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Gene Therapy Updates for Inherited Retinal Dystrophies

Introduction

Inherited retinal dystrophies (IRDs) encompass a group of genetically diverse disorders, each uniquely influencing distinct retinal cell pathways and retinal areas. IRDs currently affect an estimated 5.5 million individuals worldwide, exerting a profound impact on the quality of life of those affected.[1] Depending on the mutated gene, typical presentations often manifest as colour or night blindness, or peripheral vision blindness progressing to complete blindness.[2] Consequently, patients grappling with IRDs face not only the physical challenges of their condition, but also endure significant psychosocial and economic repercussions.[3]

Historically, IRDs were diagnosed and classified based solely on clinical characterization, with no available treatment options. However, advances in genetic characterization have led to the identification of over 270 causative genes, enabling the development of more targeted therapies aiming to restore the function of these mutated genes.[2] It is therefore not surprising that this remains an active field of research, aiming to find treatments that can potentially slow down, halt, or even reverse vision loss.

This review aims to provide an updated summary of the current state of IRD treatments, and to discuss recent advancements and emerging therapeutic strategies. The main classifications that will be explored are macular dystrophies; stationary cone dystrophies; rod-cone dystrophies; Leber congenital amaurosis (LCA); and chorioretinal dystrophies. In this review,

Disease	Gene/vector delivery	Phase	Status	Sponsor	Trial number
X-linked Retinoschisis	RS1/rAAV Intravitreal	I	Recruiting	Zhongmou Therapeutics	NCT06066008
	RS1/AAV.SPR Subretinal	I/II	Recruiting	Atsena Therapeutics Inc.	NCT05878860
	RS1/rAAV2 Intravitreal	I/II	Completed	Applied Genetic Technologies Corp	NCT02416622
	RS1/AAV8 Intravitreal	I/II	Active, not recruiting	National Eye Institute (NEI)	NCT02317887
Achromatopsia	CNGA3/rAAV Subretinal	I/II	Recruiting	STZ eye trial	NCT02610582
	CNGA3/rAAV Subretinal	I/II	Active, not recruiting	Applied Genetic Technologies Corp	NCT02935517
	CNGA3/AAV2 Subretinal	I/II	Completed with results	MeiraGTx UK II Ltd	NCT03758404
	CNGB3/rAAV Subretinal	I/II	Active, not recruiting	Applied Genetic Technologies Corp	NCT02599922
	CNGB3/AAV2 Subretinal	I/II	Completed with results	MeiraGTx UK II Ltd	NCT03001310
Retinitis Pigmentosa	RLBP1/AAV8 Subretinal	I/II	Active, not recruiting	Novartis Pharmaceuticals	NCT03374657
	PDE6A/rAAV Subretinal	I/II	Active, not recruiting	STZ eye trial	NCT04611503
	PDE6B/AAV2 Subretinal	I/II	Recruiting	Coave Therapeutics	NCT03328130
	RPGR/AAV Intravitreal	I	Recruiting	Frontera Therapeutics	NCT05874310
	RPGR/AAV capsid variant Intravitreal	I/II	Active, not recruiting	4D Molecular Therapeutics	NCT04517149
	RPGR/rAAV2 Subretinal	I/II	Recruiting	Applied Genetic Technologies Corp	NCT03316560
	RPGR/rAAV2 Subretinal	II/III	Not yet recruiting	Applied Genetic Technologies Corp	NCT04850118
	RPGR/AAV2/5 Subretinal	I/II	Completed	MeiraGTx UK II Ltd	NCT03252847
	RPGR/AAV5 Subretinal	III	Recruiting	Janssen Research & Development, LLC	NCT04671433
	RPGR/AAV5 Subretinal	III	Recruiting	Janssen Research & Development, LLC	NCT04794101
	RPGR/AAV8 Subretinal	I/II	Completed	NightstaRx Ltd, a Biogen Company	NCT03116113
	MERTK/rAAV2 Subretinal	I	Completed	King Khaled Eye Specialist Hospital	NCT01482195
	USH2A/AON Intravitreal	I/II	Completed	ProQR Therapeutics	NCT03780257
	USH2A/AON Intravitreal	II	Terminated	ProQR Therapeutics	NCT05085964
	USH2A/AON Intravitreal	II/III	Active, not recruiting	ProQR Therapeutics	NCT05158296
	USH2A/AON Intravitreal	II/III	Terminated	ProQR Therapeutics	NCT05176717
	RHO/AON Intravitreal	I/II	Active, not recruiting	ProQR Therapeutics	NCT04123626

Disease	Gene/vector delivery	Phase	Status	Sponsor	Trial number
Leber Congenital Amaurosis	RPE65/rAAV2 Subretinal	I	Active, not recruiting	University of Pennsylvania	NCT00481546
	RPE65/rAAV2 Subretinal	I	Completed	Spark Therapeutics	NCT00516477
	RPE65/rAAV2 Subretinal	I	Completed	Hadassah Medical Organization	NCT00821340
	RPE65/rAAV2 Subretinal	I/II	Completed	Applied Genetic Technologies Corp	NCT00749957
	RPE65/rAAV2 Subretinal	I/II	Completed	Nantes University Hospital	NCT01496040
	RPE65/rAAV2 Subretinal	I/II	Completed	University College, London	NCT00643747
	RPE65/rAAV2 Subretinal	III	Active, not recruiting	Spark Therapeutics	NCT00999609
	RPE65/AAV2/5 Subretinal	I/II	Completed	MeiraGTx UK II Ltd	NCT02781480
	RPE65/AAV9 Subretinal	I	Recruiting	Xinhua Hospital, Shanghai Jiao Tong University School of Medicine	NCT06088992
	REP65/AAV9 Subretinal	I/II	Recruiting	HuidaGene Therapeutics Co., Ltd.	NCT05906953
	CEP290/CRISPR/Cas9 Subretinal	I/II	Active, not recruiting	Editas Medicine, Inc.	NCT03872479
	CEP290/AON Intravitreal	I/II	Terminated	ProQR Therapeutics	NCT03913130
	CEP290/AON Intravitreal	I/II	Completed with results	ProQR Therapeutics	NCT03140969
	CEP290/AON Intravitreal	II/III	Active, not recruiting	ProQR Therapeutics	NCT03913143
	CEP290/AON Intravitreal	II/III	Recruiting	ProQR Therapeutics	NCT04855045
Choroideremia	REP1/AAV Intravitreal	I	Active, not recruiting	4D Molecular Therapeutics	NCT04483440
	REP1/rAAV2 Subretinal	I/II	Completed	University of Oxford	NCT01461213
	REP1/AAV2 Subretinal	I/II	Completed with results	Spark Therapeutics	NCT02341807
	REP1/rAAV2 Subretinal	I/II	Completed	University of Alberta	NCT02077361
	REP1/AAV2 Subretinal	II	Completed	University of Oxford	NCT02407678
	REP1/AAV2 Subretinal	II	Completed with results	Byron Lam	NCT02553135
	REP1/AAV2 Subretinal	II	Completed	STZ eye trial	NCT02671539
	REP1/AAV2 Subretinal	II	Completed with results	Biogen	NCT03507686
	REP1/AAV2 Subretinal	III	Completed	Biogen	NCT03496012

Table 1. Comprehensive overview of clinical trials for targeted therapies in common inherited retinal diseases (as of January 1, 2024).

Phase III clinical trials (registered on clinicaltrials.gov) were selected for literature analysis. In cases where no Phase III trials were available, Phase I or II clinical trials with results were analyzed. Stationary rod dystrophies as well as progressive cone and cone-rod dystrophies will not be discussed, as available studies for these disorders are limited to the preclinical phase (**Table 1**).

Gene Therapy

Gene therapy involves the introduction or modification of genetic material within cells to replace the function of mutated genes. The eye is an ideal target for gene therapy because of its tight blood-ocular barrier, making it relatively immune privileged. In addition, the retina is readily accessible, and a patient's response to therapy can easily be monitored through clinical examinations and imaging. Managing monogenic autosomal-recessive and X-linked mutations is facilitated by the loss of function of these abnormal proteins.[4] Conversely, dominant mutations are less amenable to genetic therapies, as the abnormal gain-of-function proteins impede the action of the correctly synthesized ones post-treatment.[4]

In gene therapy, three main approaches are used to address mutations. The first, and most prevalently used, is gene augmentation.[4] This technique is uniquely employed for monogenic recessive or X-linked inherited diseases, and introduces a wild type copy of the pathogenic gene into target retinal cells, thereby augmenting the production of a functional protein.[4] Second, gene editing may be used for dominant mutations.[4] This involves the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas9) technology, where a gene-specific guide RNA is linked to a Cas9 endonuclease and identifies, cuts and removes specific portions of DNA to be replaced.[4] The downside to this technique, however, is the potential of creating novel mutations.[4] Last, gene inactivation can also be used for dominant mutations.[4] Here, small interfering RNAs (siRNAs) or antisense oligonucleotides (AONs) can correct or block the production of the mRNA transcribed from the mutated DNA gene.[4]

Subretinal and intravitreal injections are the most common modes of delivery. Subretinal injections are used for outer retinal targets and require smaller amounts to achieve a therapeutic effect.[5] They are locally administered between photoreceptors and the RPE layer, and complications resemble those of pars plana vitrectomy.[5] Intravitreal injections are used for inner retinal targets, but are more immunogenic and it is harder to transduce photoreceptors and RPE cells because of the barrier effect from the inner limiting membrane.[5]

Apart from AONs, genetic therapy is delivered to target retinal cells via viral or non-viral vectors. Within viral vectors, adeno-associated vectors (AAV) have a smaller gene size carrying capacity (4.5 kb to 4.9 kb) and do not integrate into the host's genome.[6] Lentiviruses (LV) carry genes up to 8 kb but integrate the host's genome, causing a small risk of insertional mutagenesis.[6] On the other hand, non-viral vectors have a lower risk of genotoxicity and immunogenicity, but have a lower specificity and are less stable than viral vectors.[6]

Macular Dystrophies

Macular dystrophies include Stargardt disease, Best vitelliform macular dystrophy (BVMD), X-linked retinoschisis (XLRS) and pattern dystrophies. In this review, Stargardt disease, BVMD and XLRS will be discussed.

