.**

Types of VRP Devices and Their Clinical Efficacy

Multiple VRP platforms have been developed over the past few years using a variety of hardware, algorithms, and luminance profiles. These vary from specialized configurations involving commercially available VR headsets to FDA-approved equipment with integrated eye tracking and custom threshold approach designs.[18]

VisuALL (OIleyes)

VisuALL is a commercially available VR head-mounted perimetry device supported by several published validation studies.[18] In a cohort of over 100 eyes, VisuALL demonstrated strong correlation with the HFA 24-2 SITA standard test across mean deviation (MD), sectoral sensitivity, and global indices.[9,18,19] One study reported no significant difference in diagnostic accuracy for detecting glaucoma between VisuALL and HFA (area under the curve [AUC] 0.98 versus 0.93, p=0.06).[9] In a small study involving 16 eyes, the VisuALL platform was found to be significantly faster than HFA, with a median difference of 69.3 seconds (p<0.001).[20] Overall, VisuALL's high diagnostic agreement with HFA and reduced test duration make it a promising tool, although preliminary studies suggested potential limitations in advanced glaucoma patients.[18]

Vivid Vision Perimetry (VVP); Suprathreshold

VVP is a suprathreshold perimetry software designed for use with commercially available VR headsets, such as the Oculus Go.[18] Two smaller studies, involving 24 and 36 eyes, respectively, demonstrated moderate to strong correlations with HFA MD values, with correlation coefficients ranging from r=0.67 to r=0.86 across different glaucoma severities.[21,22] While early data from the VVP Swift and VVP-10 protocols are promising, further validation studies are required to elucidate whether VVP is sufficiently sensitive to detect early-stage glaucoma.[18,21,22]

Toronto Portable Perimeter (TPP)

The TPP combines a smartphone with a VR headset and an associated mobile application using a ZEST-based thresholding strategy.[23,24] In a study of 150 eyes from 91 glaucoma patients, the TPP was compared to the HFA 24-2 SITA protocol and showed strong agreement in Bland-Altman analyses of MD, pattern standard deviation (PSD), visual field index, and test duration.[23] Differences between the devices were small, suggesting that while further validation studies are needed, the TPP is a promising platform for VR-based perimetry.

VirtualEye

The VirtualEye platform features a head-mounted OLED microdisplay with integrated eye tracking and offers both manual and visual grasp modes.[25] In the visual grasp mode, the direction of the patient's gaze is used to indicate stimulus detection, eliminating the need for manual clicking. In a study by Wroblewski and colleagues involving 62 participants (59 eyes tested in manual mode, 40 eyes tested in visual grasp mode) VirtualEye (in both modes) was compared with HFA 24-2 SITA. They found that the VirtualEye platform accurately detected large visual field defects. However, it demonstrated reduced sensitivity, particularly for high dB stimuli.[25] Despite this limitation, VirtualEye showed reasonable agreement with the HFA SITA protocol.

Advanced Vision Analyzer (AVA)

The AVA platform uses a liquid crystal head-mounted display with eye tracking and offers three testing strategies: Full Threshold, Elisar standard, and Elisar Fast.[26,27] Two studies with a combined sample size of 272 participants assessed the efficacy of the AVA platform against

Category	Advantage	Disadvatage
Patient Interaction	Patients report fewer complaints, and the test is generally better tolerated than SAP.	Some patients find the headset heavy, particularly during longer testing sessions.
	Built-in language support improves cooperation.	Difficulty accommodating patients with blurry vision, even with corrective lenses.
	Automated voice prompts reduce the need for continuous technician guidance, and reminders help patients in maintaining fixation during testing.	During head-levelling or calibration, patients may see a blank screen without any notification.
Workflow and Training	The VRP workflow is more streamlined than that of the HFA due to fewer instructions needed from the technician.	VR controller batteries drain quickly and need to be removed after use to preserve their charge.
	The system is easy to learn and operate with minimal training.	
Device Flexibility	The device is portable and can be used in multiple settings, and is not restricted to a specific testing room. Additionally, for patients who find the headset heavy, the test may be conducted while they are reclined.	

Table 2. Staff-reported Advantages and Limitations of Virtual Reality-Based Perimetry in Clinical Practice; *courtesy of Abdullah Al-Ani, MD, PhD, Derek Waldner, MD, PhD, and Andrew Crichton, MD, FRCSC*

Abbreviations: SAP: standard automated perimeters; **VR:** virtual reality; **VRP:** virtual reality perimetry.

the HFA 24-2 and 10-2 protocols.[26,28] These comparisons yielded moderate to high correlations for several parameters, including MD, PSD, and mean sensitivity.[18,26,28] Moreover, the AVA accurately differentiated glaucomatous from non-glaucomatous eyes, suggesting a promising role for this platform in both diagnosing and monitoring glaucoma patients.

Radius

The Radius platform features a lightweight headset with a 10 cd/m^2 background luminance and employs a proprietary RATA-standard threshold testing strategy.[18] In a study by Bradley et al., which included 100 adult glaucoma patients–half with suspect or mild glaucoma and half with moderate or severe glaucoma–Radius showed a strong correlation with the HFA 24-2 protocol (r=0.94 for MD) and shorter test duration (298 versus 341 seconds, respectively).[29] Additionally, the study showed excellent concordance in glaucoma staging (kappa=0.91-0.93), supporting the non-inferiority of Radius compared to HFA within the study population.[29]

Virtual Field on Oculus Go

Virtual Field is an FDA-approved VRP software that operates on the Oculus Go headset using a fast threshold strategy.[10] In a study by Phu and colleagues involving 95 eyes from 95 participants (41 controls and 54 with glaucoma) the platform demonstrated strong correlations with the HFA 24-2 SITA Standard test for MD (r=0.87) and PSD (r=0.94), with minimal bias observed in Bland-Altman analysis.[10] This study also showed that this VR platform had better reliability indices (lower fixation losses and false-positive rates) and significantly faster test completion times compared to HFA.[10]

RetinoLogik (RVF100)

Developed by the Canadian startup RetinoLogik, based in Calgary, the RVF100 is a VRP platform that operates on the Pico Neo 3 Pro Eye headset and features a background luminance

of 10 cd/m^2. The RVF100 uses a proprietary thresholding algorithm that integrates statistical inference with age-correlated data. Early clinical adoption across several ophthalmology offices in Canada has been positive, with strong patient feedback. Preliminary usability surveys conducted by the authors (data not shown; manuscript under review) indicated that over 90% of participants preferred the RVF100 over traditional HFA testing. Several validation studies are currently underway globally to further evaluate the efficacy of the RVF100 in glaucoma care.

