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Penetrating vs Lamellar Keratoplasty - Indications for Treatment

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How to Improve the Evaluation and Management of Glaucoma among General Practitioners

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Introduction

Glaucoma is a term that describes a group of ocular disorders characterized by intraocular pressure-related optic neuropathy. It is normally associated with increased intraocular pressure (IOP). The term "ocular hypertension" is used for people with consistently raised IOP without any associated optic nerve damage. Conversely, the term 'normal tension' or 'low tension' glaucoma is used for those with optic nerve damage coupled with visual field loss, but normal or low IOP.

Glaucoma is classified into congenital (developmental) or acquired, and sub-classified into open-angle and angle-closure types according to the mechanism by which aqueous outflow is impaired with respect to the anterior chamber angle configuration. Another classification is primary vs. secondary; in the latter a recognizable ocular or non-ocular disorder contributes to elevation of IOP.

Worldwide, glaucoma affects up to 2% of those over the age of 40 years, and up to 10% over the age of 80; 50% may be undiagnosed. In a population of European or African ethnic origin, primary open-angle glaucoma (POAG) is the most common form. On a worldwide basis, primary angle-closure (PACG) constitutes up to half of cases, with particularly high prevalence in individuals of Far Eastern descent.

Glaucoma has been called the "silent thief of sight" because the loss of vision often occurs gradually over a long period of time, and symptoms only occur when the disease is quite advanced. Since changes are usually irreversible, treatment is aimed at preventing further loss. Globally, glaucoma is the second-leading cause of blindness after cataracts. It is also the leading cause of blindness among African Americans. If the condition is detected early enough, it is possible to arrest the development or slow the progression with medical and surgical means, and here comes the role of a general practitioner (GP).

A GP is a medical practitioner who treats acute and chronic diseases and provides preventive care and health education to patients. There are variations in the role of a GP according to countries or even within countries. In urban areas of developed countries their roles are much focused on the care of chronic health problems, treatment of acute non-life threatening diseases, early detection and referral to specialized care of serious diseases and preventative care as health education or immunization. Meanwhile, in rural areas of developed countries or in developing countries, a GP may be routinely involved in pre-hospital emergency care, the delivery of babies, some hospital care in community hospitals and perform low complexity surgical procedures.

The Role of a GP in Glaucoma

With the increasing age of the general population, the number of people suffering from glaucoma is set to rise by at least a third in the next 20 years. Therefore the role of a GP in the diagnosis, treatment and follow up of glaucoma patients is increasing day-by-day.

In general, a GP plays an important role as a representative of the patient in secondary care. He or she has a very significant role in educating patients in order to improve their compliance and their life style, particularly for those with advanced disease who are prone to falls and accidents due to problems with glare, dark adaptation and peripheral vision.

In family practice, a GP should educate family members how to take care of their patients, how to use medications, keep on follow-up visits, and encourage them for screening themselves for glaucoma. In the case of 'shared care' system for glaucoma, only the GP will have the knowledge of the possible interactions between the medications used to control glaucoma and any other conditions for which the patient might be receiving treatment in addition to the local and systemic side effects of glaucoma medications. A GP should have the basic
knowledge to figure out the risk factors of glaucoma, the clinical manifestations of congenital, open angle and angle closure types of glaucoma. However, the role of a GP differs according to the type of glaucoma.

**Primary Open Angle Glaucoma (POAG)**

POAG is a chronic simple glaucoma, is usually bilateral disease with adulthood onset affecting both sexes equally. It is the most prevalent type of glaucoma in individuals of European and African ethnic origin.³

**Risk Factors**

Risk factors include high IOP (the higher the IOP the greater the likelihood of glaucoma) thin corneas; retinal diseases such as retinal vein occlusion, rhegmatogenous retinal detachment and retinitis pigmentosa; age, it is common in older individuals; race, it is more common, develops earlier, and more difficult to control in black individuals than in whites; family history; myopia; and vascular diseases such as systemic hypertension, hypotension, cardiovascular disease, diabetes and vasospastic conditions like migraine and Raynaud’s disease.³,14-16

**Diagnosis**

Diagnosis of glaucoma is straightforward in the presence of three parameters, elevated IOP, structural damage to the optic nerve head (optic disc), and characteristic defects in visual field.¹⁷ The normal range of IOP is 10-21 mmHg. In normal tension glaucoma, the IOP is within the normal range, but the other two parameters are present. Structural damage to the optic disc is expressed as cup/disc (C/D) ratio. The normal ratio is 0.35 in small discs, and 0.55 in large ones. Only 2% of the population have a C/D ratio greater than 0.7. Therefore, 0.4 can be used as a cut-off point in the screening process by a GP. On the other hand, asymmetry of 0.2 or more between the two eyes in an individual should also be regarded with suspicion, though it is critical to exclude a difference in overall disc size.³ Figures 1 and 2 show normal C/D ratio with different optic disc sizes. Figure 3 shows abnormal C/D ratio in glaucoma.