Stargardt disease

Inherited in an autosomal recessive manner, **Stargardt** affects 1:8000 to 1:10,000 individuals, making it a leading cause of juvenile macular degeneration.[7] Patients affected by this dystrophy often have a mutated ATP-binding cassette sub-family A gene (ABCA4).[7] Lack of this protein causes toxic accumulation of bisretinoid compounds in the RPE, leading to RPE dysfunction and causing visual impairment.[7] The main obstacle in developing therapies for this gene is its large size (6.8 kb).[7] Preclinical studies are currently exploring the use of non-viral delivery systems such as covalently closed and circular DNA (C3DNA).[7] Studies on porcine and non-human primate retinas have provided evidence of sustained ABCA4 protein expression up to six months post-treatment, showing promising results for possible human applications in the future.[7]

Best Vitelliform Macular Dystrophy

Best disease is usually inherited in an autosomal dominant pattern and affects 1:10,000 individuals.[8] It is caused by a mutation in the BEST1 gene, responsible for the expression of the transmembrane protein Bestrophin 1, which is

greatly implicated in the calcium homeostasis of the RPE.[9] Best disease evolves through six stages, from the subclinical/previtelliform phase where the fundus appears normal, to the vitelliform stage with classic egg yolk lesions on the macula, gradually evolving toward the atrophic stage.[9] The most commonly reported symptoms are vision dimness, metamorphopsia and scotoma, but these symptoms vary largely between individuals.[9] Although genetic testing is needed for definitive diagnosis, there are no available pre-clinical or clinical gene therapy studies.

X-linked retinoschisis

X-linked retinoschisis causes predominant central vision loss in 1:5,000 to 1:25,000 males and is associated with a mutation in the retinoschisin 1 gene (RS1).[10] This retinoschisin membrane protein is involved in retinal cell layer organization and cell adhesion, explaining why patients develop macular schisis that may even extend to the peripheral retina.[10] As opposed to subretinal injections, intravitreal gene therapy delivery is the preferred approach, as patients have a higher predisposition to retinal detachments.[10] Although preclinical studies have shown effective gene augmentation therapies in non-human models, the results of two Phase I/II trials introducing AAVs intravitreally (AAV8-RS1) showed inflammation in almost all patients with no improvement in visual function.[10]

Stationary Cone Dystrophies

Stationary cone dystrophies such as achromatopsia and blue cone monochromatism represent a group of IRDs characterized by a stable and non-progressive impairment of cone photoreceptors. As achromatopsia is the more classic example, it will be discussed in this review.

Achromatopsia

Achromatopsia (ACHM) is an autosomal recessive, inherited disorder affecting approximately 1:30,000 people.[11] It is characterized by the early, insidious loss of photoreceptor cones, leading to vision loss; colour blindness; hemeralopia; photophobia; and nystagmus.[11] Approximately 90% of patients with ACHM carry mutations in the cyclic nucleotide-gated channel alpha 3 (CNGA3) or beta 3 (CNGB3) gene, which encodes essential components of the phototransduction cascade.[11] Although there are currently no approved therapies, ongoing Phase I and II AAV gene augmentation clinical studies, including two that have shown gains in visual acuity and contrast sensitivity in all nine treated patients with CNGA3 mutations, are underway.[12]

Rod-cone Dystrophies

Rod-cone dystrophies include retinitis pigmentosa (RP), Usher syndrome, enhanced S-cone syndrome, and Bietti crystalline dystrophy. In this review, RP and Usher syndrome will be discussed.

Retinitis pigmentosa

Retinitis pigmentosa is the most common IRD, affecting 1:4,000 people.[13] It can be inherited through autosomal dominant, autosomal recessive, or X-linked genetic patterns, reflecting its complex genetic etiology. It is characterized by primary rod and secondary cone Degeneration.[13] Symptoms include nyctalopia, followed by progressive peripheral visual field loss.[13]

Accounting for up to 15% of all RP cases, X-linked RP is the most severe form of the condition.[13] Seventy to seventy-five percent of these patients have mutations in the GTPase regulator gene (RPGR), a protein involved in ciliary transport and critical in maintaining photoreceptor integrity.[13] In a Phase I/II dose escalation gene augmentation trial (AAV2/5-RPGR), six out of seven patients treated with low or intermediate doses showed stability or improvement in retinal sensitivity at 12 months.[14] In the higher dose cohort however, two out of three treated patients showed signs of inflammation and no signs of visual improvement.[14]

The USH2A gene codes for usherin, a protein necessary for basement membrane and photoreceptor integrity.[15] In patients with Usher syndrome Type 2a and some non-syndromic forms of RP, mutations have been found in the USH2A exon 13, leading to clinical studies using an AON designed to skip this exon (QR-421a).[15] In the STELLAR study, all 20 treated patients had visual acuity improvement, objectified by an average gain of six letters or improvement in total retinal sensitivity at 48 weeks post-treatment.[15] There were no reported serious adverse events.[15]

Leber Congenital Amaurosis

Commonly inherited in an autosomal recessive manner and affecting 1:50,000 to 1:100,000 people, **LCA** is one of the most severe

forms of retinal dystrophy.[16] In addition to severe vision loss, patients often have accompanying sensory nystagmus, near-absent pupillary response, and a non-detectable electroretinogram response.[17] Voretigene neparvovec-rzyl (AAV2-hRPE65v2) is currently the only FDA approved gene therapy for IRDs. Recent surgical technique enhancements avoid bleeding and inadvertent macular hole formation.[18] This subretinal gene augmentation therapy targets biallelic RPE65 mutations frequently found in LCA type 2 patients, accounting for up to 16% of all LCA cases.[16] The RPE65 gene is responsible for converting trans-retinyl esters to 11-cis-retinols, and its dysfunction leads to an inability to regenerate pigments in photoreceptors.[16] Recent clinical studies have demonstrated sustained partial rescue of photoreceptor function for up to four years post-treatment.[16] This was objectified via multi-luminance mobility tests, visual field testing, and full-field stimulus tests.[16] The most commonly reported adverse event post-treatment was central retinal thinning.[19]

In type 10 LCA, the gene encoding the centrosomal protein 290 (CEP290) is frequently mutated, leading to faulty photoreceptor cilia function.[20] In Phase 1b and II clinical trials, AONs (QR-110) have been used to correct the faulty mRNA before protein translation.[20] Five out of 11 treated patients showed a -0.3 logMAR improvement in visual acuity one year post-treatment; the most common adverse event was the development of cataracts.[20] A Phase III trial has been completed, although its results are yet to be released.[21] In addition, there are ongoing Phase I/II clinical trials using the CRISPR-Cas9 system to eliminate the IVS26 mutation in this same CEP290 gene.[21]

Chorioretinal Dystrophies

Chorioretinal dystrophies are a distinct subgroup of IRD characterized by progressive degeneration in both the choroid and retina. The most prevalent example, choroideremia (CHM), will be discussed in this review.

Choroideremia

CHM is an X-linked recessive dystrophy affecting 1:100,000 to 1:200,000 males.[22] It is characterized by the centripetal loss of photoreceptors, RPE cells and the choriocapillaris, even reaching the fovea in severe cases.[23] Patients begin to report nyctalopia and peripheral vision loss in late childhood, progressing to near-complete vision loss by the age of 40.[23] Choroideremia is caused by a mutation in the CHM gene, which encodes the Rab escort protein 1 (REP1), an enzyme essential for intracellular trafficking of vesicles.[23] A recent Phase III STAR study treating one eye per patient with an either low or high dose of timrepigene emparvovec (BIIB111/AAV2-REP1) allowed patients to gain in visual acuity when compared to the control eye.[22] However, the number of treated patients meeting this three-line improvement did not reach statistical significance, which is why there has been no regulatory approval.[22] In Phase I and II clinical trials, there were rare cases of adverse events, with two cases of retinal holes over a non-functional retina and one case of intraretinal immune response.[22]

Conclusion

In summary, ongoing research endeavours are focused on the development of sustainable gene therapies for IRDs, previously considered untreatable. The primary challenges include the development of delivery methods with reduced immunogenicity, ensuring enduring treatment effects, and establishing therapies that minimize host mutagenesis. Optimal treatment candidates appear to be patients with early-stage diagnoses and gradual disease progression, as these factors provide a broader window for treatment before the degeneration of target cells. This article provides an overview of a select number of ongoing clinical studies, indicating a cautious yet hopeful outlook for the future of IRD treatments.

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Recent Advances in the Evaluation and Treatment of Primary Angle Closure Disease

Introduction

In the realm of ophthalmology, the clinical management of angle closure remains a disputed topic. An aging population, underperformance of gonioscopy, and a paucity of clear guidelines about management have contributed to the rising number of patients with primary angle closure glaucoma (PACG). The global prevalence of PACG based on a meta-analysis published in 2014 was 0.50%, with the highest prevalence occurring in Asian populations. This study also projected that the number of people with PACG worldwide will increase to 32 million by the year 2040.[1] PACG is a visually devastating disease; around a quarter of individuals worldwide and one out of nine individuals in the United States with newly diagnosed PACG are affected by blindness (visual acuity of 20/200 or less).[2,3] The rising burden of the visual morbidity associated with untreated PACG highlights the urgent need for more clearly defined, evidence-based practice guidelines in angle closure care.

Classification

While angle closure comprises a spectrum of disease, categorical definitions of primary angle closure disease (PACD) have been established to aid in its scientific study and clinical care. The current classification consists of the following categories: primary angle closure suspect (PACS); primary angle closure (PAC); primary angle closure glaucoma (PACG); and acute primary angle closure (APAC).[4] PACS is defined as 180 or more degrees of non-visible pigmented trabecular meshwork on gonioscopy in the absence of elevated intraocular pressure (IOP) greater than 21 mmHg and optic nerve damage (**Figure 1**). PAC shares similar findings as PACS except there is presence of peripheral anterior synechiae (PAS) and/or elevated IOP greater than 21 mmHg. PACG is defined as PAC with concurrent examination findings consistent with glaucomatous optic neuropathy. APAC is defined as an acute episode of PAC with elevated IOP greater than 21 mmHg.

Angle Closure Diagnosis

Dark-room dynamic gonioscopy remains the clinical standard for evaluating the anterior chamber angle and detecting patients at risk for PACG. The American Academy of Ophthalmology (AAO) Preferred Practice Pattern guidelines for primary open angle glaucoma (POAG) and PACG both emphasize the importance of gonioscopy in patients undergoing evaluation for glaucoma. They also note that ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) (**Figure 2**) can aid in the diagnosis.[5]

Despite its importance, gonioscopy tends to be underperformed by eyecare providers. Hertzog et al reported a gonioscopy rate of 51.3% at initial evaluations of patients with moderate to severe glaucomatous damage, a number that is supported by more recent studies on gonioscopy.[6,7,8] The rate of gonioscopy was found to be even lower (less than one-third) in patients who presented with an episode of APAC who were previously evaluated by an ophthalmologist or optometrist in the preceding two years.[9] The diagnosis of PACS prior to the diagnosis of PACG was associated with lower risk of blindness, showing that earlier detection of angle closure via gonioscopy yields more favourable outcomes.[2] Therefore, the importance of performing angle evaluations in all patients suspected of glaucoma cannot be ignored.