Limitations and Future Directions

While VRP holds tremendous promise in revolutionizing visual field testing, particularly by improving accessibility, patient comfort, and cost-effectiveness, the technology remains in its early stages compared to SAP and is subject to several limitations. In general, VRP platforms have higher test-retest variability than SAP, especially in pointwise sensitivity and global indices.[10] Additionally, because VRP is a relatively new technology, it relies on normative databases that may not be as robust or well-validated as those established in SAP.[10]

Hardware limitations also pose a challenge for VRP platforms. Their performance is at least partially limited by the quality of the headset hardware, which may restrict luminance ranges—even when paired with well-optimized software algorithms—potentially impacting VRP performance.[11,30] Furthermore, while several VRP platforms demonstrate a moderate to strong correlation with SAP for global indices and mean sensitivity, pointwise sensitivity correlations are often weaker. This raises concerns regarding discrepancies in fine-detailed virtual field mapping and its implications for clinical decision-making.[9] As VRP technology continues to evolve, particularly in the era of artificial intelligence, many of these limitations are expected to be addressed. We anticipate that with further development and validation, VRP has the potential to become a reliable and scalable adjunct, or even an alternative, to traditional SAP in selected clinical settings.

Summary

Despite all of the discussed advantages, VRP technologies remain in the early stages of development. Considering the current limitations and available literature, it remains uncertain whether VRP possesses sufficient reliability and sensitivity to replace SAP as the gold standard in glaucoma care. Validation studies are ongoing worldwide to further characterize the functionality, sensitivity, and reliability of VRP platforms in various patient populations. Given its flexibility in both testing posture and setting, VRP may be particularly beneficial for patients who are unable to undergo conventional perimetry. It may also serve as the only practical option in inpatient or low-resource environments.

At present, while VRP is not a replacement for SAP, the technology should be regarded as a valuable adjunct, especially in select populations. With ongoing advancements and further clinical validation, VRP holds the potential to become a powerful standalone tool for monitoring functional progression in patients with glaucoma.

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D.W.: None declared.
A.C.: None declared.

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Approach to The Patient With Hypertensive Uveitis and Uveitic Glaucoma

Carol Tadrous, MD, FRCSC

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

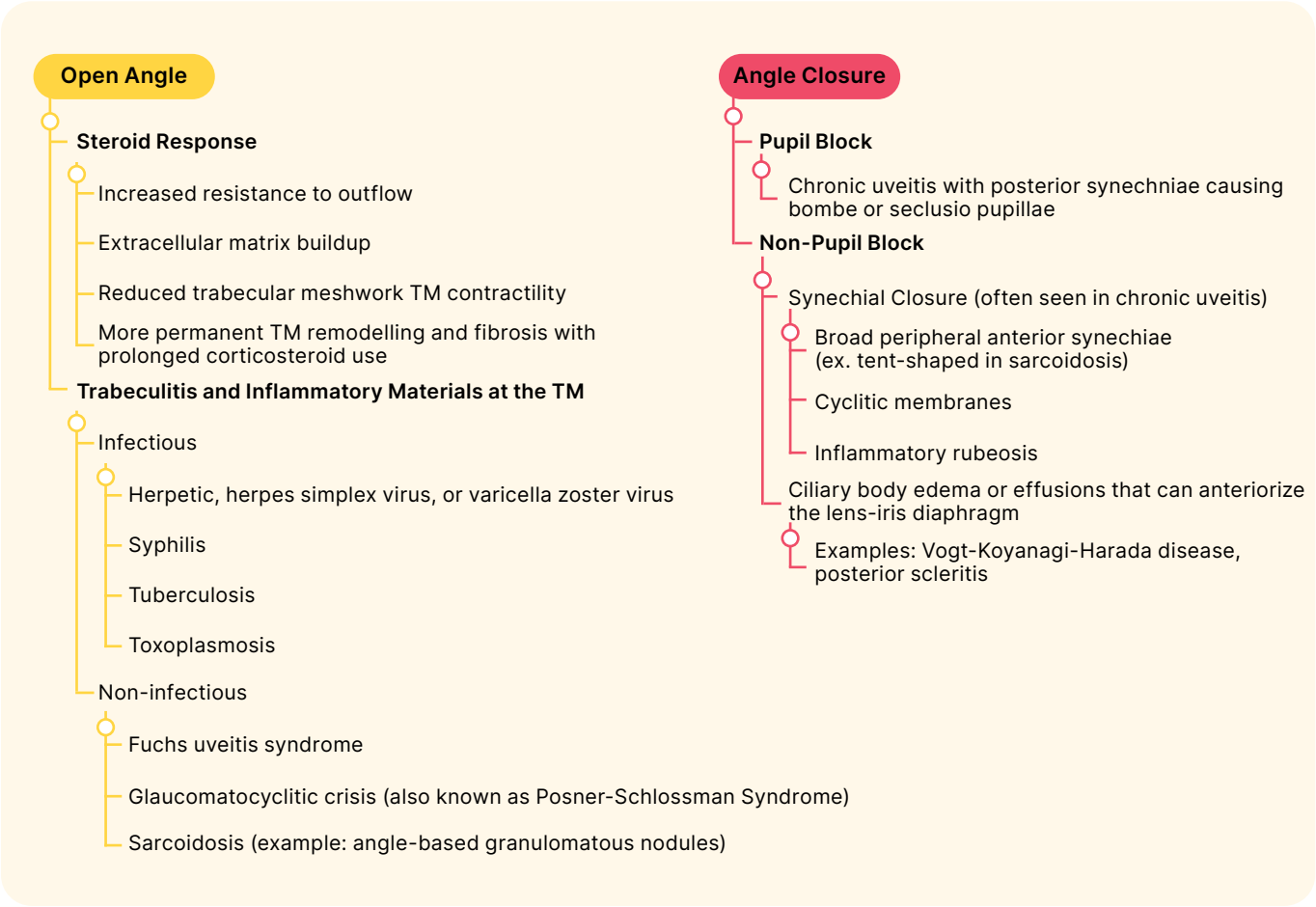

Figure 1. Mechanism of elevated intraocular pressure in uveitis.[8,9,21]; *courtesy of Carol Tadrous, MD, FRCSC*

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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Unmasking Ocular Rosacea: Diagnostic Challenges and Evolving Management

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Introduction

Ocular rosacea is a chronic inflammatory condition affecting the eyes, and is often associated with cutaneous rosacea. It is a common yet frequently underdiagnosed disorder that can lead to significant ocular morbidity and, in severe cases, vision loss.

Case Report

A 49-year-old male with a known history of acne rosacea **(Figure 1)** presented with bilateral interstitial keratitis, characterized by subepithelial scarring and neovascularization. A comprehensive workup, including serologic testing for syphilis and a full rheumatologic evaluation, yielded unremarkable findings. During follow-up, the patient experienced a single episode of corneal infectious ulcer, attributed to contact lens wear, which resolved without significant sequelae. Over 15 years of follow-up, his condition has remained stable with ongoing treatment, including oral doxycycline, topical fusidic acid ointment, fluorometholone, and cyclosporine. Imaging studies have demonstrated bilateral irregular astigmatism, corneal thinning, and stromal scarring **(Figure 2)**. The patient declined corneal transplantation.

