CLINICAL HANDBOOK

Ocular Surface Disease IN Glaucoma Patients

Théa

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Preface

Glaucoma is a complex and progressive eye disease that can lead to irreversible vision loss if left untreated. While the primary focus in managing glaucoma has traditionally been on lowering intraocular pressure to prevent optic nerve damage, recent research has shed light on the significant role that ocular surface disease plays in the management and progression of glaucoma.

The ocular surface, comprising the cornea, conjunctiva, and tear film, plays a crucial role in maintaining the health and function of the eye. Ocular surface disease encompasses a wide range of conditions, including dry eye syndrome, blepharitis, and meibomian gland dysfunction, all of which can impact the ocular surface and exacerbate the symptoms of glaucoma.

This handbook aims to provide a comprehensive overview of ocular surface disease in glaucoma, exploring the intricate interplay between these two conditions as we understand it today and offering insights into the latest advancements in diagnosis and management, thus assisting ophthalmologists to find their way around the different aspects of ocular surface disease in glaucoma patients.

We truly hope this clinical handbook serves as a reference guide for healthcare professionals to better understand ocular surface disease in glaucoma patients and utilize the advice and recommendations given herein in the real-world management of patients suffering from this multifactorial condition. By enhancing our understanding of the relationship between these conditions and implementing evidence-based strategies for their management, we can improve the quality of life and visual outcomes for individuals affected by glaucoma and ocular surface disease.

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List of abbreviations

Abbreviation	Definition
ADDE	Aqueous-Deficient Dry Eye
ADES	Asian Dry Eye Society
AED	Allergic Eye Disease
AKC	Atopic Keratoconjunctivitis
ALT	Argon Laser Trabeculoplasty
BAK	Benzalkonium Chloride
BDNF	Brain-Derived Neurotrophic Factor
CAI	Carbonic Anhydrase Inhibitor
CCT	Central Corneal Thickness
CDR	Cup to Disc Ratio
CM	Confocal Microscopy
DED	Dry Eye Disease
EDE	Evaporative Dry Eye
EGS	European Glaucoma Society
5-FU	5-Fluorouracil
GPC	Giant Papillary Conjunctivitis
GQL-15	Glaucoma Quality of Life-15
GTR-OSD	Glaucoma Therapy-Related Ocular Surface Disease
HA	Hyaluronic Acid
HLA-DR	Human Leukocyte Antigen-D-Related
HIV	Human Immunodeficiency Virus
IL	Interleukin
IOP	Intraocular Pressure
IPL	Intense Pulsed Light
LASIK	Laser-Assisted In Situ Keratomileusis
LGP	Laser Gonio Puncture
LT	Laser Trabeculoplasty
MAP	Mitogen-Activated Protein
MCP	Monocyte Chemoattractant Protein
MGD	Meibomian Gland Dysfunction
MIBS	Minimally Invasive Bleb Surgery
MIGS	Minimally-Invasive Glaucoma Surgery
MMC	Mitomycin C

Abbreviation	Definition
MMPs	Matrix Metalloproteinases
NEI	National Eye Institute/Industry
NF-kB	Nuclear Factor Kappa B
NGF	Nerve Growth Factor
NICE	National Institute of Health and Clinical Excellence
NPDS	Non-Penetrating Deep Sclerectomy
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
ONH	Optic Nerve Head
OSD	Ocular Surface Disease/Disorder
OSDI	Ocular Surface Disease Index
PACG	Primary Angle-Closure Glaucoma
PF	Preservative Free
PGA	Prostaglandin Analog
POAG	Primary Open-Angle Glaucoma
PPA	Peripapillary Atrophy
PXF	Pseudoexfoliation
RGC	Retinal Ganglion Cell
RNFL	Retinal Nerve Fiber Layer
SAP	Standard Automated Perimetry
SLP	Scanning Laser Polarimetry
SLT	Selective Laser Trabeculoplasty
TBUT	Tear Breakup Time
TFOS	Tear Film & Ocular Surface Society
TFOS DEWS II	Tear Film & Ocular Surface Society Dry Eye Workshop II
TIMP	Tissue Inhibitor of Matrix Metalloproteinase
TNF-α	Tumor Necrosis Factor-α
UK	United Kingdom
VKC	Vernal Keratoconjunctivitis

Ocular Surface and Ocular Surface Disease

Definition of Ocular Surface Disease

The ocular surface encompasses a complex system that includes the epithelial layers of the conjunctiva and cornea, the lacrimal and meibomian glands, as well as their supporting connective tissue (basal matrix) and tear layer (apical matrix). Additionally, it involves the eyelashes and their associated glands (Moll and Zeis), components of the eyelids responsible for blinking, and the nasolacrimal duct (Gipson, 2007). Any dysfunction or disease affecting one or more of these interconnected structures can lead to ocular surface disease (OSD).

Ocular surface disease (OSD) is highly prevalent in the general population, and its incidence rises with age to 30% in the general population aged 50 years and older *(Stapleton et al., 2017)*.

OSD is characterized by its high prevalence in patients with glaucoma and ocular hypertension *(Leung et al., 2008)*.

OSD causes significant morbidity and has a negative impact on treatment compliance, quality of life, and surgical outcomes *(Broadway, 1994; Pisella et al., 2004; Chawla et al., 2007; Pouyeh et al., 2012)*, rendering OSD a global public health problem.

OSD includes blepharitis, Dry Eye Disease (DED) and Allergic Eye Disease (AED) *(Amescua et al., 2019; Messmer, 2022; Lorenzana-Blanco et al., 2023; Patek et al., 2023)*.

Blepharitis

One of the most common chronic inflammatory diseases of the eyelid margin is blepharitis. Blepharitis can result in irreversible changes to the eyelid margin and even vision loss from corneal ulceration, neovascularization, or superficial keratopathy. Over the years, blepharitis has been categorized by a variety of classification systems, with the most recent classification to be dependent on the anatomic location *(Amescua et al., 2019)*. The traditional categories of staphylococcal and seborrheic blepharitis include anterior blepharitis, which affects the follicles and base of the eyelashes. Meibomian gland dysfunction (MGD) constitutes the main etiology for posterior blepharitis, which affects the posterior lid margin (the segment that contacts the cornea and bulbar conjunctiva) *(Pflugfelder et al., 2014)*.

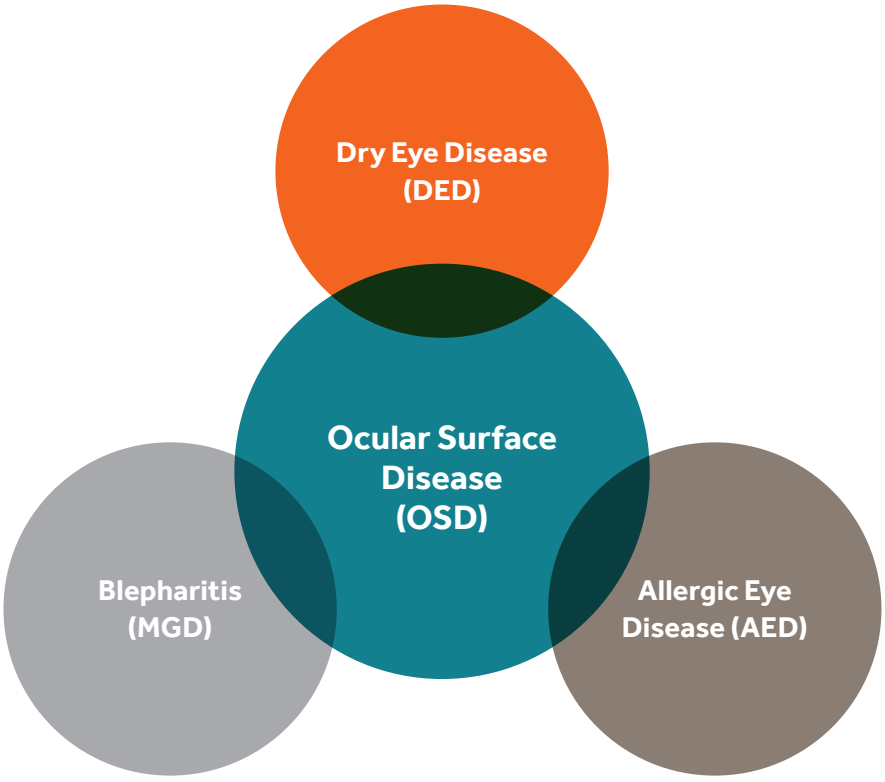
Dry Eye Disease (DED)

There are significant differences in the prevalence of DED, which ranges between 5% and 34% of the population. A number of reasons, including geographical location, study population changes, and a lack of consistent diagnostic criteria, are responsible for the significant global discrepancy in prevalence *(Hantera, 2021)*. DED is characterized by a loss of homeostasis, leading often to hyperosmolarity or osmolar instability of the tear film, damage to the ocular surface epithelia, inflammation of the lacrimal gland and ocular surface, and abnormalities in neurosensory function. DED is classified into two groups: aqueous-deficient with decreased tear production and hyperevaporative with excessive tear film evaporation *(Lemp, 2007; Craig et al., 2017)*.

The Asian Dry Eye Society (ADES) also recognizes a third subtype, characterized by decreased wettability of the cornea and conjunctiva, related to a deficiency in membrane-associated mucin. *(Tsubota et al., 2020)*.

Allergic Eye Disease (AED)

Ocular allergies are a group of disorders caused by inflammation of the cornea. Of these, 15–25% of the population suffers from seasonal allergic conjunctivitis and perennial allergic conjunctivitis, which are the most common ocular allergies. Atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC) are more severe disorders. The latter, known as GPC, has been linked to several allergy diseases even though it is actually a response to repeated irritation. The immunoglobulin E-mast-cell system, which is activated by allergens that cause histamine release and subsequent proinflammatory mediators like prostaglandins, leukotrienes, and cytokines, is responsible for mediating ocular allergies. This system ultimately recruits neutrophils, macrophages, and eosinophils, and causes a late-phase reaction in the conjunctival tissues. These events cause the inflammatory response manifested by swelling (chemosis), ocular injection (redness), itching (pruritus), and tearing, and a possible white ropey discharge *(Kimchi et al., 2020 ; Leonardi et al., 2021)*.



Definition of Dry Eye Disease

According to the Tear Film & Ocular Society Dry eye Workshop II (TFOS DEWS II), DED is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological role (Craig, Nelson, et al., 2017).

Ocular Surface Disease (OSD) and DED are closely interrelated and are used interchangeably as terms. However, it is imperative to highlight the distinction between these two medical terms.

An important function of the ocular surface is to protect the eye from injury, infection, and desiccation *(Ramos et al., 2015)*.

The lacrimal functional unit is composed of the lacrimal glands (both main and accessory), the ocular surface and the interconnecting sensory and autonomic innervation (Figure 1) *(Stern et al., 2004; Yazdani et al., 2019)*.

Dysfunction or disturbance of any component of the lacrimal unit can alter the quality or quantity of tears, and thus cause derangement of tear film homeostasis, resulting in DED symptoms.

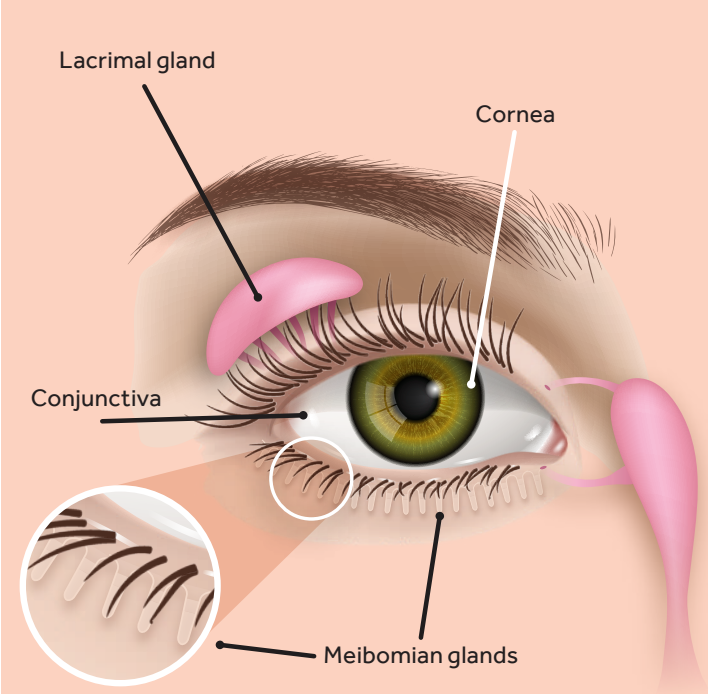


Figure 1: Schematic representation of the main glands of the lacrimal functional unit *(Yazdani et al., 2019)*.

A clinical decision algorithm, based on the current knowledge of the pathophysiology of DED, seeks to provide accurate classification of potential DED *(Craig, Nichols, et al., 2017)*, (Figure 2). The classification scheme is based on the predominant, but often overlapping, etiologies of aqueous deficient and evaporative dry eye (Figure 2). In more detail:

— DED exhibits both symptoms and signs and can be differentiated from other OSD with the use of triaging questions and ancillary testing. Symptomatic patients without clinical signs do not fall into the DED group but are differentiated into pre-clinical dry eye or neuropathic pain (non-OSD). Asymptomatic patients with demonstrable signs are differentiated into patients with poor corneal sensitivity, or those with prodromal signs, who are at risk of developing manifest DED with time or provocation, for example following ophthalmic surgery (Figure 2).

— Etiological classification of DED: Aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) are the two most frequent conditions, which are not mutually exclusive. ADDE can occur without evident signs of EDE and conversely *(Craig, Nichols, et al., 2017)* (Figure 2).

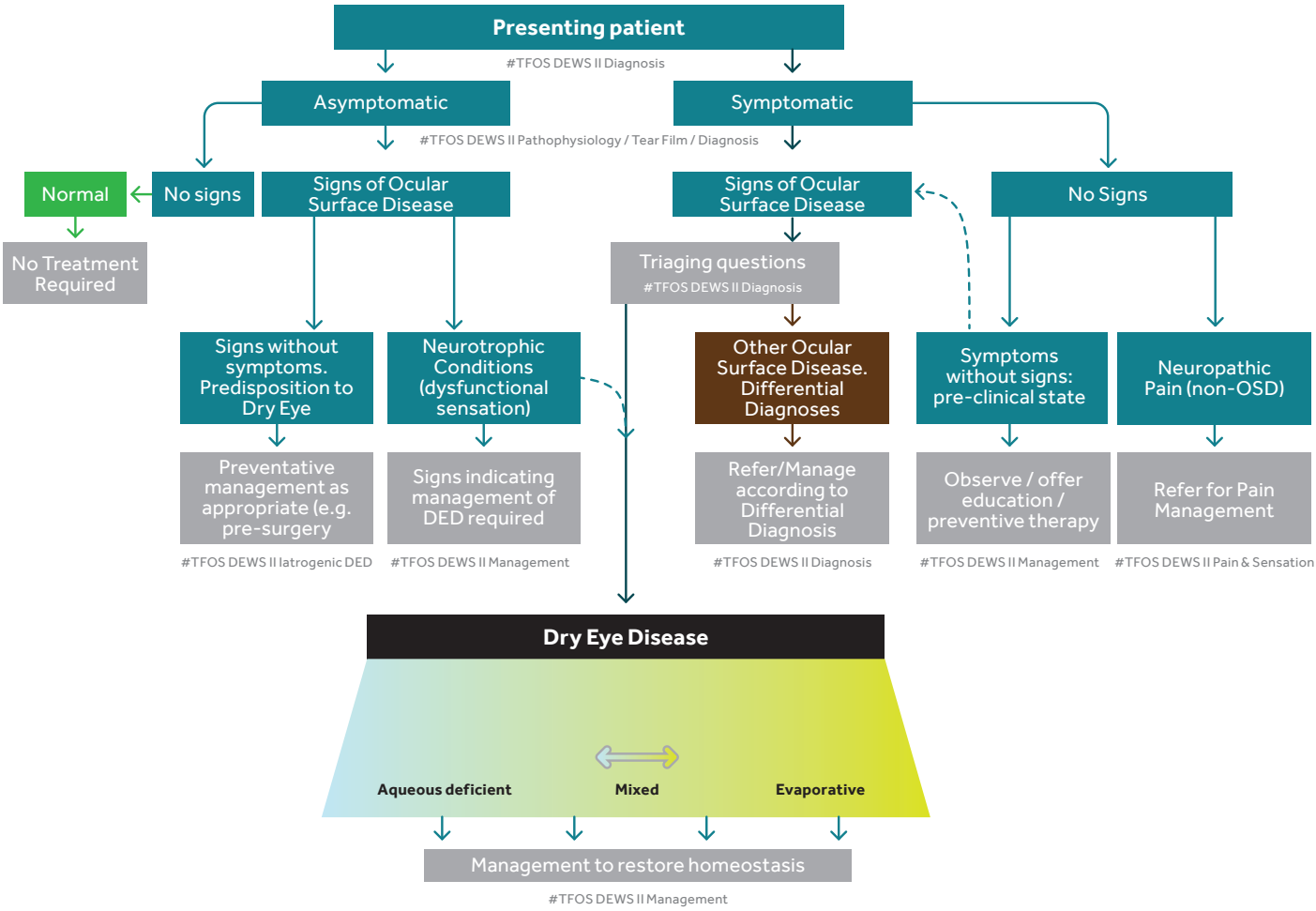


Figure 2: Classification of dry eye disease (DED). OSD: Ocular Surface Disease. *(Craig, Nichols, et al., 2017)*.

Pathophysiology of Ocular Surface Disease

Amongst the currently identified core mechanisms of the ocular surface desiccation, leading to dry eye disease are **tear film hyperosmolarity** and **tear film instability**. They can initiate, amplify, and potentially change the character of dry eye over time to other OSD.

Tear osmolarity is not a constant value *(Murube, 2006)*. Also diurnal variation occurs *(van Setten, 2019)*. If osmolarity rises in situations of a low, aqueous tear flow, or due to excessive evaporation, or a combination of these events, hyperosmolarity develops.

Tear hyperosmolarity causes cell stress related damage to the surface epithelium leading to the activation of various inflammatory events at the ocular surface, a release of inflammatory mediators into the tears, and an increased **tear film instability**. Hyperosmolarity associated processes apparently constitute core events of the so called vicious circle of dry eye disease *(Baudouin et al., 2014, Bron et al., 2017; Craig, Nelson, et al., 2017)*.

The two main types of DED (Figure 3) are EDE and ADDE, where EDE and mixed EDE/ADDE forms account for more than 80% of cases *(Messmer, 2015)*:

— In ADDE, tear hyperosmolarity results when lacrimal secretion is reduced, in conditions of normal evaporation from the eye. Around 10% of patients with dry eye have a solely aqueous-deficient disorder.

Moreover, variations in osmolarity and osmokinetics in ADDE can influence ocular surface sensitivity, leading to additional pathologies. Diurnal osmolarity variations and frequent osmotic shifts challenge ocular surface homeostasis, triggering inflammatory responses and cellular stress that may amplify dry eye symptoms. Specifically, osmotic cycles can stress corneal epithelial cells, sometimes beyond their osmoadaptive capacity, leading to altered protein synthesis, inflammation, and even apoptosis over time *(van Setten, 2024)*.

— In EDE, tear hyperosmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland.

ADDE:

EDE:

Figure 3: Pathogenesis of Aqueous Deficient Dry Eye (ADDE) and Evaporating Dry Eye (EDE).