Angle Closure Management

In the recent past, a few clinical studies have recommended dramatic changes to the paradigms of angle closure management. The standard of care for eyes with mild angle closure (PACS) has been laser peripheral iridotomy (LPI). The Zhongshan Angle-Closure Prevention (ZAP) Study was a landmark randomized, controlled trial

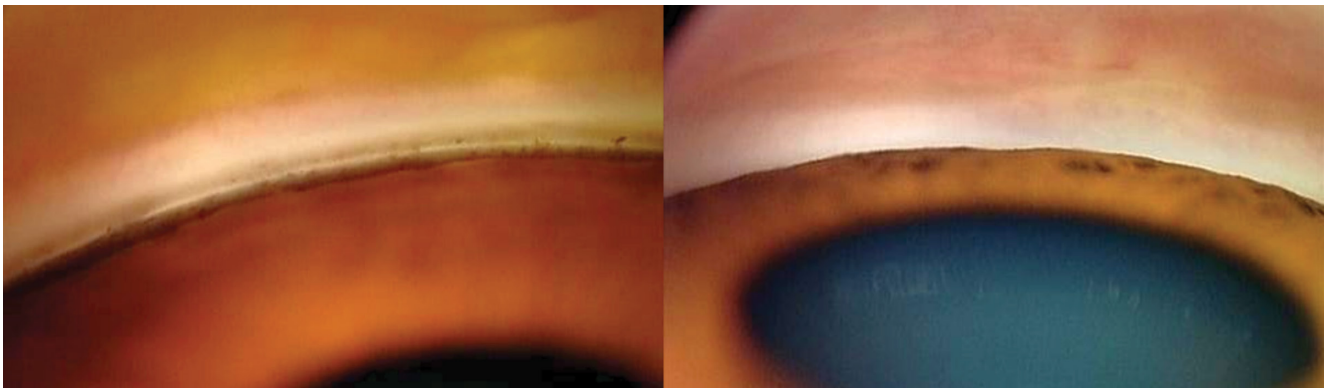

Figure 1. Gonioscopic view of the anterior chamber angle showing an open angle with visible pigmented trabecular meshwork (left) and closed angle with non-visible pigmented trabecular meshwork (right); *image courtesy of Benjamin Y. Xu, MD, PhD and Alanna James, MD.*

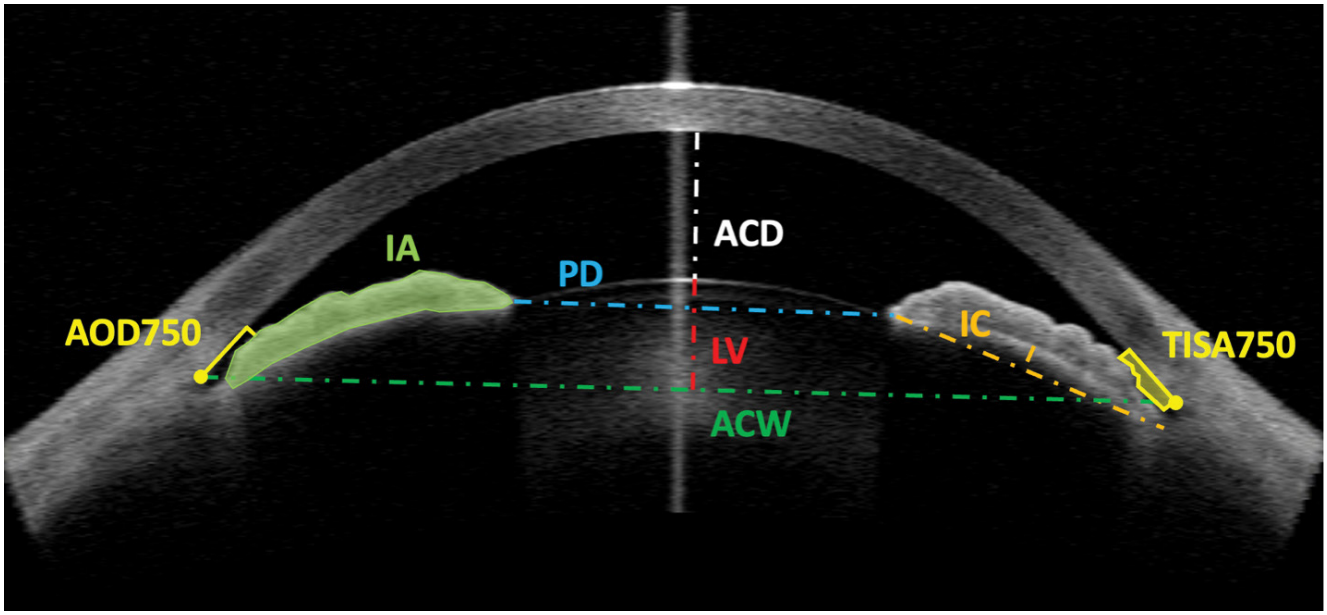

Figure 2. Representative anterior segment OCT (AS-OCT) image with ocular biometric parameters marked; *image courtesy of Benjamin Y. Xu, MD, PhD and Alanna James, MD.*
AOD: angle opening distance; **TISA:** trabecular iris space angle; **IA:** iris area; **PD:** pupillary diameter; **LV:** lens vault; **ACW:** anterior chamber width; **ACD:** anterior chamber depth; **IC**: iris curvature.

conducted in Guangzhou, China that enrolled 889 bilateral primary angle-closure suspects. Participants received an LPI in one eye and the contralateral eye served as a control. The primary outcome measure was progression to PAC, which was defined as an IOP greater than 24 mmHg, the formation of at least one clock hour of PAS, or an episode of acute angle closure crisis (AACC). The initial study, published in 2019, presented the six-year data.[10] A follow-up study reported the 14-year progression rates from the ZAP trial.[11] Overall, LPI significantly lowered the risk of progression (largely due to development of PAS), which was three times lower in treated versus control eyes (hazard ratio = 0.31) after 14 years. The risk of progression after 14 years was low (1.4% per eye year), although it was slightly higher than in the primary six-year ZAP trial analysis (0.8% per eye year). The ZAP trial authors recommended against wide-spread LPI for PACS

due to the low overall risk of progression to PAC in both the six- and 14-year studies. Although this overall risk is low, there are still patients who developed PAC, which is associated with higher risk for PACG and risk of severe vision loss.[9] Therefore, a system of risk stratification for PACS is crucial to identify patients who would benefit from earlier LPI or other interventions.

More recent work has focused on identifying high-risk cases of PACS. Using data from the six-year ZAP trial, Xu et al proposed a method of risk stratification for untreated PACS eyes using ocular biometric measurements.[12] AS-OCT and A-scan ultrasound data from 643 subjects were analyzed, of whom 609 were non-progressors and 34 were progressors. The authors found narrower angle width and flatter iris curvature measured by AS-OCT; older age at baseline were significant predictors of progression to PAC (**Figure 1**). Interestingly, a smaller cumulative gonioscopy score (a sum of gonioscopy grades from all four quadrants) was not associated with progression, which highlights the limitations of gonioscopy in risk stratifying untreated PACS eyes.

While significantly fewer PACS eyes that received LPI progressed to PAC in the ZAP trial, it remains important to identify treated eyes at higher risk that may benefit from closer monitoring. Therefore, Bao et al recently used gonioscopy and AS-OCT data from the ZAP trial to characterize the anatomic effects of LPI on PACS eyes and identify biometric risk factors for angle closure in treated PACS eyes.[13] The authors found only around a quarter of treated PACS eyes still fit the definition of PACS after LPI treatment. They also found that persistent PACS despite LPI and narrower angle width measured by AS-OCT were both predictive of progression to PAC.

One limitation of current discoveries in the field of angle closure is their reliance on measurements obtained by AS-OCT imaging, a technology that is not as widely available as other forms of testing used in the diagnosis and monitoring of glaucoma, such as visual fields and posterior segment OCT. However, AS-OCT technology is becoming more commonplace as it is incorporated into modern biometers for intraocular lens calculations. In addition, recent advances using artificial intelligence (AI) have automated the biometric measurement process in modern AS-OCT devices, such as the ANTERION OCT System (Heidelberg Engineering, Heidelberg, Germany). These AI algorithms approximate expert-level measurements of biometric parameters, making biometric analysis of AS-OCT images accurate and convenient.[14]

Recent advances in angle closure diagnosis and evaluation have been accompanied by similar advances in treatment paradigms. Treatment options for angle closure include LPI and lens extraction; and, in the setting of elevated IOP or glaucoma, other glaucoma procedures such as trabeculectomy and glaucoma drainage implants. The AAO Preferred Practice Pattern guidelines on PACD recommend medical treatment and LPI in the setting of APAC, but also note that pupillary block, which is alleviated by LPI, plays a role in most cases of chronic angle closure. These guidelines also mention that lens extraction could be considered in some patients with PAC and PACG prior to traditional glaucoma surgery.[5]

Several studies have shown that removal of the crystalline lens widens the anterior chamber angle in eyes with angle closure, which is often accompanied by a decrease in IOP.[15,16,17] However, while lens extraction is an obvious first-line treatment for angle closure eyes with visually significant cataracts, its role in eyes with clear lens or non-visually significant cataracts is less apparent. This topic was explored by the EAGLE trial, a landmark randomized, controlled trial published in 2016 in which participants with clear lenses (VA better than 20/40) and PAC with elevated IOP (>30 mmHg) or PACG were randomized to either clear lens extraction or LPI with topical medical treatment.

Participants who underwent clear lens extraction had significantly lower mean IOP (by 1.2 mmHg) and higher scores on quality-of-life questionnaires. Lens extraction was also found to be more cost effective. In addition, only one patient who had clear lens extraction had irreversible loss of vision in comparison to three patients who received standard care.[18] In a separate study comparing clear lens extraction to trabeculectomy in patients with PACG, lens extraction yielded a significant reduction in synechial angle closure, and increases in anterior chamber depth and angle width in eyes without visually significant cataracts.[19] While there is significant evidence to support earlier extraction of clear lenses in angle closure eyes, there are barriers in real-world clinical practice due to insurance coverage issues, loss of accommodation in younger patients, and patient aversion to surgery.