There are several instruments and devices to measure the IOP, some are hand-held tonometers, others are machines or devices to be used with machines. Examples for the hand-held tonometers are the Tonopen (Figure 4), the iCare (Figure 5), and the Schiotz (Figure 6).³ Although the latter is now seldom used in clinical practice, it is the cheapest and can be used by a GP.

A direct ophthalmoscope is an essential instrument in the GP daily practice. By this device, the GP can evaluate the C/D ratio.

Although visual field needs to be estimated by sophisticated machines, still the confrontation test is a simple and
or close the eyes for about 3 minutes after instillation to enhance the efficacy of the medications.

The main role of a GP during the treatment of a POAG patient is monitoring the IOP and observing adverse side effects of medications. The target pressure and the follow-up visits should be determined by an ophthalmologist in coordination with the GP. In case of an above-target IOP and/or a fluctuating IOP, the patient should be referred to the ophthalmologist. A GP has to be aware of potential adverse side effects of medications. Beta blockers can cause postural hypotension, bronchospasm and worsening of asthma, impotence, heart block and congestive cardiac failure. Acetozolamide may cause nausea, paraesthesia, electrolyte disturbances and renal stones. Prostaglandins are capable to induce an increase in melanin pigmentation in the iris, blurred vision, redness of the eyelids and anterior uveitis, upper respiratory tract infection symptoms, chest pain and miscarriages. In case of side effects, the patient should be referred to the ophthalmologist.

In screening for POAG, there are general recommendations that a GP should follow. Optic disc examination with an ophthalmoscope is useful when screening for glaucoma in a family practice. A patient with IOP > 21 mmHg should be referred to an ophthalmologist. Fundoscopy and IOP measurement should be a routine in medical examination on persons older than 40 years.
Primary Congenital Glaucoma (CG)

PCG affects 1:10 000 births; 65% of patients are boys. The clinical features depend on the age of onset and the level of IOP. Both eyes are affected in 75% of cases although involvement is frequently asymmetrical. 3

The patient may present with corneal haze, which is often the first sign noticed by the parents and it is the cause behind photophobia, blepharospasm and lacrimation that the patient is suffering from. Buphthalmos or large globe is the second important sign that happens due to elevated IOP prior to the age of 3 years. PCG should be suspected whenever corneal diameter is > 12 mm. It is rare to see a C/D ratio > 0.3 in CG. 3 A GP may be the first practitioner to see a child with PCG, and he or she should put this diagnosis at the top of the differential diagnosis list of lacrimation, large globe, large cornea or cloudy cornea, and should refer the child to an ophthalmologist.

Early assessment and surgical intervention is essential in CG to prevent structural damage to the optic disc and allow visual rehabilitation.

Primary Angle Closure Glaucoma (PACG)

Diagnosis

It is an emergency case. The patient usually comes with painful red eye, blurred vision, headache and, frequently nausea and vomiting. The patient usually gives a history of similar attacks. Signs include impaired visual acuity, red painful eye, hazy cornea, semi-dilated non reacting pupil, and hard palpated eye in addition to nausea, vomiting and headache. 3 Sometimes, the patient may present in a stage when such symptoms and signs are improving and the attack is resolving, it is therefore the good history taking that reveals the diagnosis. 19

Risk Factors

Risk factors for developing PACG include: age (usually 60 years and older); gender, females are commonly affected 3-4 times more than males; race, far eastern are at higher risk whereas black patients are at lower risk; refraction especially hyperopia; and finally short axial length, shallow anterior chamber and nanophthalmos. 5

Emergency Treatment

In addition to the important role that a GP may play in the diagnosis of this emergent case, he or she should initiate the medical therapy before referring the patient. The patient should assume a supine position; acetazolamide 500 mg is given IV if IOP > 50 mmHg and orally if IOP is < 50 mmHg, and if treatment is IV an additional oral dose may be given; topical apraclonidine 1% (if available), timolol 0.5%, prednisolone 1% or dexamethasone 0.1% to the affected eye leaving 5 minutes between each instillation; and analgesic and an antiemetic. After controlling the attack and the IOP decreased, subsequent medical treatment can be given including: pilocarpine 2–4% one drop to the affected eye, repeated after half an hour, and one drop of 1% as prophylaxis into the fellow eye then continued every 6 hours; topical steroid (prednisolone 1% or dexamethasone 0.1%) every 6 hours if the eye is acutely inflamed; and timolol, apraclonidine and oral acetazolamide may be continued if necessary until the patient reaches a consultant. 3

Conclusion

A GP is an important link in the medical chain of glaucoma management. He or she can contribute to early diagnosis of the disease and to treatment control by educating the patient and his family, monitoring the disease and the side effects of the medications, and referring the patient to the ophthalmologist when necessary.
Penetrating vs Lamellar Keratoplasty—
Indications for Treatment

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Since the 1905, first penetrating keratoplasty (PK) procedure, corneal transplantation surgery has evolved. Nowadays, penetrating keratoplasty is being replaced by lamellar techniques. The risks associated with “open-sky” surgical procedures and the postoperative complications inherent to PK have resulted in a mounting interest and use of this new lamellar surgical approach.