Risk Factors and Symptoms of Ocular Surface Disease

Several risk factors have been reported to be associated with the development of OSD (Figure 4), *(Bron et al., 2017; Craig, Nelson, et al., 2017; Gomes et al., 2017)*:

Sjögren's Disease and associated autoimmune diseases

- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Systemic Sclerosis

Inflammatory (Sarcoidosis, and ocular Graft-versus-Host disease)

Other Disorders (Meige Syndrome, Diabetes Mellitus)

Lacrimal gland deficiency

- Blocking sensory drive to lacrimal gland that is essential to maintain osmolar homeostasis

Medication Use

- Antihistamines, antimuscarinics, beta-blockers, diuretics, psychotropic drugs, anticholinergics, antiandrogens

Dry eye due to cancer therapy

- Chemotherapeutics and radiation therapy

Lymphoma

Age- and Sex-related

Refractive Surgery including LASIK surgery

Contact Lens Wear

Low humidity, high room temperature and poor air quality

Figure 4: Key Risk Factors Contributing to the Development of Ocular Surface Disease (OSD).

Many OSD symptoms are common between DED, blepharitis, Meibomian glands dysfunction (MGD) and ocular allergies or result from ocular surgery (Figure 5), *(Bron et al., 2017; Gomes et al., 2017)*. In patients with glaucoma, the development and progression of OSD symptoms is closely linked to the use of anti-glaucoma medication (frequency and number of eye drops) *(Batra et al., 2014)*. This has been specifically shown for benzalkonium chloride (BAK), a common preservative in anti-glaucoma medications *(Pisella et al., 2004)*.

Dry, gritty, sandy sensation	**Redness**	**Foreign body sensation**
Tearing	**Ocular pain**	**Itching, Burning**
Mucous Discharge	**Sensitivity to light**	**Fluctuation of vision**
	Contact lens intolerance	

Figure 5: Key Ocular Surface Disease (OSD) symptoms.

Key Learning points

— Ocular surface disease (OSD) is a common global health issue; its incidence increases with age, reaching 30% in the general population aged ≥50.

— OSD includes chemical and thermal burns, blepharitis, dry eye disease (DED) and allergic eye disease (AED).

— According to the TFOS DEWS II, Dry Eye is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis, accompanied by ocular symptoms.

— Tear hyperosmolarity and tear film instability constitute the core mechanisms of the dry eye process.

— DED is classified as aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE), with overlapping etiologies.

— In glaucoma patients, the progression of OSD symptoms is often significantly influenced by the anti-glaucoma medication itself or, more commonly and specifically, by the preservatives in the eye drops, particularly benzalkonium chloride (BAK)

Introduction to Glaucoma

Glaucoma is one of the most common sight threatening conditions, characterized by an optic neuropathy associated with structural damage to the optic nerve and progressive degeneration of retinal ganglion cells *(Foster, 2002; Weinreb et al., 2014; Jayaram et al., 2023)*. Glaucoma is the leading cause of global irreversible blindness. In 2013, the number of people (aged 40-80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040 *(Tham et al., 2014)*.

The aqueous humor is drained through two independent pathways: the trabecular meshwork and uveoscleral outflow pathway (Figure 6). An imbalance between aqueous humor production and its outflow causes a rise in intraocular pressure (IOP) that can damage the optic nerve in the back of the eye, leading to progressive loss of the visual field and potentially visual dysfunction and blindness (Figure 6).

Elevated intraocular pressure is identified as main pathological force of glaucoma. Pressure reduction is hence prime target for these patients. Primary open-angle glaucoma (POAG) is subdivided depending on eye pressure and normal tension glaucoma does take a considerable toll in vision loss of the world population *(Langbøl et al., 2024)*. In the following we address mainly the issue of elevated pressure in the eye as it is here where eventually surgery is needed to reduce the pressure. It is this surgery that could lead to severe deterioriation of the ocular surface balance and, eventually dry eye.

Development of Glaucoma

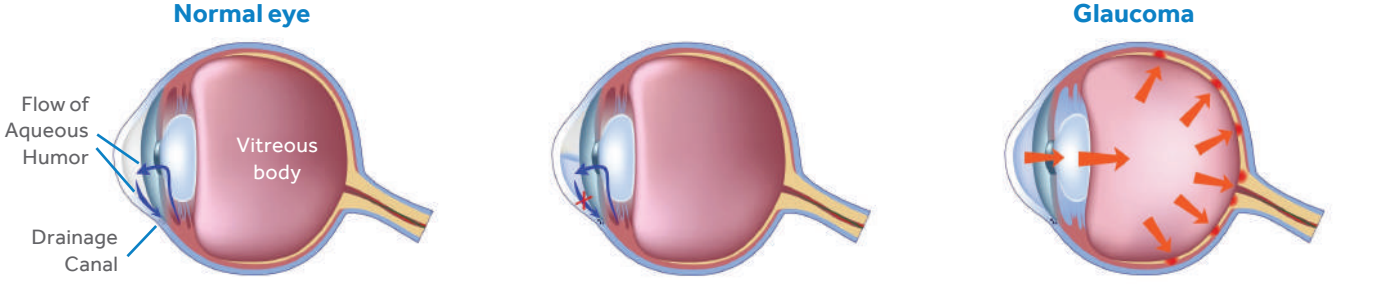


Figure 6: Schematic difference in aqueous humor flow between the normal eye and the glaucomatous eye and its consequences for the eye (Image from https://meetcaregivers.com/glaucoma-signs-symptoms-prevention).

Glaucoma can be classified into 3 subtypes presented in Figure 7.

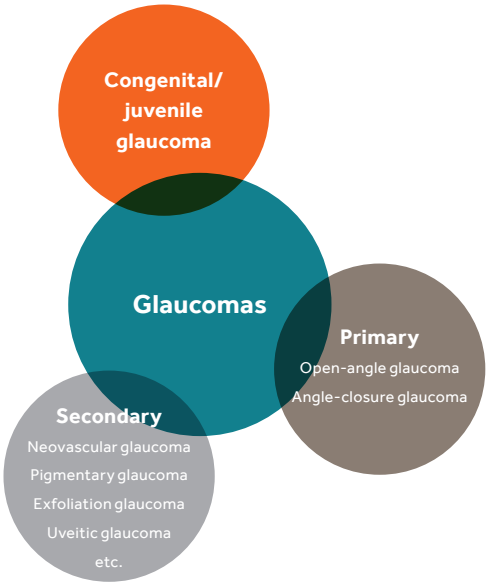


Figure 7: Subtypes of glaucoma (EGS guidelines, 2021).

The two most common forms of glaucoma are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), with the former approximately seven times more common than the latter in the United States and Europe *(Gupta & Chen, 2016)*.

The normal aqueous humor flow is depicted in Figure 8A. In POAG, there is increased resistance to aqueous outflow through the trabecular meshwork (Figure 8B) *(Gupta & Chen, 2016)*.

In PACG, access to the drainage pathways is obstructed by either appositional or synechial angle closure (clinically relevant if there is more than 180 degrees of the angle occluded) (Figure 8C) *(EGS Guidelines, 2021)*.

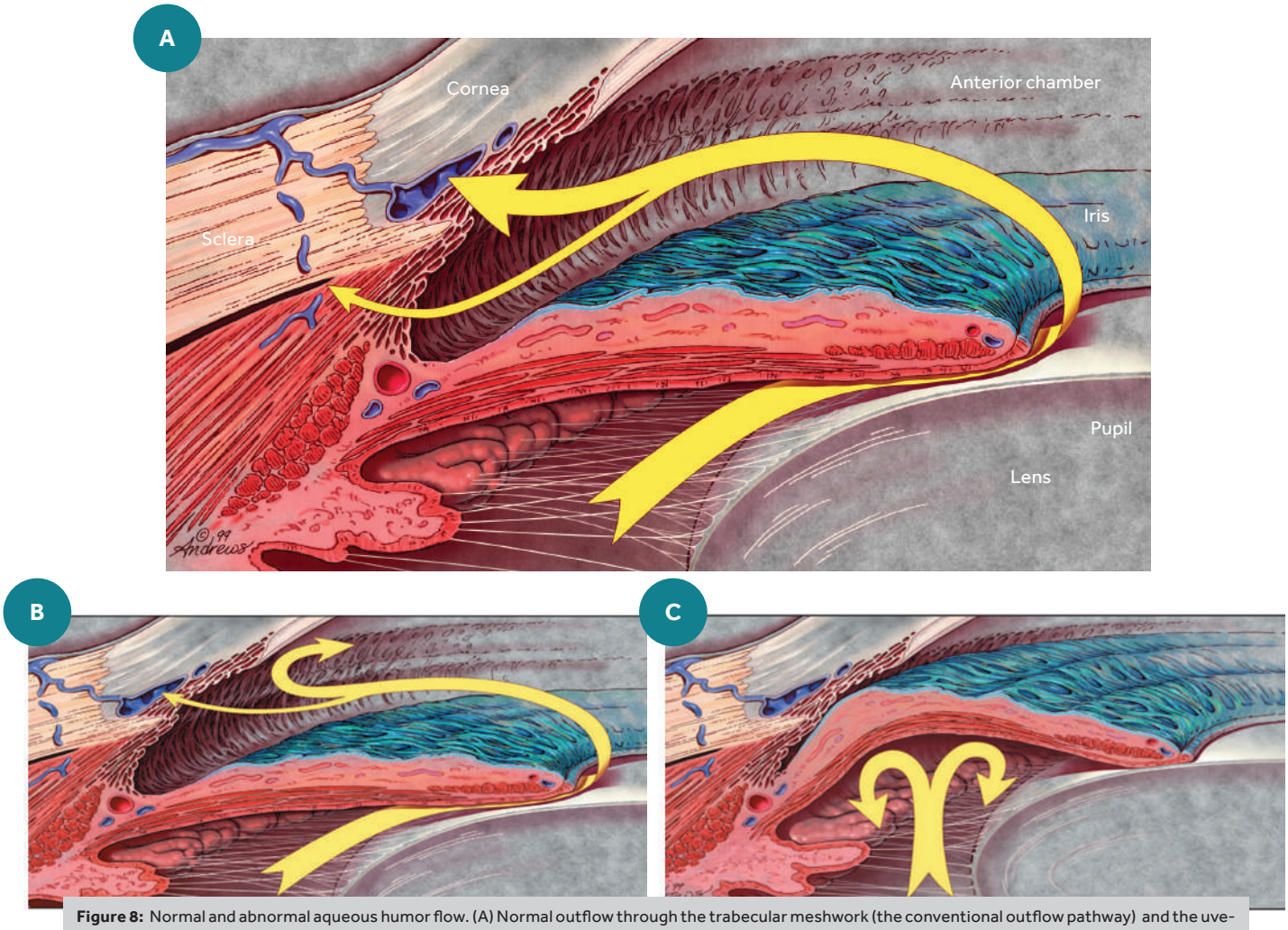


Figure 8: Normal and abnormal aqueous humor flow. (A) Normal outflow through the trabecular meshwork (the conventional outflow pathway) and the uveoscleral routes (the unconventional outflow pathway) and related anatomy. Most aqueous flow is through the trabecular meshwork. Each pathway is drained by the eye's venous circulation. (B) In primary open-angle glaucoma, aqueous outflow by these pathways is diminished about 85%. (C) In angle-closure glaucoma, the iris is abnormally positioned so as to block aqueous outflow through the anterior chamber (iridocorneal) angle (adapted from *Gupta & Chen, 2016*).

Risk Factors Contributing to Glaucoma

Although factors contributing to glaucoma progression have not been fully characterized, risk factors for OAG are presented in Table 1 *(Kwon et al., 2009, Weinreb et al., 2014, Lee et al., 2021)*.

Ocular risk factors and signs

Intraocular Pressure (IOP)

— Elevated baseline IOP

Optic disc

— Narrowing or loss of neuroretinal rim

— Disc hemorrhage

Myopia

Decreased ocular perfusion pressure

Non-ocular risk factors

Increasing age

African descent

Hispanic ancestry

Family history

Genetics

— Myocillin

— Optineurin

— Apolipoprotein

— Etc, depending on the glaucoma subtype

Migraine

Corticosteroids

Table 1: Key Risk Factors contributing to the development of Primary Open-Angle Glaucoma (POAG)

Pathogenesis of Glaucoma

Although the pathogenesis of primary open-angle glaucoma is not fully understood, the elevated IOP is related to retinal ganglion cell dysfunction and potentially death *(Huang et al., 2005)*.

Lowering IOP is the only evidence-based treatment to decrease glaucoma progression). Elevated IOP has been shown to induce oxidative stress and ischemia. This may lead to activation of microglia and macroglia, potentially causing dysfunction of the retinal ganglion cells (Figure 9) *(Baudouin et al., 2021)*.

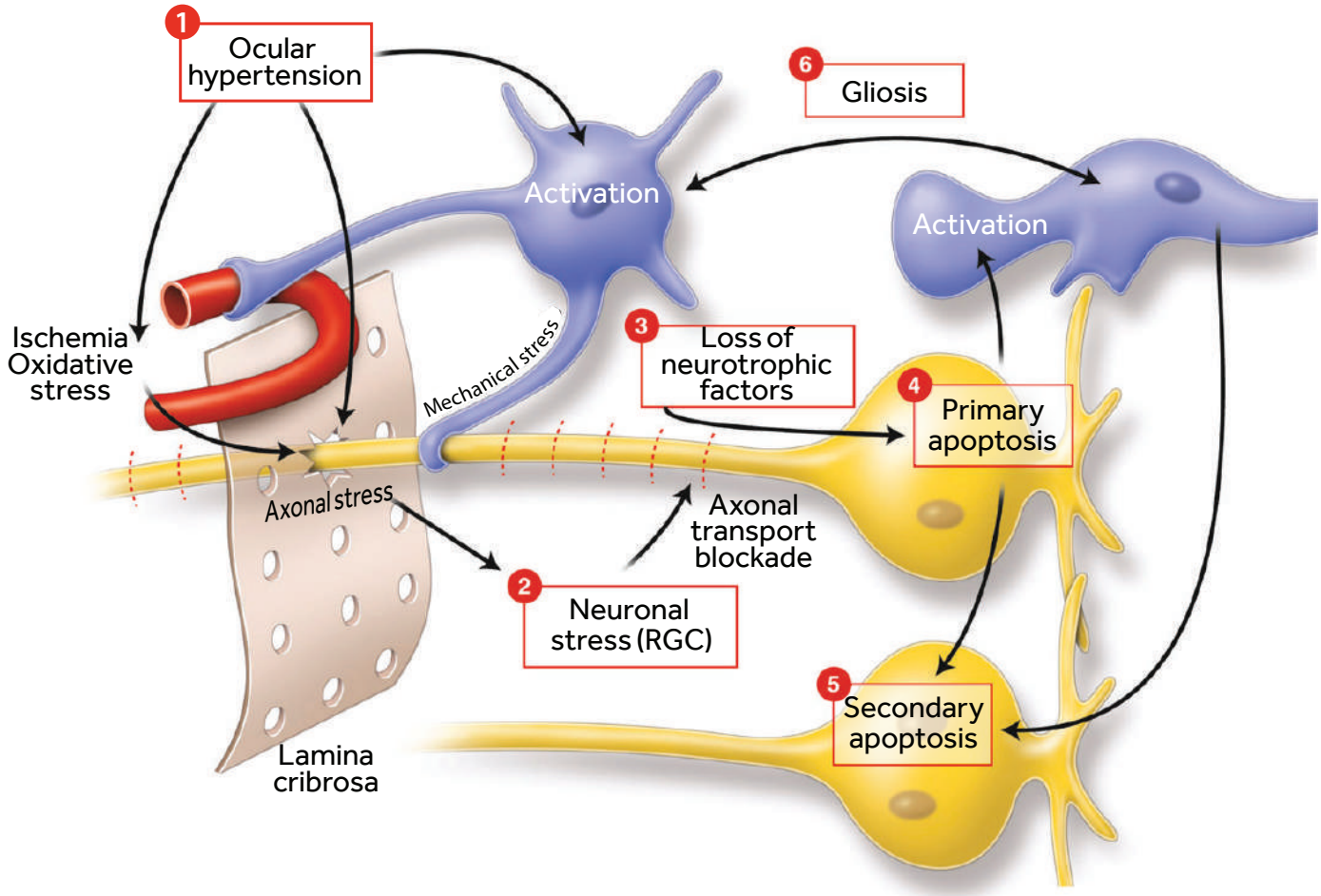


Figure 9: Schematization of potential pathophysiological principles involved in glaucomatous degeneration of retinal ganglion cells Adapted from *Denoyer, 2014*.

For many years, glaucoma was characterized by a statistically elevated IOP. However, the concept that a statistically elevated IOP is a defining feature of glaucoma has been universally discarded. This is based on several studies documenting the typical loss of retinal ganglion cells and typical visual field loss in patients with glaucoma with a statistically normal IOP and studies that conversely document individuals with a statistically elevated IOP without signs of glaucoma.

Among many hypotheses, one suggested mechanistic pathway for how IOP can lead to retinal ganglion cell loss and thus glaucomatous optic neuropathy is shown in the Figure 10:

Thus, although IOP is one of the major risk factors for the development and worsening of glaucoma, elevated IOP does not define glaucoma, which is consensually defined by a progressive loss of retinal ganglion cells and their axons, associated with visual field loss *(Foster, 2002; Weinreb et al., 2014)*.

