European University Professors of Ophthalmology

EUPO 2017

& Cornea, Conjunctiva Refractive surgery

In conjunction with SOE 2017
Centre de Convencions
Internacional de Barcelona

June 9-10, 2017
Barcelona, Spain

EUPO Office • Kapucijnenvoer 33 • 3000 Leuven • Belgium • www.eupo.eu

The sequence of the EUPO courses

2017	Barcelona (SOE)	Cornea, Conjunctiva and Refractive Surgery
2016	Nice (EVER)	Neuro-ophthalmology and Strabismus
2015	Vienna (SOE)	Uveitis and Glaucoma
2014	Nice (EVER)	Retina
2013	Copenhagen (SOE)	Cornea, Conjunctiva and Refractive Surgery
2012	Leuven	Neuro-ophthalmology and strabismus
2011	Geneva (SOE)	Uveitis & Glaucoma
2010	Athens	Retina
2009	Amsterdam (SOE)	Cornea, Conjunctiva and Refractive surgery
2008	Geneva	Neuro-ophthalmology and strabismus
2007	Vienna (SOE)	Glaucoma and uveitis
2006	Ghent	Retina
2005	Berlin (SOE)	Cornea
2004	Nijmegen	Neuro-ophthalmology and strabismus
2003	Madrid (SOE)	Glaucoma and uveitis
2002	Erlangen	Retina
2001	Istanbul (SOE)	Cornea
2000	Leuven	Neuro-ophthalmology and strabismus
1999	Stockholm (SOE)	Glaucoma and uveitis
1998	Amsterdam (ICO)	Chorioretina
1997	Budapest (SOE)	Cornea, conjunctiva, lids, orbit
1996	Athens	Neuro-ophthalmology and strabismus
1995	Milano (SOE)	Uveitis, lens, glaucoma
1994	Montpellier	Retina
1993	Santiago de Compostella	The external eye
1992	Brussels (SOE)	Neuro-ophthalmology and strabismus
1991	Torino	Uveitis, lens, glaucoma
1990	Bonn	Chorioretina
1989	Leuven	The external eye and orbit
1988	Nijmegen	First EUPO course

Gabriel Van Rij, President of EUPO

Dear colleagues,

It is my pleasure to welcome you to the 30th annual Course of the European Professors of Ophthalmology (EUPO) on Cornea, Conjunctiva and Refractive Surgery in Barceona, Spain 9-10 June 2017.

We are delighted that a superior international faculty, who are all leaders in their field, accepted our invitation.

These invited lecturers come from Europe and from around the world. They will present an unsurpassed scientific programme.

The course follows a tradition established in 1988 by Professor Deutman.

After this course it was decided to organize a course once a year in different places in Europe.

Later it was decided that in the year of a congress of the European Society of Ophthalmology (SOE), the course would be organized in connection with the European Congress of Ophthalmology.

Most of the ophthalmology curriculum should be covered in the EUPO Courses within a four-year period in order to permit residents and ophthalmologists to have an overview of basic and clinical knowledge of the eye during this four-year period.

The EUPO course book will be published on line and will be avalable before the course. Resident scan benefit most by reading the MCQ's and handouts before attending the course. I welcome you to Barcelona and thank you for making the EUPO Course 2017 a memorable event.

Gabriel van Rij, MD, PhD
President of EUPO

available on www.eupo.eu

EUPO 2017
Cornea, Conjunctiva and Refractive Surgery

EUPO 2016
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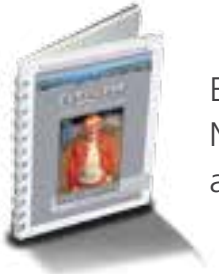

EUPO 2008
Neuro-Ophthalmology and Strabismus

EUPO 2007
Uveitis

EUPO 2006
Retina

European University Professors of Ophthalmology

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Programme EUPO 2017
Friday June 9, 2017

Course directors: Friedrich Kruse, Jesús Merayo-Lloves, Gabriel van Rij

• Morphology, anomalies and tumors — 08:35 - 10:15

		Course	Page
• 08:35	Opening by Gabriel van Rij, Netherlands		
• 08:45	Morphology of the normal human cornea *BERTA A - Hungary*	1	10
• 09:15	Corneal disorders in children and congenital anomalies of the cornea *MURTA J - Portugal*	2	19
• 09:45	Tumors of the cornea and conjunctiva *SEREGARD S - Sweden*	3	25

• Break — 10:15 - 11:00

• Inflammatory and non-inflammatory — 11:00 - 12:30

		Course	Page
• 11:00	Role of inflammation in ocular surface disease *PLEYER U - Germany*	4	30
• 11:30	Dry eye and clinical disease of tear film, diagnosis and management *MERAYO-LLOVES J - Spain*	5	56
• 12:00	Non-inflammatory corneal pathology, Salzmann and Terrien *IRKEÇ M - Turkey*	6	59

• Lunch — 12:30 - 14:00

Programme EUPO 2017
Friday June 9, 2017

Course directors: Friedrich Kruse, Jesús Merayo-Lloves, Gabriel van Rij

• Ocular surface reconstruction and keratoplasty		14:00 - 15:40 Course	Page
• 14:00	Young Ophthalmologists		
• 14:10	Corneal transplantation: Anterior lamellar *GÜELL J - Spain*	7	82
• 14:40	Ocular surface reconstruction *RAMA P - Italy*	8	85
• 15:10	Corneal transplantation: Posterior lamellar *KRUSE F - Germany*	9	94

• Break	15:45 - 16:15

• Corneal translantation immunology, corneal examination and keratoprosthesis		16:15 - 17:45	
• 16:15	Corneal examination, keratoconus and dystrophies *BELIN M - USA*	10	97
• 16:45	Keratoconus and pellucid marginal degeneration *MALECAZE F - France*	11	158
• 17:15	Corneal dystrophies *TUFT S - United Kingdom*	12	161

• End	17:45

Programme EUPO 2017
Saturday June 10, 2017

Course directors: Friedrich Kruse, Jesús Merayo-Lloves, Gabriel van Rij

• Bacterial, fungal and acanthamoeba **08:00 - 09:30**

• Break and exhibition **09:30 - 10:00**

• SOE 2017 Opening Ceremony **10:00 - 11:30**

• SOE Keynote lecture: **13:15 - 14:00**
Evolution of retinal surgery by Bill Aylward, UK

Programme EUPO 2017
Saturday June 10, 2017

Course directors: Friedrich Kruse, Jesús Merayo-Lloves, Gabriel van Rij

		Course	Page
• Dry eye, eyelids and contact lenses			**14:15 - 15:45**
• 14:15	Meibomian gland dysfunction *MURPHY C - Ireland*	16	227
• 14:45	Assesment and step by step management of allergic eye disease *LARKIN F - United Kingdom*	17	232
• 15:15	Therapeutic use of contact lenses in ocular surface disease *KOPPEN C - Belgium*	18	243
• Break			**15:45 - 16:15**
• Keratoprosthesis and refractive surgery			**16:15 - 17:45**
• 16:15	Keratoprosthesis *LIU C - United Kingdom*	19	249
• 16:45	Intra stromal refractive lenticule extraction *HJORTDAL J - Denmark*	20	255
• 17:15	Quality of vision after refractive surgery *AZAR D - USA*	21	260
• End of the EUPO Course			**17:45**

Evaluation form and Certificate of Attendance

The evaluation forms should be returned to registration desk and the certificate of attendance for EUPO 2017 will be emailed to all delegates after the EUPO Course.