Discussion

Acne rosacea is a common, chronic skin disorder characterized by telangiectasia, persistent erythema, papules, pustules, and sebaceous gland hypertrophy. It primarily affects the central areas of the face, including the forehead, cheeks, and nose.[1]

Ocular rosacea is estimated to affect up to 75% of patients with acne rosacea, although this number may be underestimated due to diagnostic challenges.[2] The condition can occur in both adults and children, with a reported age range of 22 months to 85 years.[3,4] Interestingly, ocular symptoms may precede or occur in the absence of cutaneous manifestations in up to 90% of cases, making diagnosis particularly challenging.[2,5]

The pathophysiology of ocular rosacea is complex and not fully understood. Recent research suggests that it involves an interplay of factors, including innate and adaptive immunity, environmental triggers, and neurovascular sensitivity.[2] The role of bacterial lipases, interleukin-1 alpha, and matrix metalloproteinases has been implicated in the development of blepharitis and corneal epitheliopathy associated with the condition.[1] Additionally, variations in the local and systemic microbiome, including Demodex infestation, may contribute to the pathogenesis, severity, and different phenotypes of rosacea.[6]

Ocular rosacea presents with a wide spectrum of signs and symptoms, often mimicking other ocular surface disorders. The most common symptoms reported include foreign body sensation and burning.[4] Clinical signs typically involve the eyelids, conjunctiva, and cornea. Frequently observed features include telangiectasia and irregular lid margins, along with meibomian gland dysfunction (MGD).[4] Chronic blepharoconjunctivitis is a hallmark of ocular rosacea, often accompanied by MGD.[7] Corneal involvement, which occurs in approximately one-third of patients, can range from mild punctate epithelial erosions to severe complications such as corneal vascularization, ulceration, scarring, and, in rare cases, perforation.[5,7] These corneal manifestations can lead to decreased visual acuity and, if left untreated, may result in permanent vision loss.[4] A study on pediatric ocular rosacea

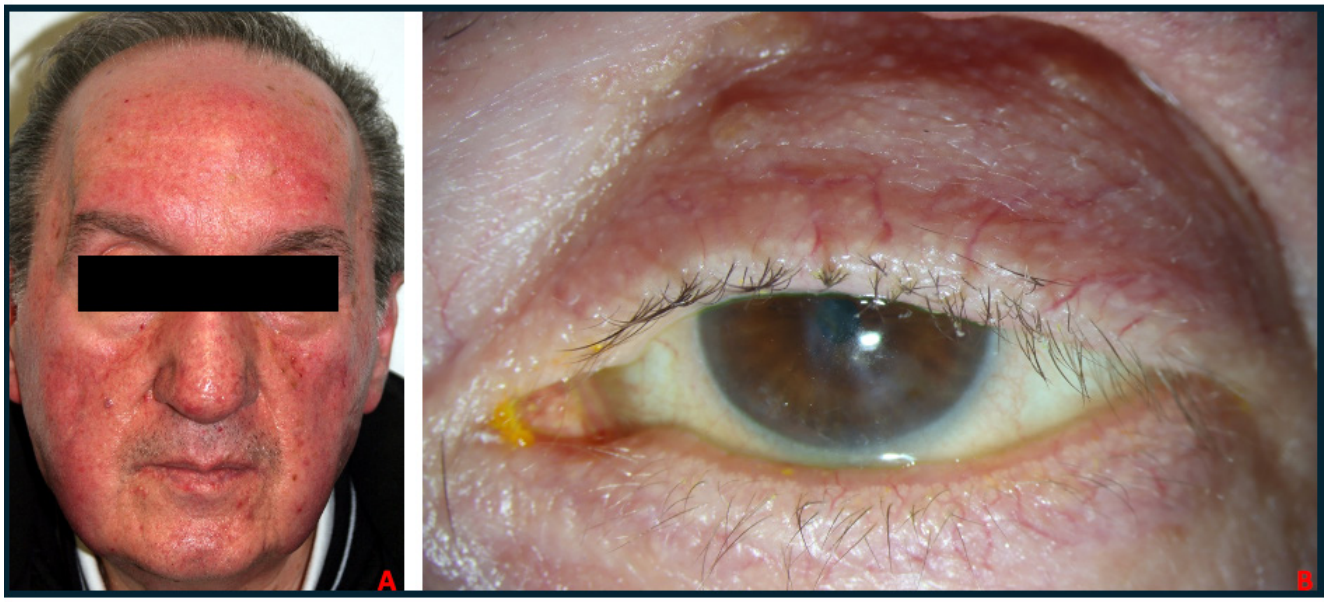

Figure 1. A) A 49-year-old male with acne rosacea affecting the central facial region, including the forehead, nose, and cheeks **B)** Examination reveals characteristic eyelid involvement, with erythema and telangiectasia; *courtesy of Anat Maytal, MD, Johanna Choremis, MD, FRCSC, and Julia C. Talajic, MD, MPH, FRCSC*

cases found that 50% of the patients exhibited sterile corneal ulcers.[8] This highlights the importance of early recognition and treatment in the pediatric population to prevent the progression of corneal pathology.

Rosacea has been associated with other systemic disorders, including cardiovascular disease, inflammatory bowel disease, migraines, and depression.[2,6,7] This underscores the need for a comprehensive approach to patient care and potential need for interdisciplinary management.

Diagnosing ocular rosacea is primarily clinical, and is based on the observation of characteristic signs and symptoms.[5] However, the absence of a specific diagnostic test and the variable presentation of the disease can lead to delays in diagnosis, particularly in patients without obvious cutaneous rosacea.[5,6] This is especially true for children, where the condition may be underrecognized.[3,6]

In vivo confocal microscopy has emerged as a valuable tool for analyzing corneal and meibomian gland structures.[9] In patients with rosacea, inflammatory cells can be observed in the corneal tissue. The meibomian glands may appear from hyperreflective to atrophic, and Demodex mites can be observed within the gland follicles. This non-invasive imaging technique can help quantify alterations in the cornea and may aid in the early detection of corneal involvement.

In 2017, the National Rosacea Society Expert Committee established an updated classification system for rosacea, which includes ocular rosacea as a distinct subgroup.[10] This classification system aids in obtaining more accurate diagnoses and guides treatment strategies.

Research has explored diagnostic approaches, such as glycomics analysis of tear fluid. One study demonstrated that tear fluid samples from rosacea patients yielded distinctive oligosaccharide patterns, which could potentially serve as an objective diagnostic marker for the disease.[11] This approach showed promising results, with a reported sensitivity of 100% and specificity of 95.2% in distinguishing ocular rosacea cases from normal controls.

Managing ocular rosacea involves a multifaceted approach, combining patient education, skin care, and pharmacological interventions.