Apart from IOP, vascular abnormalities, such as i.e. insufficient blood supply and reduced ocular blood flow, have been identified as a pathogenetic mechansim of glaucoma, independent of IOP pathogenesis of glaucoma is diverse. This mechanism is linked with vascular dysregulation leading to both low perfusion pressure and insufficient autoregulation, despite IOP. Ocular perfusion pressure and its fluctuations should be tested in glaucoma patients, even in case of normal IOP. *(Alexandrescu et al., 2010; Mursch-Edlmayr et al., 2021; Flammer et al., 2002)*. Inflammation has also been proposed as a potential causal factor in the pathogenesis of glaucoma. *(Vohra et al., 2013; Baudouin et al., 2021).*

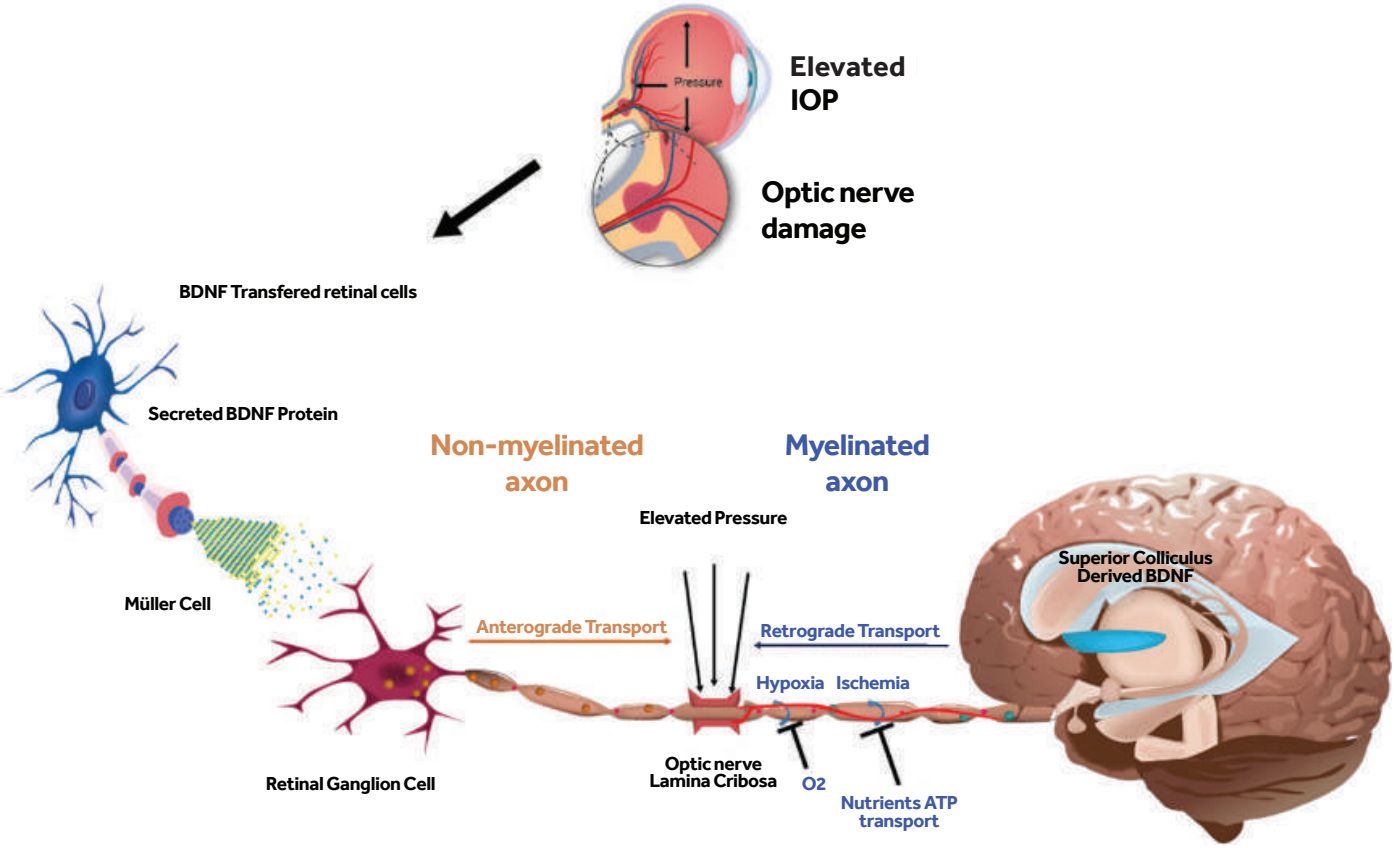


Figure 10: The optic nerve head is damaged by increased intraocular pressure (IOP). A change in the choroidal, anterograde and retrograde obstruction of axonal transport in the Optic Nerve Head (ONH), where the axons leave the eye, is triggered by increased pressure in the lamina cribrosa from the optic nerve. This reduces the transmission of trophic signals, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BNDF), from terminal axons to the cell bodies of neurons, as well as the transport of oxygen and nutrients to the retina's layers, which results in ischemia and hypoxia. Axons of non-myelinated retinal ganglion cells are highly active and energy dependent, which is associated with a high number of mitochondria in this optic nerve segment. Axoplasmic flow from the lateral geniculate nucleus and the superior colliculus to the retinal ganglion cells is altered by changes in energy supply, contributing to the reduction in neurotrophins and axon damage. Muller cells may have neuroprotective effects after damage due to the release of neurotrophic factors, such as BDNF. IOP: Intraocular Pressure (Reproduced from *Evangelho et al., 2019*).

Key Learning points

— Glaucoma is one of the most common sight-threatening eye conditions and the leading cause of irreversible blindness worldwide. It is defined as progressive optic neuropahty associated with structual damage to the retinal ganglion cells with characteristic loss of the visual field .

— The two most frequent types of glaucoma are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). POAG can be subdivided into phenotypes with and without increased IOP. In many cases, there is a resistance in the drainage system despite a normal anatomy. PACG is characterized by an anatomical obstructed drainage pathway due to appositional or synechial angle closure.

— Risk factors for POAG include elevated IOP, increasing age, family history, genetics and use of corticosteroïds. Risk factor other than IOP are *e.g.* myopia.

Ocular Surface Disease and Glaucoma

Ocular Surface Disease Prevalence in Glaucoma Patients

The prevalence of OSD is notably high among patients with glaucoma, primarily as a result of the treatments used *(Nijm et al., 2023)*.

Leung et al, 2008

59% of patients with glaucoma or ocular hypertension reported dry eye symptoms, while severe symptoms were reported by 27% of patients.

Patients with primary open-angle glaucoma or ocular hypertension who were on IOP-lowering medication regimen developed mild (48.4%), moderate (21.3%) and severe (13.8%) DED.

Ghosh et al 2012

Significant increase in the prevalence of dry eye signs was observed in the glaucoma population (70.3%, compared with controls, 33%).

Baudouin et al 2013

51% of patients with glaucoma showed significant dry eye symptoms, including mild to moderate in 30% of patients, and severe in 21%.

Mylla Boso et al 2020

73% of the patients suffering from glaucoma reported severe symptoms of dry eye.

Monjane & Makupa 2020

Prevalence of dry eye in patients with glaucoma was 79.7%. Severity of DED was mild, moderate and severe for 22.1%, 16.0% and 61.9% of the patients, respectively.

Signs and Symptoms of Ocular Surface Disease in Glaucoma Patients

Common ocular symptoms and signs reported by glaucoma patients undergoing treatment with topical medications are outlined in Table 2 (adapted from *Jaenen et al., 2007)*:

Ocular Surface Disease symptoms

- **Ocular discomfort**
- **Foreign body sensation**
- **Stinging or burning**
- **Dry eye sensation**
- **Tearing**
- **Eyelid itching**
- **Eye redness**
- **Photosensitivity**
- **Increased blinking**
- **Blurred vision**

Ocular Surface Disease signs

- **Decrease in tear clearance**
- **Blepharitis**
- **Eczema**
- **Abnormal Schirmer test**
- **Conjunctival Hyperemia**
- **Lid margin vascularization**
- **Cornea/Conjuctiva staining**
- **Decreased corneal sensation**
- **Abnormal tear osmolarity**
- **Abnormal tear break-up time test**
- **Meibomian Gland Dysfunction (MGD)**

Table 2: Common ocular symptoms and signs in glaucoma patients treated with topical medications.

Key Learning points

— A high incidence rate of Dry Eye Disease (DED) is observed among glaucoma patients.

— Use of topical glaucoma medications is commonly associated with ocular discomfort, eye redness, decreased corneal sensation, photosensitivity, and abnormal tear osmolarity.

Glaucoma Treatment

Glaucoma typically progresses without noticeable symptoms in its early stages. Only in advanced stages, after significant visual field loss has occurred, do patients begin to notice issues, such as tipping a coffee cup or stumbling over steps. When symptoms occur, the loss of visual function is thus pronounced, which is why there is often at the same time a reduction in quality of life and a reduced ability to perform daily activities, such as driving a car *(Weinreb et al., 2014)*.

IOP-lowering is, this far, the sole proven effective intervention for treating glaucoma even if elevated IOP is not the only risk factor of glaucoma. It has also been shown to be effective in glaucoma patients with IOP within the "normal" range. *(Garg & Gazzard, 2020)*.

Although treatment is usually initiated with IOP-lowering eye drops, laser trabeculoplasty, minimal invasive glaucoma surgery (MIGS), non-penetrating and penetrating surgery may also be used to slow disease progression *(Garg & Gazzard, 2020)*.

Treatment With Eye Drops

Several different classes of pressure-lowering medications are available (Table 3).

Class of anti-glaucoma medication	Active ingredients	
	Formulated as preserved eye drops	Formulated as Preservative-Free (PF) eye drops
Prostaglandin analogs	Latanoprost, bimatoprost, travoprost, tafluprost	Latanoprost, travoprost, tafluprost, bimatoprost (as single unit dose)
Beta-blockers	Timolol, levobunolol, carteolol, levobetaxolol, betaxolol, metipranolol	Timolol, levobunolol, Bataxolol (as single unit dose)
Alpha-adrenergic agonists	Brimonidine, apraclonidine	Brimonidine
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide	Dorzolamide
Miotic agents or Cholinergic agonists	Pilocarpine, carbachol	Pilocarpine
Rho-Kinase Inhibitors	Netarsudil, ripasudil	-

Table 3: Classes of medications used to lower IOP *(Weinreb et al., 2014; Schuster et al., 2020; Wang et al., 2023)*.

A network meta-analysis on topical first-line drugs demonstrated that prostaglandin analogs achieve the greatest reduction in intraocular pressure (IOP), followed by beta-blockers, alpha2-adrenergic agonists, and carbonic anhydrase inhibitors *(Li et al., 2016)*. In addition, Rho kinase inhibitors have entered the market *(Clement Freiberg et al., 2022)*. A meta-analysis has shown that these modalities are non-inferior to beta-blockers in reducing IOP *(Wandji et al., 2024)*.

Miotic drugs can be a further alternative but are now hardly ever used as the treatment of first resort *(EGS guidelines 2021)*.

Prostaglandin analogues and carbonic anhydrase inhibitors lower IOP during both the day and night, while beta-blockers and alpha-adrenergic agonists are largely effective only during the day *(EGS guidelines 2021)*.

Topical treatments such as eye drops can have significant systemic side effects. They have been described in particular during the use of topical beta-blockers, which are contraindicated in patients with a history of chronic pulmonary obstructive disease, asthma or bradycardia *(Weinreb et al., 2014)*. Although a population-based cohort study recently indicated that topical beta-blocker is not associated with increased risks of cardiovascular and respiratory diseases in patients with glaucoma, ophthalmologists are still advised to prescribe topical beta-blockers with caution *(Chen et al., 2020)*.

Glaucoma eye drops and their ocular surface adverse effects

The adverse effects of preservatives in IOP-lowering eye drops on the ocular surface and their involvement in OSD development have been thoroughly investigated.

Most prescribed anti-glaucoma eye drops contain preservatives to prevent microbial contamination and biodegradation, thus maintaining drug's potency as well as prolonging its shelf life *(Kaštelan et al., 2013)*.

BAK is one of the most used preservatives in eye drops.

BAK is a quaternary ammonium compound that acts as a detergent whose antimicrobial activity arises from its ability to lyse and disrupt cell membranes. Hence, it impacts the tear film by disrupting the lipid layer, causing evaporation of its aqueous component, increasing epithelial permeability and reducing the tear-film breakup time, leading to dry eye symptoms *(Baudouin et al., 2010; Kaštelan et al., 2013; Kestelyn et al., 2019)*.

The pathogenic results of BAK's long-term use are summarized in Figure 11. *(Jaenen et al., 2007; Sarkar et al., 2012; Kaštelan et al., 2013; Cetinkaya et al., 2015 - ref: PMID: 37302545)*.

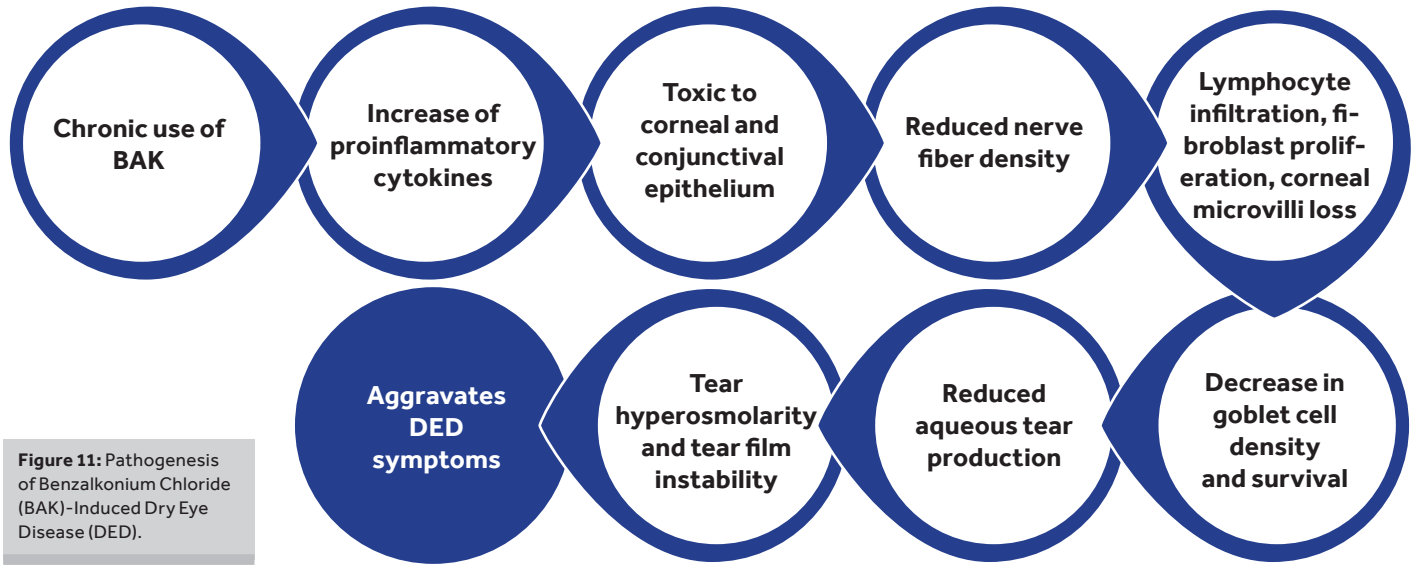


Figure 11: Pathogenesis of Benzalkonium Chloride (BAK)-Induced Dry Eye Disease (DED).

From another viewpoint, the mechanisms of toxic reaction on the ocular surface by BAK are illustrated in Figure 12 *(Debbasch et al., 2001; Pisella et al., 2004; Kaštelan et al., 2013)*.

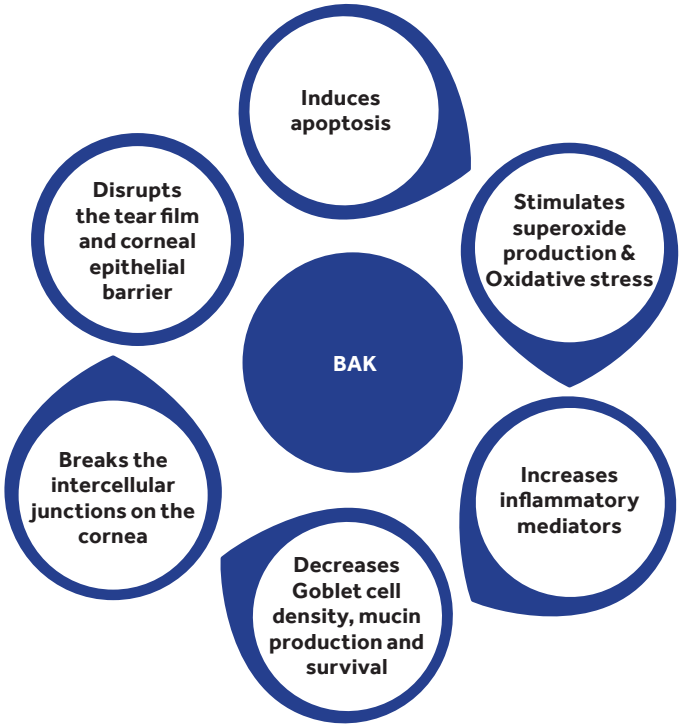


Figure 12: Mechanisms of Benzalkonium chloride (BAK)-induced toxicity on the ocular surface.

In vitro study has demonstrated that even at the 0.01% concentration used in most eye drops, BAK induces oxidative stress by stimulation of superoxide production that promotes apoptosis, (Figure 13) *(Debbasch et al., 2001)*.

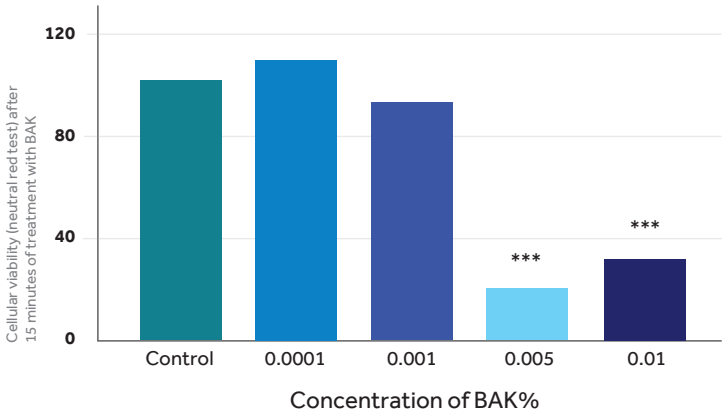


Figure 13: Cultured conjunctival cells incubated with varying concentrations of Benzalkonium chloride (BAK). Note that cellular viability significantly decreases (*** p <0.001) with increased concentrations of BAK *(Debbasch et al., 2001)*.

Several strategies are being developed for alternative approaches to reduce or eliminate the use of preservatives in anti-glaucoma eye drops (Figure 14), *(Baudouin et al., 2010; Bagnis et al., 2011)*.

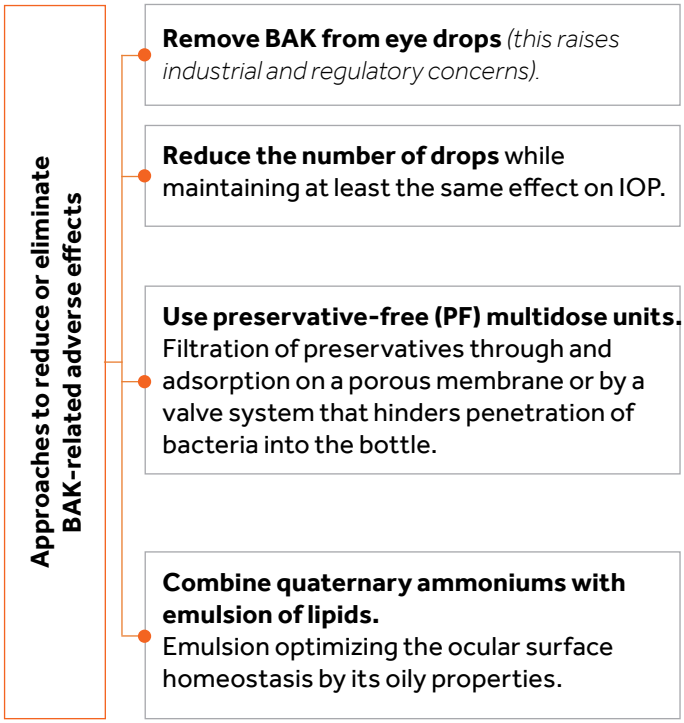


Figure 14: Approaches to reduce or eliminate Benzalkonium chloride (BAK)-related adverse effects. IOP: Intraocular Pressure.

The target IOP should be achieved with the least number of medications and minimum adverse effects. When medical treatment does not achieve adequate IOP reduction with acceptable adverse effects, laser or incisional surgeries are indicated *(EGS guidelines 2021)*.

Associated risk factors for Ocular Surface Disease development with Eye Drops in glaucoma patients

High risk of developing OSD, including DED, has been associated with:

— long-term use of IOP-lowering anti-glaucoma medication containing preservatives (BAK) (Table 4) *(Erb et al., 2008; Baudouin et al., 2010; Ghosh et al., 2012; Baudouin et al., 2013; Rossi et al., 2013)*

— multitherapy (Table 4) (*i.e.*, receiving more than one medication (multiple eye drops) *(Erb et al., 2008; Rossi et al., 2009; Baudouin et al., 2010; Ghosh et al., 2012; Baudouin et al., 2013; Rossi et al., 2013)*

— glaucoma surgery such as trabeculectomy (Table 4) *(Baudouin et al., 2012; Lee et al., 2013; Lam et al., 2015)*

Two strategies may be considered when OSD develops in glaucoma patients:

— Additive strategy, which involves alleviating symptoms with Preservative-free (PF) lubricant eye drops, antiallergic drugs and/or corticosteroids. If using corticosteroids IOP must be carefully monitored.

— Substraction strategy, which includes the identification and removal of potentially toxic eye drops, such as eye drops, anti-glaucoma (e.g., stop brimonidine) or switch to a PF medication *(Dubrulle et al., 2018)*. For additional information, please refer to "Clinical Cases, Case Study 2" section, below.