Deep anterior lamellar keratoplasty (DALK) has become the method of choice vs. PK in cases of keratoconus, dystrophies and anterior corneal opacities, providing the recipient eye’s endothelium (i.e., the so-called “host” endothelium) is undamaged and in good condition. In this respect, DALK has proven to be a safe and effective alternative to PK for these patients. Nonetheless, it is worth pointing out that corneal opacities associated with a disrupted endothelium are rather common (traumatism, herpes keratitis…); in those cases PK still is the technique of choice. Moreover, the keratoconus cases that nowadays we scheduled for a lamellar procedure are very advanced cases, as long as intracorneal ring segments and cross-linking have helped us to get most keratoconus patients ahead, so perforations are more prone to occur during a DALK procedure (Figure 1), which again force surgeons to re-evaluate the procedure into a PK as they go along.

Similarly, the various forms of endothelial keratoplasty (EK), such as Descemet-Stripping Automated Endothelial Keratoplasty (DSAEK) and Descemet’s Membrane Endothelial Keratoplasty (DMEK) (Figure 2) have become the techniques of choice in those cases of corneal edema secondary to endothelial decompensation, providing the stroma remains in good condition. Pseudophakic bullous keratopathy has recently emerged as a leading cause of endothelial keratoplasty. However, the patients with a long duration of bullous keratopathy could not benefit from this technique because of the permanent stromal scarring.
that can affect their vision after the surgery.\(^{(7)}\) So a PK must therefore be considered, also in scenarios with high-risk of endothelial graft dislocation (either in DSAEK or DMEK), such as aphakia, anterior chamber lens\(^{(8-10)}\) or the presence of glaucoma drainage device.\(^{(11)}\)

Consequently, even though lamellar approaches are nowadays the prevailing techniques, PK is still used in many occasions with excellent outcomes. However, success of PK depends on many preoperative, intraoperative and postoperative factors and it is not free from disadvantages: open-sky surgery, high postoperative corneal astigmatism, weak wound, glaucoma, allograft rejection, loss of endothelial cells with time. Postkeratoplasty glaucoma (PKG) is one of the challenging issues important for the survival of the graft.\(^{(12)}\) The incidence of PKG has been reported to range between 8.5\% and 34\%.\(^{(13,14)}\) Also allograft rejection, that is the leading cause of graft failure after PK,\(^{(15,16)}\) is a main concern, despite the methods have been developed to decrease its risk.\(^{(17,18)}\) For this reason, many ophthalmologists have begun to move towards lamellar techniques, trying to preserve patient’s own healthy cornea. In this situation, two new concepts arises: we should avoid late-stage disease presentations, where all the layers of the cornea will be affected, and try to perform the lamellar procedure in an early stage, the opposite of what we were used with PK. Another new concept that we have to bear in mind is what we consider a good outcome in terms of visual acuity after lamellar procedures. In spite of the clinical and theoretical advantages of lamellar keratoplasty, visual outcomes have not always been ideal due to the tissue interface. In our opinion, it could be preferable worse visual results but keep patient’s own healthy cornea. Currently, this is not really an important issue since deep lamellar keratoplasty surgery removes almost all of the recipient stromal tissue, so the risk of scarring in the interface and subsequent poor visual outcomes is much reduced. There are studies that have already shown no differences among both techniques.\(^{(19)}\) Regarding endothelial keratoplasty, with the new DMEK approach that avoids a stroma-to-stroma interface (Figure 3), superior visual outcomes have been achieved compared to DSAEK,\(^{(20)}\) although in DMEK, donor preparation and handling in the anterior chamber is more surgically challenging than in DSAEK.

In summary, there is an exciting future affecting keratoplasty surgery. Nowadays, we have knowledge and resources that allow us to perform less invasive surgeries for our patients. The development of DSAEK and DMEK has greatly influenced eye banks, surgery and patient outcomes, and the femtosecond laser may find a place also in corneal transplantation. However, penetrating keratoplasty will still be used in many cases, and, despite long experience, it has failed to match outcomes on other areas of clinical transplantation, mainly in those high-risk cases where immunological privilege has been eroded. Thus, we need better regional and systemic immunosuppression for allograft rejection, alternative therapies and techniques that avoid high intraocular pressure, new devices, as femtosecond laser, in order to help us to improve our surgical technique... Also artificial corneas for corneal anterior lamellar transplantation may become a viable option within the next decade and human endothelial cell culturing, as several groups are now actively working on, will likely change the way we face these diseases.
References


OCT Indications in Posterior Infectious Uveitis

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The advantages of Optical Coherence Tomography (OCT) in the diagnosis and follow-up of retinal conditions have led to a large variety of possibilities. Modern OCT equipments perform real time, in vivo biopsies of the retina and the neighboring structures such as the vitreous and the choroid with 3-µm accuracy. Regarding posterior uveitis, and more specifically infectious uveitis, OCT has become a useful tool in the evaluation of retinal complications associated with uveitis providing accurate information on the condition.