MCQ's

1. Which of the folowing statements is true for the Bowman's layer of the cornea?

a. It's composing collagen molecules are different from the corneal stroma.
b. It contains keratocytes that can transform into fibroblasts.
c. It does not regenerate, when injured or damaged.
d. It separates the stroma from the endothelial layer.

2. Which of the following statements characterizes the Dua's membrane best?

a. It is clearly distinguishable on light microscopy sections stained with H-E from the stroma.
b. It does not have any practical significance in corneal transplantations.
c. It was discovered at the beginning of the 20th century.
d. It can be separated from the Descemet mebrane by pumping an air buble into the deepest layers of the corneal stroma.

3. Which of the following stements is true for the normal human cornea?

a. The cornea is responsible for 10 % of the total refractive power of the eye.
b. The human cornea is asheric in shape, steeper in the center and flatter in the periphery.
c. Healthy corneas are thicker in the center and thinner near the limbus.
d. Endothelial cells of the cornea can regenerate, this ability dcreases with age.

Introduction

The both the oral and the written part of the course on corneal diseases and corneal surgery starts with the description of the morphological and histolological characteristics of the normal cornea. Residents should start their studies with this subject, because a wellbased and detailed knowledge of the normal corneal stuctures is essential for the study of pathological changes to be found and recognized in the cornea, either on the macroscopic or on the microscopic level. In certain countries the study of corneal pathology is a part of the resident training in Ophthalmology. Such information help the residents to recognize corneal diseases both in vivo, using the slitlamp, both on stained sections using the microscope. Proper knowledge of corneal morphology is essential to evalute the findings gained using modern diagnostic instruments (cornal topograph, specular microscope, in vivo confocal microscope, pachymeter, anterior segment OCT, UBM, Scheimpflug cameras and instruments such as Pentacam and CorVis), as well as to be able to perform surgery on the cornea (different types of corneal transplantation, and refractive surgical interventions). Not only a thorough knowledge of corneal morphology can help the use of diagnostic instruments, and the performance of corneal surgeries, but also experiences, research and developmental work in the field of corneal diagnostics and corneal surgery, constantly increase our knowledge on the structure and function of the cornea as a whole and that of different layers and parts of the cornea in health and in disease.

Anatomy

The average diameters of the cornea are: 12 mm and 11.5 mm in the horizontal and in the vertical axis, respectively. This results in a 0.5 diopter, on an average, with the rule astigmatism, that is called physiological astigmatism.

Histology

1. Epithelium

The corneal epithelium has three layers (surface cell layer, wing cell layer and basal cell layer) that consist of different types of cells. The surface cells are flat, are present in 2-3 layers, have flat nuclei and are joined together by bridges (zonula occludens). The surface of the outermost cells is increased by microvilli in order to facilitate the adsorption of mucin, that makes the corneal surface more hydrophyllic. The wing cells have 'wing like' extensions and are arranged in 1-2 layers. The basal cells form a single layer, are of columnar shape with nuclei located near to the apex of each cel, are able to devide and are the source of the wing celss which in turn when shifted towards the surface become superficial cells (Figure 1, 2A).

1. Bowman's layer

Bowman's layer is only a superficial layer of the stroma, with special compact structure, acellular, does not regenerate when injured or damaged.

2. Stroma

Is composed of collagen fibrils of uniform size, extending across the the entire cornea, forming bundles and layers (lamellae) in a parallel and criss-crossed manner, as well a corneal cells (keratocytes) (Figure 2C) and extracellular matrix, that is composed of glycoproteins and glycose-aminoglycans. Rather special characteristic of the corneal stroma is transparency (optical clarity) which is related to its highly oriented structure and its dehidrated state.

3. Descemet's membrane

Descemet's membrane is composed of thin collagen fibrils arranged in lattice forming way. Its anterior layer, that shows bands on electorne microscopic picture, develops during the intrauterine life, while the posterior layer is slowly growing, synthetized by the endothelial cells throughout life. Descemet's membrane acts as a basement membrane of the corneal endothelium.

4. Endothelium

Endothelium is a single layer of hexagonal cells covering the inner surface of the cornea (Figure 1, 2D). It plays a basic role in maintaining the deturgenscens of the cornea by a continuous pumping of water and ions from the stroma to the aqueous humor in the anterior chamber. The number (density) of corneal endothelial cells decreases with age. As the endothelial cells are not able to regenerate. The integrity of the endothelial cell layer is mantained by streaching out of the neighbouring cells covering the place of a dying cell.

5. Dua's layer

Dua proposed that a 5th layer exists between the corneal stroma and Descemet's membrane. To prove the existence of this layer, Dua et al. carried out corneal sparation experiments on donated human corneas. They separated corneal layers by pumping small air bubbles in between them, and then removing and replacing the different layers. By injecting even smaller bubbles, they were able to reveal the new Dua's layer, whose unique structure they confirmed also with electron microscopy.

The human cornea contains sensory nerve fibers originated from the trigeminal nerve and sympathetic axons from the superior cervical ganglion. Stromal nerve bundles enter the cornea at its periphery and before penetrating the Bowman's membrane, they compose the subepithelial plexus. After dividing into several smaller branches, subbasal plexus nerves innervate the corneal epithelium and form nerve terminals with a considerably higher density in the central cornea than in the periphery (Figure 2B). Corneal nerves have a pivotal role in maintaining the functional and morphological

integrity of the ocular surface. The healthy human cornea is avascular, it is supplied by the anterior ciliary artery and the facial artery. At the limbus, peripheral cornea connects to the opaque sclera (Figure 3).

Structure related characteristics

The special microstructure, regulation and physiology of the normal human cornea are responsible for its complex functions. Cornea is the principal refracting component of the eye contributing two-thirds of the total refractive power. Corneal avascularity, the special arrangement of collagen fibers and interfibrillar spacing in the stromal layer as well as intact endothelial function are essential in maintaining corneal transparency. Endothelial cell density and morphology are important markers of the corneal health since these hexagonal cells act like active fluid pumps and have barrier function and are responsible for preserving corneal deturgescence. Impairment of endothelial function leads to corneal swelling and loss of transparency. The fundamental functions of the normal cornea are light transmission, refraction (with the pre-corneal tear film) and protection. Healthy corneas show larger thickness values towards the limbus (Figure 4, 5). This phenomenon could be explained by the growing amount of collagen fibers and the transversely oriented anchoring lamellae in the periphery. Due to its unique microstructural composition and organization, cornea exhibits viscoelastic behaviour which is important to understand the biomechanical changes in different corneal diseases and after refractive surgery (Figure 6). The human cornea is aspheric in shape, steeper in the center and flatter in the periphery. Apart from the curvature of the anterior and posterior cornea, surface elevation (ie. the height of a surface point relative to a best-fit reference shape) represents a clinically useful parameter in identifying corneal disorders (Figure 5).