— Future strategies could involve incorporating treatments like intense pulsed light (IPL) therapy for glaucoma patients, alongside other emerging approaches for managing DED and OSD.

Chronic use of anti-glaucoma medication containing preservatives

After 1 year of receiving anti-glaucoma eye drops, about 45% of patients developed DED, while after 15 years, the rate increased to 58.9% *(Erb et al., 2008)*

57% of patients treated with ocular medications for glaucoma for at least 10 years had dry eye symptoms *(Baudouin et al. 2013)*

Multitherapy

50.9% patients who used one type of anti-glaucoma eye drop developed dry eyes, while 65.3% of those receiving four different anti-glaucoma eye drops *(Erb et al., 2008)*

39% and 40% of patients developed dry eye with two and three drugs, respectively, while only 11% of patients who received one eye drop developed dry eyes *(Rossi et al., 2009)*

71% of patients treated with 3 or more glaucoma medications developed DED, while 54% and 38% who were treated with two medications or were in monotherapy, developed DED, respectively *(Baudouin et al. 2013)*

Patients undergone trabeculectomy

Trabeculectomy is suggested to have the deleterious effects on ocular surface including conjunctival epithelial spongiosis and reduced number of conjunctival goblet cells *(Baudouin, 2014; Lee et al. 2013)*

Tear film osmolarity was shown to be increased in post-trabeculectomy patients even after 6 months without preserved medications compared to subjects without glaucoma and DED *(Lee et al. 2013)*

Preoperative-compromised ocular surface and dry eye symptoms can be exacerbated after glaucoma filtration surgery disruption of the ocular surface *(Lam et al. 2015)*

Table 4: Risk factors for developing Ocular Surface Disease (OSD) in glaucoma patient. DED: Dry Eye Desease

Correlation between multitherapy and the long-time use of BAK on the increased incidence of dry eye symptoms in glaucoma patients has been demonstrated in clinical studies (Figure 15).

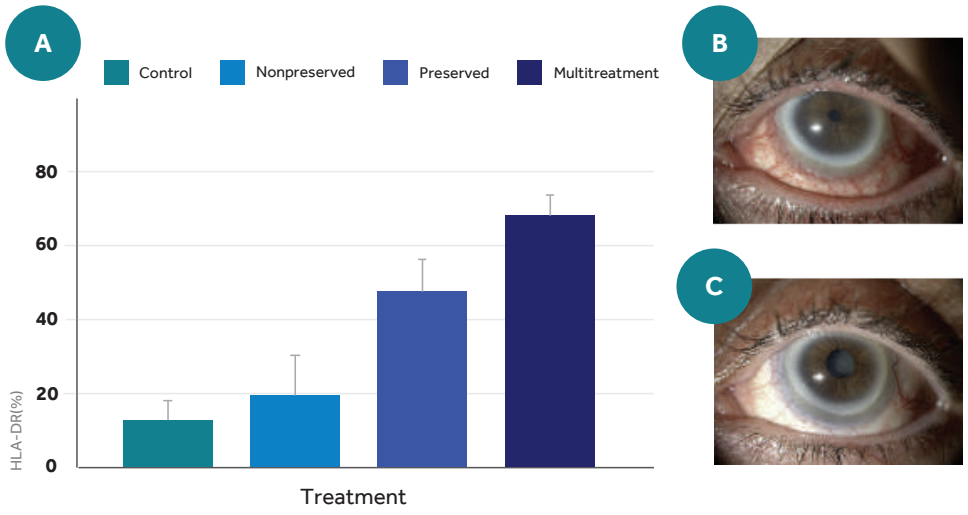


Figure 15: (A) Comparative expression of HLA-DR class II antigens using flow cytometry in impression cytology specimens in normal subjects and glaucomatous patients treated with unpreserved or preserved beta-blocker or receiving multiple therapy. (B) Example of toxic reaction resulting from long term use of multiple treatment for glaucoma: note that limbus is distended, hyperemic from inflammatory infiltrates. (C) Few weeks after surgery and treatment, the ocular surface rapidly recovered (Adapted from *Baudouin et al., 2010*).

Association between the severity of DED and the number of daily anti-glaucoma eye drops has been demonstrated (Figure 16).

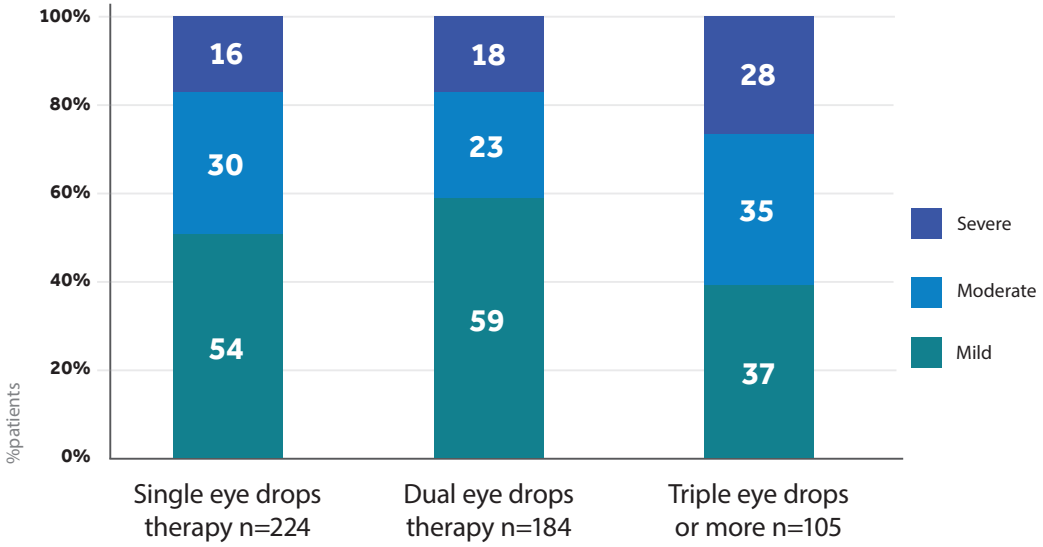


Figure 16: Severity of Dry Eye Disease (DED) in relation to the number of eye drops. Note the higher percentage of severity when three or more drops are applied to patients with Primary Open Angle Glaucoma (POAG) / Ocular Hypertension (OHT) *(Baudouin et al., 2013)*.

OSD can exacerbate IOP control through chronic inflammation of the ocular surface, and substituting preserved eye drops with PF drops can improve both OSD and IOP control.

— In a series of 4 patients with inadequately controlled POAG and OSD administration with PF equivalents of topical anti-glaucoma medications resulted in a clinically and statistically significant improvement in OSD symptoms and signs as well as in a statistically significant reduction in the mean IOP *(Batra et al., 2014)*.

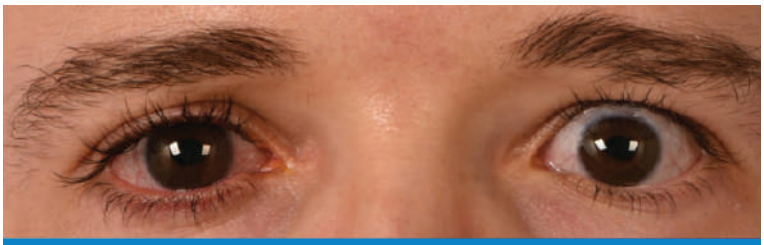
— Standard concentrations of BAK range from 0.015% to 0.02% in ophthalmic solutions, however, toxicity has been demonstrated at concentrations as low as 0.005% *(Vaede et al., 2010)*.

BAK concentration	Ocular effects
0.004%	Significant reduction of the lachrymal tear film
0.005%	Direct toxicity on superficial cells with epithelial erosion
0.007%	In-vitro conjunctival epithelial cell lysis in 90 -100 sec
0.01 %*	Important epithelium alteration, stimulation of limbal and conjunctival infiltration of inflammatory cells
0.02%	Corneal cicatrisation delay
0.1%	Destruction of the endothelium and irreversible corneal oedema in case of intracameral injection
0.1 to 0.5%	Major toxic keratitis, epithelial metaplasia, corneal infiltration of inflammatory cells, and neovascularization induced by repeated administration in rat
1 to 2% (in animals)	Total destruction of the anterior segment (conjunctiva and cornea) in less than one week

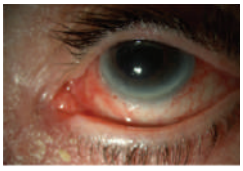
* The most frequent concentration used.

Table 5: Dose-dependent toxicity of Benzalkonium chlorid (BAK) on the ocular surface (Adapted from *Vaede et al., 2010*).

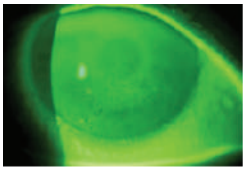
Chronic use of BAK is one of the major factors leading to ocular surface inflammation and damage as outlined in the clinical examples Figure 17:



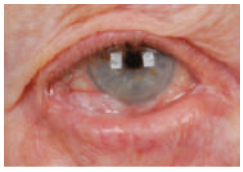
Post-surgical difference between left eye, eye drops-free after trabeculectomy and right eye severely affected by topical treatment



Eczematous eyelid: allergic reaction to topical drug



Weakly symptomatic toxic keratopathy marked by extended fluorescein staining



Toxic pseudopemphigoid with eyelid retraction and symblepharon

Figure 17: Ocular Surface Disease (OSD) in patients with glaucoma (Adapted from *Baudouin et al., 2021*).

Chronic inflammatory response associated with BAK toxicity, may reduce success of glaucoma surgery due to:

— fibrosis of the bleb

— increase in subepithelial macrophages, lymphocytes, mast cells and fibroblasts, indicating a strong positive correlation between glaucoma eye drops and surgical failure *(Sherwood et al., 1989; Souchier et al., 2006; Lemp MA, 2007; Kaštelan et al., 2013)*.

Laser Trabeculoplasty Treatment

Ab interno: Surgery without known OSD affection

Laser treatment can be recommended on an equivalent basis to topical monotherapy and especially in patients with intolerance to eye drops *(EGS guidelines 2021)*. Laser trabeculoplasty is a laser treatment modality performed in OAG to lower IOP by inducing biological changes in the trabecular meshwork, resulting in increased aqueous outflow *(Weinreb et al., 2014; Garg & Gazzard, 2020)*.

Argon laser trabeculoplasty (ALT) was the first version of LT developed in 1979. Subsequently, selective laser trabeculoplasty (SLT), which uses much lower energy exposures with minimal permanent tissue damage, has superseded ALT to become the principal laser treatment modality for IOP-lowering. First introduced by Latina & Park in 1995, SLT uses a 532nm Q switched, frequency doubled Nd:YAG laser that is able to deliver a short laser pulse duration (3 ns) (Figure 18), *(Alon, 2013; Garg & Gazzard, 2020)*.

Laser trabeculoplasty is suggested to cause an inflammatory response. For example, an increase in the recruitment and number of macrophages in the trabecular meshwork, or an increased expression and secretion of both IL-1β and TNF-α, which mediate increased trabecular stromelysin expression observed following photodisruption. This could cause remodeling of the extracellular matrix and subsequently modify the structure of the trabecular meshwork. Consequently, these reactions leads to increased outflow of aqueous humor through the trabecular meshwork to the canal of Schlemm *(Alon, 2013)*.

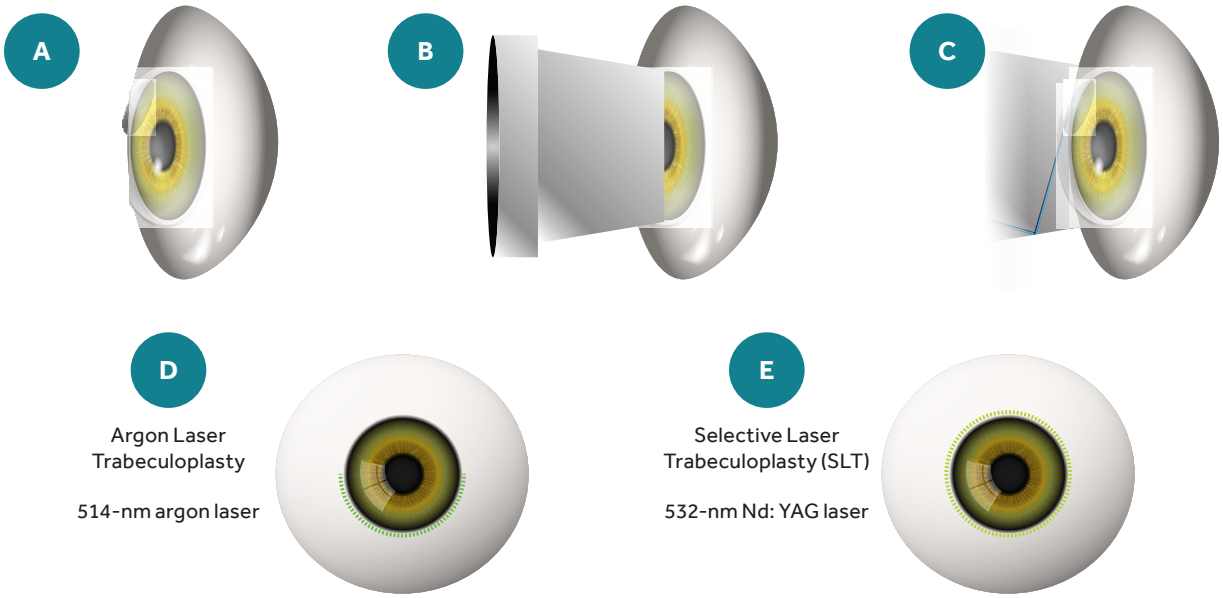


Figure 18: Illustration of the laser trabeculoplasty procedure. (A) Eye is numbed with eye drops and (B) a special laser lens is placed on the eye to help control the direction of laser beams. (C) After indentifying angle structures, the laser burns are placed on the trabecular meshwork. (D) The original laser trabeculoplasty procedure applies argon laser of 514 nm wavelength on half of the meshwork circle in one treatment. (E) The newer technique (SLT) uses a solid-state laser of 532 nm wavelength. The pulse energy of SLT is about 100 times lower than the traditional argon laser. SLT selectively targets pigmented cells while leaving the rest of the trabecular meshwork tissue intact. Therefore, it can be applied to 360 degrees of the meshwork in one treatment and is considered safe to be repeated. Images adapted from https://www.alilamedicalmedia.com/-/galleries/all-animations/eyes-and-vision-videos/-/medias/ec93f517-7eef-443a-917c-3cffbc10cfa5-laser-trabeculoplasty-animation.

Minimally-Invasive Glaucoma Surgery Treatment

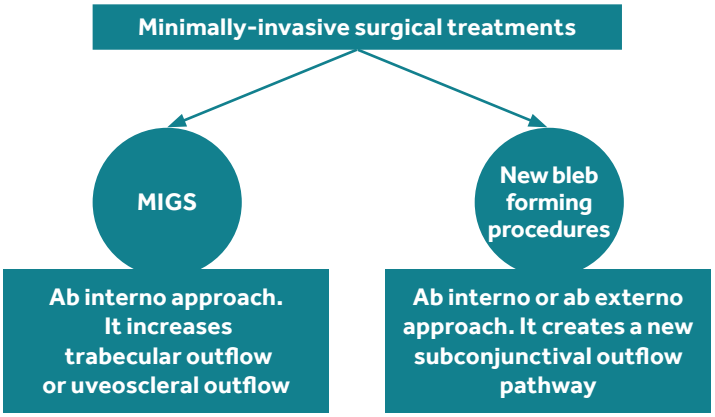


Figure 19: Minimally-Invasive Glaucoma surgery (MIGS) and new bleb forming procedures *(EGS guidelines, 2023; Galvez-Olortegui et al., 2024).*

Ab interno: Surgery with or without potential OSD affection

Over the last several years new devices for minimally-invasive glaucoma surgery (MIGS) were developed and have gained interest *(Bhartiya et al., 2019)*. The term MIGS refers to a group of surgical procedures - excluding the ab-interno bleb-forming procedures - which share five main characteristics (Figure 19) *(EGS guidelines, 2023).*

- An ab interno approach through a clear corneal incision which spares conjunctiva of incision
- A minimally traumatic procedure to the target tissue
- An IOP-lowering efficacy that justifies the approach
- A high safety profile avoiding serious complications compared to other glaucoma surgeries
- A rapid recovery with minimal impact on the patient's quality of life

Figure 20: The five main characteristics of minimally-invasive glaucoma surgery (MIGS).

MIGS is intended to achieve lower IOP in patients with glaucoma with shorter surgical time, and ideally to achieve a medication sparing effect. All devices work by increasing the outflow of aqueous humor from the anterior chamber, either by directly accessing Schlemm's canal or shunting aqueous humor to the suprachoroidal, supraciliary or subconjunctival space *(Pillunat et al., 2017; Glaucoma Society of France; Balas and Mathew, 2023)*.

Despite their benefits, these devices have limitations, including potentially less effective intraocular pressure (IOP) reduction compared to traditional surgeries, uncertainty regarding long-term outcomes, and questions about cost-effectiveness *(Balas and Mathew, 2023)*.

Newer bleb-forming procedures, also referred to as minimally invasive bleb surgery (MIBS), lower intraocular pressure by implanting a device that creates a subconjunctival outflow pathway for aqueous humor drainage *(EGS guidelines, 2023)*. This new filtration site is also named a "bleb" (described in the chapter on trabeculectomy). MIBS are less invasive than traditional filtering glaucoma surgery and offer advantages such as reduced tissue manipulation and shorter surgical times. These procedures may be a suitable option for patients with cataracts and mild to moderate glaucoma who do not require a very low target intraocular pressure *(Kolko et al., 2023; Galvez-Olortegui et al., 2024)*. Depending on the device, they can be inserted using an ab interno or ab externo technique. The most frequent reason for surgical failure is bleb fibrosis, which may necessitate postoperative bleb revision to restore drainage *(Ontario Health, 2024)*.

Major Glaucoma Surgery

Advanced or major surgery may be recommended if eye drops or laser treatment have not been effective *(EGS guidelines 2021)*.

Known surgical methods in the management of POAG can be distinguished based on whether they result in the formation of a filtering bleb and the bleb's position within the eye.

A filtering bleb is a new filtration site. Anterior filtering blebs are typically visible as an elevated area located peripherally from the limbus. The morphological alteration following visualization of the success of such filtration surgery is the formation of a filtration site, also named a "bleb" to which aqueous humor is drained into and from where it should diffuse to the environment such as the lymph and subtenon space for absorption *(Razeghinejad & Spaeth, 2011; van Setten et al., 2018)*. In posterior filtering bleb, aqueous humor is drained toward the posterior subconjunctival spaces where the risk of fibrosis is less.

Surgical methods in the management of POAG may be categorized in 3 groups described in Figure 21 *(Glaucoma Society of France; Kumar et al., 2022)*.

— (A) Ab externo filtration surgeries with anterior filtering bleb, which are further divided into: (a) penetrating (trabeculectomy) and (b) non-penetrating glaucoma surgeries, such as non-penetrating deep sclerectomy (NPDS).

— (B) Ab externo filtration surgery with posterior filtering bleb using drainage implants, which consist of a tube connected to a large plate positioned on the sclera behind the equator and around which a bleb will form.

— (C) Ab externo filtration surgery techniques without filtering bleb, including viscocanalostomy and canaloplasty.

When IOP values are high and remain uncontrolled, surgical treatment with a scalpel cannot be avoided in many patients to efficiently reduce IOP, whereby all surgical techniques aim to create an alternative outflow for the aqueous humor.