OCT is particularly useful in the diagnosis and follow-up of retinal changes such as macular edema, exudative retinal detachment and choroidal neovascularization, as well as quantification of retinal thickness and monitoring the therapeutic response. It is a non invasive, easy to perform test that does not require pupillary dilation and provides much information about the retina in a few minutes. OCT is very useful especially in uveitic patients in whom macular edema is suspected. Posterior infectious uveitis can be classified in four subgroups: bacterial, fungal, viral and those caused by parasites. Toxoplasmosis, toxocariasis, cysticercosis and onchocerciasis are caused by parasites. Tuberculosis, syphilis, leptospirosis and leprosy cause bacterial uveitis. Candidiasis, histoplasmosisis, coccidioidomycosis, sporotrichosis cause fungal uveitis and cytomegalovirus, herpes simplex, rubella and Epstein Barr-virus cause viral uveitis (Figure 1).

In these conditions, the inflammation of the posterior segment will involve the retina, the choroid or both, inducing changes that will affect visual acuity. Macular edema is the most important and frequent change, causing visual loss in more than 30% of the cases that can be significant in almost 10% of the cases. Uveitic macular edema is usually related to inflammatory changes involving the blood-retinal barrier. Macular edema may occur in any patient with uveitis, though it tends to be more severe in patients with pars planitis or sarcoidosis. In these cases, posterior segment biomicroscopy is unable to detect all the cases with early macular edema; however, OCT permits the identification of these cases. Furthermore, there is no direct relationship between visual acuity and the type or severity of macular edema. There are three different patterns of macular edema: focal, diffuse or cystic. Once again, OCT is key in the detection and early classification of macular edema. Even though these patterns are very similar to those previously reported in other conditions such as diabetic retinopathy, we can assume that the process that leads to their appearance is different, since it is caused by inflammatory mediators affecting deeper and vascular structures of the retina, such as prostaglandins, interleukins or vascular endothelial growth factor. We know that the earlier the diagnosis of macular edema, the better the prognosis will be. OCT scans show hypo reflective areas associated with the accumulation of fluid, and retinal thickening quantified as foveal thickness and increased volume of the OCT analysis cube (Figure 2).

In cases of macular edema associated with serous retinal detachment, we can observe a hyper reflective (red or yellow) line. We should bear in mind that chronic macular edema tends to damage the photoreceptor layer and induce retinal fibrosis, that will jeopardize visual improvement. Early treatment is usually followed by macular recovery in more than 95% of the cases. The main advantages of OCT in these cases are not only its great accuracy, but also its reproducibility permitting a trustworthy follow-up (Figure 3).
One of the most frequently seen posterior infectious uveitis is toxoplasma choroiditis. We have argued for a long time whether diagnosis should be based upon lab results or upon clinical observation. Experience shows that clinical observations usually go before lab results. Chorioretinal examination is followed by OCT, revealing minimal structural changes associated with this condition. Therefore, a clinically visible active lesion presenting with blurred borders appears at the OCT as a hyper reflective lesion with retinal thickening. The enface map and the 3D rendering show these changes clearly. A decreased reflectivity of the external layers such as the retinal pigment epithelium (RPE) can also be observed as well as choroidal or choriocapillary hypo reflectivity. The appearance of multiple hyper reflective areas in the vitreoretinal interface close to the lesion is also characteristic. These hyper reflective areas are 100 to 150 µm wide. Non-active or healed lesions look completely different, as retinal thinning combined with posterior hyaloid detachment. In the case of congenital toxoplasmosis, intraretinal cysts with increased RPE reflectivity can be observed. Syphilis and tuberculosis cause inflammatory subretinal lesions that appear as hyper reflective and thickened RPE at OCT (Figure 4).

OCT provides an accurate evaluation of retinal changes allowing an adequate follow-up, as well as early detection of subtle changes such as epiretinal membranes or vitreo-macular traction that may require surgery in order to preserve visual acuity. High resolution OCT technology allows a better understanding of structural changes associated to inflammation in uveitis, more specifically those occurring in the vitreoretinal interface.

New OCT devices such as enface OCT will provide increased information about the choriocapillaris, in order to understand uveitis associated changes, thus improving the accuracy of diagnosis, permitting a faster therapeutic decision making.

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The accurate measurement of corneal astigmatism has been the topic of many recent presentations due to the increasing prevalence of toric IOLs and femtosecond LRI technology. These procedures benefit from clear defined and accurate corneal astigmatism measurements. The alignment of the IOL and LRI with the steepest corneal meridian together with the selection of the appropriate power and degree of arc are key factors in determining patient satisfaction.

Many surgeons rely on corneal astigmatism measurements from a number of instruments. These can include the Zeiss IOL Master, Haag-Streit Lenstar LS900, topography and manual keratometry. From these multiple readings a single magnitude and meridian must be chosen to best represent the corneal shape, which can be challenging as magnitudes and meridian usually vary between devices. It is important to remember that each of these instruments measures the corneal astigmatism in a slightly different manner.