Suggested reading:

- Anatomy of the Human Eye http://www.missionforvision.org/2005/10/cornea-histology.html

- Morphology of the Human Eye http://www.missionforvision.org/2005/10/cornea-histology.html

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Legends to figures

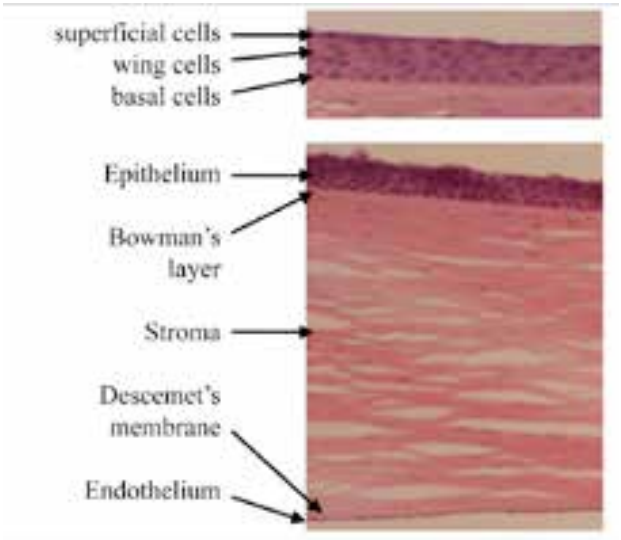

Figure 1. Histology of the normal cornea: Five layers of the cornea (bottom) and the different cellular layers of the corneal epithelium (top).

A. Corneal epithelial cells in the basal epithelium

B. Hyperreflective fibers represent the sub-basal nerve plexus

C. Corneal stroma: hyperreflective keratocyte nuclei and processes

D. Monolayer of hexagonal endothelial cells

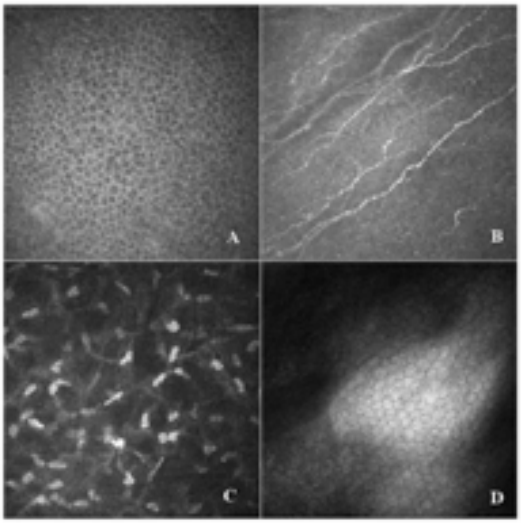

Figure 2. Cellular structures of the normal cornea imaged with in vivo confocal microscopy.

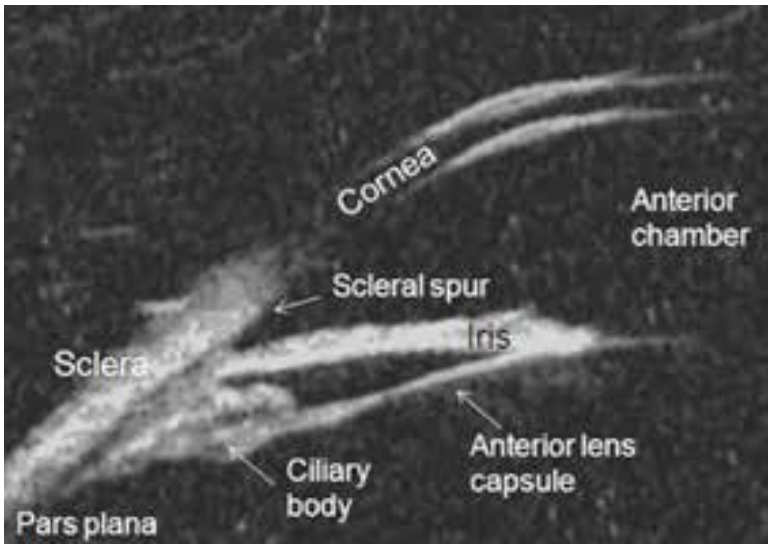

Figure 3. 35 MHz ultrasound biomicroscopy image of the normal eye.

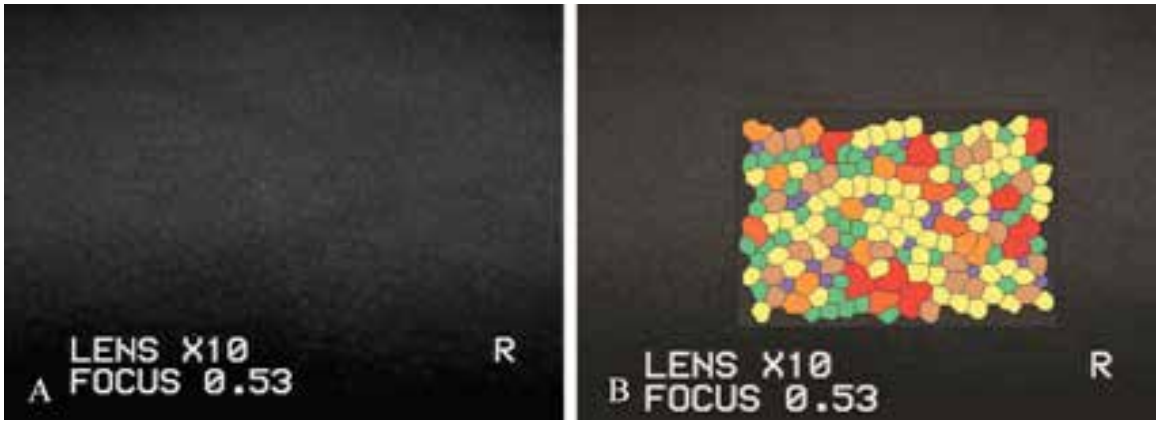

Figure 4. Endothelial photograph (A) and image analysis (B) made by a contact specular microscope. Endothelial cell density: 2900 cells/mm2, mean cell size: 343 µm2, coefficient of variation: 0.38, corneal thickness: 530 µm.

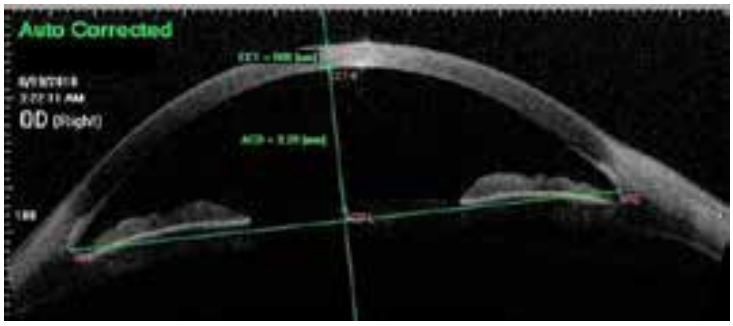

Figure 5. Fourier domain anterior segment optical coherence tomography imaging of the cornea, anterior chamber, iris, anterior lens and irido-corneal angle. Please note the normal central pachymetry (CCT, central corneal thickness) and anterior chamber depth (ACD).