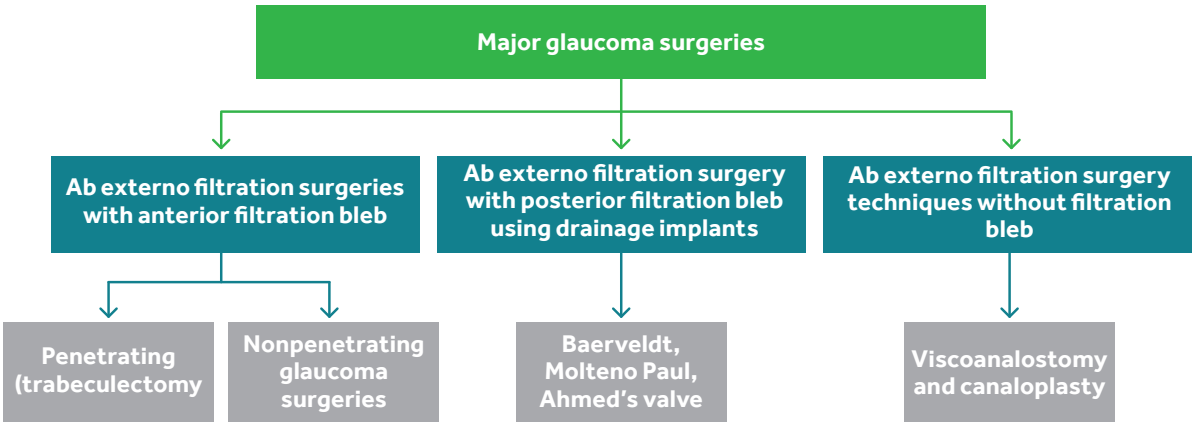


Figure 21: Categories of major surgical methods.

Trabeculectomy Treatment

Ab Externo: Surgery with OSD affection

Trabeculectomy is an effective surgical procedure for reducing IOP in patients with POAG (EGS guidelines 2021).

The classical filtration operation, trabeculectomy, is the most common type of surgery and is a penetrating eye surgery which goes back to 1960s, as described by Sugar in 1961 and Cairns in 1968 *(Sugar, 1961; Cairns et al., 1968)*. It is a standard surgical procedure that has been widely practiced for over 40 years. It consists of an excision of a small portion of the trabecular meshwork and adjacent corneoscleral tissue to provide a drainage route for aqueous humor from within the eye underneath the scleral flap to the subconjunctival space where it is absorbed. In other words, a surgical pathway is cut through all tissues to allow a straight passage from the lumen of the anterior chamber to the subtenonal space of the bleb (Figure 22), *(Razeghinejad & Spaeth, 2011)*. All filtration surgeries share the common feature of creating a filtration site.

Although trabeculectomy effectively decreases IOP for a substantial period, it can be accompanied by a number of short- and long-term complications such as hypotony, choroidal effusion, hyphema, bleb leakage, and in rare case endophthalmitis, blebitis and retinal detachment. In addition, the bleb may become fibrotic or scarred, leading to a failure of the surgery to control IOP.

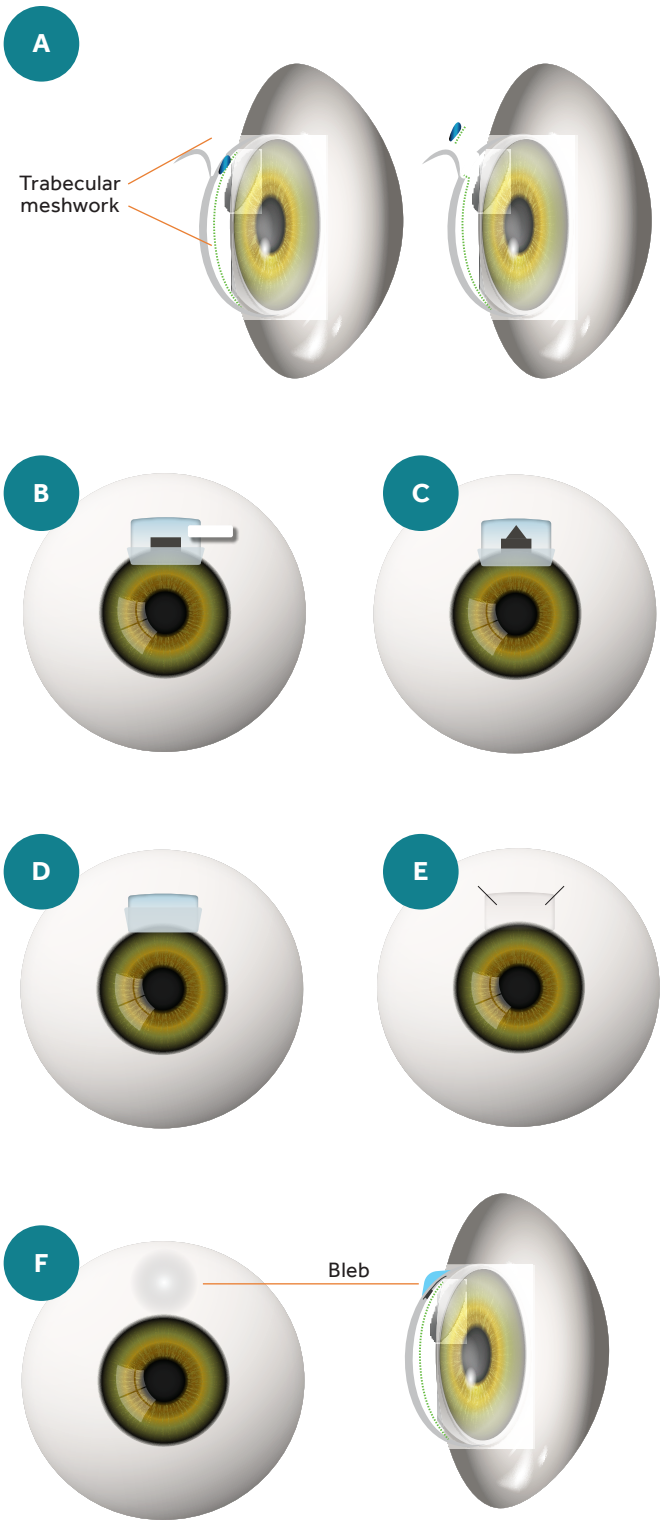


Figure 22: Illustration of trabeculectomy procedure. (A) Removing part of the trabecular meshwork and creating a new escape route for the aqueous humor. (B) Incision in the conjunctiva, a small flap is created in the sclera and a small piece of tissue under the flap, including part of the trabecular meshwork is removed. (C) This allows aqueous humor from inside the eye to flow out which lowers Intraocular pressure (IOP). (D,E) The flap is placed back down against the sclera and stitched to protect the drainage pathway. (F) After trabeculectomy the fluid flows out from the eye into a reservoir underneath the conjunctiva, called a 'bleb'. Images adapted from https://www.drchelvinsng.com/trabeculectomy-surgery/, http://www.alilamedicalimages.org/2014/06/16/trabeculectomy/.

Non-Penetrating Deep Sclerectomy Treatment

Ab Externo: Surgery with OSD affection

In 1964 Krasnov introduced the non-penetrating glaucoma surgery, that is revolutionizing the care of glaucoma patients for more than two decades *(Razeghinejad & Spaeth, 2011)*.

Non-penetrating filtering surgical procedures, in which aqueous is allowed to filter out without the removal of a full-thickness block of trabecular tissue, also aim to control IOP e and have the reputation of being safer than trabeculectomy. The most widely practiced non-penetrating surgical procedures for glaucoma are viscocanalostomy and deep sclerectomy *(Eldaly et al., 2014)*.

The non-penetrating deep sclerectomy has become an increasingly popular alternative to standard trabeculectomy throughout the world *(Al Obeidan, 2009; Kumar et al., 2022)*. The non-penetrating deep sclerectomy is far more delicate, consisting essentially in the opening approach of the Schlemm's canal from the outside (ab externo) leaving a thin membrane of the outerwall of the Schlemm's canal as a soft barrier to prevent excessive outflow of aqueous humor (Figure 23), *(Al Obeidan, 2009; Razeghinejad & Spaeth, 2011)*.

The advantage of non-penetrating glaucoma surgeries is that they prevent complications related to a sudden decrease in IOP *(Kumar et al., 2022)*. Such hypotony constitutes a potentially vision threatening complication with, amongst others, the development of chorodial detachment (Razeghinejad & Spaeth, 2011). Deep sclerectomy has also the advantage of the option of postoperative IOP adjustment with the Laser Gonio Puncture (LGP) *(van Setten, edition 2018)*, allowing to reconstitute the efficiency of the filtration site even seven years after surgery. The disadvantage, however, of deep sclerectomy is that it is very time consuming to learn and to master.

Deep sclerectomy remains a filtering procedure for which success often requires bleb formation. Fibrosis at the operation site is the main reason for failure of both trabeculectomy and non-penetrating deep sclerectomy (Figure 24). The formation and extent of a bleb varies which poses a challenge for adequate lubrication of the tear film. Subsequently, attrition is maximized and possibly triggers fibrosis of the bleb which has a strong impact on the destiny of the functionality of the bleb *(van Setten et al., 2018)*.

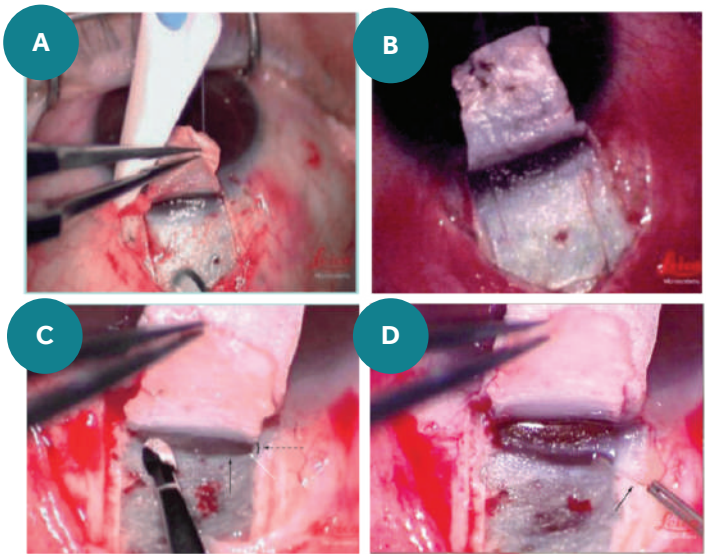


Figure 23: Illustration of non-penetrating deep sclerotomy. (A) The superficial flap is dissected and advanced ypo 1-1.5 mm into clear cornea. (B) The deep scleral flap is outlined, leaving a step of sclera on the two lateral and posterior borders of the floor of the superficial flap. (C) Dissection of the deep sclera flap leaves a very thin scleral layer on the uveal tissue (creation of the trabeculo-Descemet's membrane (dotted arrow); solid arrow indicates scleral spur and white arrow indicates Schlemm's canal just anterior to the scleral spur). (D) Illustration of the peeling of the floor of the Schlemm's Canal (Adapted from *Al Obeidan, 2009*).

Scar formation, *i.e.* fibrosis of the filtering path or site, is one of the main reasons for failure of glaucoma filtration surgery *(van Setten, 2018)*. To prevent fibrosis, use of antimetabolites such as 5-fluorouracil (5-FU) or mitomycin C (MMC) has been proposed. Application of antimetabolites during surgery or injections during the postoperative period increase the effectiveness of these surgeries, but their use increases the risk of the development of grave complications including bleb leakage, blebitis and endophthalmitis *(Tan, 2001; Rulli et al., 2013; Kumar et al., 2022).*

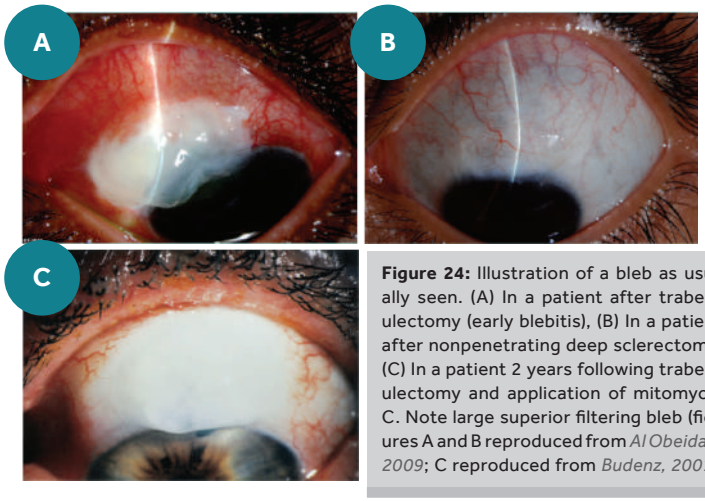


Figure 24: Illustration of a bleb as usually seen. (A) In a patient after trabeculectomy (early blebitis), (B) In a patient after nonpenetrating deep sclerectomy, (C) In a patient 2 years following trabeculectomy and application of mitomycin C. Note large superior filtering bleb (figures A and B reproduced from *Al Obeidan, 2009*; C reproduced from *Budenz, 2001*).

Association Between Ocular Surface Disease And Creation of Bleb

OSD, such as DED, is common in patients with functioning filtering blebs following trabeculectomy. Patients with a functioning filtering bleb frequently complain of eye irritation, burning and foreign body sensation *(Lee et al., 2013; Ji et al., 2016)*.

Blebs can become increasingly large in size and height and cause ocular pain, discomfort, burning, foreign body sensation, and tearing, a feature of bleb dysesthesia (Figure 25), *(Budenz et al., 2001; Janz, 2001)*.

Randomized controlled trials on participants undergoing standard trabeculectomy for POAG compared to deep sclerectomy showed that filtering bleb height can interfere directly with tear instability *(Neves Mendes et al., 2012)*.

A cross-sectional, case-comparison study of seventy glaucomatous patients who had undergone trabeculectomy more than 6 months prior showed that the patients with functioning blebs presented higher corneal staining scores and lower TBUT values and greater tear film instability than the control group and the values for microcysts and bleb heights were significantly higher in the DED group. More patients in the study group complained of dryness, a gritty or sandy sensation and redness *(Ji et al., 2016)*.

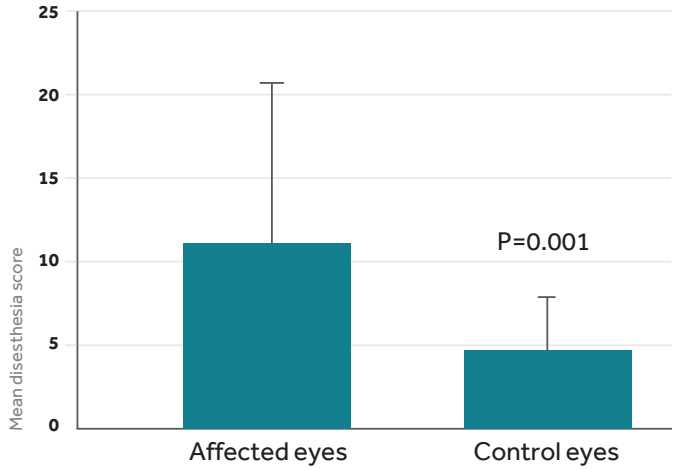


Figure 25: Total dysesthesia scores in post-trabeculectomy eyes with glaucoma filtering blebs compared with eyes without filtering blebs. Patients were asked to score the frequency (0 to 5) and severity (1 to 5) on dysesthesia symptoms. Discomfort from filtering blebs is quite common with 67% of eyes with glaucoma filtering blebs reporting dysesthesia (Adapted from *Budenz et al., 2001*).

Association Between Filtration Surgery and Ocular Surface Disease

Ab interno: Surgery without or with potential OSD affection

A case-controlled study including 133 eyes, showed that trabeculectomy and chronic use of preserved anti-glaucoma eye drops significantly increased tear film osmolarity. Post-trabeculectomy patients were more than four times as likely to experience dry eye symptoms (OR = 4.24) *(Lee et al., 2013)*.

Trabeculectomy is suggested to have deleterious effects on ocular surface including conjunctival epithelial spongiosis and reduced number of conjunctival goblet cells *(Baudouin, 2012; Lee et al., 2013)*.

Ocular surface changes take place in post-trabeculectomy patients as observed in a group of post-trabeculectomy patients (at least 6 months after surgery) where TBUT, corneal fluorescein staining, and rose bengal staining were worse compared to normal controls *(Neves Mendes et al., 2012)*.

Trabeculectomy may also compromise tear function due to the use of antimetabolites (such as MMC) which may have negative impact on corneal epithelium *(Lee et al., 2013; Lam et al., 2015)*. For example, MMC used during surgery to minimize postoperative scarring has been reported to cause corneal epitheliopathy and limbal stem cell deficiency. The irregular corneal surface and increased inflammatory cells that result from the corneal epithelial abnormalities may be related to the poor quality of the tear film *(Lee et al., 2013)*.

Trabeculectomy and non-penetrating glaucoma surgeries continue to be the Holy Trinity for the glaucoma surgeon. If these techniques fail, and repeated surgery is not successful, then the option left is implantation of tubes or cyclodestructive laser surgery *(Razeghinejad & Spaeth, 2011)*.

Key Learning points

— Glaucoma is typically treated with a variety of Intraocular Pressure (IOP)-lowering medications formulated as preserved and preservative-free (PF) eye drops, including prostaglandin analogs, beta-blockers, alpha-adrenergic agonists, carbonic anhydrase inhibitors, Rho kinase inhibitors, miotic agents or cholinergic agonists.

— Benzalkonium Chloride (BAK) is a commonly used preservative in eye drops, which has been shown to disrupt the lipid layer of the tear film, causing evaporation of its aqueous component, increasing epithelial permeability and reducing the tear-film breakup time, leading to dry eye symptoms and toxic reaction on the ocular surface. Chronic BAK use leads to ocular surface inflammation and damage, potentially reducing glaucoma surgery success.

— The prevalence and severity of ocular surface disease (OSD) increase with the number of daily anti-glaucoma eye drops used by patients with Primary Open-Angle Glaucoma (POAG) or Ocular Hypertension (OHT).

— Laser trabeculoplasty is a laser treatment option that may be preferred to topical monotherapy for patients with intolerance to eye drops. It is used in POAG and OHT to reduce IOP by inducing biological changes in the trabecular meshwork, leading to enhanced aqueous outflow.

— Minimally-invasive glaucoma surgery (MIGS) is intended to reduce IOP in patients with glaucoma with shorter surgical time, and ideally to achieve a medication sparing effect.

— Surgical methods for the management of POAG can be classified as Ab Interno filtration surgeries, creating no (viscocanalostomy and canaloplasty) or minor ocular surface anomalies (MIGS) and Ab Externo filtration surgeries with formation of a filtering site, so-called "bleb" [penetrating (trabeculectomy) and non-penetrating glaucoma surgeries (deep sclerectomy)].

— Common to all surgical techniques is the potential creation of a filtration site, regardless of whether its shape, form and design is defined as a bleb or whether the filtration area varies greatly. Common to all filtration sites is the anatomical predisposition to trigger deterioration of topical lubrication and thus the characteristics of localized anatomical dry eye *(van Setten, 2017)*. Here, some of the main triggers for potential surgical failure, especially fibrosis, are triggered by processes such as friction and attrition *(van Setten, 2020)*. Therefore, additional, optimized and continuous lubrication is required.