This recent data suggests it is reasonable to perform lens extraction for patients who have PAC or PACG. However, the data does not clarify

the role of clear lens extraction for patients with PACS. Given the data from the ZAP trial, we know there is a low risk of progression from PACS to PAC; therefore, the risks and costs of clear lens extraction may not be warranted. The AAO Preferred Practice Pattern guidelines note that LPI may be considered to reduce the risk of developing PAC; alternatively, patients may be provided with education and return precautions, and followed for progression to PAC. The guidelines also list factors that may motivate a provider to consider performing LPI over observation: medication usage that could provoke APAC, symptoms suggestive of intermittent APAC, difficulty accessing prompt eye care, history of poor compliance, or the need for frequent dilated eye exams.[5] While the risks of LPI are low, possible complications include corneal edema, posterior synechiae, visual disturbances, and elevated IOP.[20]

Conclusion

There has been an abundance of high-quality research conducted in the field of angle closure focused on establishing evidence-based detection, monitoring, and treatment guidelines. While gonioscopy remains the current clinical standard for evaluating angle closure eyes, AS-OCT is a promising tool for evaluating patients with angle closure, both prior to and following treatment. These advances will enhance clinicians' ability to utilize treatments that effectively alleviate angle closure, such as LPI and lens extraction. However, further longitudinal studies on angle closure in diverse, high-risk populations are needed to determine how frequently at-risk patients should be monitored, the benefits of earlier angle closure detection, and what additional objective data may be useful to deliver more precise care to patients at risk for PACG.

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Corneal Lumps and Bumps

Introduction

Patients present to the ophthalmologist with various corneal pathologies, and it is imperative to differentiate the benign from the malignant at the slit lamp to provide them proper guidance and treatment. These conditions tend to play a more significant role in the pre-operative cataract evaluation as they typically affect post-operative visual rehabilitation. In this review, we aim to examine the differentiating factors of the many lumps and bumps that affect the cornea and the available ways for surgeons to treat them in Canada.

Pterygium

Pterygium is one of the most common degenerations of the bulbar conjunctiva that invades the cornea causing astigmatism and ocular surface inflammation.[1-3] Its prevalence is higher in certain populations with excessive long-term exposure to ultraviolet light such as outdoor workers, but its exact pathogenesis and underlying causes are not completely understood.[1]

Clinical Features

While most pterygia are asymptomatic and only cause cosmetic concern, some may lead to refractive changes when impinging on the visual axis and cause significant visual disturbances. Others may cause surface inflammation and irritation decreasing quality of life (QOL).[1-3] Pterygium is generally associated with an increased prevalence of dry eye.[2]

Diagnosis

Slit lamp examination: Triangular or wing-shaped fibrovascular connective tissue overgrowth of the bulbar conjunctiva and invading the cornea. It can be associated with subepithelial corneal scarring but usually does not involve any thinning of the limbus and cornea.[1-3]

Corneal topography: The degree of flattening of the curvature along the axis of the lesion is directly dependent on the size of the pterygium and is related to the induced refractive astigmatism.[4,5] Pterygia invading the limbus for more than 1.5mm–2mm in length tend to cause refractive disturbance.[5]

Management

Management is usually divided into **1)** Medical management of any associated ocular inflammation and associated refractive error; **2)** Surgical management of growing ocular surface lesion.[2,3,6] Within the conservative approach in patients who have a stable pterygium, UV protection plays a major role, as well as modifying dry eyes risk factors with heavy lubrication and associated anti-inflammatory topical medications as needed.[2,3] Mitigating these factors not only helps improve QOL for those patients but also prevents growth of the lesion overtime.

Surgical Management, on the other hand, is reserved for patients who exhibit any one of the following features:

- Growth over time of the pterygium toward the visual axis
- Decrease in vision secondary to induced astigmatism
- Cosmetically bothersome lesion
- Pre-operatively for any refractive surface or intraocular surgery especially cataract surgery
- Ocular discomfort and conjunctival inflammation[3,6-8]

Multiple surgical techniques have been employed to manage pterygium excision. The current consensus is to avoid any technique that leaves the sclera bare as the recurrence rate induced by post-operative inflammation is quite elevated.[3,7] Advancing conjunctival tissue over bare sclera is preferred and can be accomplished using multiple techniques that vary depending on the lesion's size, tissue availability and surgeon preferences.[6–9]

Conjunctival autografting tends to be the gold standard procedure with better cosmetic results and lower recurrence rates.[3,7] Amniotic membrane grafting is also a valid approach for larger scleral bed defects and can help preserve the natural superior conjunctiva.[3,6,7] Clinical studies have studied the use of fibrin glues versus suturing techniques to approximate conjunctival

tissues. Fibrin sealants show decreased postoperative inflammation compared to sutures with less associated risks of recurrence.[3,7] **Table 1** summarizes the recurrence rates associated with each technique.

Pterygium excision techniques	Recurrence rate
Bare Sclera Technique	38%–88%
Primary Closure	40%–70%
Conjunctival Autograft	5%–20%
Conjunctival Autograft with fibrin sealant	0%–10%
Amniotic Membrane Grafting	14%–27%

Table 1. Pterygium recurrence rates depending on the surgical technique used for reconstruction of ocular surface.[3,7]

Complications of Pterygium Surgery

Recurrence remains the most challenging component of pterygium surgery and is related to increased surface inflammation. Most recurrences occur 3–6 months after surgery. Risk factors for recurrence include demographic factors such as continuous UV exposure; dry eyes and ocular surface inflammation; older age; and darker skin pigmentation.[7,10] They also include surgical factors such as use of conjunctival sutures, retained Tenon's layer over scleral bed.

Peri-operative adjuvant management aims to decrease rates of recurrence.[3,6,9] Using post-operative anti-inflammatory management (topical corticosteroids or cyclosporine) for a -3 to 6-month period is important in decreasing rates of inflammation. Intraoperative use of anti-fibroblastic agents such as Mitomycin C (MMC) 0.02% for 1–3 minutes can help inhibit the proliferation of fibroblasts. Clinical studies have demonstrated its efficacy even in primary pterygium cases.[9,10] Other adjuvant treatments with less proven efficacy than MMC include the use of perioperative 5-Fluorouracil (5-FU) to decrease progression of disease or sub-conjunctival injections of monoclonal antibodies against vascular endothelial growth factors (anti-VEGF).[6,7]

Ocular Surface Squamous Neoplasia (OSSN)

Ocular Surface Squamous Neoplasia (OSSN) is on the differential of many conjunctival and corneal lesions occurring on the surface. Although OSSN is rare, it is a slowly progressive disease ranging from pre-malignant to malignant epithelial cells and leads to ocular surface damage. The incidence of OSSN is reported as 0.1–35 cases/1,000,000 people.[11] OSSN can start as a corneal and conjunctival intraepithelial neoplasia (CIN) and lead to squamous cell carcinoma (SCC) when it invades the basement membrane.[12]

Clinical features

Risk factors associated with OSSN progression include UV light exposure, history of human papilloma virus (HPV); human immunodeficiency virus (HIV) infection; smoking us; and history of OSSN or skin cancers.[12,13]

Alarming features raising suspicion for malignancy transformation are the lesion's appearance (gelatinous, leukoplakic, papilliform, presence of pigmentation), its location (tarsal, forniceal or caruncular lesions being more suspicious) and its multifocality.[13,14]

Diagnosis

Slit lamp examination: The above clinical features are associated with higher risks of conjunctival intraepithelial neoplasia (CIN) and malignancy transformation especially when they occur unilaterally. The presence of feeder vessels around the lesions is also another factor to keep in mind. Positive staining with Rose Bengal stain on exam is a clinical tool that helps differentiate these lesions. Leukoplakic adherent white-gray corneal lesions can also be characteristic of squamous cell disease.[14]

Anterior Segment Optical Coherence Tomography (AS-OCT): This imaging technique shows characteristic hyperreflectivity and thickened epithelium with an abrupt transition from normal to abnormal tissue (**Figure 1**) which help to differentiate it from other conjunctival lesions such as pterygium.[15]

Management

In current practice, the gold standard for diagnosis of OSSN is histopathologic specimen by incisional or excisional biopsy. AS-OCT has the potential to provide a non-invasive evaluation of the conjunctiva and cornea with high axial

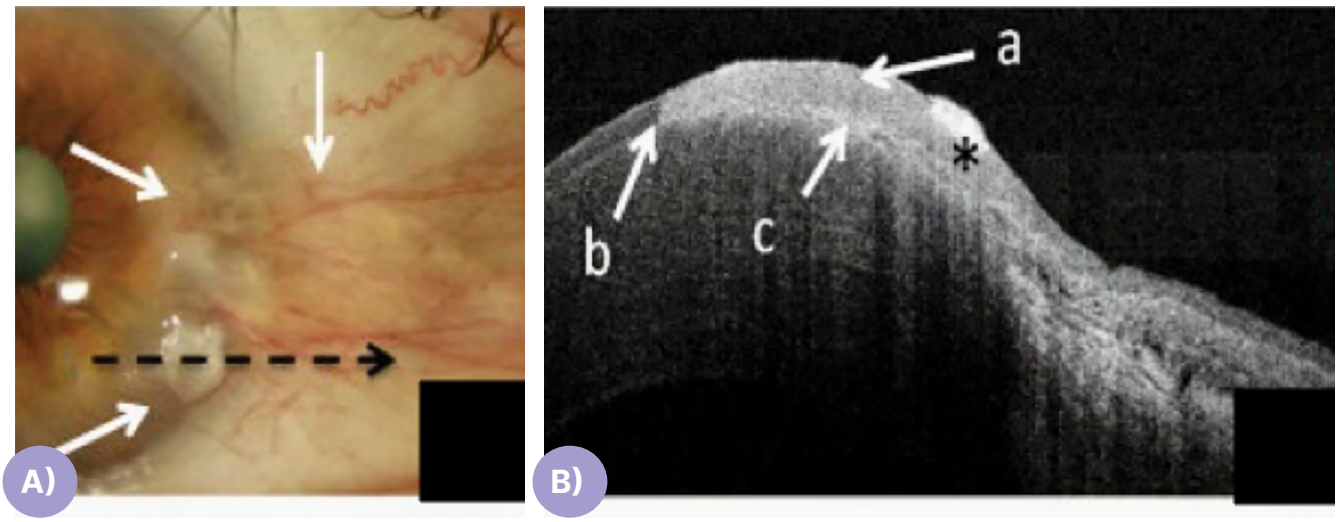

Figure 1. A) slit-lamp photo demonstrating gelatinous, leukoplakic, and papillary OSSN, respectively (white arrows). The black dotted arrows represent the direction and location of the AS-OCT taken.
B) AS-OCT shows a thickened hyperreflective epithelium (arrow a). Note the abrupt transition between abnormal and normal epithelium (arrow b). A plane of cleavage between the lesion and the underlying tissue is also noted (arrow c); *adapted from Kieval et al.*[15]

	Concentration	Dosing	Endpoint
Interferon alpha-2-b (IFN)	1 MIU/mL	1 drop every 6 hours	4–6 months or until clinical resolution of lesions
Mitomycin C (MMC)	0.4 mg/mL	1 drop 4 times daily for 1 week and drug holiday for 1 week	Until clinical resolution of lesions, or failure to respond within 2 months
5-Fluorouracil (5FU)	1%	1 drop 4 times daily for 1 week and drug holiday for 3 weeks	Until clinical resolution of lesions, or failure to respond within 2 months

Table 2. Various topical pharmacotherapies available for primary treatment of OSSN or adjuvant therapy in patients with margin positive disease.
Abbreviations: MIU/mL: Million International Unit per microlitre, **Mg/mL:** milligrams per microlitre.[11,16]

tissue resolution and allows examination of the morphological and histological features of tissues.