Topographers display a simulated keratometry (Sim K) value based on data obtained from the 3mm region of the anterior cornea – this in itself can vary depending on whether a steep or flat cornea is being measured. For a steep cornea the Sim K measurement will be determined from a different more central region of the cornea to that of a flat cornea.

The Sim K is determined using data from one Placido ring or from a Scheimpflug camera. In a significantly irregular cornea the limitation of the asymmetrical and/or non-orthogonal data collected can lead to inaccurate measurements.

IOLMaster measures the keratometry at 2.5mm corneal diameter using 6 points measured 5 times with each acquisition. Again an irregular cornea will present a somewhat imprecise and variable measure of the magnitude and orientation of corneal astigmatism.

Lenstar has more measurement points and uses a 32 pattern marker on two concentric rings (1.65 and 2.3mm in diameter). This instrument can also provide Placido topography of the central 6mm optical zone.

The Manual Keratometer measures corneal astigmatism at 3.2mm diameter using mires projected by light onto the cornea. Since each instrument measures corneal astigmatism in a different manner and position of the cornea, one should not expect to obtain the same value for the one eye from several devices. What is of paramount importance is consistency – so that pre and postop measurements of corneal astigmatism are performed using the same instrument and where possible the same operator, to minimize any potential variability.

The corneal astigmatism measurements provided by the currently used instruments mentioned are taken at particular points on the cornea. A new parameter known as corneal topographic astigmatism (CorT) can be calculated using all the raw data obtained by the topography system – not limited to the 3mm zone of the cornea (Figure 1). In this study anterior topographic data were captured using an Atlas 9000 system (Carl Zeiss Meditec). The study assessed 486 virgin eyes with an age range of 19-64 years. A best fit sphero-cylindrical curve was fitted to the data and a vector mean of the astigmatism values was obtained for the whole cornea. The CorT was found to correspond more accurately in magnitude and orientation to manifest refractive cylinder than any of Sim K, Manual Keratometry, Corneal Wavefront (CorW) and Paraxial Corneal Matching (PCM) (Figure 2). The ocular residual astigmatism (ORA) magnitude and its standard deviation were used to assess how closely each measure of corneal astigmatism matched the manifest refractive cylinder and its variability.

The ORA is defined as the vectorial difference between the corneal astigmatism and the refractive cylinder at the cor-
Figure 1. Incorporating all the valid topography ring data captured into the calculation of corneal astigmatism can be more accurate than Sim K which is based on one Placido ring.

Figure 2. The best range of Placido rings to generate CorT by examining the standard deviation of the ORA mean was number 0 to 17 in the AtlasTM 9000 (Carl Zeiss Meditec). CorT has the smallest variability of the ORA compared with other measures of corneal astigmatism which included Sim K, Manual K, Corneal Wavefront (CorW) and paraxial corneal matching (PCM).

The calculation of CorT will be implemented into topographers in the near future using the iASSORT® software. This will include a CorT value of the total corneal power including the posterior cornea in the topographers that are able to measure it.

Furthermore, by dividing the cornea into two hemi divisions, two CorT values can be calculated. These two CorT values, one for the superior cornea and one for the inferior can then provide a vectorial measure of corneal irregularity known as topographic disparity (TD). In this way, a standardized parameter can be compared across all topography systems for corneal irregularity instead of the various individual measures currently that are different for each system.

Using CorT, consistent values are obtainable for surgical procedures and analysis for both regular and irregular corneas undergoing surgery. This also enables nomogram refinement to be more precise and result in better outcomes.

**Financial Disclosure:** Dr. Alpins and Mr. Stamatelatos have a financial interest in ASSORT® Surgical Management Systems.

**References**

The Herpes Simplex Virus (HSV) is a DNA ubiquitous virus, which has humans as its only natural reservoir. Most of the human population shows serologic evidence of herpetic infection by middle age and it has been estimated than one third of the world population suffers from recurrent HSV infection. Two different types of HSV have been described based on virus-specific antigens. Type 1 (HSV-1) and type 2 (HSV-2) were thought to be site-specific, although nowadays they indistinctively cause herpetic disease with similar clinical characteristics and locations, including ocular disease.

The eye is a particular target for HSV, as it can affect almost every structure and create the most varied clinical appearances, not only by primary infection, but also by its ability to undergo multiple recurrences through reactivation from latent virus presence in ganglionic neurons (including the trigeminal ganglion), that migrate via retrograde axonal transport following primary infection. For the purpose of this article, we will focus on the diagnosis and management of HSV affecting the different layers of the cornea.

Anatomical Classification

HSV can affect all layers of the cornea, including the epithelium, stroma and endothelium. We will address each layer separately, although combinations thereof are not uncommon.

EPITHELIUM

Infectious epithelial keratitis (IEK) may manifest as:
1. Corneal vesicles
2. Dendritic ulcer
3. Geographic ulcer
4. Marginal ulcer

All these manifestations result from active viral disease, with the dendritic ulcer being the most common. Other than the marginal ulcer, they represent a continuum of progressive HSV epithelial keratitis.