The first-line of defence in managing rosacea is patient education and preventive measures. Patients are advised to avoid specific triggers that can exacerbate symptoms, such as certain foods (including alcohol, caffeine, and spicy foods), environmental factors, and stress. Proper skin care is essential, involving the use of moisturizers to decrease transepidermal water loss and sunscreen to block ultraviolet light.[12]

Pharmacological interventions play a crucial role in managing ocular rosacea, and are typically implemented in a step-wise manner based on the severity of symptoms and clinical findings.[12] Initial therapy often includes supportive

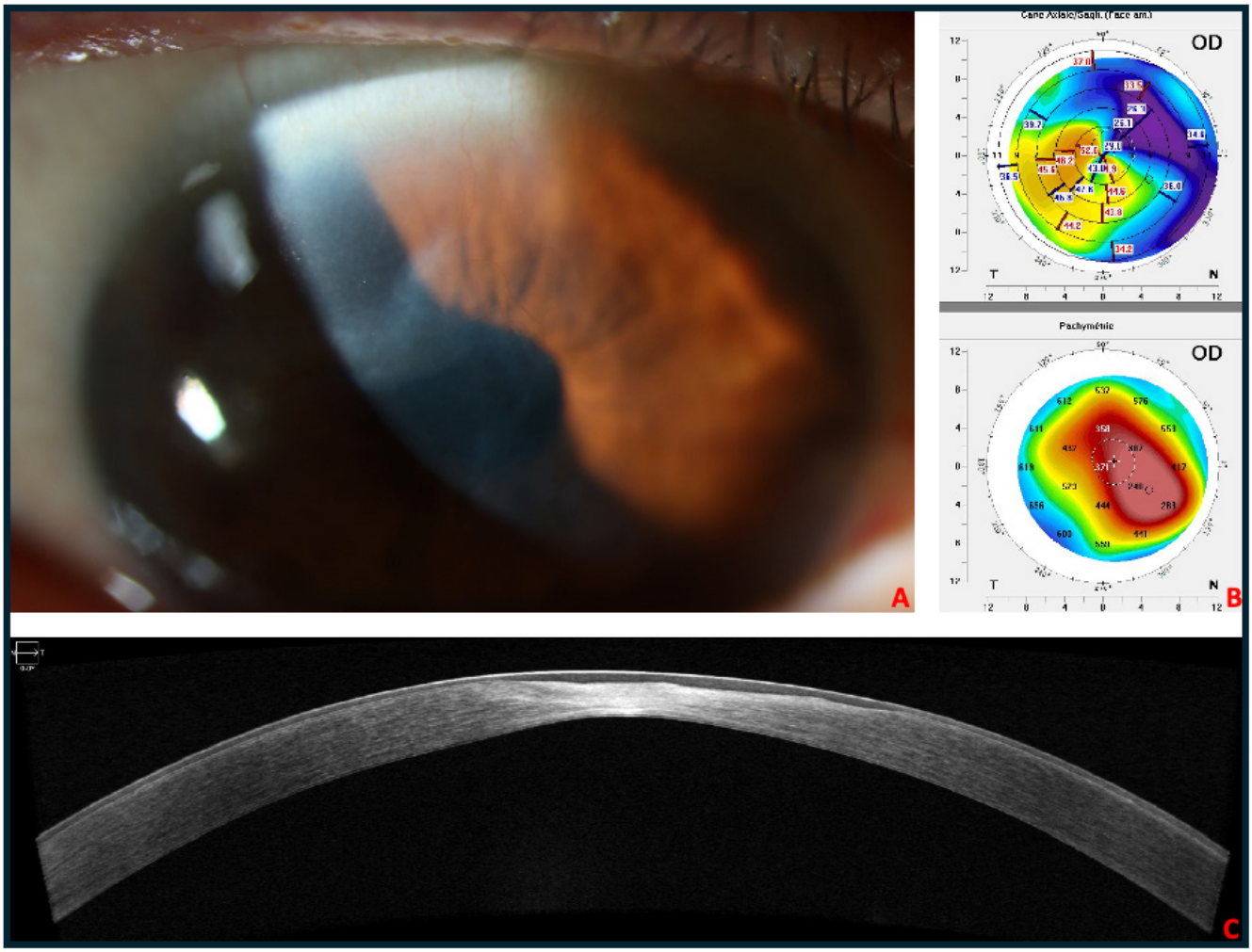

Figure 2. A) Corneal involvement is evident, with stromal scarring and neovascularization observed. **B)** Pentacam corneal tomography demonstrates irregular astigmatism and significant thinning. **C)** Anterior segment optical coherence tomography reveals a central hyperreflective area consistent with stromal scarring; *courtesy of Anat Maytal, MD, Johanna Choremis, MD, FRCSC, and Julia C. Talajic, MD, MPH, FRCSC*

measures such as preservative-free lubricants and warm compresses to improve meibomian gland function.[13,14] Topical antibiotic ointments, particularly erythromycin, are also frequently used to combat the underlying inflammation and bacterial component associated with ocular rosacea.[15] For patients who remain symptomatic despite first-line measures, a short course of low-dose topical corticosteroids, such as loteprednol or fluorometholone, may be introduced and gradually tapered.[16] At this stage, adding immunomodulatory therapy, such as topical cyclosporine, is often considered to address underlying inflammation and support long-term disease control.[17]

For more severe cases, systemic antibiotics, particularly tetracyclines such as doxycycline, are often prescribed.[1,2] These antibiotics not only have antimicrobial properties but also inhibit matrix metalloproteinases, downregulate cytokines, and suppress angiogenesis, among other anti-inflammatory mechanisms.[18] Even low-dose, slow-release forms of doxycycline have demonstrated significant improvements in ocular symptoms, with effects lasting 6 to 17 months after discontinuing treatment.[19] However, long-term treatment is limited due to side effects involving the gastrointestinal system, photosensitivity, and tooth discoloration in young children.[19] Interestingly, while tetracyclines are widely used, the optimal dosing regimens and treatment efficacy specifically for ocular rosacea have not been rigorously studied.

Recent advancements in understanding the pathogenesis of rosacea have led to new treatment targets. Researchers are exploring

the role of the microbiome, including Demodex infestation, in the development and severity of rosacea, which has led to novel therapeutic approaches.[6] Lotilaner ophthalmic solution 0.25% (XDEMVY®) has emerged as a promising treatment for Demodex blepharitis, receiving FDA approval in July 2023.[20] This novel GABA-Cl inhibitor has demonstrated significant efficacy in eradicating Demodex mites.[21] Clinical trials have shown that lotilaner not only reduces collarette grades and mite density but also improves erythema due to Demodex blepharitis, with effects lasting up to a year after treatment completion.[22,23]

For patients with MGD, intraductal meibomian gland probing has emerged as an effective technique. This procedure has shown significant improvements in symptoms such as discomfort, tearing, and blurred vision, with patients reporting a decreased need for artificial tears and oral medications.[24]

Intense pulsed light (IPL) therapy has emerged as a promising treatment for ocular rosacea, offering relief for patients suffering from associated dry eye disease and MGD.[25,26] This treatment works by delivering high-intensity light pulses to the affected areas, which can help improve the function of meibomian glands and reduce inflammation.[27,28] IPL treatment regimens for ocular rosacea typically involve multiple sessions spaced several weeks apart. A typical protocol begins with three monthly treatments using initial settings of a 560-nm filter, pulse durations of 2.4 and 6.0 ms separated by a 15-ms delay, and a starting fluence of 25 J/cm.[2,29] The optimal treatment parameters may vary depending on the specific IPL system used and the patient's individual characteristics. IPL has also been shown to be effective against Demodex mites. A study observing the real-time effects of IPL on a live Demodex mite demonstrated complete immobilization and destruction of the organism following IPL application.[30]

Radiofrequency (RF) irradiation has also shown promise as a potential treatment for ocular rosacea, particularly in addressing the underlying inflammatory and angiogenic processes.[31] The treatment has been found to reduce keratinocyte proliferation in the epidermis and decrease the expression of pro-inflammatory cytokines and angiogenesis-related factors, including vascular endothelial growth factor (VEGF), a potent angiogenic factor implicated in rosacea pathogenesis. However, the optimal dosing and maintenance protocols for both IPL and RF treatments have yet to be established to ensure sustained long-term efficacy. Furthermore, the necessity of continuing adjunctive therapies such as tetracyclines, corticosteroids, or cyclosporine remains to be determined.