If diagnosis is established clinically, treatment can include topical pharmacotherapy alone or surgical excision. In a recent meta-analysis, there was no difference in tumor recurrence rates between proceeding with primary pharmacotherapy and surgery.[11] **Table 2** outlines the topical treatments available with their adopted dosing.[11,16] While Interferon alpha-2-b (IFN) is the most tolerated treatment in terms of side effects profile, its worldwide shortage is causing a significant shift in treatment protocols toward 5-fluorouracil (5FU) management. In a recent review, 5FU was shown to be a good substitute for IFN treatment.[14] Mitoymycin C (MMC) is usually reserved as management of last resort due to its high ocular surface toxicity and side effects.[11]

OSSN is routinely removed surgically using a no-touch technique removing 4 mm to 5 mm margins, with alcohol epitheliectomy of the cornea. Cryotherapy and topical chemotherapy applied to the conjunctival margins is important to clean out the area before conjunctival reconstruction.[17]

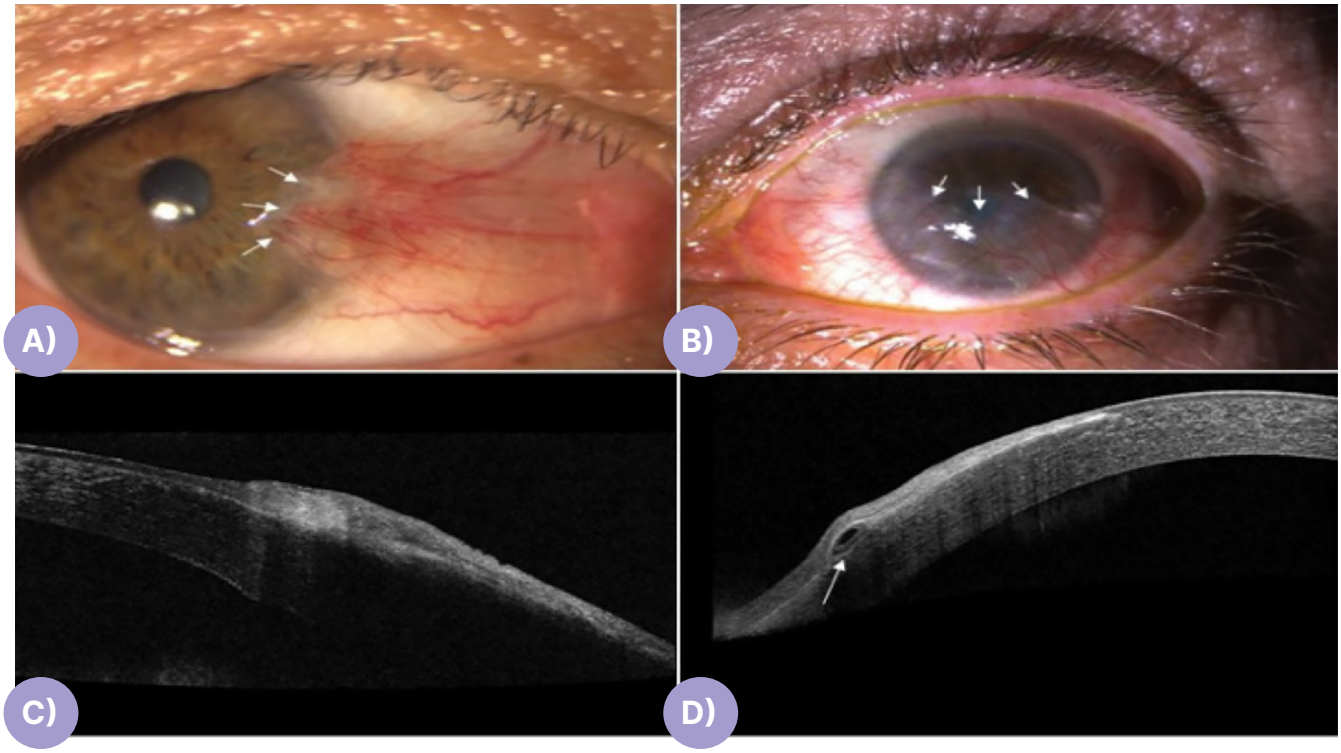

Figure 2. Clinical features of pterygium and pseudo-pterygium. **A)** Pterygium in slit-lamp (arrow); **B)** pseudo-pterygium in slit-lamp (arrow); **C)** AS-OCT of pterygium with no epithelial cleavage plane. **D)** AS-OCT of pseudo-pterygium with well- demarcated normal epithelial cleavage plane and membrane overgrowing cornea (arrow); *adapted from Urbinati et al.*[18]

Pseudo-Pterygium

Pseudo-pterygium is a secondary pathology related to damage that occurs to the limbal epithelium. It is characterized by conjunctival adhesion to the peripheral cornea in areas of limbal stem cell deficiency and can occur in any quadrant.[18,19]

Etiology

Etiologies leading to pseudo-pterygium formation include:

- Eye trauma
- Corneal degenerations such as marginal Terrien's degeneration
- Corneal burns (thermal, chemical or gas)
- Iatrogenic limbus pathology due to ocular surgery
- Chronic inflammation due to infections, ocular cicatricial pemphigoid or rosacea[18]

Diagnosis

Slit lamp examination: Reveals a fibrovascular growth of the conjunctiva over areas of limbal cell deficiencies. The lesions typically are associated with concurrent corneal thinning, and ocular surface inflammation and scarring. They can occur anywhere around the cornea.[18,19]

AS-OCT: Lesions show an overgrowing membrane over an intact corneal epithelium in pseudo-pterygium. A clean cleavage plane is a characteristic feature differentiating it from a pterygium that can invade a thickened corneal epithelium (**Figure 2**).[18,19]

Management

Management includes primarily treating the underlying condition causing the limbal stem cell deficiency before any surgical intervention is advised. Medical management includes ocular surface optimization and chronic topical immunomodulatory agents. Surgery is reserved for patients who have visual disturbance related to the ocular scarring and can include lysis of the adhesions, excision of the scarred conjunctival

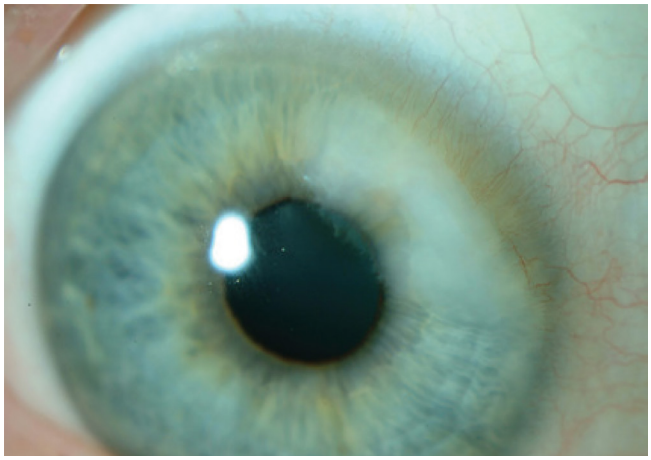

Figure 3. Slit lamp photography of elevated grayish opacification in the perilimbal area with associated increased vascularization characteristic of PHSCD; *adapted from Jarventausta et al.*[24]

tissue, and coverage of the defect through a free conjunctival graft or amniotic membrane.[18]

Nodular and Subepithelial Degeneration

Salzmann's nodular degeneration (SND) is a rare, non-inflammatory condition that affects the corneal epithelium. It is characterized by mid-peripheral nodularity anterior to Bowman's layer of the cornea.[20-22] Typically, these nodules are bilateral and are more prevalent in female patients (72%) and in older age groups.[20-22] Histologically, SND is a dense hyalinization occurring between the epithelium and Bowman's layer and occurs with thinning of the overlying epithelium and late disruption of Bowman's layer with duplication of membranes.[21,22] Most patients are asymptomatic, although some may present with significant ocular surface irritation and foreign body sensation.

A variant of this condition is called peripheral hypertrophic subepithelial corneal degeneration (PHSCD). These patients have bilateral, symmetrical, perilimbal, hypertrophic, subepithelial corneal opacification that is always associated with limbal neovessels (**Figure 3**).[23,24]

Etiology

The exact cause SND and PHSCD is not well understood, but risk factors associated with ocular surface inflammatory conditions such as dry eye, chronic blepharitis, previous interstitial keratitis, meibomian gland dysfunction have been established. Long term contact lens wear, trauma and previous ocular surgeries have also been associated with SND.[21,22,25]

Diagnosis of Nodular Degenerations

Slit lamp examination: Nodules appear as bluish-white subepithelial elevations that may occasionally stain with fluorescein. They typically range from 2mm–4mm in size. The nodules may appear in any part of the cornea, and their location depends on the underlying risk factor. Some cases have been reported with circumferential peripheral corneal involvement.[20-22]

Corneal Topography: Peripherally located nodules can cause flattening of the central cornea and a hyperopic change. Irregular astigmatism can also be seen with multifocal nodularity.