Diagnosis

Even though in every infectious process the clinician would like to have microorganism confirmation, viruses affecting the cornea are very difficult to demonstrate in a clinical setting, therefore careful examination aided by some diagnostic tools will, in most instances, suffice to allow a management plan to be determined. Laboratory tests are only indicated in complicated or uncertain cases and in all cases of suspected neonatal herpes infection.

Slit lamp Exam: Dendritic ulcers have a branching shape, with terminal bulbs and characteristic swelling at the epithelial margins.

Staining: IEK constitutes a true corneal ulceration, extending beyond the basement membrane through Bowman’s layer; therefore it stains positively with Fluorescein, delineating the dendritic lesions (Figure 1 A - B). This feature helps to differentiate HSV ulcers from other confounding epithelial lesions such as varicella-zoster pseudodendrites or healing epithelial defects. Rose Bengal and Lissamine Green can both be used to stain devitalized cells, and will be especially absorbed by cells at the ulcer’s margins, therefore helping with the diagnosis.
Polymerase Chain Reaction (PCR): Although very sensitive and specific, logistic requirements make this technique very difficult to implement in a standard clinical setting.

Management

Even though HSV IEK is a self-limited condition, the use of antivirals has been shown to provide faster recovery times, especially in immunocompromised patients. Several antivirals have been used in the management of IEK, from the almost historical Idoxuridine and Viradabine, to the current commonly used Trifluridine (TFT), Acyclovir and Gancyclovir. Topical Trifluridine and Acyclovir, as well as oral Acyclovir (400 mg) administered 5 times a day have shown equivalent efficacy in the treatment of HSV IEK. Considering the relatively wide safety profile, we strongly favor oral antiviral treatment in order to avoid local corneal toxicity secondary to frequent topical administration and duration of treatment, especially in patients with an already compromised ocular surface, such as in neurotrophic corneas or post-keratoplasty. Treatment duration can vary depending on the host’s response but we recommend maintaining the antiviral for no less than 14 days.

Currently, newer oral antivirals are available which require less frequent dosing which can aid in patient compliance. Valacyclovir, a prodrug of Acyclovir with higher bioavailability and Famciclovir can be used twice a day in the treatment of IEK with suggested equivalent efficacy.

If IEK persists after 14 days of aggressive antiviral therapy, resistance to treatment must be suspected, and alternatives such as vidarabine need to be considered. Some strains of HSV have the ability to mutate its thymidine kinase, therefore preventing activation and decreasing the antiviral capabilities of both acyclovir and trifluridine.

Prophylaxis

Recommendations for antiviral prophylaxis vary among clinicians, but there is agreement that patients undergoing 2 or more herpetic recurrences in 1 year and post-keratoplastic patients secondary to HSV would most likely benefit from it, with a significant reduction on the frequency of recurrences. The rate of recurrence is significantly higher in patients with
atopy or HIV infection. The accepted dosage is Acyclovir 400 mg twice a day or Valacyclovir 500 mg once a day.

**STROMA**

Stromal keratitis is one of the most common causes of infectious corneal blindness and is associated with the greatest visual morbidity. This disease can be subdivided into 2 separate entities:

1. **Necrotizing stromal keratitis:** characterized by stromal infiltration, ulceration and necrosis, this condition is secondary to direct viral invasion and replication, with a subsequent severe inflammatory response which can potentially aid in further destruction of the corneal stroma.
   a. **Diagnosis:** diagnosis is made based on the clinical features described above. In general no additional tests are required, other than bacterial and fungal cultures to rule out these differential diagnoses in this setting.
   b. **Management:** since this condition involves active viral replication, antivirals, such as Acyclovir 400 mg 5 times a day or Valacyclovir 1g twice a day should be administered as soon as possible. Even though stromal destruction is also related to the inflammatory response, topical steroids should be used with caution, since they can favor stromal melt and perforation.

2. **Immune stromal keratitis:**
   a. **Diagnosis:** viral stromal antigens can trigger an antibody-antigen and complement immunologic inflammatory response, resulting in stromal inflammation and subsequent corneal haze, scarring (Figure 2) and neovascularization with lipid deposits. Once again the clinical picture will enable the diagnosis and the need for further testing is generally not required (Figure 3 A-B).
   b. **Management:** steroids are required in this condition, either topically for mild and moderate stromal keratitis, or combined topically and orally for severe immune stromal inflammation. Even though antivirals at therapeutic

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**Figure 2:** Slit lamp photograph of corneal scarring secondary to Herpes simplex virus.

**Figure 3A-B:** A) Slit lamp photograph of herpes simplex virus immune stromal keratitis. Note the neovascularization and dense corneal inflammation. B) Slit lamp photograph of herpes simplex virus immune stromal keratitis. Note the slit beam demonstrating deep stromal neovascularization and inflammation with intact normal epithelium.
dosages did not prove to be beneficial in healing time, it is recommended to use concomitant oral antiviral prophylaxis in order to prevent severe epithelial keratitis if a patient would develop IEK while on topical steroids.