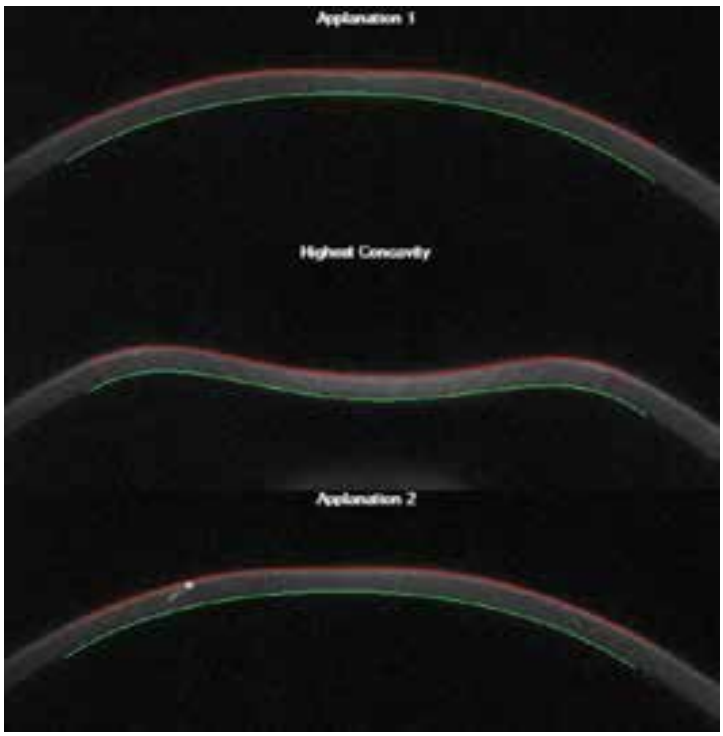

Figure 6. Corneal biomechanical measurement: Scheimpflug-image of corneal deformation response to an air impulse recorded with CorVis ST.

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MCQ answers page 10

1. **Answer: c**

2. **Answer: c**

3. **Answer: b**

MCQ's

1. Which one of the following regarding abnormalities of corneal size and shape is false?

a. Megalocornea is defined as a cornea whose horizontal diameter is greater than 12 mm.
b. The majority of megalocornea is bilateral and seen in men.
c. Simple megalocornea is associated with other ocular abnormalities
d. Cornea plana is usually associated with significant hyperopia.
e. Acute hydrops can be associated with keratoglobus.

2. What are the clinical features that distinguish congenital hereditary endothelial dystrophy (CHED) from congenital glaucoma:

1. Corneal thickness.
2. Corneal diameter.
3. Epithelial edema.
4. Intraocular pressure.
5. Corneal topography.

a. 1, 2 and 5.
b. 2 and 5.
c. 2 and 4.
d. 5 only.
e. 1, 2, 3, and 4.

3. The earliest sign of Wilson's disease is:

a. Copper deposition in far periphery Descemet's membrane.
b. Sunflower cataract.
c. Kayser-Fleischer ring.
d. Ocular hypertension.
e. Decrease of visual acuity

02 - Corneal disorders in children and congenital anomalies of the cornea, MURTA J - Portugal

Corneal disease is still today the most common cause of blindness in the world. Diseases affecting the cornea and anterior segment in children differ little from diseases in adults with the exception of congenital and development abnormalities.

The initial 6 weeks, until the closure of the embryonic fissure, are the most critical period for ocular development. Arrest of development during this period leads to severe ocular anomalies and greatly impaired visual acuity (anophthalmia, congenital cystic eye, congenital aphakia, typical colobomas, etc).

The congenital anomalies of the anterior segment are present at birth, usually bilateral, but often asymmetrical, in approximately 3/100,000 newborns. The etiology can be genetic, infectious, inflammatory, traumatic, toxic or a combination of these factors, which most often affect the normal ocular development between the sixth and sixteenth weeks of gestation, when differentiation of the anterior segment occurs. Different structures in the anterior segment are subject to common influences, so that development abnormalities of one component are often accompanied by abnormalities of others. The development anomalies of the anterior segment are often difficult to classify and new classifications have been proposed.

However precise diagnosis is necessary in order to predict the natural history of the disease, to look for associated ocular and systemic abnormalities, to give genetic counselling and to initiate appropriate treatment. The following will be briefly described: **Abnormalities in corneal size and shape:** Microcornea, Megalocornea, Keratoglobus, Cornea Plana; **Abnormalities in corneal development leading to a visually opaque cornea:** Sclerocornea, Peripheral Anterior Chamber Cleavage Abnormalities (Axenfeld's Anomaly, Axenfeld's Syndrome, Rieger's Anomaly, Rieger's Syndrome), Central Anterior Chamber Cleavage Abnormalities (Central posterior Keratoconus, Peters Anomaly), **Inborn Errors of Metabolism, Corneal Dystrophies** present at or shortly after birth (Congenital Hereditary Endothelial Dystrophy, Posterior Polymorphous Dystrophy, Congenital Hereditary Stromal Dystrophy, Posterior Amorphous Corneal Dystrophy), **Congenital Glaucoma** and **Epibulbar Tumors** (Dermoid, Osseous Choristomas). We will also discuss a classification system of congenital corneal opacification from a perspective of pathogenesis, surgery and prognosis will be discussed.

We will also consider **corneal manifestations of systemic diseases** (diseases of abnormal carbohydrate metabolism, diseases of abnormal protein metabolism, diseases of abnormal lipid metabolism, avitaminosis, interstitial keratis secondary to syphilis, tuberculosis and virus, Wilson's disease, Refsum's syndrome) and different forms of **atopic and vernal keratoconjunctivitis**.

Keratoconus, the most common ectatic corneal disease, appears in the early adolescent years and can progress in the late teens into the twenties. It may be seen with other conditions such as allergic disease, *retinitis pigmentosa*, Down, Alport or Marfan syndromes.

Pediatric microbial keratitis is a rare but potentially devastating disease. The condition is similar to the adult version but is often characterized by a more severe inflammatory response; herpes simplex and bacteria (*pseudomonas aeruginosa, staphylococcus aureus and α-hemolytic streptococci*) are more common, with fungi being less frequent.

Ocular trauma and child abuse will also be covered. The former is second only to cataracts as the most common cause of visual impairment and the most frequent cause of unilateral blindness among children.

Also discussed will be the management of corneal opacities in children (team approach, preoperative examination, the use of new instrumentation such as high-frequency ultrasound or anterior segment optical coherence tomography, indications for surgery like keratoplasty, lamellar keratoplasty, iridectomy or keratoprosthesis) as well as ectatic diseases (crosslinking, intracorneal rings). Penetrating keratoplasty is indicated in children who have significant unilateral or bilateral corneal opacities that prevent visual development. Otherwise they would develop dense amblyopia. In cases of significant congenital corneal opacities, surgery should be performed within the first 3 months of life to reduce the degree of amblyopia. Poor prognostic factors include bilateral disease, concomitant infantile glaucoma, lensectomy and vitrectomy at the time of the surgery, previous graft failure, extensive goniosynechiae and corneal vascularisation.

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MCQ answers page 19

1. **Answer: c**

2. **Answer: c**

3. **Answer: a**

MCQ's

1. **Which of the following is often used to treat a 4 mm area of conjunctival intraepithelial neoplasia encroaching onto the cornea:**

   a. radiotherapy
   b. systemic chemotherapy
   c. local chemotherapy
   d. enucleation

2. **A 3 mm juxtalimbal conjunctival pigmented lesion featuring small cysts in a 10-year old child is most likely a:**

   a. conjunctival naevus
   b. conjunctival melanocytic neoplasia
   c. conjunctival melanoma
   d. conjunctival rhabbomyosarcoma

3. **The so-called conjunctival lymphangioma is a (an):**

   a. neoplastic tumour with potential to seed metastases
   b. vascular malformation
   c. reactive lesion typically arising after trauma
   d. angiomatous intraocular lesion with extraocular growth onto the conjunctiva

Tumours largely include neoplasia and reactive mass-like lesions. Neoplastic lesions may be benign or malignant. Malignant lesions are characterized by the capacity to invade basement membranes and the potential to generate metastases. Metastatic disease is caused by cells which invade lymphatics or blood vessels, survive in the circulation and then attach to the vessel wall and extravasate at a distant site. For this reason, malignant lesions which are confined to the epithelium (i.e. without signs of break of basement membrane invasion) do not have the capacity to generate metastatic spread. Such lesions are typically referred to as carcinoma-in-situ or melanoma-in-situ. Nearly all tumour-like lesions of the cornea and conjunctiva actually derive from the conjunctiva, and any corneal lesion is usually caused by secondary tumour invasion of the cornea.