AS-OCT: This imaging technique shows bright, hyperreflective, subepithelial deposits above the Bowman layer. The epithelium overlying those lesions is thinned out, and the demarcation of the Bowman's layer can be lost in more severe disease (**Figure 4**).[20-22]

Management

Medical management is applicable in most cases with aggressive ocular surface treatments including lubrication and meibomian gland dysfunction therapy. Long-term topical immunomodulation with cyclosporine and/or lifitegrast might be indicated to decrease the risks of disease progression and symptoms.[20-22] In more severe cases with associated vision loss surgery is an option. Restoring the proper anatomy of the cornea has been shown to improve corneal curvature and hence visual outcomes.[26] Procedures can vary from manual superficial keratectomy (SK) to excimer laser assisted phototherapeutic keratectomy (PTK). With SK, the epithelium overlying the lesion is denuded using alcohol 20% or flat blades; the lesion is peeled off using forceps.[22,27] In PTK surgery, excimer laser is applied on top of SK to deal with corneal haze (25–75 micrometers can be ablated with or without masking within the central 6 mm of the cornea).[26] PTK has been shown to improve lines of vision and decrease recurrence rates of these lesions (22% recurrence rate with SK versus 3.8% with PTK). Adjuvant MMC 0.02% applied intra-operatively has been shown to reduce recurrence of SND.[22,26,28]

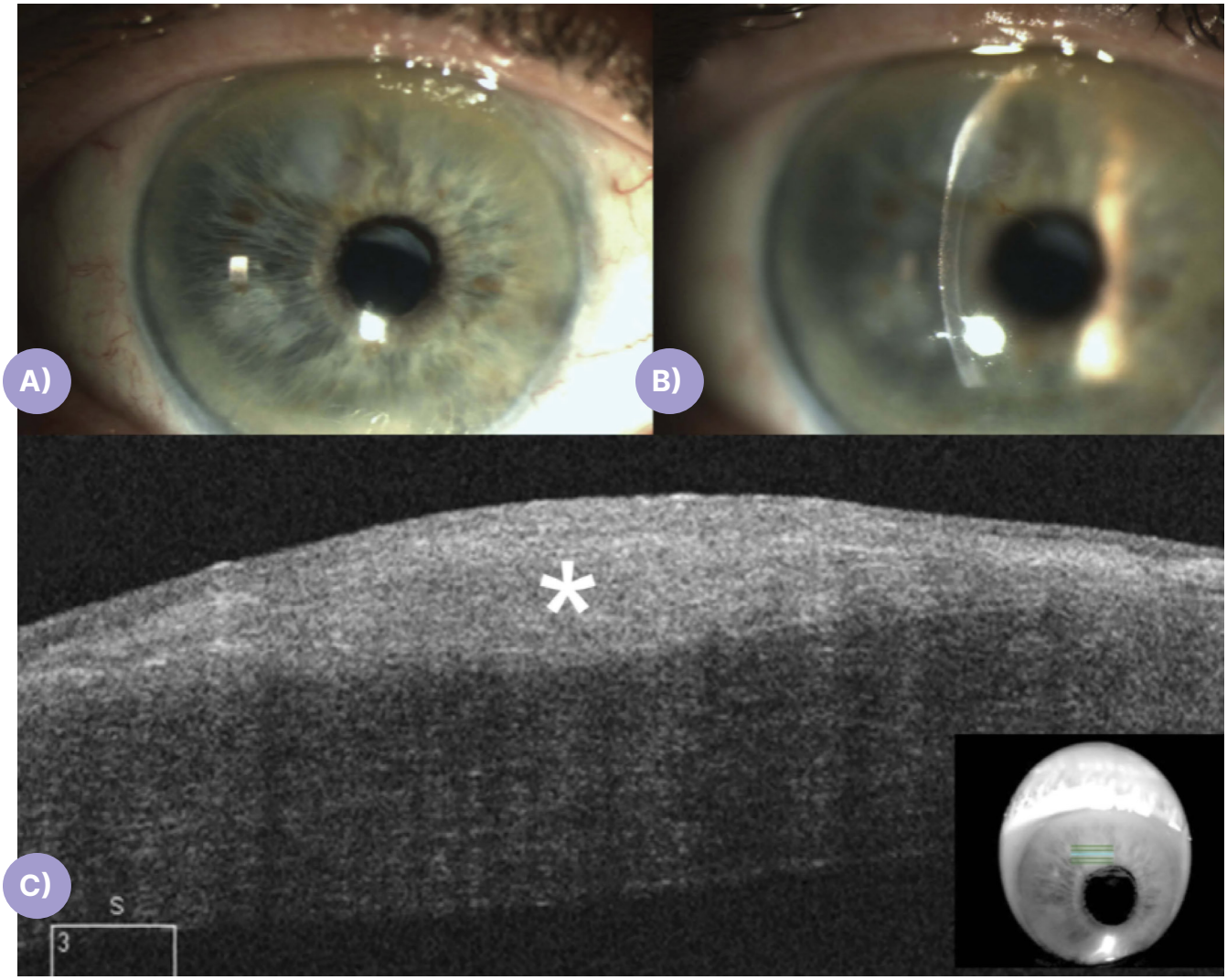

Figure 4. A) Slit lamp photography of SND at 11 o'clock in mid-peripheral cornea demonstrating elevated grayish opacity. **B)** Slit beam image showing hyperreflective subepithelial lesion. **C)** AS-OCT demonstrating subepithelial lesion (Asterisks) with thinning of overlying epithelium and poorly demarcated Bowman's layer; *image adapted from Paranjpe et al.*[22]

Visual Rehabilitation with Corneal Lumps and Bumps

As most of these lesions not only affect corneal curvature but also cause significant corneal haze and opacities, they are usually associated with disruption in visual acuity and visual potential. The more centrally involved the lesion is, the greater the effect on the vision. For lesions causing astigmatism changes such as SND and pterygia/pseudo-pterygia, visual rehabilitation includes excision of lesions followed by spectacle or contact lens correction of astigmatism.[5,7,29] Typically, corneal curvature stabilizes 3–6 months after surgery allowing for changes in refractive error to stabilize. In patients with associated visually significant cataract, it is advised to delay surgical assessment of keratometry and biometry for 3–6 months after surface procedures have been performed for optimal outcomes.[4,5,29] For corneal scarring related to these lesions, visual potential might be improved with using rigid or scleral contact lenses. In rare cases where a patient's visual acuity is not improved with conservative measures, therapeutic lamellar keratoplasty might play a role in improving outcomes.[22]

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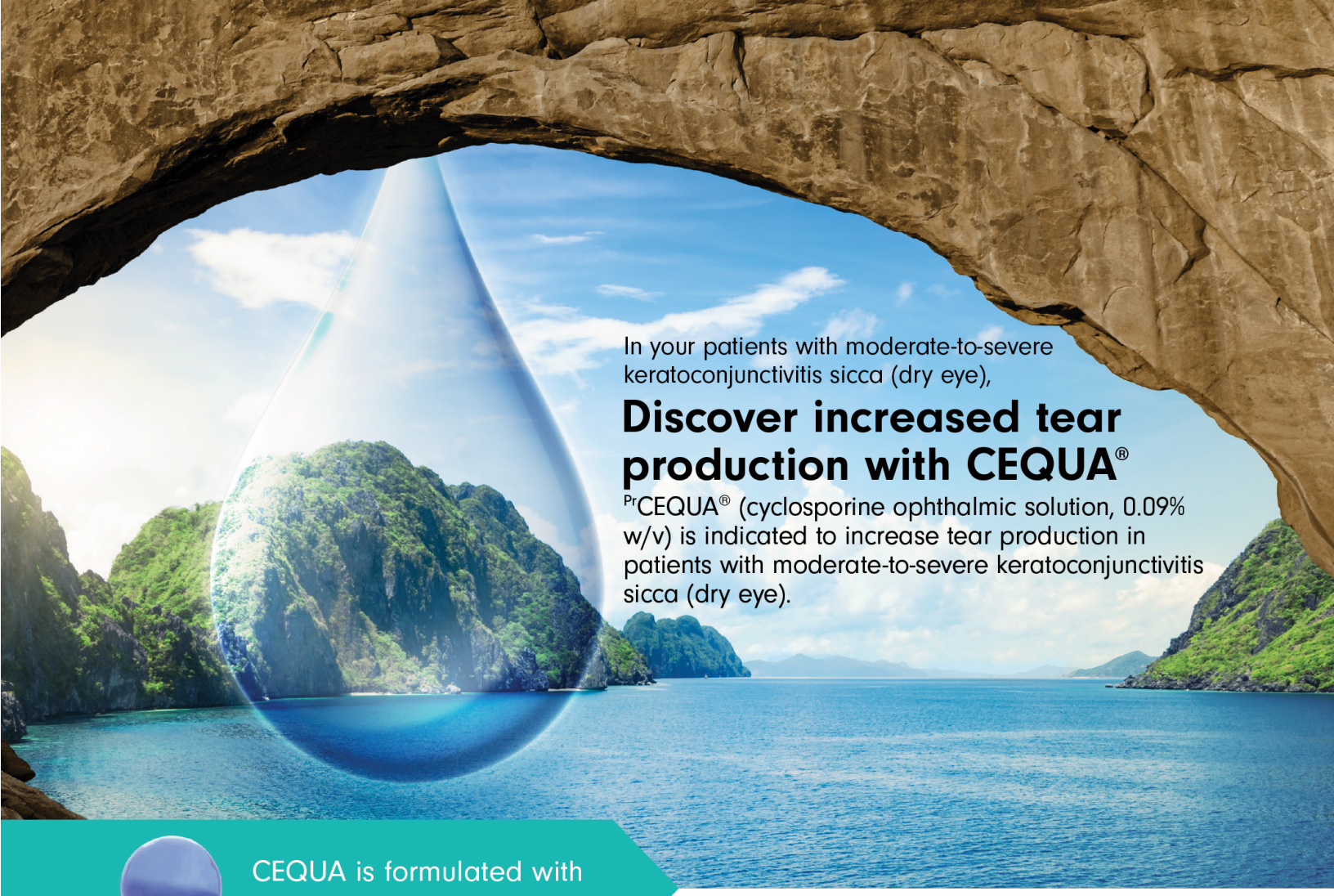

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Retinal Artery Occlusion and Neurovascular Risk

Introduction

An occlusion of the central retinal artery (CRA) or one of its branches can lead to severe acute vision loss. Patients rarely recover functional visual acuity (VA) in the affected eye, however good visual recovery can occur in transient retinal artery occlusion (RAO). Several treatment strategies have been described in the acute setting of a retinal artery occlusion (RAO). However, to date, no evidence- based treatments exist for this condition.[1] Recently, several clinical studies have emphasized the higher risk of stroke and cardiovascular events (CVE) in patients with RAOs.[2] As a result, urgent assessment of neurovascular risk factors in the context of an acute RAO is widely recommended.[2]

Definition

RAO refers to disruption of blood flow to the inner retinal layers leading to ischemia. RAO is further classified as a central retinal artery occlusion (CRAO) or a branch retinal artery occlusion (BRAO), based on the size and location of the retinal artery involved.

The definition of a stroke by the American Stroke Association is “brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury”.[3] While, retinal tissue and brain tissue are morphologically distinct, and tolerate acute ischemia differently, RAO is recognized as a type stroke by several professional bodies.[4,5]

Epidemiology and Risk Factors

The incidence of RAO is 1–2 per 100 000, and rises to 10 per 100,000 over the age of 80. Men have a slightly higher incidence than women.[5] The incidence of asymptomatic branch retinal emboli is far higher, and has been reported as 2.9% in patients aged 50 and over.[6]

RAO is associated with a myriad of vascular risk factors. There is a high prevalence of obesity, hypertension, tobacco use, hypercholesterolemia, and diabetes in CRAO patients.[5] In 30%–40% of cases, CRAO is associated with ipsilateral

internal carotid artery stenosis of greater than 70%.[7] The heart, aortic arch and great vessel can also cause emboli that block the central retinal artery or one of its branches.[5] Atrial fibrillation (AF) is more common in CRAO patients, when compared to age- and sex-matched controls. Furthermore, RAO patients with AF are more likely to have a recurrent stroke.[2] Therefore, promptly investigating RAO patients for vascular risk factors is of utmost importance.