Prophylaxis

As with IEK, the HEDS study showed that antiviral prophylaxis with Acyclovir 400 mg twice a day was successful in decreasing the likelihood of stromal recurrence of the disease. We strongly encourage clinicians to maintain long-term antiviral prophylaxis, since one fifth of patients with external ocular HSV infection will develop stromal keratitis. Alternatively, Valacyclovir 500 mg a day can successfully be used for the same purpose.

ENDOTHELIUM

Diagnosis

As with stromal disease, the clinical picture of endothelial herpetic disease plays a key role in diagnosis. Common findings of herpetic endotheliitis are keratic precipitates with overlying stromal edema, anterior uveitis and trabeculitis with increased intraocular pressure (Figure 4). This entity can be subdivided into 3 different categories: disciform, diffuse or linear, depending on the configuration of the keratic precipitates and the pattern of corneal edema.

Management

Since the pathogenesis of this condition involves active viral replication and concomitant endothelial immune inflammation, both aggressive antiviral and anti-inflammatory therapies need to be started. The HEDS study suggested that oral antivirals were more effective than topical treatment in this setting. Therefore, we recommend either Acyclovir 400 mg 5 times a day or Valacyclovir 1 gram twice a day to stop active viral replication. In terms of antiinflammatory therapy, topical steroids with good anterior chamber penetration should be promptly started. We normally suggest hourly topical 1% Prednisolone or 0.1% Dexamethasone with a slow taper. In cases of severe endotheliitis, and especially in the linear subtype, oral steroids could be added to the topical regimen.¹

HEDS Study in a Glance(4-7)

HEDS-I: The purpose of this double-blinded randomized landmark clinical trial was to evaluate:

a. The efficacy of topical steroids in treating HSV stromal keratitis in conjunction with topical Trifluridine.

b. The efficacy of oral acyclovir in treating HSV stromal keratitis in patients receiving concomitant topical steroids and Trifluridine.

c. The efficacy of oral acyclovir in treating HSV iridocyclitis in conjunction with treatment with topical steroids and Trifluridine.

Results

a. Patients who received prednisolone phosphate drops had faster resolution of the stromal keratitis and fewer treatment failures.

b. There was no apparent benefit in the addition of oral acyclovir to the treatment regimen of a topical steroid and a topical antiviral.
c. The trend in results suggests a benefit in adding oral acyclovir to the treatment of HSV iridocyclitis in patients receiving topical steroids and Trifluridine prophylaxis.

**HEDS-II:** This second landmark study wanted to determine:

a. Whether early treatment with oral acyclovir of HSV IEK prevents progression to the blinding complications of stromal keratitis and iridocyclitis.

b. The efficacy of low-dose oral acyclovir in preventing recurrent HSV eye infection in patients with previous episodes of HSV eye disease.

c. The role of external and behavioral factors on the induction of ocular recurrence of HSV eye disease.

**Results**

a. No benefits from the addition of oral acyclovir to treatment with topical Trifluridine in patients with HSV IEK, in preventing the development of stromal keratitis or iritis.

b. Oral acyclovir reduced by 41% (50% for stromal disease) the probability that any form of ocular herpes would return in patients who had the infection in the previous year.

c. No statistical importance was attributed to any of the plausible risk factors for ocular HSV recurrence, such as stress, systemic infection and eye injuries.

**Did you Know?**

1. Topical alpha interferon has shown success in shortening the healing period of IEK in combination with antivirals.

2. Topical Acyclovir and Ganciclovir are less toxic than Trifluridine for the treatment of IEK.

3. Valacyclovir has been associated with thrombotic thrombocytopenic purpura/hemolytic uremia syndrome in severely immunocompromised patients.

**Management Pearls**

1. Oral and topical antivirals have proven similar healing rates in the treatment of IEK.

2. Treatment of immune stromal keratitis and endothelial disease related to HSV requires topical steroids (with or without oral steroids) and oral antivirals.

3. Antiviral prophylaxis is recommended in recurrent disease and special cases such as keratoplasty secondary to herpetic disease.

**References**


Pearls and Tips in Retinal Detachment Surgery with 23, 25 and 27g Vitrectomy Systems

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The introduction of microincisional vitreous surgery (MIVS) has dramatically transformed the way we perform vitreous surgery. It is the most relevant innovation in the field of vitreoretinal surgery during the past decade. MIVS technology has changed the subspecialty of vitreoretinal surgery and its individual procedures from lengthy and cumbersome to elegant, efficient procedures. Since its initial description by Eugene de Juan in 2002, optimized vitrectomy machines and instrumentation have made us efficient and more proficient surgeons.

At its inception many surgeons resisted the adoption of MIVS. This was mostly due to the limitations of the existing technologies available to support it. At present, according to the PAT survey of 2013, 54.1% of surgeons perform 23g, 41.9% perform 25g vitrectomy, and only 3.7% perform 20g. Like all new procedures, a learning curve exists which can be reduced with the appropriate tips and tricks.