The tumours of the cornea and conjunctiva may for practical reasons be divided into melanocytic and non-melanocytic lesions. Most melanocytic lesions are pigmented, but a substantial proportion (e.g. approximately 30% of conjunctival naevi are non-pigmented). Similarly, non-melanocytic lesions may show pigmentation (e.g. squamous cell carcinoma of the conjunctiva presenting in individuals with heavy skin pigmentation).

Melanocytic lesions of the conjunctiva arise from melanocytes typically lodged in the basal part of the conjunctival epithelium or sometimes in the conjunctival stroma. The most common lesion is the acquired conjunctival naevus, which typically presents as a thin, pigmented or non-pigmented lesion in the limbal or juxtalimbal region. This lesion rarely undergoes transformation to malignant melanoma, but may be excised for cosmetic reasons.

Individuals with abundant skin pigmentation often feature bilateral and symmetrical conjunctival pigmentation of the limbal region. This is a normal variant referred to as ethnic or racial melanosis and should not be confused with primary acquired melanosis (PAM). The PAM typically features a unilateral flat pigmentation without cysts. The borders are not sharply defined and lesions may have satellites or be multifocal. Up to 50% of PAM featuring cytological atypia may progress into (invasive) malignant melanoma. In contrast, PAM without atypia has a very small risk (if any) for malignant transformation and these two entities are distinctly different. Some authors argue that PAM with severe atypia equals melanoma-in-situ and recently melanocytic intraepithelial neoplasia (MIN) has been suggested to replace the concept of PAM with atypia. To assess the presence of atypia, biopsy of the conjunctival lesion is usually required even though cytological sampling by an exfoliative smear is advocated by some authors.

Malignant melanoma is a very rare tumour typically occurring in the limbal or juxtalimbal region of middle-aged or elderly individuals. Sometimes, a melanoma may arise from the tarsal, forniceal or caruncular conjunctiva. Thus, a complete examination of the entire conjunctival sac including the tarsal conjunctiva is warranted in patients evaluated for conjunctival malignant disease. Treatment of malignant melanoma of the conjunctiva is usually surgical taking care to provide adequate surgical margins

and to avoid seeding of tumour cells during surgery. Large conjunctival defects may be covered by amniotic membrane grafts. Adjunctive treatment may include cryotherapy, topical chemotherapy (typically using mitomycin) or brachytherapy. Primary orbital exenteration has not been shown to improve survival, but exenteration may sometimes be required to control local disease. Metastatic disease appears in some 30% of patients usually confined to the ipsilateral regional lymph nodes or salivary glands (in particular the ipsilateral parotid gland). Lymph nodes may be monitored by simple palpation or imaging by ultrasound. Any lymph node suspected of harbouring metastatic disease may be surgically excised or studied by cytology after sampling using a fine-needle aspiration biopsy. Confirmed spread to the lymph nodes may be managed by radical neck dissection. Later in the course of disease, systemic spread to distant sites occurs. Patients with malignant melanoma of the conjunctiva or PAM with atypia should have period ophthalmic follow-up for life.

Non-melanocytic lesions of the conjunctiva include a wide variety of neoplastic and reactive mass-like lesions. Conjunctival intraepithelial neoplasia (CIN) typically occurs in the limbal region of elderly patients and tends to encroach onto the cornea. Once referred to as Bowen's disease this in-situ carcinoma has traditionally been managed surgically. Local recurrence is common but recently excellent results have been reported using topical chemotherapy (5-fluorouracil, mitomycin or more recently using topical interferon). The CIN rarely progress to invasive squamous cell carcinoma, but once this takes place the lesion carry a potential to seed metastases, usually to the ipsilateral regional lymph nodes. The carcinomas of the conjunctiva also include the rare, but highly aggressive mucoepidermoid carcinoma and the poorly differentiated spindle cell carcinoma. Rarely, neoplastic disease may secondarily invade the conjunctiva from the neighbouring skin or adnexal structures.

Reactive, and usually non-pigmented, mass-like lesions include the fleshy, heavily vascularized so-called pyogenic granuloma (often occurring at the site of previous surgery or chalazion), the limbal dermoid (actually a choristomatous type of lesion; i.e. a congenital lesion composed of normal cells not usually occurring at the location), conjunctival papilloma, and lymphangieectasia.

In summary, the conjunctiva and cornea is the site of origin for a wide variety of neoplastic and reactive mass-like lesions. Some of these lesions may masquerade as others, but it is important to make a correct diagnosis as some lesions are associated with systemic spread and may even cause death by disseminated disease. The majority of lesions are, however, benign. Management depends on the specific type of lesion encountered and is typically surgical, even though a number of adjunctive therapies like cryotherapy, topical chemotherapy and brachytherapy are available. More recently introduced techniques like sentinel lymph node biopsy may be helpful to diagnose malignant lesions with early metastatic spread.

Classification of some epidermal and stromal tumours of the conjunctiva

Non-melanocytic	Benign lesions	Squamous papilloma
		Keratoacanthoma
		Pyogenic granuloma
		Oncocytoma
		Lymphocytic hyperplasia
		Lymphangiectasia
		Lymphangioma
	Premalignant	Actinic keratosis
		Conjunctival intraepitelial neoplasia
	Malignant	Squamous cell carcinoma
		Mucoepidermoid carcinoma
		Lymphoma
		Kaposi sarcoma
Melanocytic	Benign	Junctional naevus
		Compound naevus
		Intrastromal naevus
		PAM without atypia
	Premalignant	PAM with atypia ('melanocytic intraepithelial neoplasia')
	Malignant	Melanoma