RAO can also be due to other causes, such as an inflammatory process, an iatrogenic cause, an infectious etiology, or a hematologic disorder. While discussion of all possible etiologies of an RAO is beyond the scope of this article, giant cell arteritis (GCA)-associated CRAO should be suspected in patients over age 50, with systemic findings such as jaw claudication, polymyalgia rheumatica, diffuse posterior neck pain, scalp tenderness, new-onset headache, or elevated inflammatory markers.[5] In 1.6% of cases, CRAO was the cause of permanent visual loss in a large cohort of biopsy-proven GCA patients.[8]

Pathophysiology

The inner retina is supplied by the CRA, a branch of the ophthalmic artery, while the outer retina is supplied by the posterior ciliary circulation. Experimental studies have shown that 60 minutes of CRA blockage produces no permanent ischemic damage; however, greater than four hours of CRA blockage produces permanent irreversible ischemic retinal damage.[4] Thus, duration of CRA blockage is an important determinant of visual outcome. Up to 20%–30% of patients have a cilioretinal artery, which originates from the posterior ciliary circulation and often supplies the fovea.[5] In such cases, a CRAO patient may present with normal VA, but a severely affected visual field.

Diagnosis

RAO is associated with sudden painless monocular vision loss. Funduscopic examination will typically show retinal whitening in the area of occlusion. In a CRAO, A cherry red spot may be visible due to the preserved choroidal circulation subfoveally, surrounded by a pale ischemic retina. In an RAO, retinal emboli and segmental blood flow through attenuated retinal arteries may also be observed. Pallid optic nerve swelling accompanying an RAO should raise suspicion for an arteritic cause (GCA). Imaging modalities such as optical coherence tomography (OCT), OCT angiography and fluorescein angiography (FA) can help identify an RAO. In an acute RAO, OCT can rapidly show thickening and irregularity of the inner layers. FA can show delayed or absent retinal perfusion; however, this imaging modality is not required to establish a definitive diagnosis.[5]

Natural History

CRAO is associated with a poor visual prognosis. Over three-quarters of patients have a VA of counting fingers or worse.[5] Approximately 18% of patients spontaneously recover VA of 20/200 or better. Colour vision, visual field and stereoacuity are also severely affected in CRAO patients. BRAO has a better visual prognosis, given that a limited area of the retina is affected.

Treatment

Patients with a suspected RAO should be sent to the nearest hospital Emergency Department (ER) for acute stroke work-up.[9]

Over the decades, numerous treatments have been attempted to restore perfusion and/or reverse retinal cell death in RAO patients.[1] Conservative approaches to improve VA in RAO include digital massage, topical IOP lowering drops, anterior segment paracentesis, carbogen inhalation, and hyperbaric oxygen therapy. To date, there is insufficient evidence to demonstrate that conservative treatment produces a better prognosis compared to the natural history of acute artery occlusions.[1]

More aggressive treatments for RAO include Nd:YAG laser embolysis and thrombolytic therapy. Non- controlled clinical studies have shown VA improvement after 24 hours with translumenal Nd:YAG laser embolysis to selectively fragment and dislodge the intravascular embolus.[1] However, these approaches have significant risks such as vitreous hemorrhage and subretinal hemorrhage. A meta-analysis of observational studies has shown a functional benefit from treatment with intravenous thrombolysis within a 4.5-hour window of CRAO onset.[1] However, serious adverse events such as intracranial hemorrhage have been reported in clinical trials evaluating intravenous thrombolysis within 20 hours of visual loss.[1] The impact of early (within 4.5hrs) intravenous thrombolysis in acute CRAO is currently being evaluated in a few prospective randomized clinical

trials in Europe. The results of these trials will help further clarify the role of intravenous thrombolysis in the management of an acute CRAO.[10,11] Intra-arterial thrombolysis via supraselective microcatheterization of the ophthalmic artery was evaluated in the EAGLE study within 24 hours of symptom onset. The rationale of this modality was to reduce systemic risk by delivering the thrombolytic drug closer to the site of occlusion. The study was prematurely stopped due to adverse events.[12] A 2023 Cochrane Review on interventions for acute non-arteritic CRAO determined that there is insufficient evidence to support the above-mentioned interventions.[1]

Secondary Prevention

For RAO patients, the objective is to prevent further vascular events. The evidence for stroke after ischemic retinal events has been steadily increasing over the last decade.[7] A U.S. study using 2013 National Medicare datasets found a 28-fold and 33-fold increased incidence of ischemic stroke in the first and second weeks following a CRAO respectively.[13] A population-based study from Taiwan found a 2.7 times higher rate of stroke within the first three years of a CRAO compared with matched controls, and the incidence was highest within the first month.[14] A Korean study reported a 70-fold increase in ischemic stroke within the first week after a CRAO.[15] In patients with acute RAO, urgent referral to the hospital ER expedites work-up, identifies high-risk patients, and facilitates early preventive treatment to reduce the risk of stroke and CVEs.[1]

Neuroimaging does not aid in the diagnosis of an acute RAO; however, it may reveal concomitant cerebral ischemia and help guide secondary prevention strategies. One study of a CRAO cohort from a tertiary care centre demonstrated radiologic evidence of stroke in 37.3% of patients.[16]

High-grade carotid artery stenosis should be identified promptly with computed tomography/magnetic resonance angiography or carotid ultrasound, and treated as symptomatic carotid stenosis. Treatment includes surgical revascularization or medical therapy, depending on the patient's surgical risk profile.[7] Secondary prevention in RAO often includes initiation of antiplatelet therapy.[2]

Further evaluation for a nidus of embolic disease in RAO includes echocardiography to identify a structural cardiac lesion and cardiac rhythm monitoring to identify AF.[2] If AF is discovered, oral anticoagulation is often recommended to prevent a stroke.[2]

RAO management requires a multidisciplinary approach involving neurology, ophthalmology and internal medicine, to control modifiable risk factors and monitor for complications.

Future Directions

Improving visual outcomes in acute RAO and reducing future vascular events remain important unmet needs. Given its relatively low incidence, robust randomized clinical trials at earlier time points are challenging to execute. Development of local networks between primary care physicians, optometrists, ophthalmologists and neurologists with stroke expertise should expedite care and facilitate recruitment for clinical trials evaluating potential treatments for acute RAO.

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Approach to Infectious Keratitis: Clinical Pearls While on Call

Introduction

Microbial keratitis is a vision-threatening infection of the cornea and an important cause of ocular morbidity that can result in blindness. It is estimated that over 1.5 million people worldwide will develop blindness from infectious corneal ulceration each year. If left untreated or treated incorrectly, it can result in progressive tissue destruction with corneal perforation or extension of the infection to the adjacent tissue. Outcomes of these patients depend on timely diagnosis and treatment with close follow-up.[1,2]

Epidemiology in Canada

An understanding of the most common pathogens and antibiotic sensitivity in various geographical areas is essential in guiding the clinical diagnosis and empirical treatment.

In a study conducted at our centre from 2006 to 2011, the microbiology of infectious corneal ulcers at tertiary centres in Vancouver, British Columbia was reviewed.[3] In 281 corneal scrapings, the positive culture recovery rate was 75%, with 27% being polymicrobial. Overall, bacterial keratitis accounted for 84.8% of culture-positive ulcers, followed by fungal (10%) and Acanthamoeba (5.2%).

The most frequent cultured organism was coagulase-negative Staphylococcus (CoNS) and thus it was also the most common gram-positive bacterium. The most common gram-negative bacteria were Moraxella species. Over time, an increase in gram-negative bacteria vs gram-positive bacteria was noted. In non-contact lens-related polymicrobial ulcers, 100% of the infections involved gram-positive bacteria, 27.7% gram-negative bacteria, and 4.3% fungi. Contact lens-related polymicrobial ulcers showed 72.7% gram-positive involvement, 9.1% gram-negative, 9.1% fungal and 9.1% Acanthamoeba.

In a 20-year retrospective case series of fungal keratitis in Toronto, Candida species accounted for 60.8% of positive fungal cultures, followed by Filamentous species at 35.3%.[4] Similar

Bacteria	Fungi	Acanthamoeba
• Contact lens use*	• Trauma with vegetative material*	• Contact lens use*
• Trauma	• Contact lens wear	• Exposure to potentially contaminated fresh water
• Contaminated ocular medications	• Corticosteroid use	
• Ocular surface disease	• Ocular surface disease	
• Previous ocular surgery	• Previous ocular surgery	
• Atypical mycobacteria: LASIK	• Systemic immunosuppression	

Table 1. Risk factors for infectious keratitis.
*Most common risk factors

results were observed in Vancouver, where 62.5% of culture-positive fungal keratitis were attributed to Candida.[5]

In other series from our institution, the most commonly isolated microorganisms in pediatric patients were Staphylococcus epidermidis and Acanthamoeba. Acanthamoeba was isolated in 67% of contact lens-related corneal ulcers, while the remaining 33% of contact lens-related corneal ulcers were associated with Pseudomonas aeruginosa.[6]

Bacteria are the most common cause of infectious keratitis in the adult Canadian population, with CoNS as the most common isolate. The prevalence of fungal keratitis and Acanthamoeba is significantly lower, although the incidence of fungal keratitis in Canada has been increasing in the last 20 years.[5]

Risk Factors

The main predisposing risk factor for the development of infectious corneal ulcers in Canada is contact lens use. In our previous study, contact lens-related ulcers were caused primarily by bacteria (67.4%), followed by parasites (20.9%) and fungi (11.6%). Furthermore, more than 80% of Acanthamoeba cases were contact lens-related.[3]

Several clinical studies have evaluated the specific risk factors for each type of infectious keratitis. For example, bacterial keratitis has been frequently associated with contact lens wear. Contact lens use has also been recognized as an emerging risk factor for fungal keratitis. In a 20-year retrospective multicentre study across Canada, patients with yeast keratitis had more ocular surface disease than those with filamentous keratitis (79% vs 28%) and were more likely to manipulate their bandage contact lenses (36% vs 6%), while patients with filamentous keratitis wore more refractive contact lenses (78% vs 19%).[7]

In children, the major predisposing factors are contact lens wear and pre-existing ocular surface conditions including blepharitis and Stevens-Johnson syndrome.[6]

Table 1 summarizes the main risk factors associated with bacterial, fungal and Acanthamoeba keratitis.