Consequences of Ocular Surface Disease in Glaucoma Patients

The consequences of glaucoma treatments, and especially PF eye drops, are outlined in Figure 26 *(Ayaki et al., 2015; Stolz et al., 2015; Stalmans et al., 2020)*:

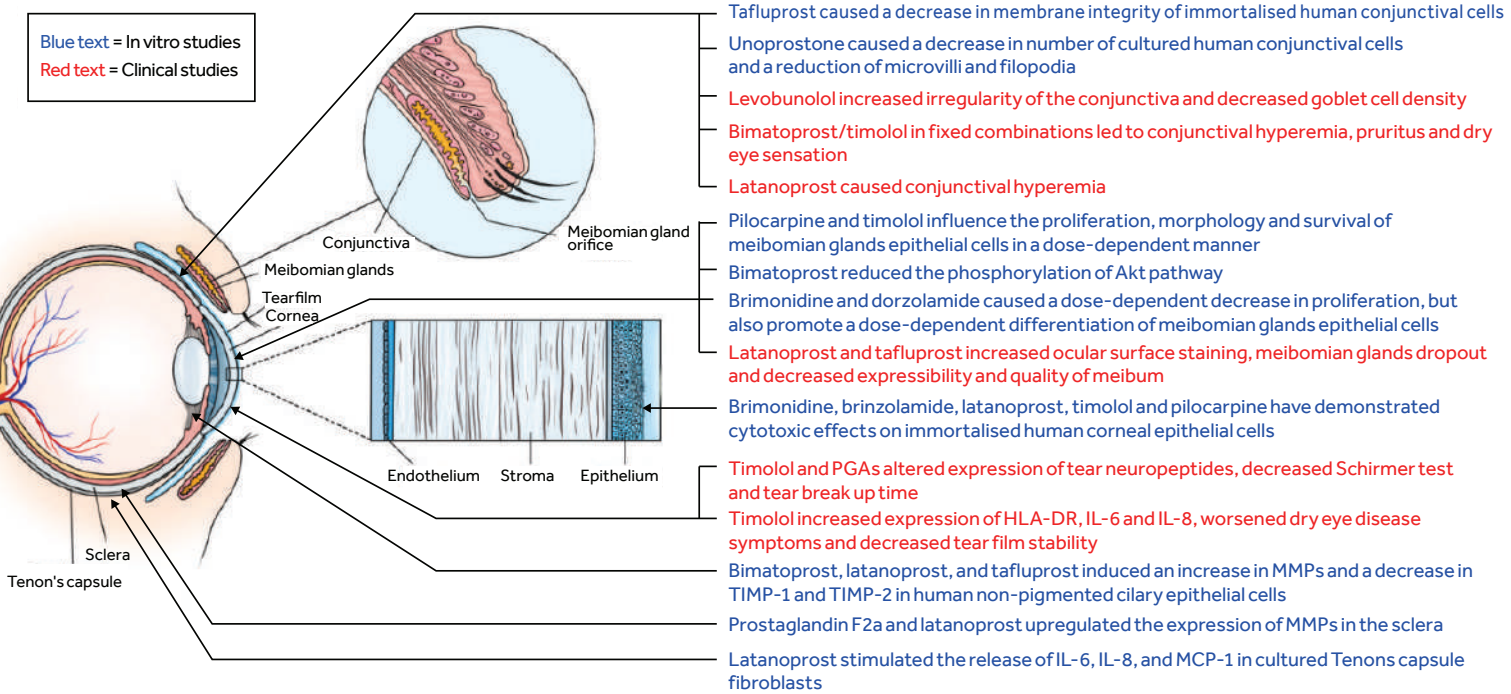


Figure 26: Effects of preservatives-free anti-glaucoma eye drops on the eye's anterior segment. Commercial formulations were used in the clinical studies, whereas active compounds were used in the studies *in vitro*. Reproduced by *Kolko et al., 2023*.

The adverse effects associated with topical anti-glaucoma medication can have a negative effect on patient adherence to therapy, the physician–patient relationship and patient's quality of life (Figure 27) *(Hopes & Broadway, 2010)*:

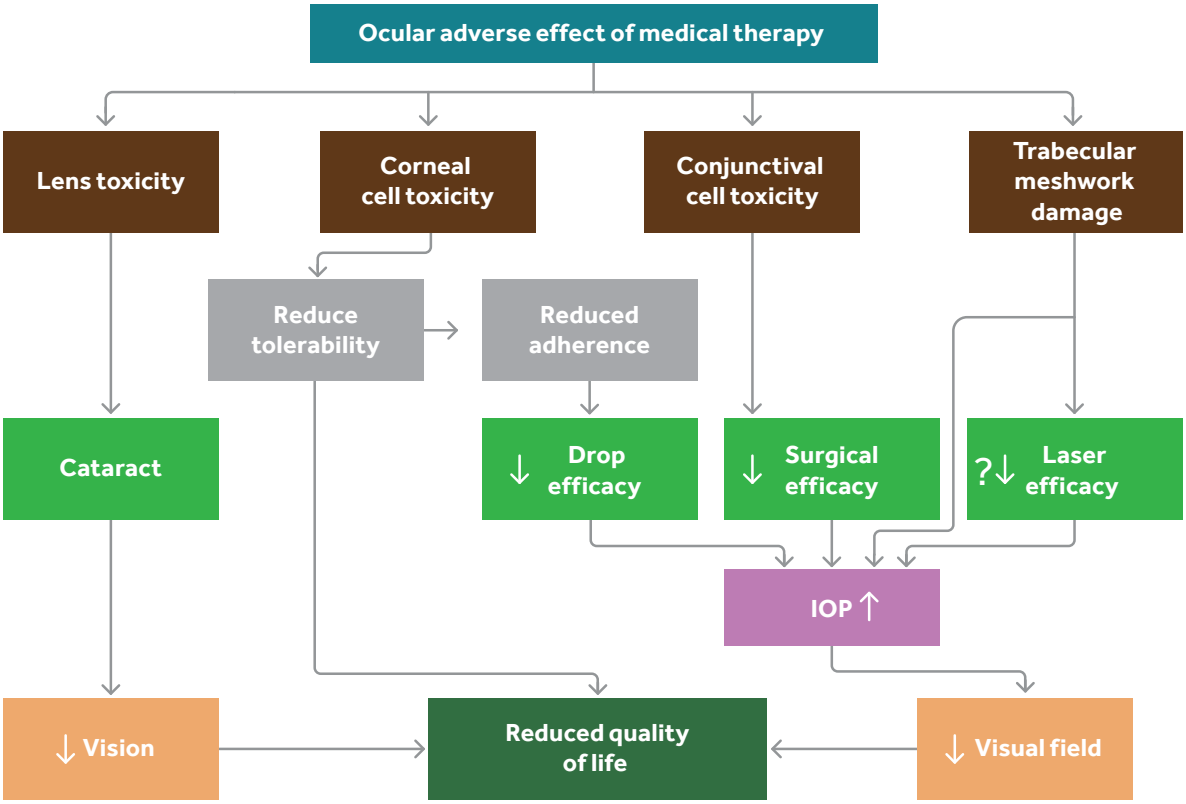


Figure 27: Chart illustrating the impact of adverse effects of anti-glaucoma eye drops on glaucoma management and patient's quality of life. IOP: Intraocular Pressure.

The impact of local anti-glaucoma medical adverse reactions on vision-related quality of life in patients with ocular hypertension or glaucoma has been investigated. Results have shown an association between impaired vision, decreased quality of life and the impact on patient satisfaction in patients with drug adverse events *(Nordmann et al., 2003)*.

— Poor vision related quality of life was associated with topical drug side effects that also impact patient satisfaction and compliance *(Nordmann et al., 2003)*.

— Prevalence of each individual side effect as reported by the COM-TOL (to assess the local side effects of the current topical treatment; *(Nordmann et al., 2003)*):

— 37.6% had no side effects, 24.9% had one, 11.6% had two, 7.0% had three, and 18.9% had four and more.

— Three side effects were reported more often by more than 20% of the patients: burning (25.4%), blurred vision (20.8%) and tearing (20.2%). (Figure 28).

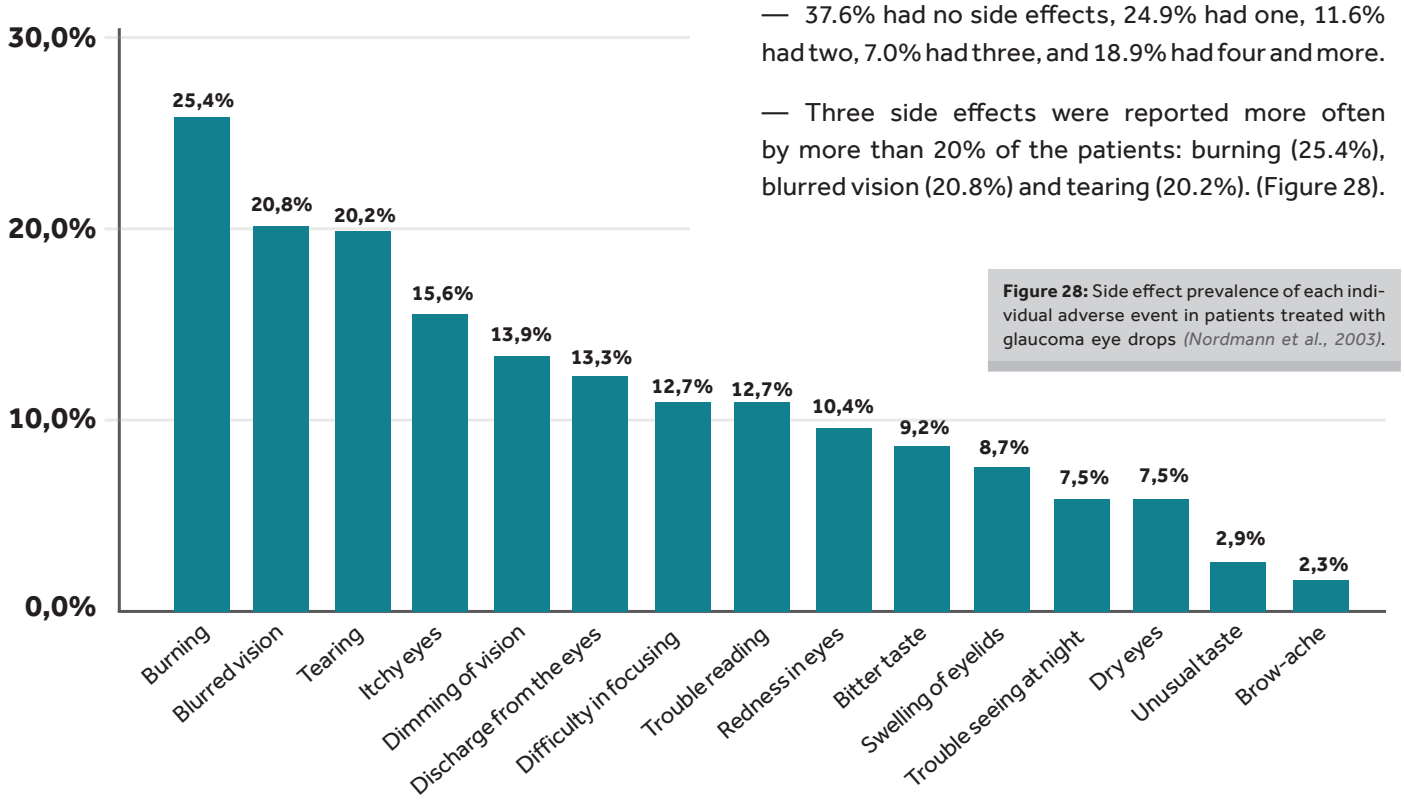


Figure 28: Side effect prevalence of each individual adverse event in patients treated with glaucoma eye drops *(Nordmann et al., 2003)*.

IOP increases with the severity of OSD (Figure 29).

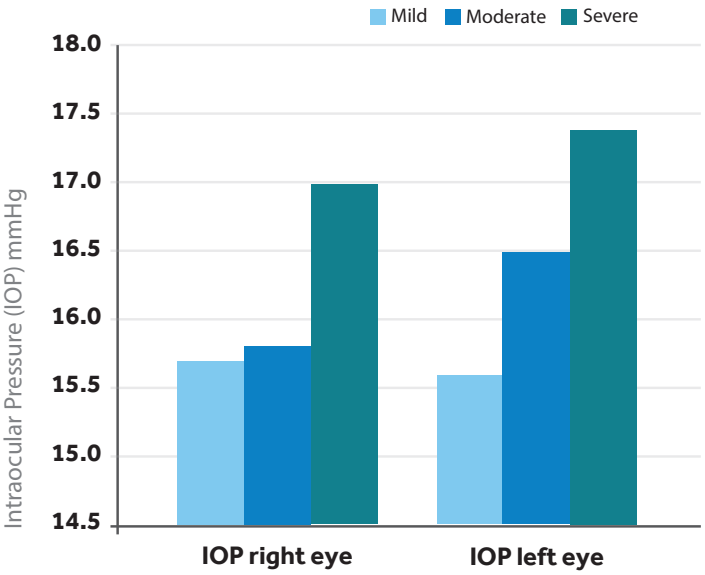


Figure 29: The increase in Intraocular Pressure (IOP) is closely linked to the severity of Ocular Surface Disease (OSD) *(Baudouin et al., 2013)*.

In addition, Skalicky and associates *(Skalicky et al., 2012)*, in a cross sectional study, investigated the relationship between OSD and glaucoma-related quality of life (QoL), glaucoma severity, and treatment in patients with POAG. One hundred twenty-four participants —patients with mild (n = 48), moderate (n = 34), or severe (n = 19) glaucoma and 23 controls (glaucoma suspects) not receiving glaucoma treatment— were enrolled. The main outcomes of the study were the Ocular Surface Disease Index (OSDI) score, the Glaucoma Quality of Life-15 (GQL-15) score, number and type of glaucoma medications, daily dose of BAK, and visual field indices. The results and the study's conclusion were the following:

— OSDI scores and the number of patients with OSD increased with increasing glaucoma severity (P < .001 and P < .005). GQL-15 scores reflected decreased QoL with increasing glaucoma severity (P < .001).

— On univariate regression OSDI was significantly correlated with GQL-15 summary score, glaucoma severity, multiple topical glaucoma medications, worse eye mean deviation and pattern standard deviation, use of topical beta blockers, topical carbonic anhydrase inhibitors, daily dose of BAK, and glaucoma filtration surgery.

Conclusion

OSD is more common in patients with increasing glaucoma severity and is associated with poorer glaucoma-related QoL and higher exposure to BAK.

Elevated IOP induces inflammation in the optic nerve and superior colliculus (Figure 30).

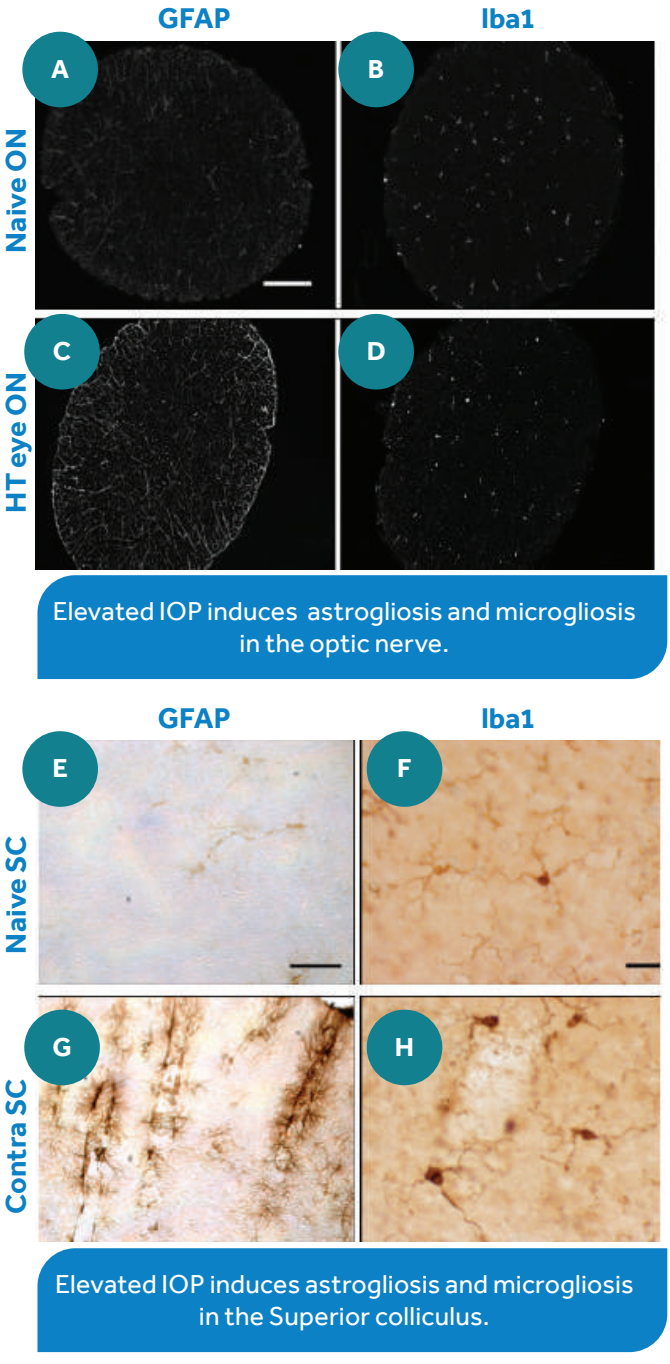


Figure 30: Elevated Intraocular Pressure (IOP) stimulates astrogliosis and microgliosis in the Optic Nerve, (A-D) and in the Superior Colliculus, (E-H). (A-D) Segments of the ONs were examined for GFAP and Iba1 expression by immunofluorescence in naïve and Hypertensive (HT) eye retinas. Scale bar = 100 µm. (E-H) Immunochemistry was performed in naïve and left SCs. In naïve SC GFAP labelling was very rare and focused around the blood vessels and under the pia mater. In left SC, dense GFAP labelling was observed, indicating astrocyte activation. In left SCs, microglia seemed to have a wider soma than in naïve SCs. Scale bar = 100 µm (GFAP) and 50 µm (Iba1). GFAP: Glial Fibrillary Acidic Protein, Iba1: Ionized calcium-binding adaptor molecule 1, IOP: Intraocular pressure *(Sapienza et al., 2016)*.

Key Learning points

— The impact of local anti-glaucoma medical adverse reactions on the vision-related quality of life of patients with ocular hypertension or glaucoma has been the starting point for substantial research.

— Research has revealed an association between decreased vision-related quality of life and topical drug side effects, which also impact patient satisfaction and compliance.

— Ocular Surface Disease (OSD) is more common in patients with increasing glaucoma severity and is associated with decreased glaucoma-related quality of life and higher exposure to Benzalkonium chloride (BAK).

Ocular Surface Disease Diagnosis in Glaucoma Patients

Clinical Tests for Glaucoma Diagnosis

Because there is no single perfect reference standard for establishing the diagnosis of glaucoma, early diagnosis can be challenging.

According to UK's National Institute of Health and Clinical Excellence (NICE) guidelines, the tests which should be offered for suspected Glaucoma or Ocular Hypertension are IOP measurement, gonioscopy and standard automated perimetry (Figure 31). Corneal thickness test can also be performed to provide insights into potential measurement errors *(Haleem et al., 2013)*.

These tests are usually followed by an Optic Nerve Head (ONH) appearance examination. Glaucoma leads to alterations in the ONH, neuroretinal rim and vasculature structure. By analyzing retinal images, anatomical changes in retina due to glaucoma can be observed. ONH appearance examination is also coupled to imaging techniques to further determine the anatomical changes in the retinal structures:

Tonometry

Intraocular Pressure (IOP) measurement

There are several techniques for tonometry. Among those techniques, Goldmann Applanation in considered the gold standard.

Pachymetry

Corneal thickness test

It is not a relevant test for glaucoma diagnosis. However, corneal thickness testing can provide insights into potential measurement errors.

Gonioscopy

To determine whether the angle is open or closed

It is an examination of the front outer edge of the eye between the cornea and the iris.