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MCQ answers page 25

1. **Answer: c**

2. **Answer: a**

3. **Answer: b**

MCQ's

MCQ's not yet received

Role of inflammation in ocular surface disease

….and its impact on the differential diagnosis and classification

Uwe Pleyer, Berlin, Germany

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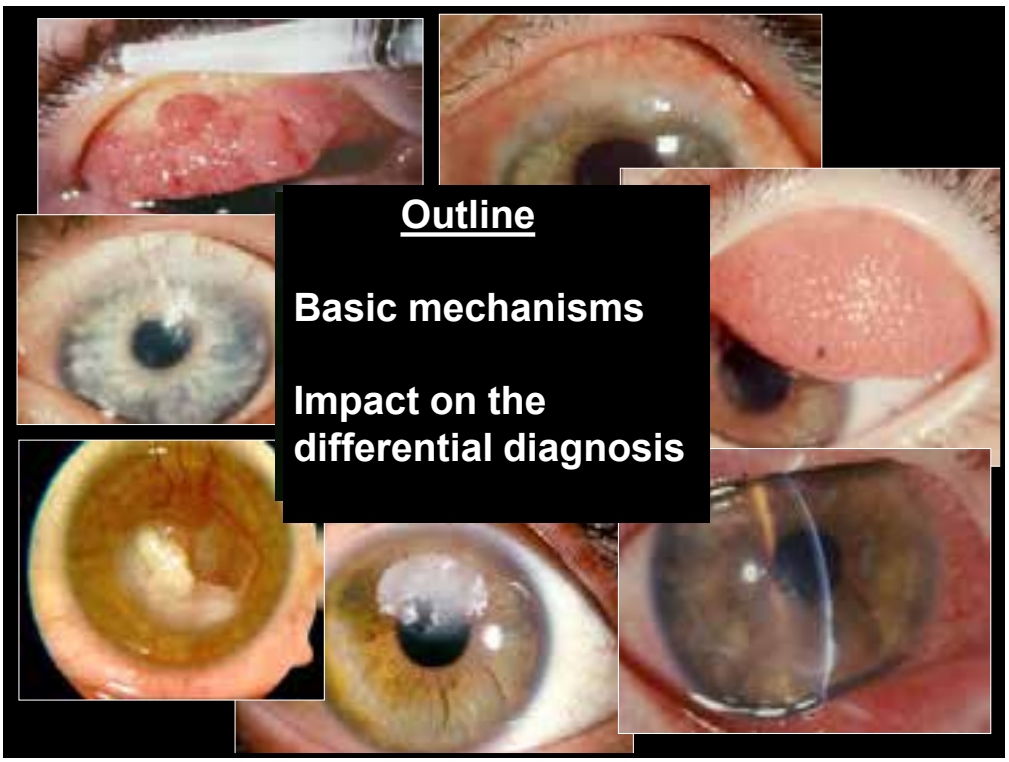
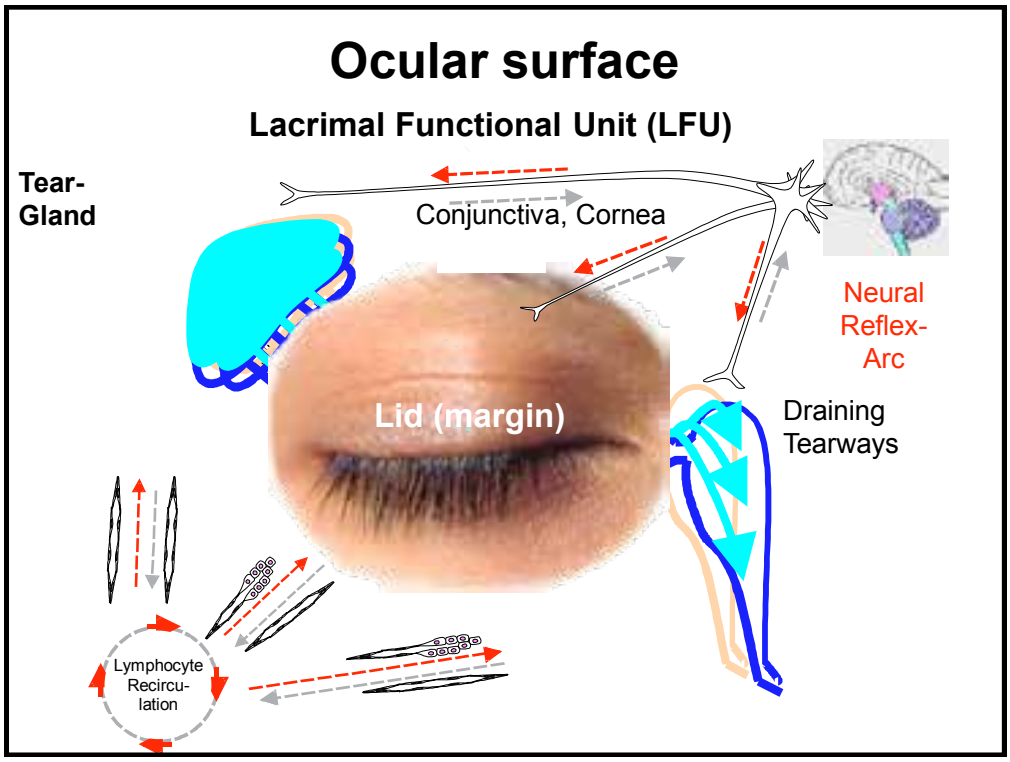
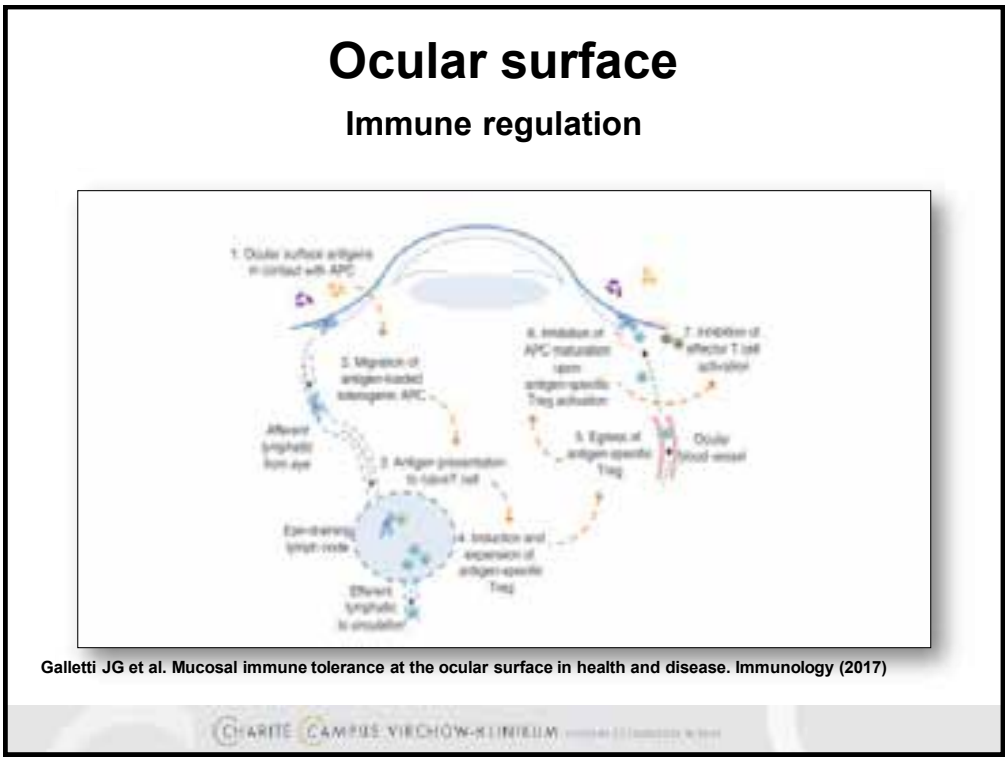
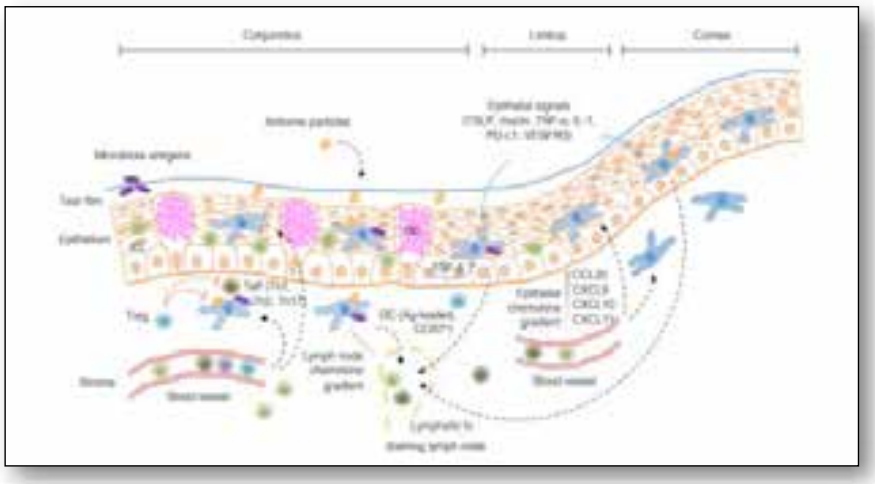