Clinical Presentation

The clinical appearance of infectious keratitis is not a reliable indicator of the causative pathogen, but can help differentiate bacterial from fungal or amoebic keratitis.

Bacterial corneal ulcers typically present as a single superficial, suppurative infiltrate associated with an epithelial defect (**Figure 1A**). An endothelial inflammatory plaque, marked anterior chamber reaction and hypopyon can be present in bacterial keratitis and are more common in gram-negative bacteria.

Fungal keratitis has a chronic or indolent clinical course, and tends to present with less dramatic signs and symptoms of an inflammatory

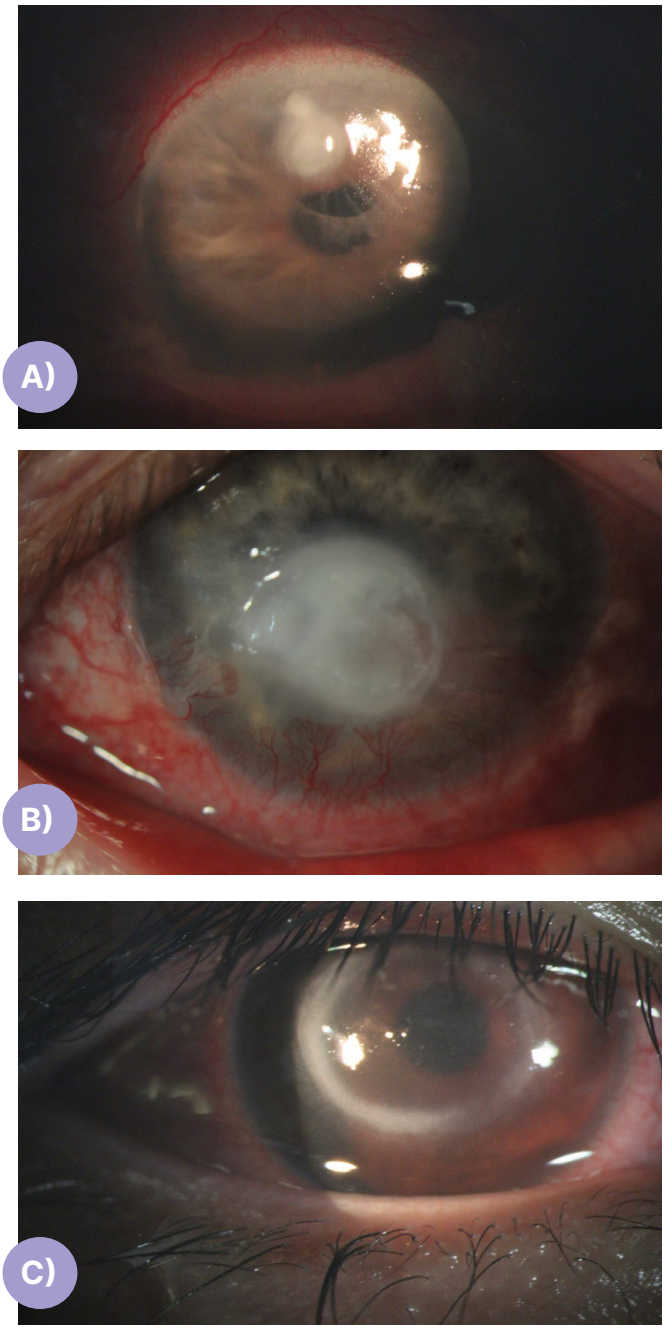

Figure 1. A) Single suppurative infiltrate with epithelial defect and mild anterior chamber reaction, suggestive of a bacterial ulcer.
B) Fungal gray-white infiltrate with irregular feathery margin in a patient with a trauma to the cornea with vegetative material. **C)** Acanthamoeba keratitis presenting with severe ocular pain, no response to topical antibiotics and a central ring infiltrate; *image courtesy of Sonia N. Yeung, MD, Alfonso Iovieno, MD, Barbara Burgos-Blasco, MD.*

response compared to infections of bacterial origin. It classically manifests as gray-white, non-suppurative multifocal or satellite infiltrates with irregular feathery or filamentous margins and a dry texture (**Figure 1B**). In the course of the disease, stromal infiltration without epithelial defect may present, as well as an endothelial plaque or hypopyon, particularly if the fungal infiltrate is deep-seated or large.[2]

Acanthamoeba keratitis typically presents with severe ocular pain that is greater than expected from clinical findings, as well as photophobia, a progressive course and no response to standard topical antimicrobial agents. Slit-lamp examination shows a spectrum of findings ranging from mild epitheliopathy to subepithelial opacities, pseudo-dendritic lesions and radial perineuritis (considered a quasi-pathognomonic sign) to a partial or complete central ring infiltrate (**Figure 1C**).[8,9]

Culture of Corneal Scrapes

Microbial culture of corneal scrapings remains the standard of care for the diagnosis of infectious keratitis. Culture positivity is significantly higher before antibiotic treatment is initiated; therefore, it should be considered the first diagnostic step. It may also be helpful to culture the contact lenses, contact lens cases and solutions if available.

According to the American Academy of Ophthalmology guidelines, specimens for culture should be obtained in the following cases: central infiltrate; large infiltrate; significant stromal involvement; corneal melting; previous corneal surgery; multiple sites of corneal infiltration; perforation; unresponsive to broad-spectrum antibiotic therapy; or atypical clinical features suggestive of fungal, amoebic or mycobacterial keratitis.[10]

Multiple corneal samples for culture on various growth media are typically used. However, this may not always be accessible to all eye care specialists, as most culture media require refrigeration and have a short shelf life. An alternative to common culture media is the ESwab (Copan Diagnostics, Inc, Murrieta, California), a nylon-tipped swab placed in 1 mL of modified Amies medium. It maintains bacterial sample viability for 48 hours. The shelf life of this swab at room temperature is 18 months. The ESwab has been validated for microbiological use, culture results being comparable to the multi-sample method.[11]

Initial Treatment

Initial treatment consists of empiric, broad-spectrum topical antibiotics that should cover the most frequent and serious pathogens in a specific geographical area and should be initiated immediately, while awaiting a definite microbiological diagnosis.

In routine corneal ulcers, topical fluoroquinolone monotherapy has excellent penetration at commercially available concentrations and provides outcomes equivalent to those of combination therapy.[8] Second generation fluoroquinolones (ciprofloxacin, ofloxacin) have excellent Pseudomonas coverage but lack useful gram-positive activity. Third- and fourth-generation fluoroquinolones (e.g., moxifloxacin, gatifloxacin, levofloxacin, and besifloxacin) have improved gram- positive and atypical mycobacterial coverage, but have limited activity against methicillin-resistant Staphylococcus aureus (MRSA). While considered generally effective against Pseudomonas in North America,[12] recent evidence may suggest an increasing rate of moxifloxacin resistance in ocular Pseudomonas isolates in British Columbia, in particular from corneal samples. Conversely, susceptibility of Pseudomonas to tobramycin has significantly increased over time and it may represent a good treatment option.[13]

A possible protocol for initial empirical treatment is the use of topical fluoroquinolone monotherapy hourly for five days while the patient is awake, followed by a taper to qid for 7–10 days if the infection is responding.[8]

Fortified antibiotics are compounded at higher concentrations than those commercially available and can be difficult to obtain. They are sometimes required in severe ulcers, particularly in large gram-positive or vision-threatening ulcers, when MRSA is suspected, or after failure of the initial therapy.

In fungal keratitis, natamycin 5% is generally recommended for filamentous fungal keratitis, particularly Fusarium. Topical amphotericin B 0.15% should be used in cases of yeast keratitis such as Candida or filamentous keratitis caused by the Aspergillus species.[14] However, recent evidence by our group shows that over 90% of Candida isolates in Canada are sensitive to fluconazole.[13]

Systemic antibiotics or antifungals are not usually necessary, but should be added to topical treatment if scleral or intraocular extension of the infection is suspected. If this is the case, fluoroquinolones are the treatment of choice in bacterial cases given their excellent ocular penetration (ciprofloxacin 250 mg bid or moxifloxacin 400 mg daily). In fungal keratitis, oral fluconazole (100 mg bid), voriconazole (200–400 mg/day), and posaconazole (800 mg/day) are good options due to their excellent intraocular penetration and broad coverage.[10,15]

The role of corticosteroid therapy for infectious keratitis remains controversial and it should be considered with caution. Corticosteroids are effective at managing the inflammation and reducing tissue destruction, but can also inhibit the host's response resulting in worse outcomes or complications. In bacterial keratitis, the use of topical corticosteroids in large central ulcers and 48 hours after initiating topical antibiotics may improve clinical outcomes.[16,17] However, this is not the case for fungal or Acanthamoeba keratitis. Therefore, when in doubt, topical corticosteroids are not initially recommended.

In addition, topical cycloplegic agents to reduce pain and the formation of synechiae and pressure-lowering medications can be used if needed. Oral doxycycline and vitamin C supplementation can be considered in severe cases to prevent keratolysis.[18]

Follow-up

Once treatment is initiated, patients should be monitored closely every 24–48 hours. The clinical response should guide patient management and if clinical improvement is noted, therapy should be continued. The first indication of a positive clinical response to antimicrobial treatment is an improvement in pain. Other signs of possible improvement are re-epithelialization; blunting of the perimeter of the stromal infiltrate; decreased density of the stromal infiltrate; improvement of corneal thinning; reduction in stromal edema; decrease of endothelial inflammatory plaque; and reduction in anterior chamber inflammation.[18,19]

If the patient appears to be worsening on treatment despite good compliance, one can consider switching to fortified broad-spectrum antibiotics if the initial therapy was fluoroquinolone monotherapy. However, if there is worsening of the clinical signs, the infection is severe or sight threatening, there is risk of perforation, or an atypical pathogen such as fungal or Acanthamoeba is suspected, the patient may need to be referred to a Corneal Unit.

Conclusion

Microbial keratitis is an ophthalmic emergency that needs to be treated imminently in order to avoid extensive visual impact. A delay in initiating appropriate therapy is the most important factor associated with a worse prognosis in corneal ulcers. Certain risk factors and clinical features may be helpful in identifying the infectious agent, but ultimately an etiological diagnosis with standard microbiology techniques is generally mandated. If deterioration is observed on close follow-up, referral to a cornea specialist or a tertiary centre should be considered.

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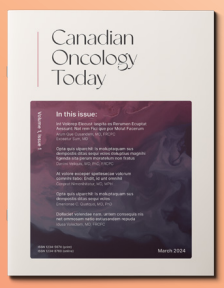

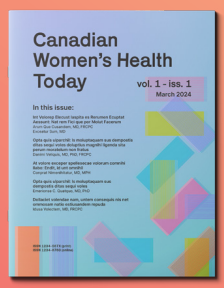

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