In cases of corneal complications, which can include vascularization, ulceration, and scarring, more aggressive treatment and close follow-up are usually necessary.[7] Topical treatments may include low-dose steroid preparations and antibiotics to control inflammation and prevent secondary infections. Oral tetracycline derivatives have also shown efficacy in managing corneal manifestations.[3,8] In severe cases, surgical interventions such as corneal transplantation may be necessary.[4]

Ideally, managing ocular rosacea would benefit from a multidisciplinary approach, involving both dermatologists and ophthalmologists.[32] Early recognition and prompt referral for ophthalmologic examination are crucial for preventing permanent eye impairment. Conversely, ophthalmologists should be aware of the potential underlying skin disease when encountering signs suggestive of rosacea.

Conclusion

In conclusion, ocular rosacea remains a complex and potentially sight-threatening condition that requires early diagnosis and appropriate management. As our understanding of the condition evolves, future research should focus on developing targeted therapies and improving diagnostic criteria. This will help ensure timely intervention and prevent potential vision loss.

NOTE: Specific indications, contraindications, warnings, precautions and safety information exist for these products and therapies. Please consult a clinician and product instructions for use prior to application. Rx only.
As with any case study, the results should not be interpreted as a guarantee or warranty of similar results. Individual results may vary depending on the patient's circumstances and condition.

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From Peel to Plug: Sealing The Gap With Surgical Innovations For Macular Hole Repair

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Historical Context and Evolution

The surgical management of macular holes (MH) has evolved significantly over the past few decades. In 1991, Kelly and Wendel revolutionized MH repair by introducing pars plana vitrectomy combined with air fluid exchange.[1] Eckardt et al. in 1997 further advanced and improved the success of macular hole closure by introducing internal limiting membrane (ILM) peeling, establishing the gold standard for idiopathic MH treatment.[2] The subsequent development of micro-incision vitrectomy systems, particularly 25- and 27-gauge instrumentation, has resulted in better wound sealing, reduced postoperative inflammation, and faster visual recovery.[3] These technological advancements laid the foundation for more complex surgical approaches, especially in complex cases such as large, recurrent, persistent, traumatic or myopic MHs. Contemporary techniques now include a variety of ILM flap methods (e.g., inverted, temporal, single-layer, and multilayered/petal flaps), autologous ILM transplantation (AILMT), human amniotic membrane (hAM) grafts, and autologous retinal transplantation (ART).[4]

Modern Techniques For Routine and Challenging Cases

Before the advent of ILM flap techniques, the standard surgical approach for MH repair involved peeling the ILM surrounding the hole. Surgeons differed in their technique preference, with some advocating for a limited ILM peel centred around the MH, while others favoured a more extensive arcade-to-arcade peel. This conventional ILM peeling approach remains the standard of care for small idiopathic MHs measuring less than 400 µm in diameter.

In recent years, a range of advanced surgical techniques have been developed to address large (>400 µm), recurrent, or otherwise complex MHs. These innovations aim to improve anatomical closure rates and enhance visual recovery, particularly in cases with poor prognostic indicators. Among these, ILM flap techniques—such as inverted, temporal, single-layer, and multilayered flaps—have become critical tools for managing challenging MHs.

Inverted ILM Flap Technique

The inverted ILM flap technique, introduced by Michalewska et al. in 2010, involves preserving a portion of the ILM attached to the edges of the MH during the peeling process, rather than removing it entirely.[5] This remaining ILM is then flipped over to cover the MH. Next, an air–fluid exchange is carried out, and patients are instructed to maintain a face-down position for 3 to 4 days.[5] The rationale behind this technique is that the ILM flap contains Müller cell fragments that promote gliosis and serve as a biological scaffold, encouraging retinal tissue to bridge the defect. Compared to conventional ILM peeling, the inverted flap technique has demonstrated higher anatomical closure rates, particularly in large MHs. In their original randomized controlled trial, Michalewska et al. reported a 98% closure rate with the inverted flap technique, compared to 88% with traditional peeling. Subsequent meta-analyses have confirmed that the inverted ILM flap technique results in superior anatomical outcomes and, in many cases, improved visual acuity for large MHs.[6,7] However, some studies have noted that visual acuity improvements may converge with standard techniques after 6 months.[8] Further multicenter randomized trials are warranted to definitively determine the functional advantages of the inverted flap in the long term.

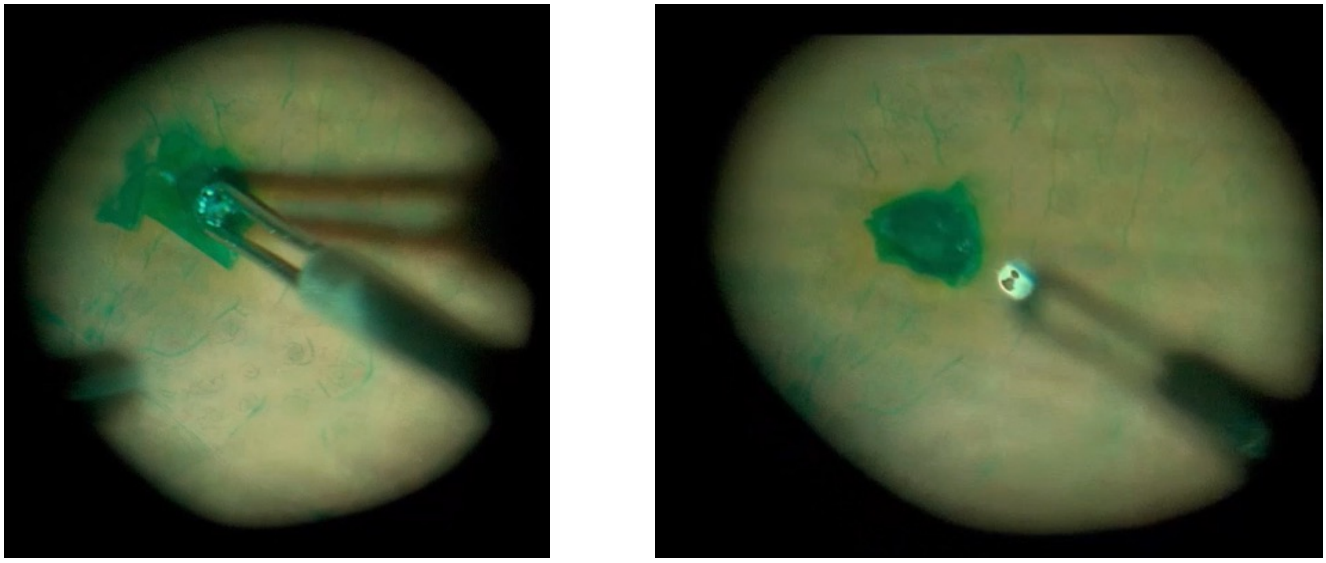


Figure 1. Intraoperative view of the multilayered or petal internal limiting membrane (ILM) flap technique, visualized with indocyanine green (ICG) staining; *courtesy of Peng Yan, MD, FRCSC*