Ocular surface
Lacrimal Functional Unit (LFU)
Tear-
Gland
Conjunctiva, Cornea
Neural
Reflex-
Arc
Lid (margin)
Draining
Tearways
Lymphocyte
Recircu-
lation


Ocular surface
Immune regulation
Galletti JG et al. Mucosal immune tolerance at the ocular surface in health and disease. Immunology (2017)

Ocular surface

Immune regulation



Galletti JG et al. Mucosal immune tolerance at the ocular surface in health and disease. Immunology (2017)

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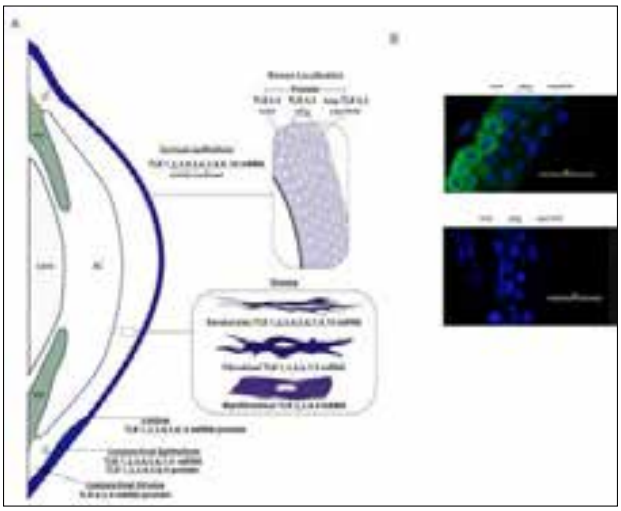
Ocular surface (Defence)



Dermott et al.
Exp Eye Res. 2010 June; 90(6): 679–687.

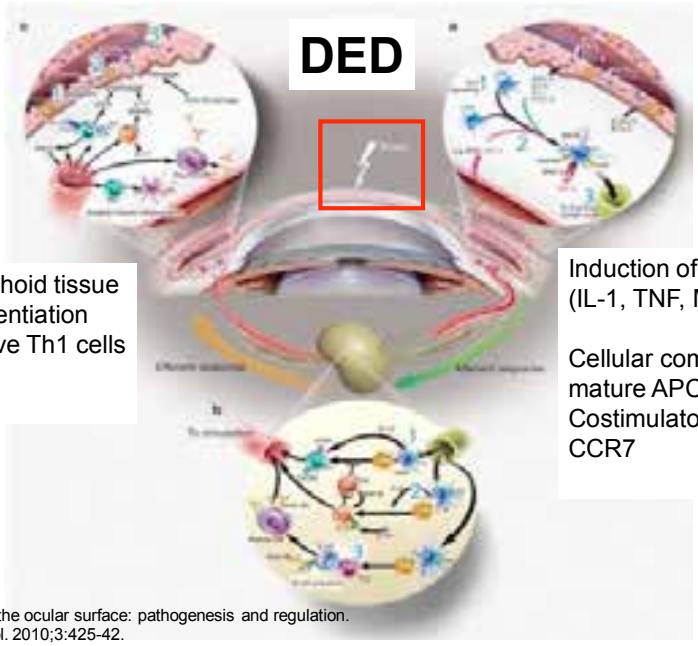
Ocular surface (Defence)

Association of TLRs with Ocular Surface Diseases

Disease	TollLikeReceptor
Herpes Simplex keratitis	TLR2,3,4,7,9
Pseudomonas keratitis	TLR4,5,9
Fungal keratitis	TLR2,4
Vernal keratoconjunctivitis	TLR4,9
Atopic Keratoconjunctivitis	TLR2
Sjögren's syndrome	TLR1 2,3,4
Non- Sjögren's syndrome	TLR2,4,5,9

Dermott et al.
Exp Eye Res. 2010 June; 90(6): 679–687.

Ocular surface



Local lymphoid tissue
Tcell differentiation
Autoreactive Th1 cells
B cells

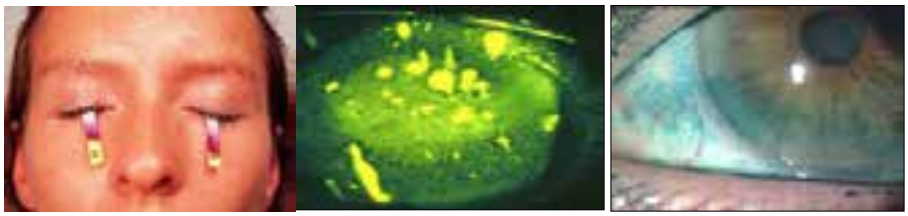
Induction of proinflam.
(IL-1, TNF, MMP)

Cellular components
mature APC
Costimulatory CD80
CCR7

Stern ME et al.
Autoimmunity at the ocular surface: pathogenesis and regulation.
Mucosal Immunol. 2010;3:425-42.

Dry eye

- **Tear deficient dry eye**
- **Evaporative dry eye**



Up to 30% in the general population !

Diagnostic „hints“

Observation (frequency and type of blink)

Key symptom?

- **Burning?**
  - **During the day ? When ?**
    - **„Already morning“** → BLEPHARITIS
    - **„Increasing evening“, while reading, computer** → **DES - SICCA**
- **Foreign body sensation?**