Standard Automated Perimetry (SAP)

It quantifies a patient's sensitivity to light stimuli across the visual field in a systematic, standardized way to detect deviations from the normal hill of vision of an age-matched control subject.

Figure 31: Glaucoma diagnostic tests based on UK's National Institute of Health and Clinical Excellence (NICE) guidelines.

Stereoscopic photographs are used to assess ONH health, providing improved detection of retinal nerve fiber layer (RNFL) and optic disc changes, including optic disc hemorrhages *(Bundez et al., 2006)*.

Confocal Microscopy (CM) employs the principle of light reflection. Here a laser is projected through a pinhole towards the area of interest and the reflections are picked up through another pinhole in front of light detector *(Haleem et al., 2013)*.

OCT, based upon interferometry, is a non-invasive, non-contact method of producing high-resolution images utilizing coherence property of light reflected from a scanned area *(Haleem et al., 2013)*.

Imaging techniques, most commonly optical coherence tomography (OCT), provide quantitative information on the amount of optic nerve fiber (retinal ganglion cell axon) loss. These techniques have improved the identification of early disease and improved the observation of progressive loss of optic nerve fiber over time *(Weinreb et al., 2014)*.

An example of OCT is shown in Figure 32:

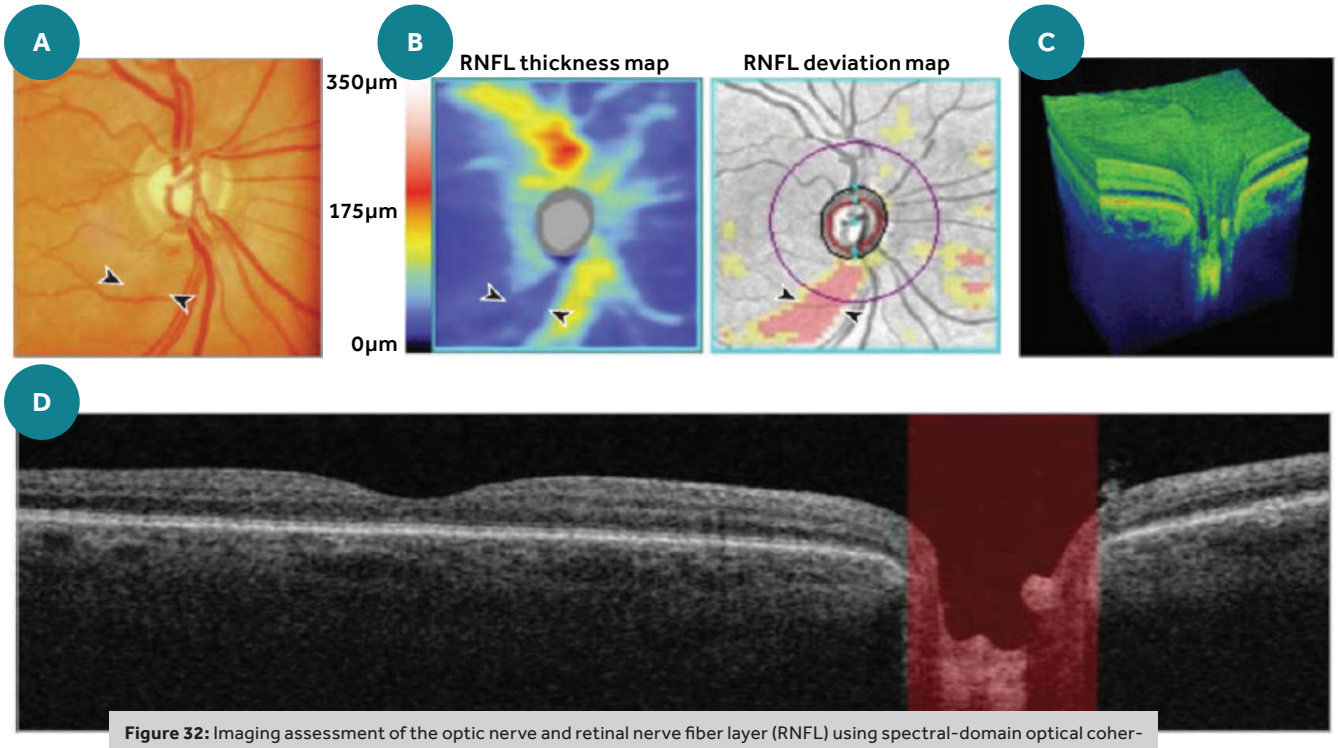


Figure 32: Imaging assessment of the optic nerve and retinal nerve fiber layer (RNFL) using spectral-domain optical coherence tomography (OCT). (A) Photo of glaucomatous Optic Nerve Head (ONH) with inferior RNFL defect (arrowheads). (B) Color-coded maps from OCT imaging (areas of thicker RNFL appear in yellow and red. Arrowheads point to RNFL defect. Deviation map compares the RNFL thickness values with a normative database and highlights the defect). (C) Three-dimensional OCT image of ONH. (D) Cross-sectional OCT image of RNFL and ONH (Adapted from *Weinreb et al., 2014*).

Characteristic changes in the appearance of the ONH and RNFL occur following retinal ganglion cell death and optic nerve fiber loss in glaucoma. A progressive exacerbation of these changes along with characteristic visual field loss constitute the most important aspects of glaucoma diagnosis (Figure 33 A-C).

Longitudinal evaluation and documentation of structural damage to the optic nerve is, therefore, one of the critical components of the diagnosis of the disease. Such an evaluation can be performed by observing the optic nerve head using an ophthalmoscope or by obtaining optic nerve head photographs (Figure 33 A-C).

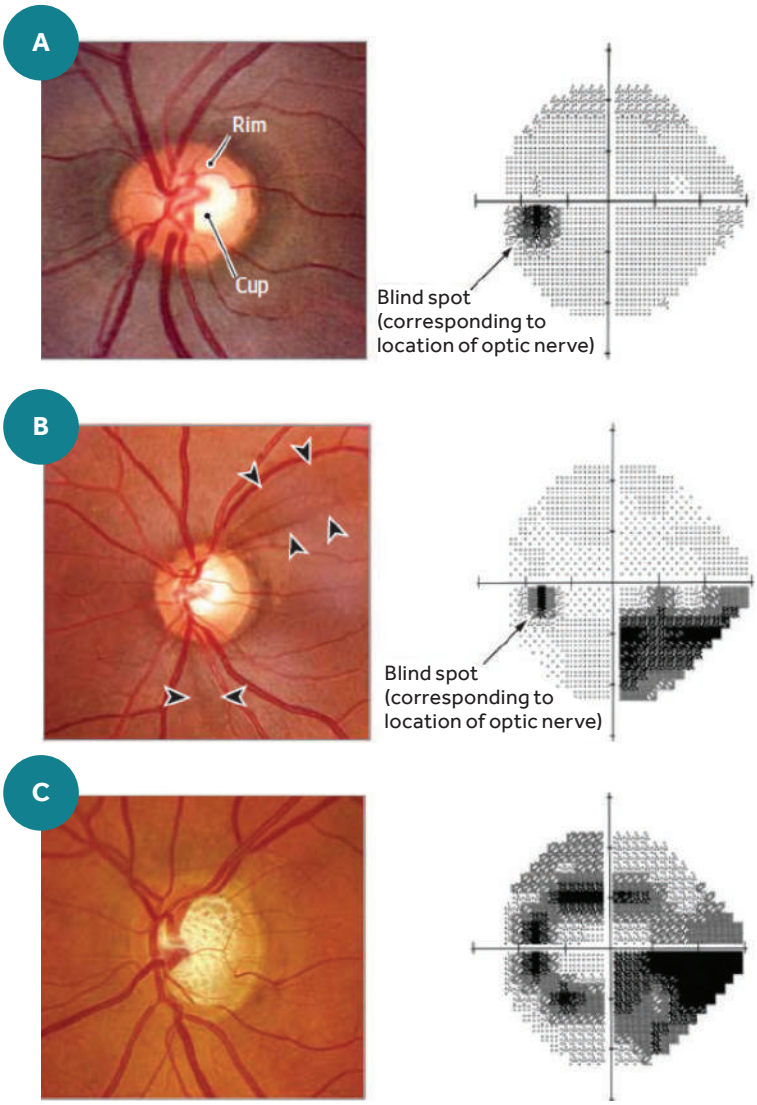


Figure 33: Normal, Glaucomatous, and Severe Glaucomatous Optic Nerve Head (ONH) and Visual Field Test Results: (A). Normal optic nerve head and Visual field Test Result: The pink area of neural tissue forms the neuro-retinal rim, whereas the central pale space corresponds to the cup. (B). Glaucomatous optic nerve head and associated inferior visual field loss: Glaucomatous optic nerve showing loss of superior neuroretinal rim (thinning) and excavation with enlargement of the cup. The arrowheads point to an associated retinal nerve fiber layer defect, which appears as a wedge-shaped dark area emanating from the ONH. The superior neural losses correspond to the inferior defect (black scotoma) seen on the visual field. There is also a small retinal nerve fiber layer (RNFL) defect inferiorly, but the corresponding hemifield of the visual field remains within normal limits. (C). Extensive neural tissue loss in severe glaucoma and associated severe visual field loss. More extensive neural tissue loss from glaucoma with severe neuroretinal rim loss, excavation, and enlargement of the cup. There is severe loss of visual field both in the superior as well as in the inferior hemifield (Adapted from *Weinreb et al., 2014*).

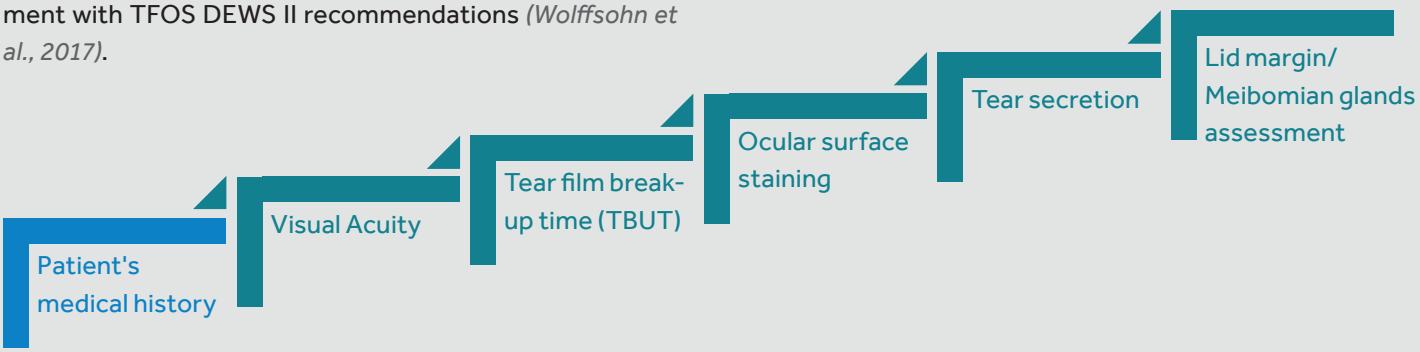
Presence of characteristic visual field defects can confirm the diagnosis, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing *(Weinreb et al., 2014)*.

Subjective identification of optic disc damage from glaucoma can be challenging, with great disagreement in the assessment observed even among glaucoma specialists *(Reus et al., 2010)*.

Deep learning models for glaucoma diagnosis have shown significant advancements using various imaging modalities and multimodal strategies, with potential applications in detecting and estimating visual field progression. However, some challenges remain before artificial intelligence is routinely employed in clinical practice *(Correia Barão et al., 2024)*.

The 6-Step Workup Process for Ocular Surface Disease Diagnosis

Ophthalmologists in clinical practice can follow a 6-step workup process that helps them diagnose OSD, in alignment with TFOS DEWS II recommendations *(Wolffsohn et al., 2017)*.



1 Patient's medical history includes evaluation of:

Family history of glaucoma.

Previous and current symptoms and signs of Ocular Surface Disease (OSD).

Previous and current treatment (use of preservative-containing glaucoma medication or artificial tears).

Evaluation of possible exposure to aggravating factors (digital device use, air-conditioning, topical and systemic treatments, systemic diseases).

2 Visual acuity

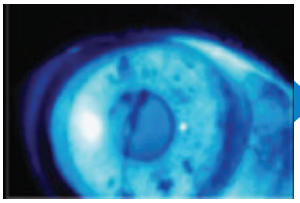
OSD can impact a patient's visual acuity due to insufficient ocular surface lubrication. This is especially relevant in glaucoma patients, as OSD-related visual acuity reduction can adversely affect visual field (VF) test results. Therefore, it is important to avoid attributing VF test deterioration solely to glaucoma progression if OSD is present. Conversely, OSD can also reduce medication adherence, meaning VF worsening in a glaucoma patient with dry eye disease (DED) should not automatically be attributed to DED alone *(Yenice et al., 2007; Figus et al., 2023)*.

3 Tear film break- up time (TBUT)

Measurement of the interval between the last complete blink and the first appearance of a dry spot or disruption in the tear film *(Messmer, 2015; Wolffsohn et al., 2017)*:

Procedure for TBUT assessment:

1. Instill one drop of non-preserved sodium fluorescein or drop from a saline wetted fluorescein strip onto the bulbar conjunctiva
2. Ask the patient to blink naturally to distribute the fluorescein
3. Within 1-3 minutes of the fluorescein instillation, ask the patient to stare straight without blinking
4. Set slit-lamp magnification at 10x, keep the background illumination intensity constant and observe the tear film over the entire cornea
5. Record (can use stopwatch) the time between last complete blink and first appearance of growing micelle. Counting slowly until the tear film break-up is acceptable for daily clinical practice
6. Once TBUT is observed, instruct patient to blink freely



> 10 sec = normal

<10 sec = dry eye

4 Ocular Surface Staining

Staining is assessed 1-3 min after the fluorescein instillation and after TBUT *(Mainstone et al., 1996; Messmer, 2015; Wolffsohn et al., 2017)*:

Procedure for ocular surface staining assessment:

- Instilation of fluorescein dye (compare TBUT)
- Slit lamp at 16x magnification / Cobalt Blue light
- Cornea: the upper eyelid is lifted to grade the whole corneal surface
- Conjuctiva:
  - grade the temporal zone (subject looks nasally)
  - grade the nasal zone (subject looks temporally)

Two recommended guidelines are predominantly followed by ophthalmologists in grading conjunctival and corneal staining (Figures 34 & 35); *(Begley et al., 2019)*.

The Oxford grading scale divides corneal and conjunctival staining into six groups according to severity from 0 (absent) to 5 (severe) for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. Dots are arranged on a log scale *(Bron et al., 2003)*.

The National Eye Institute/Industry (NEI) scale divides the cornea into five zones (central, superior, temporal, nasal, and inferior) and for each zone, the severity of corneal fluorescein staining is graded on a scale from 0 to 3 *(Begley et al., 2019)*.

Staining with lissamine green/ rose bengal are used in patients with early to moderate DED while corneal sodium fluorescein is used for moderate to severe DED *(Bron et al., 2003)*.

Oxford grading scale

Panel	Grade	Descriptor
A	0	Absent
B	I	Minimal
C	II	Mild
D	III	Moderate
E	IV	Marked
>E	V	Severe

NEI grading scale

Conjuctiva Staining		Corneal Staining
Lissamine Green	Rose Bengal	Sodium Fluorescein

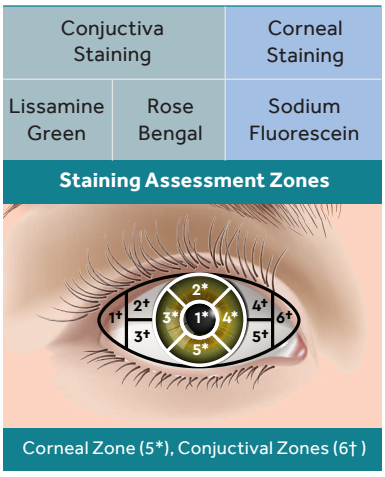


Figure 34: The Oxford and National Eye Institute/Industry (NEI) grading scales for estimating conjunctival and corneal staining, and thus severity of Dry Eye Disease (DED) (Figure adapted from *Chien et al., 2017*; https://www.aao.org/image/neiindustry-grading-system, https://www.aao.org/image/oxford-grading-system).

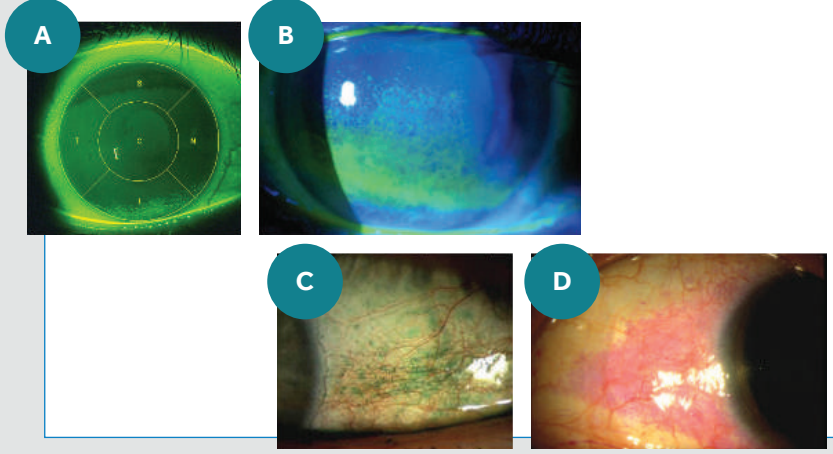


Figure 35: Example of conjunctival and corneal staining. (A) Schematic illustration of the five corneal zones: C, central zone; S, superior zone; I, Inferior zone; T, temporal zone; N, nasal zone (B) Moderate-to-severe corneal fluorescein staining in a patient with aqueous deficiency. (C) Moderate-to-severe lissamine green staining of the temporal aspect of the conjunctiva. (D) Moderate rose bengal staining of the conjunctiva in the temporal region with a classic pattern for keratoconjunctivitis sicca. (Adapted from *Milner et al., 2016; Woods et al., 2018*).

5 Tear secretion evaluation

The tear meniscus height is a simple technique to indirectly assess tear volum (Figure 36) *(Messmer, 2015; Wolffsohn et al., 2017)*:

Procedure for tear meniscus height assessment:

- Fluorescein instillation
- Observe lower tear meniscus height with the slit lamp in the center of the eyelid
- Compare to slit beam height
- Photographed at 120 magnification/ slit lamp cobalt blue filter

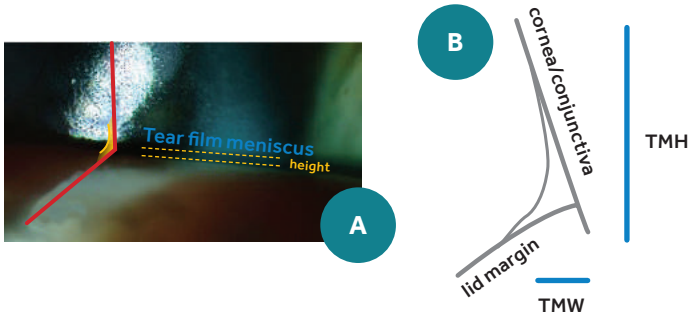


Figure 36: (A) Photography of tear meniscus height. (B) Schematic representation of tear meniscus.

The Schirmer test measures the secretions of the lacrimal gland.

In the Schirmer I test, calibrated filter paper strips (Figure 37) are placed in the conjunctival sac of the temporal third of the lower eyelid and, with the patient's eyes closed, wetting of the strip is measured after 5 minutes. In the Jones basal secretion test, the test is performed like the Schirmer I test, but after topical anesthesia.

Value of <5mm is pathological, whereas >15mm is normal.

In the Schirmer test II, the test is performed with nasal stimulation. Test results are subject to marked inter- and intraindividual fluctuations. In theory, this test measures only the basal secretion, without reflex tears *(Messmer, 2015)*.