Case Selection

For a surgeon who is comfortable with 20g, the transition to 23g is simpler since the feel and rigidity of the instruments resembles 20g. Once a surgeon is comfortable with 23g the switch to 25g occurs almost automatically. For surgeons beginning to perform vitrectomy de novo, I would encourage them to begin with 25g since 27g vitrectomy is becoming available and smaller gauges will be the future. As with any new technology, one should select the simpler cases initially until one feels comfortable with all the steps of the procedure, and slowly increase their complexity. The ideal cases to begin with are simple vitrectomies with low risk of iatrogenic breaks: macular puckers, simple vitreous hemorrhages and opacities. As the surgeons comfort level increases, more complex cases can be tackled. Some surgeons, myself included, feel that 25g and 27g, with the slighter vitreous cutters are ideal for the more complex retinal detachment cases because of the enhanced finesse and control they offer.

Wound Construction

MIVS systems utilize trocar/cannulas, and their use can be cumbersome initially. The wound construction is important to prevent the cannulas from slipping out of the eye during the procedure, prevent suprachoroidal infusion of fluid, and provide a self-sealing wound without leakage at the end of the case. This not only prevents hypotony and perioperative bleeding, but reduces the incidence of endophthalmitis, as well as obviating the need for suturing at the end of the case. For the trocar/cannula placement, displacing the conjunctiva and making an angled wound results in optimized closure.

Vitrectomy for Retinal Detachment

The incremental benefit of utilizing the 25 and 27g cutters is in the more complicated cases- diabetic traction detachments and PVR detachments. The vitrectomy set-up is performed in a similar manner, as with 20g except that instruments are placed through trocars. Multifunction instruments are rarely necessary since new chandeliers in 25g and 29g provide superb illumination to allow for bimanual techniques (Figure 1).

Smaller vitreous cutters with openings closer to the tip and with machines with very high cut rates allow for these to be used as multifunction tools. Shaving of membranes from the surface can be performed with high cut rates and reduced aspiration. This is useful in cases with PVR detachments and in diabetic traction detachments. Membranes
can be dissected with the probe similarly to what occurs with scissors (Figure 2). Suction can be utilized to use the cutter as forceps to lift membranes and detach the posterior hyaloid. The cutter can also be used as a flute needle and to blow out blood with the reflux mode available in some machines, as well as to aspirate fluid from retinal breaks and to perform a gas/fluid exchange. The 25g and 23g cutters can be used to engage and remove large blood clots and lens fragments by utilizing low cut rates (Figure 3). All these maneuvers are not possible with the larger and less delicate 20g instruments. Valved cannulas and IOP control provide a controlled vitreous environment and reduce intra-operative bleeding and optic nerve damage from unstable IOP during the vitrectomy. Segmentation, delamination, dissection and shaving of membranes can all be performed uni-manually with the smaller cutters to remove membranes and traction on the retina (Figure 4).
Wound Closure

Adequate wound closure is essential in all vitreous surgery and it begins with optimal wound construction. Nevertheless the management of the wounds at the end of the case is relevant. Some surgeons prefer performing a partial air/fluid exchange at the end of the procedure so that the air bubble tamponades the wounds from the inside. If leakage is noted through a sclerotomy, a suture should be placed on that sclerotomy to provide complete closure. This prevents hypotony and its associated complications of bleeding, choroidal formation and potential endophthalmitis. In the past reports of an increased incidence of tears and endophthalmitis was reported with MIVS. These results were possibly due to inadequate wound construction and closure and limited vitrectomies with poor illumination during the learning curve and initial stages of this technology. Lihteh Wu with the Panamerican Collaborative Study Group (PACORES) retrospectively reviewed over 33,000 pars plana vitrectomies to assess the incidence of endophthalmitis among the different gauges and no statistically significant difference in incidence of endophthalmitis was found between 20g, 23g and 25g vitrectomies.

Transition Pearls

A concern and barrier for many surgeons in transitioning to MIVS is the cost involved in replacing all their existing 20g instrumentation. There are three points in this respect. First, the need for use of ancillary instrumentation is markedly reduced when utilizing MIVS; I have not used scissors in several years. Second, one can use 23g, 25g or 27g trocars except in the sclerotomy in the dominant hand, and open that sclerotomy 20g. This allows for the use of 20g instruments like foreign body forceps, viscodissection setups or fragmatomes. In a case started in small gauge, if the need arises during the case, the conjunctiva can be opened and the sclerotomy enlarged to 20g to allow for the required instruments. Thirdly, an important point relative to the cost of new instrumentation is the efficiency the system provides. MIVS allows for a surgeon to be able to perform more cases in less time with reduced turnover lag. Time being our most precious, irreplaceable commodity; the value of the optimal efficiency is priceless.

MIVS with 23,25 or 27g is a wonderful technology that allows for exquisite precision and control during complicated vitrectomy procedures. At present improved 25g technology does offer the best control with minimal invasiveness. In the future 27g will have a significant role in a number of pathologies. Do not be afraid to embrace this technology, MIVS will dramatically enhance your efficiency, outcomes and total operating room experience as a vitreoretinal surgeon.

References

2. PAT survey 2013, American Society of Retinal Specialists.
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