Temporal Inverted ILM Flap

To further minimize surgical trauma, Michalewska et al. later introduced the temporal inverted ILM flap technique, a modification designed to reduce the extent of ILM peeling and better preserve the retinal nerve fiber layer.[9] In this approach, the peel begins on the temporal side of the MH and spans an area approximately equivalent to two optic disk diameters, leaving the nasal side of the fovea attached. This modified method has demonstrated comparable MH closure rates and improvements in visual acuity to those achieved with the original inverted ILM flap technique.[9] Notably, a randomized controlled trial published in 2023 reported a lower incidence of dissociated optic nerve fiber layer (DONFL) appearance postoperatively associated with the temporal technique. DONFL is seen as numerous arcuate retinal striae running along the optic nerve fibers in the macular area and has been considered to be related to ILM removal. However, functional outcomes such as best-corrected visual acuity and retinal sensitivity were comparable to those achieved with standard ILM peeling in holes larger than 250 µm.[10] This technique may be especially useful in eyes where minimizing trauma to the inner retina is a priority, such as in younger patients, those with thinner retinas, or those with concerns involving the preexisting nerve fiber layer.

Single-layer ILM Flap

The single-layer ILM flap technique, introduced by Shin et al., represents a refinement aimed at reducing excessive tissue layering while maintaining anatomical efficacy. This technique involves positioning a thin, single-layer ILM flap over the MH, assisted by perfluoro-n-octane (PFO) to stabilize the flap during surgery.[11] Unlike the original inverted flap technique, which creates a multilayered fold, this method avoids excessive tissue buildup and ensures a more physiological scaffold over the fovea. In initial studies, it achieved favourable results, with anatomical closure in 10 out of 12 eyes and significant improvement in visual acuity over 6 months, suggesting it is a simpler yet effective alternative. Further studies have confirmed the technique's effectiveness for large MH,[12] and found that the single-layered inverted ILM flap was better than ILM peeling for the closure of large MHs.[13]

Multilayered/petal Flaps

The multilayered or petal ILM flap technique **(Figure 1)** is another innovative variation designed to enhance scaffold stability over large MHs. Often referred to as the "flower-petal" technique, it involves creating multiple ILM segments that are inverted and layered sequentially over the hole to form a thickened, multilayered construct.[14,15] This approach provides a robust platform for glial proliferation and tissue remodelling, especially in cases where hole size, chronicity, or high myopia reduce the likelihood of spontaneous closure. In

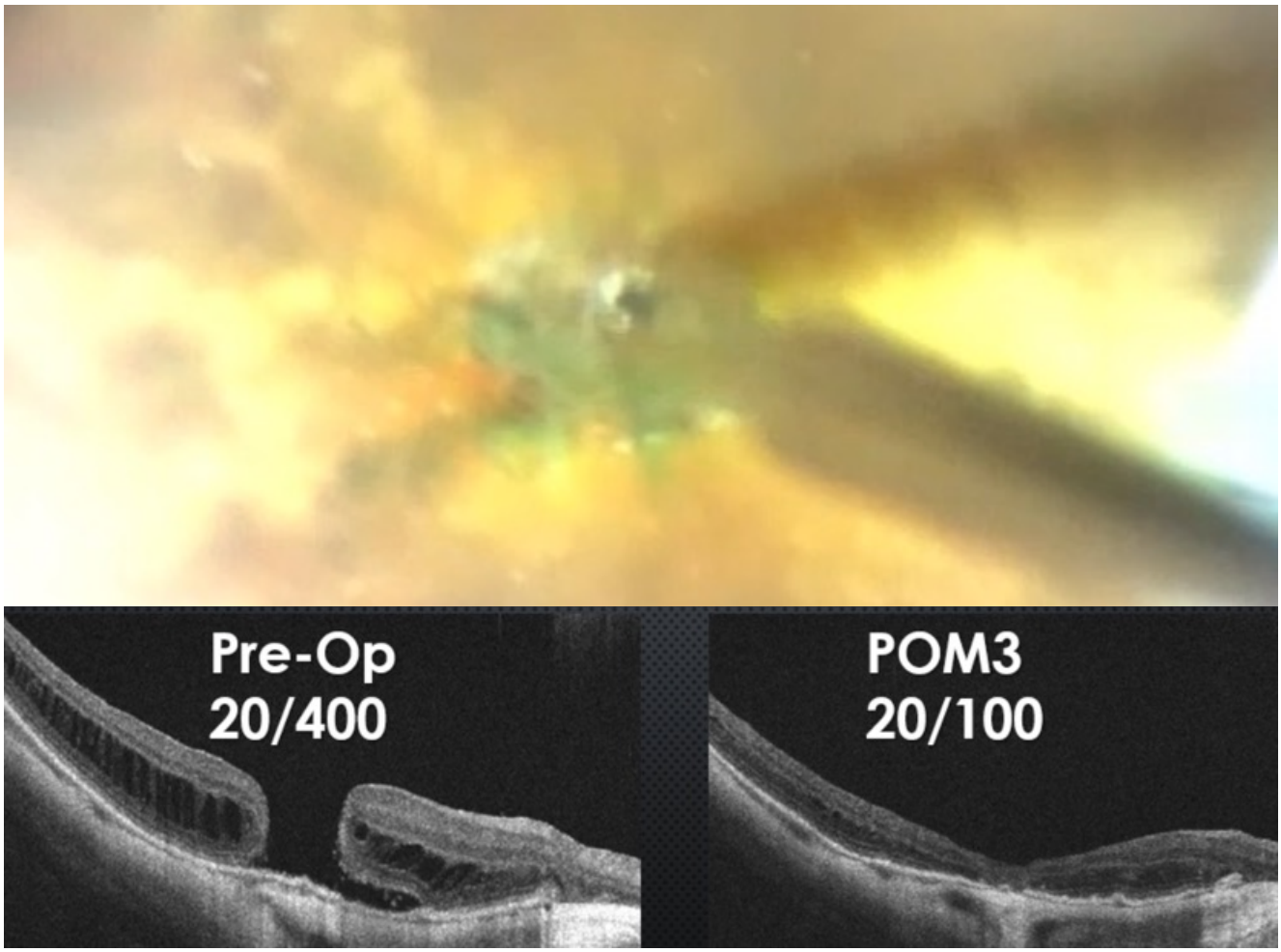


Figure 2. In myopic macular hole (MH) repair, an autologous internal limiting membrane (ILM) graft is harvested from a separate retinal area and transplanted into the MH. Postoperative outcomes show successful MH closure and improved visual acuity; *courtesy of Peng Yan, MD, FRCSC*

a study of 103 eyes with large full-thickness MHs (average minimum linear diameter of 712 µm), Joshi et al. performed this method under PFO and achieved an anatomic closure rate of 92.2%.[16] This approach may be especially beneficial for highly myopic eyes with posterior staphyloma, where the ILM is often fragmented or discontinuous.[16] While PFO is frequently used to stabilize the multilayered flaps during surgery, surgeons can use alternative anchoring methods, such as autologous blood or platelet plugs to anchor the flaps in place, which offers an alternative strategy when PFO use is not feasible or desired. This technique may be best suited for very large, chronic, or myopic holes where standard inverted or single-layer flaps are insufficient to promote closure.