A common consensus among the experts is utilizing the Schirmer Test without local anesthesia due to difficulties in clinical differentiation between Schirmer test I+II.

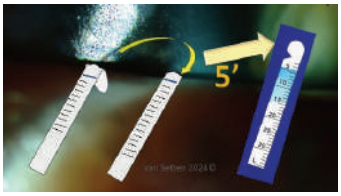


Figure 37: Schirmer test to measure tear secretion.

6 Lid margin/Meibomian glands evaluation

Lid margins are carefully inspected for signs of thickness, irregularity, notching or telangiectasia.

The number of Meibomian orifices in the central 1 cm of the lid and the percentage of orifices that are blocked is noted.

The quality of Meibomian secretion is assessed. Normally, the secretion should have the consistency of olive oil.

The volume, the type of expressed secretion and the expressibility are evaluated (Figure 38); *(Bron et al., 1991; Foulks & Bron, 2003)*).

Volume
(score the diameter of the largest pool expressed)

Expressed secretion:

0 = clear
1 = cloudy
2 = granular — **abnormal**
3 = solid

Expressibility:

0 = minimal
1 = light
2 = moderate — **abnormal**
3 = heavy

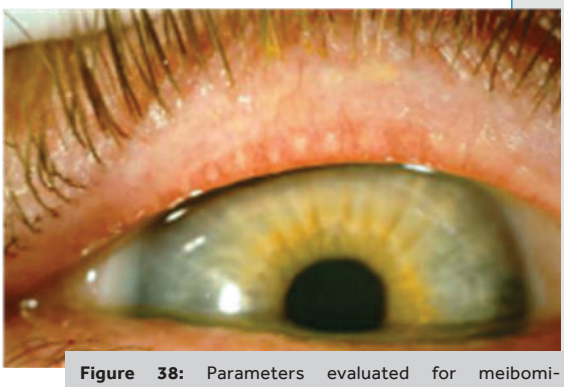


Figure 38: Parameters evaluated for meibomian glands evaluation. Picture of simple obstructive meibomian gland dysfunction (MGD) with pouting of orifice, loss of definition of cuff, and plugging (Modified from *Bron et al., 1991; Foulks & Bron, 2003)*.

Key Learning points

— Early diagnosis of glaucoma remains a challenge, with no single golden reference standard available.

— Tonometry, pachymetry, gonioscopy, and perimetry are among the tests recognised by the UK's National Institute of Health and Clinical Excellence (NICE) for the detection of glaucoma or ocular hypertension. The aforementioned tests are usually followed by an Optic Nerve Head (ONH) appearance examination.

— Imaging techniques, such as Optical Coherence Tomography (OCT), are mainly used for the detection of anatomical changes in the retinal structures caused by glaucoma.

— In clinical practice, a 6-step workup process, including assessment of patient's medical history, visual acuity, tear film break-up time (TBUT), ocular surface staining (lissamine green/rose bengal or sodium fluorescein staining and grading with the Oxford and the National Eye Institute/Industry scale), tear secretion (tear meniscus height, Schirmer test), and lid margin/meibomian glands status (number of meibomian orifices, quality of meibomian secretion), is used for the proper diagnosis of ocular surface disease (OSD).

Management of Ocular Surface Disease in Glaucoma Patients

- Switch to PF treatments with similar efficacy and a better safety profile.

- Lid hygiene monitoring, use of PF artificial tears and ocular lubricants.

- Use of PF antihistamines and avoidance of allergenic or OSD-triggering treatments, such as chemical preservatives in topical ocular therapies (eye drops, ointments, contact lens solution, etc.) *(Bielory et al., 2020)*.

- Use of PF topical steroids.

Note: Topical corticosteroids are associated with side effects, such as increased IOP and may induce glaucoma – An alternative approach to this challenge involves the use of mild or soft steroids, such as hydrocortisone, or nonsteroidal anti-inflammatory (NSAID) agents.

- Use of topical insulin eye drops *(Cid-Bertomeu et al., 2024)*

- Use of autologous serum eye drops.

-Use of calcineurin inhibitors (cyclosporin A, tacrolimus or picrolimus).

-Use of oral antibiotics, such as doxycycline.

-Use of treatments for coincidental skin diseases (*e.g.* rosacea).

Preservative-Free Benefits over Preserved Application of Topical Anti-Glaucoma Eye Drops

BAK-free (including PF) anti-glaucoma eye drops have become available.

Several reports have confirmed the advantages of BAK-free anti-glaucoma eye drops and demonstrated that adverse reactions induced by the BAK and other preserved medications may be reversible and offer clinically relevant long-term benefits for glaucoma patients *(Kaštelan et al., 2013, Kestelyn et al., 2019)*.

Data from previous studies show that, in the short-term, switching to topical PF glaucoma therapies alone improves symptoms *(Jaenen et al., 2007; Baudouin et al., 2010; Stalmans et al., 2020)*, tolerability *(Pflugfelder & Baudouin, 2011; Holló et al., 2018; Konstas et al., 2021)*, subclinical ocular surface inflammation *(Boboridis & Konstas, 2018; Mohammed et al., 2020; Goldstein et al., 2022)*, ocular surface health and IOP control *(Konstas et al., 2023)*.

PF monotherapies are non-inferior in terms of IOP-lowering efficacy, as are PF fixed combinations, when compared to preserved therapies. For example, this has been demonstrated for latanoprost, bimatoprost, brimonidine and the fixed combinations latanoprost/tomolol and brimonidine/timolol *(Day et al., 2013; Rouland et al., 2013, Economou et al., 2018; Aptel et al., 2019; Kim et al., 2021; Kim et al, 2023; Munoz-Negrete et al., 2024)*.

The toxicity of BAK has an effect at three different anatomical levels of the eye *(Kaštelan et al., 2013, Kestelyn et al., 2019)*:

— Ocular surface

— Trabecular Meshwork

— Retina

Overall, preservative-free (PF) benefits include:

- Reduction of adverse events
- Better tolerability
- **Better outcome & Quality of life**
- Lower rate of inflammation
- Protection of the ocular surface from side effects
- **Dry eye management**

Key Learning points

— Preservative-free (PF) eye drops must be considered for glaucoma patients.

— Results from switch studies show improved signs and symptoms of Ocular Surface Disease (OSD) when antiglaucoma eye drops are changed from Benzalkonium chloride (BAK)-preserved to PF formulations.

— *In vitro* and *in vivo* studies demonstrate PFdrops result in the least disruption to the ocular surface at both clinical and cellular levels.

— A number of clinical studies revealed that PF anti-glaucoma eye drops are as effective as therapies with preservatives.

— Improvement of quality of life for glaucoma patients after switching to PF antiglaucoma eye drops is demonstrated by the reduction of the level of severity in hyperaemia, ocular signs and symptoms.

Use of Hydrocortisone

The use of mild or soft steroids, such as hydrocortisone, is highly indicated in patients with OSD, where a long-lasting anti-inflammatory treatment is advisable *(Aragona et al., 2021)*.

This treatment can be considered safer than other types of corticosteroid molecules. However, it is always mandatory to check IOP and the lens status during treatment (Figure 39).

A retrospective review demonstrated that topical applications of PF hydrocortisone 0.335% twice daily for 2 weeks significantly improved clinical signs and symptoms in patients with mild to moderate DED *(Elabjer et al. 2020)*

In a prospective study, patients with chronic DED and ocular surface inflammation received preservative-free hydrocortisone 0.335% which resulted in reduced ocular inflammation and decreased OSDI score with no change in IOP *(Kallab et al. 2020)*

Figure 39: Examples of studies applying hydrocortisone (soft corticosteroid) for relieving symptoms of Dry Eye Disease (DED). IOP: Intraocular Pressure; OSDI: Ocular Surface Disease Index; PF: Preservative-free. *(Elabjer et al., 2020; Kallab et al., 2020)*.

Preoperative Management

Improvement of the ocular surface and reduction of inflammation prior to glaucoma surgery should be considered aiming at the optimization of the ocular surface condition (preconditioning) *(Broadway et al., 1996)*.

The use of preservatives should be avoided or reduced in patients with severe glaucoma or requiring multiple therapies, in patients most likely to undergo surgery, and those with clinically impaired ocular surface, such as dry eyes, allergic reactions, or blepharitis *(Baudouin, 2012)*.

Patients with severe glaucoma, who are most likely to undergo surgery, or those with clinically impaired ocular surface in need of multiple therapies, should avoid or minimize the use of preserved eye treatments, as these are partially or entirely responsible for changes in the ocular surface *(Baudouin, 2012)*.

Various studies have demonstrated the clinical advantage of PF eye drops prior to glaucoma surgery (Figure 40) *(Broadway et al., 1996; Breusegem et al., 2010; Baudouin, 2012)*.

Treatment before glaucoma surgery

- Preoperative 1% fluorometholone eye drops one month before surgery can improve the ocular surface and the success rate of filtration surgery *(Broadway et al., 1996)*.
- Indomethacin (unpreserved) and fluorometholone (preserved) eye drops administered 1 month before filtering surgery in glaucoma patients also reduced subclinical conjunctival inflammation as measured by ocular surface HLA-DR expression *(Baudouin et al., 2002)*.
- Ketorolac eye drops administered for 1 month in patients with uncontrolled Intraocular Pressure (IOP) before surgery were shown to be associated with improved trabeculectomy outcome *(Breusegem et al., 2010)*.

Figure 40: Preoperative treatments to optimize ocular surface and surgical outcomes in glaucoma patients.

Postoperative Considerations

Filtration surgery can alter the ocular surface and dry eye symptoms may be provoked *(van Setten, 2018)*.

Sophisticated techniques should be applied in order not to create high bulging blebs leading to a condition of anatomical dry eye and triggering processes favoring attrition and secondary scar formation *(van Setten, 2018)*.

Attrition is the process of reducing the strength or effectiveness through sustained attack or pressure. Epitheliopathy of the bleb is the result of friction caused by attrition. This occurs on the ocular surface of the surgically created protruding bleb, which is constantly exposed to the eroding forces of the environment and lid movement *(van Setten, 2018)*.

Attrition may lead to mechanical stimulation and fibrosis threatening the functionality of the bleb and enhancing inflammation, resulting in dysregulation of tear production and blink reflex *(van Setten, 2018)*.

Topically applied high molecular weight 0.15% hyaluronan eye drops on subbasal corneal nerves in patients suffering from severe DED for eight weeks promotes corneal nerve growth acting as a neurotrophic agent *(van Setten et al., 2020)*.

The viscoelastic and mucoadhesive properties of hyaluronan eye drops minimize the friction between the moving eyelid and the surface of the eyeball during blinking, thus reducing known stimuli of ocular surface inflammation (Figure 41).

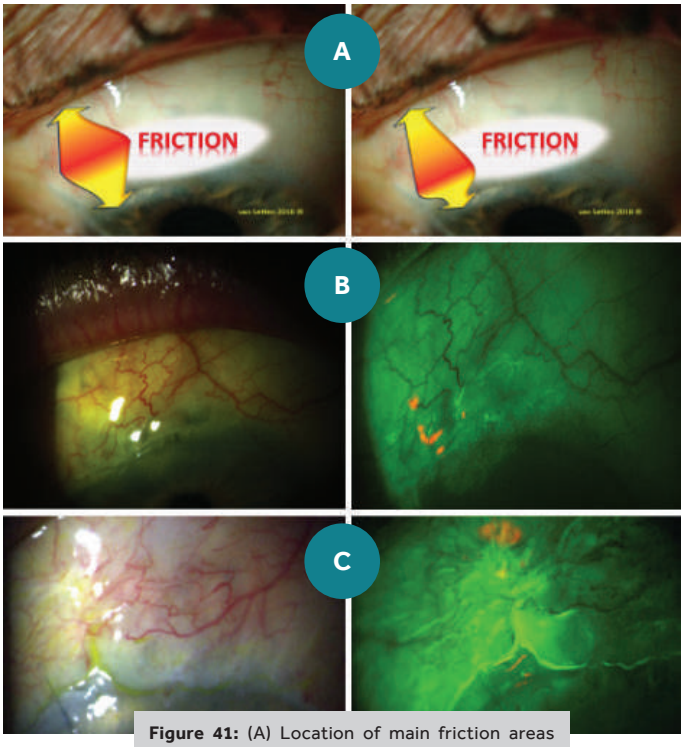


Figure 41: (A) Location of main friction areas on the bleb surface (schematic). (B) Localized punctate staining at the downhill side of the bleb towards the limbus. (C) Localized staining over a cystic area of the bleb *(Van Setten, 2018)*.

Postoperative Management

The ocular surface and the morphology of filtering blebs should be routinely evaluated in postoperative patients.

In general, can be considered as first-line treatment according to the 2021 guidelines of the European Glaucoma Society (EGS):

— Avoidance of repeated exposure to BAK.

— Use of PF artificial tear fluid substitutes and lubricants (Figure 42).

— Use of PF artificial tears 6-8x/day.

— Chronic application of hyaluronic acid to decrease attrition *(van Setten et al., 2020)* and contribute to the survival of the drainage sites such as recommended for deep sclerectomy *(van Setten, 2018)*.

— Antibiotics to be administered for 2-3 weeks, while topical steroids (preferably PF) should be used for 12 weeks after filtration surgery.

Cyclosporine A 0.05%

In an interventional, randomized study, patients receiving cyclosporine A 0.05% following trabeculectomy demonstrated after 6 months statistically significant decrease in OSDI with less severity of dry eye symptoms and significant reduction of ocular pain

Preservative-free (PF) eye drops

In patients following phacoemulsification, PF-trehalose, when used as part of a combined postoperative therapy (with dexpanthenol gel), was effective against dry eye syndrome (improved OSDI, TBUT, conjunctival hyperemia, corneal confocal tomography) *(Astakhov & Tkachenko, 2016)*

The high-molecular-weight absorbable biosynthetic cross-linked HA viscoelastic gel was as safe and effective as low-dose MMC in trabeculectomy. Similar results were observed for postoperative IOP reduction and bleb morphology over 1 week, 1 month, 3 months, 6 months, and 12 months *(Mudhol & Bansal, 2021)*

In a retrospective study, following trabeculectomy the group which was administered PF trehalose and HA had improved IOP control, postoperative complications, and bleb morphology compared to control group *(Sen et al., 2021)*

Figure 42: Postoperative management of glaucoma patients. HA: Hyaluronic Acid; IOP: Intraocular Pressure; MMC: Mitomycin; OSDI: Ocular Surface Disease Index; TBUT: Tear Break-Up Time.

Clinical Cases

Clinical cases are important to give an insight on the typical history and initial examination of various ophthalmic disorders. A thorough review of previously reported case series can help a physician recognize and describe the typical presentation of common conditions affecting the anterior and posterior segments of the eye, consider a range of multiple etiologies when examining patients with eye or vision problems, including trauma, infection, congenital abnormalities, autoimmunity, vascular issues, metabolic deficiencies, and environmental causes, recall the basic pathophysiology underlying numerous ophthalmic conditions, evaluate the significance of clinical findings in relation to common ophthalmic diseases, formulate a differential diagnosis after reviewing the patient's history and ocular exam and identify which laboratory tests or exams are appropriate to confirm and evaluate specific ophthalmic diagnoses.

CASE STUDY 1

(Batra et al., 2014)

4 patients referred for a glaucoma surgery

Despite 3 anti-glaucoma treatments

1. Intraocular Pressure (IOP) uncontrolled (35 mmHg)
2. Poor tolerance

Therapeutic Escalation

1. Addition of anti-allergic preserved eye drops
2. Addition of preserved anti-inflammatory eye drops
3. Addition of topical Carbonic Anydrase Inhibitor (CAI)

Interruption of preserved eye drop

1. Palpebral hygiene
2. Artificial tears
3. Oral doxycycline (50mg)
4. Anti-glaucoma Preservative-free (PF) eye drops

Ocular surface near-normal, with a reduction in hyperemia, meibomian gland dysfunction and superficial keratopathy

Improvement in the IOP control

No need for surgery

The use of a combination approach comprising medical treatment to manage the Ocular Surface Disease (OSD) in patients with Primary Open Angle Glaucoma (POAG) may lead to an improvement in the IOP control and the management of glaucoma.

CASE STUDY 2

(Dubrulle et al., 2018)

10 patients with uncontrolled glaucoma associated with Ocular Surface Disease (OSD) and referred for filtering surgery

Despite maximal anti-glaucoma treatments (from 2 to 6 therapies)

1. Uncontrolled Intraocular Pressure (IOP)
2. Progression of glaucoma
3. Poor tolerance
4. An affected ocular surface

The Therapeutics used

1. Preserved anti-glaucoma eye drops
2. Addition of preserved anti-inflammatory or topical corticosteroids
3. Addition of carbonic anhydrase inhibitor (CAI)

Interruption of preserved eye drop

1. Glaucoma Preservative-Free (PF) eye drops
2. PF artificial tears
3. Lid hygiene
4. Oral doxycycline (50 mg) when necessary
5. PF non-steroidal anti-inflammatory drugs (NSAID)

Improvement of the ocular surface (the mean Oxford score decreased from 1.7 ± 0.67 to 0.4 ± 0.51 (-76.5%; P<0.001)

Improvement in the IOP control (the mean IOP significantly decreased from 23.75 ± 9.98mmHg to 15.15 ± 4.75mmHg).

However, for two patients IOP was not sufficiently reduced after treatment and they finally underwent filtering surgery

Reduction of the number of IOP lower medications (from 3.7 ± 1.06 at presentation and 2.8 ± 0.63 after intervention)

The hyperemia decreased by 67% (from 2.0 ± 0.82 to 0.65 ± 0.41)

Reduction or removal of preserved eye drops replaced by PF products.

Treatment of OSD improves the ocular surface status and the IOP control, with no more or fewer anti-glaucoma drugs.

Summary Keypoints

— Optimizing glaucoma therapies involves switching to preservative-free (PF) eye drops, avoiding allergenic or Dry Eye Disease (DED)-triggering treatments, maintaining ocular hygiene, and using doxycycline, cyclosporine A, corticosteroids, or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), when needed.

— PF options are recommended for glaucoma patients, especially those with multi-drug therapy or with DED. Studies demonstrate improved Ocular Surface Disease (OSD) symptoms after switch from Benzalkonium chloride (BAK)-preserved drops to PF formulations, and minimal disruption to the ocular surface.

— PF formulations are recommended as a first-line treatment to preserve the ocular surface from OSD.

— Preserved and PF anti-glaucoma treatments have the same efficacy, with better tolerability for PF therapies.

— The benefits of BAK-free anti-glaucoma eye drops include the reduction in potentially reversible adverse reactions, improved tolerability and quality of life, reduced rate of inflammation and protection of the ocular surface against side effects.

— Mild or soft steroids, such as hydrocortisone, are widely recommended in patients with DED for relieving clinical signs and symptoms since they are considered safer than other types of corticosteroid molecules.

— Preoperative optimization should involve topical treatment transition from preserved to PF eye drops, which might require several months.

— Regarding postoperative management, the European Glaucoma Society (EGS) Guidelines of 2021 recommend avoidance of repeated exposure to BAK, use of PF artificial tears 6-8 times daily, use of high viscosity lubrication agents, as well as topical steroids, preferably PF, for up to 3 months after surgery or cyclosporine A for longer periods.

— The functionality of any filtration area or bleb is dependent on proper lubrication of the surface. This could mean lifelong application of lubricating agents.

— Clinical cases suggest OSD treatment for Primary Open Angle Glaucoma (POAG) patients, since it can improve Intraocular Pressure (IOP) control and glaucoma management and reduce the need for additional anti-glaucoma drugs, as well as switching from preserved eye drops to PF products.

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