Despite the high anatomical success rates associated with primary MH surgery, persistent, recurrent, or refractory MHs remain a significant challenge for vitreoretinal surgeons. These cases are often characterized by larger hole diameters, higher degrees of myopia, increased chronicity, and minimal residual ILM, all of which negatively impact the likelihood of successful closure. In response, a variety of advanced surgical techniques and supportive agents have been developed to improve outcomes in these difficult scenarios.

Subretinal Balanced Salt Solution (BSS) Injection

The technique of creating subretinal fluid to shift the released retina towards the center of refractory macular hole has been described in literature.[17] The mechanism involved in this technique includes: the release of centripetal force by ILM removal, followed by the release of RPE-photoreceptor adherence to mobilize retina

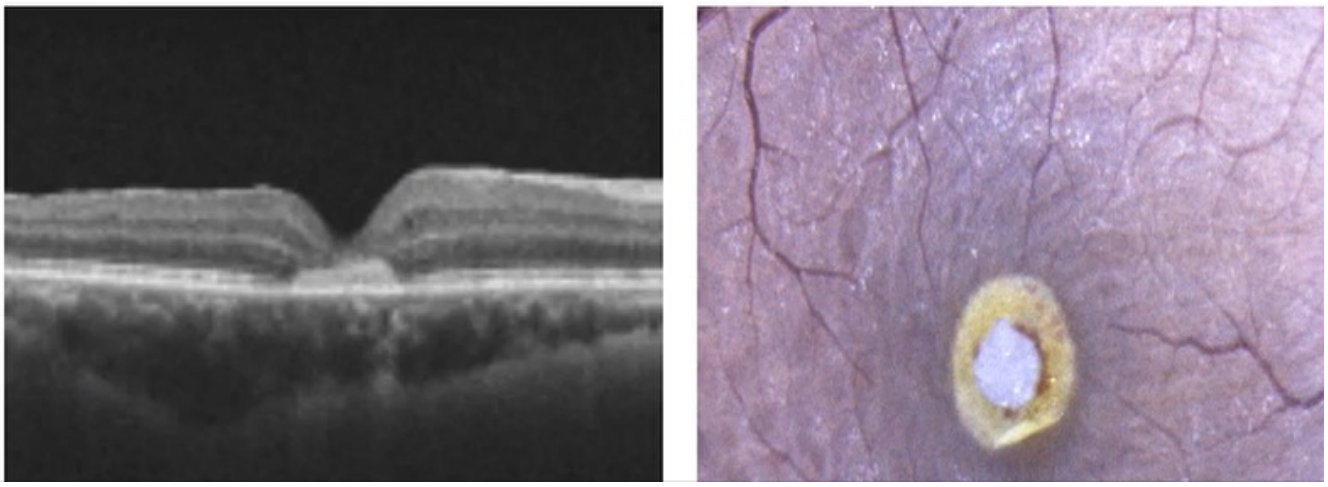


Figure 3. A human amniotic membrane graft is inserted into subretinal space as a plug over the macular hole (MH). Optical coherence tomography illustrates the role of the amniotic membrane in assisting with MH closure; *courtesy of Peng Yan, MD, FRCSC*

from epiretinal and subretinal adhesions, then stretching the retina with subretinal fluid and tactile massage to enlarge retinal surface covering large macular holes. Small studies have reported success of 78% of closure of refractory macular hole using subretinal BSS injection with objective visual improvement with no complications.[18]

Autologous ILM Transplantation

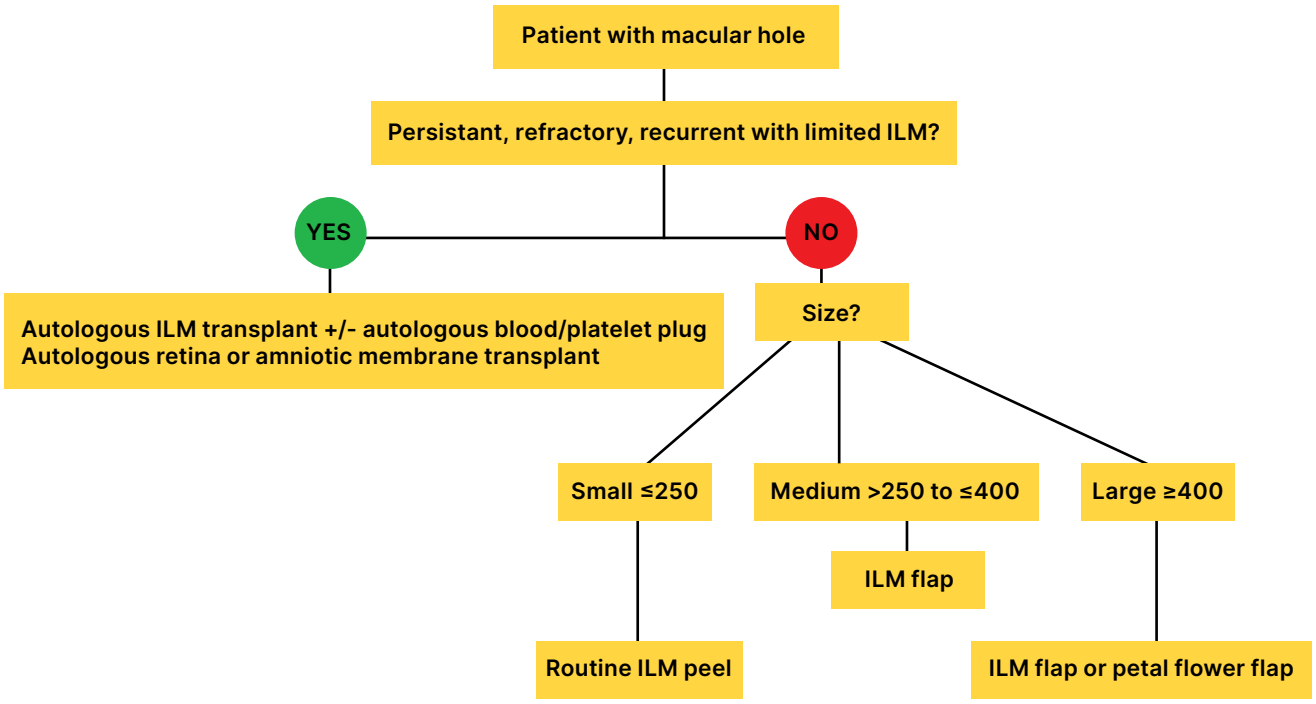
In patients who lack sufficient ILM around the MH for secondary surgery, Morizane et al. introduced autologous ILM transplantation **(Figure 2)**. This method involves harvesting a small ILM flap from a different retinal area and placing into the MH, using viscoelastic to anchor it, followed by gas tamponade.[19] This method achieved a 90% closure rate and visual improvement in 80% of eyes. Studies have demonstrated that AILMT can achieve high closure rates and is associated with minimal complications.[20–22] A limitation of this technique is that the free ILM flaps are prone to displacement and are positioned in the MH in a non-physiological orientation, which might limit their ability to promote glial cell growth. One way to help minimize this effect is to use autologous blood or platelet plugs to prevent displacement of the ILM. Additionally, this approach may not restore the neurosensory retina across the hole.

Autologous Retinal Transplantation

First described by Grewal and Mahmoud in 2016, the ART technique involves transplanting a segment of the patient's own retina to cover the MH.[23] This technique involves harvesting a free flap of autologous neurosensory retina and positioning it over the refractory MH, where it serves as both a mechanical plug and a biological scaffold to promote glial proliferation and tissue integration.[23] ART is particularly useful in cases with no residual ILM, chronic holes exceeding 750 µm, or in eyes associated with high myopia and retinal atrophy. A multicenter international study reported an 87.8% anatomical closure rate and a mean visual acuity improvement of 0.08 logarithm of the Minimum Angle of Resolution (logMAR) in eyes with full-thickness MH refractory to prior vitrectomy with ILM peel and tamponade.[24] A meta-analysis published in 2024 involving 322 cases demonstrated a 94% overall closure rate and significant improvement in postoperative visual acuity across all subgroups of large MHs, including refractory MH, high myopia associated with MH, primary MH, and MH with retinal detachment.[25] While ART has demonstrated excellent anatomical success, visual outcomes can be variable due to potential disorganization of the outer retina and disruption of photoreceptor alignment. Nevertheless, ART remains a powerful salvage technique for cases where traditional or ILM-based strategies are not feasible.

Human Amniotic Membrane Grafts

The hAM is the innermost layer of fetal membranes. It possesses anti-inflammatory, anti-fibrotic, and pro-regenerative properties. In this technique **(Figure 3)**, hAM is inserted as a plug into the epiretinal or subretinal space over the MH, where it acts as a biological scaffold to support



Flow diagram of the surgical decision-making algorithm for macular hole management; *courtesy of Peng Yan, MD, FRCSC*

Abbreviations: ILM: internal limiting membrane

tissue repair and cell proliferation, helping to achieve hole closure.[26]

A retrospective analysis of large MHs (>400 µm) or reoperations following unsuccessful ILM peeling, has shown a 100% closure rate with a single hAM intervention and no recurrences, along with a median of three lines of visual improvement.[26] A 2023 meta-analysis involving 103 eyes treated with hAM after failed vitrectomy and ILM peeling reported a 66% improvement in visual acuity and a 94% MH closure rate.[27] Cryopreserved hAM grafts have shown better outcomes than dehydrated grafts.[27]

Surgery Guided by Optical Coherence Tomography (OCT) Features

With an expanding array of surgical techniques available, selecting the optimal approach for MH repair increasingly relies on a detailed preoperative assessment, particularly using OCT. OCT offers high-resolution cross-sectional imaging that enables precise evaluation of MH characteristics—including size, shape, retinal thickness, and the presence of associated pathologies such as epiretinal membranes (ERMs). For small MHs measuring less than 400 µm, the standard ILM peel technique remains an effective technique of choice. However, for larger MHs, evidence suggests that the inverted ILM flap technique is likely to yield better anatomical outcomes.[6,7] In addition, a meta-analysis involving over 1,400 eyes showed that the inverted ILM flap technique results in significantly higher closure rates than ILM peeling alone. This advantage was consistent across various full-thickness MH sizes, including myopic eyes, and those complicated by retinal detachment.[28] A systematic review and meta-analysis reported that the inverted ILM flap technique provides superior anatomical closure and better short-term visual outcomes in large idiopathic MHs compared to traditional ILM peeling, ART, or ILM insertion.[29] While ART has been shown to be effective in treating refractory MHs, large hAM grafts, though associated with high closure rates, tend to result in less favourable visual acuity outcomes.[29] This meta-analysis recommends the inverted ILM flap technique as the preferred approach for large idiopathic MHs, while ART and hAM grafts are considered effective alternatives for refractory cases.[29] Thus, for large MH cases greater than 400 µm, the inverted ILM flap is the approach of choice provided sufficient ILM remains. In refractory MHs larger than 750 µm or in cases where the ILM is insufficient, ART or hAM grafts are the recommended approaches.

Additional OCT-derived features also guide surgical decision making:

- Chronicity: MHs persisting for more than 3–6 months often exhibit signs of retinal thinning, glial remodelling, and reduced tissue elasticity. In such cases, techniques such as inverted flaps, ILM free flaps, or ART are more suitable than standard ILM peeling.[30]
- ERM presence: ERMs exert tangential traction that can prevent hole closure. Their removal is essential, and in combined cases, more aggressive approaches such as inverted flaps or grafting should be considered to minimize recurrence.[31]
- Lamellar macular holes (LMH): Differentiating between tractional LMH (typically associated with highly reflective ERMs) and degenerative LMH (characterized by lamellar hole-associated epiretinal proliferation, or LHEP) is crucial. In degenerative LMH, traditional peeling can risk converting the defect into a full-thickness hole. Modified techniques, such as LHEP embedding combined with ILM flap inversion, have shown promise in reducing complications.[32]

Key strategies to minimize anatomical failure and optimize visual outcomes in MH surgery begin with a thorough preoperative assessment. OCT should be used to evaluate key features such as hole size, traction, ERM presence, and chronicity. Early surgical intervention is important, as shorter symptom duration is associated with higher closure rates and better visual recovery. Intraoperatively, careful use of vital dyes (indocyanine green [ICG], brilliant blue, or triamcinolone) and controlled endoillumination can help reduce retinal toxicity during ILM peeling. Surgical technique should be individualized—typically using the inverted ILM flap for large idiopathic holes, and ART or hAM grafts for refractory or recurrent cases. Postoperatively, the use of long-acting gas tamponades such as SF_6, combined with face-down positioning, can enhance closure. However, recent studies suggest that high closure rates can still be achieved without strict prone positioning when extensive ILM peeling is performed.[33]

Conclusion

MH surgery has evolved into a highly effective and nuanced discipline, driven by advances in imaging, instrumentation, and surgical techniques. Innovations such as the inverted ILM flap, ART, and hAM grafts have significantly improved outcomes, particularly in complex and refractory cases. Current evidence supports the inverted ILM flap as the preferred approach for large idiopathic holes, while ART and hAM grafts offer viable solutions when ILM is unavailable or if previous surgical attempts have failed.

Achieving successful outcomes in MH surgery now depend on individualized, OCT-guided surgical planning. Key factors such as hole size, chronicity, ILM availability, and associated pathologies must also be carefully evaluated. As both imaging and surgical technologies continue to advance, precision-based, tailored interventions are becoming the standard of care, offering patients the best possible anatomical and visual results in even the most challenging cases.

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