Dry eye

Tear deficient dry eye

Sjögren sydrome

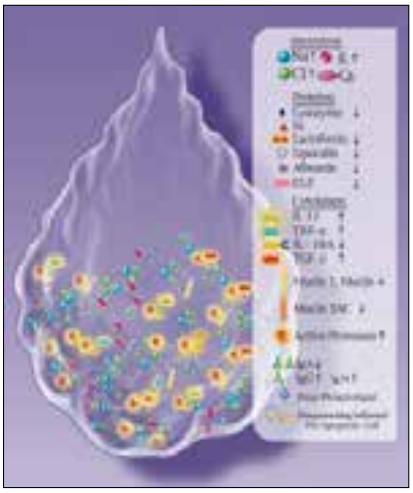
1°

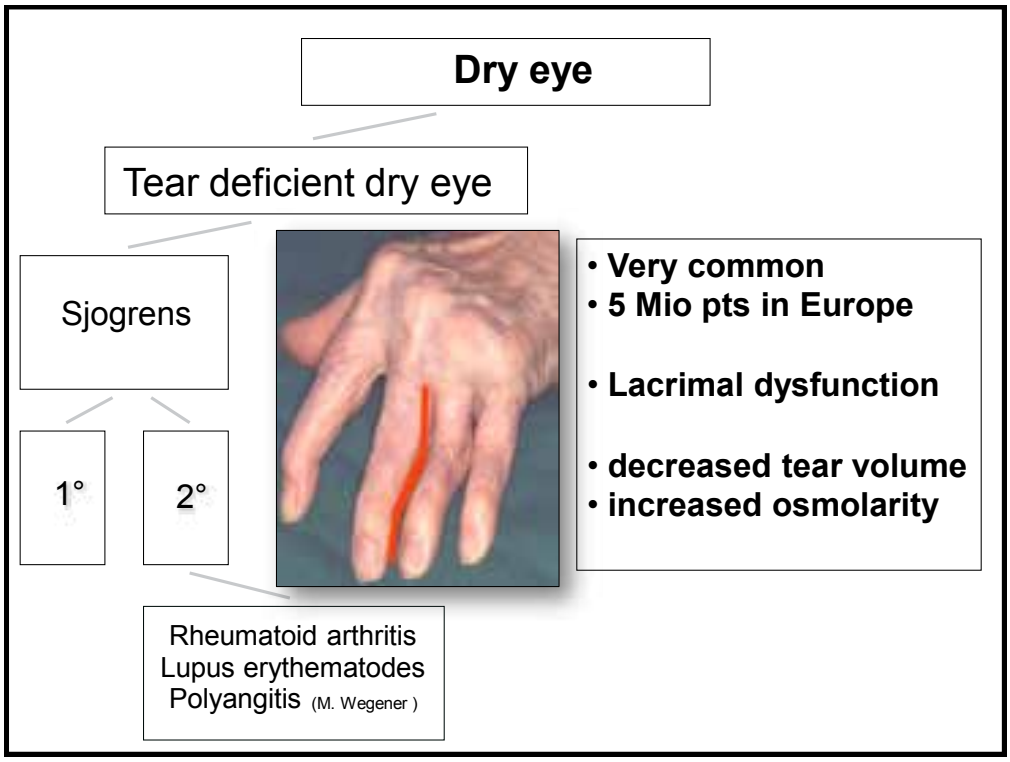
- **2nd most common rheumatol. disorder**
- **Female : male = 19 : 1**
- **Exocrinopathy**
- **Autoimmune (-Ro,- La)**
- **CD4 + Infiltration**
- **? EBV, Hept. C, HTLV**

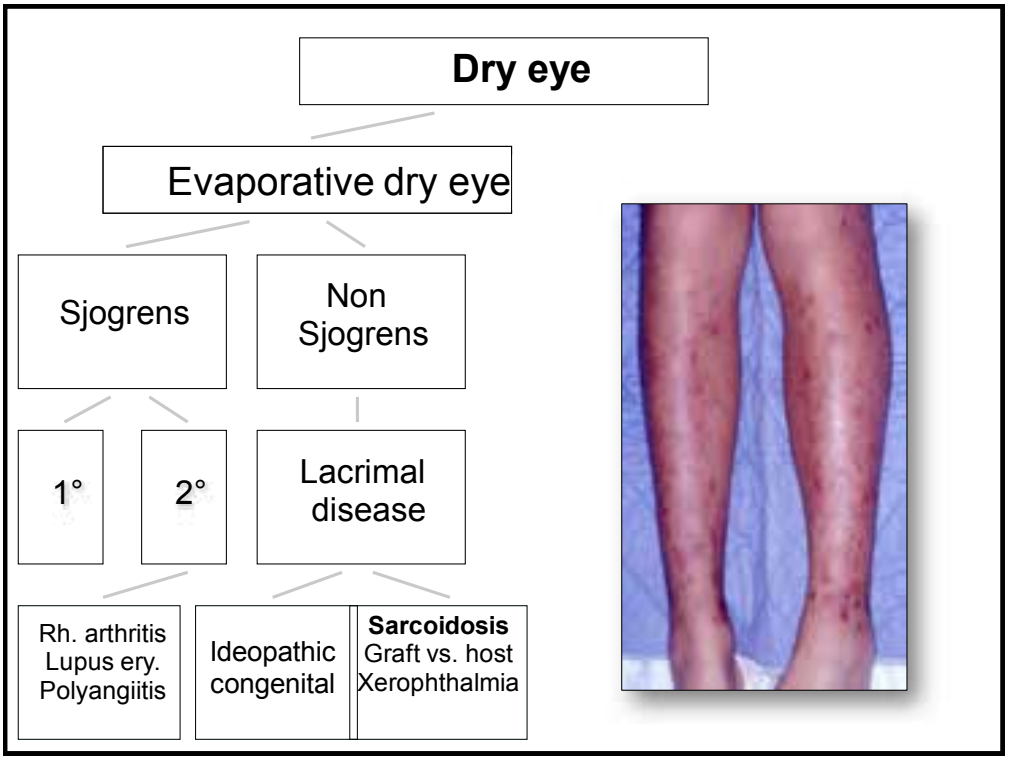
Dry eye

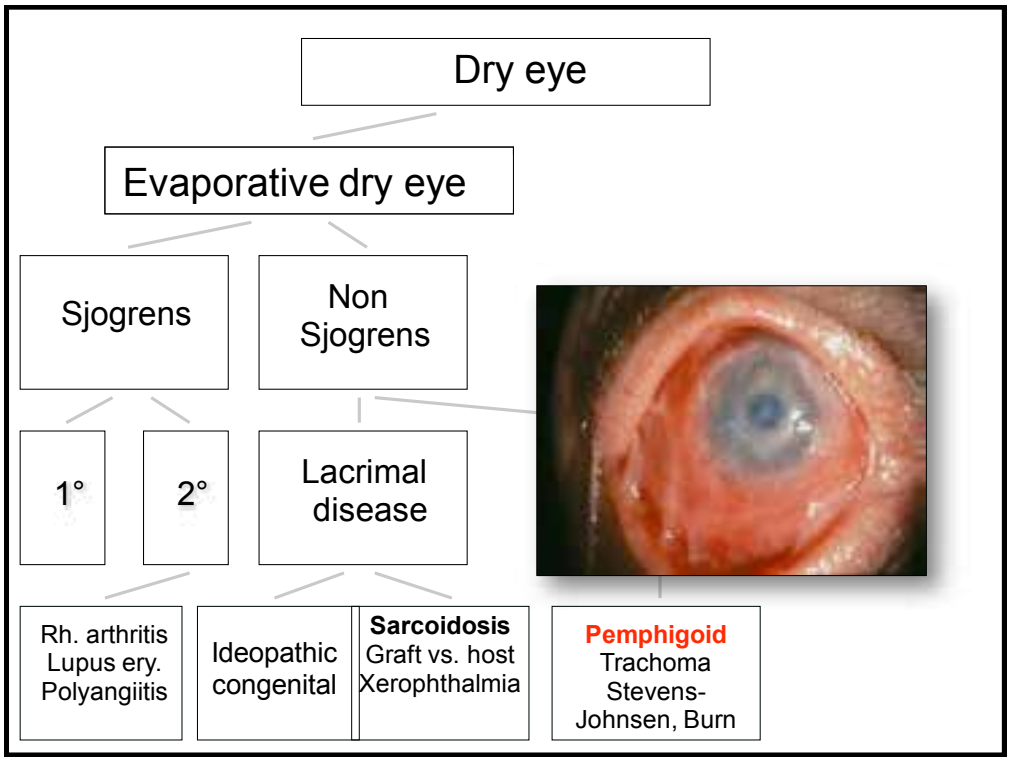
Tears in Sjøgrens Syndrome

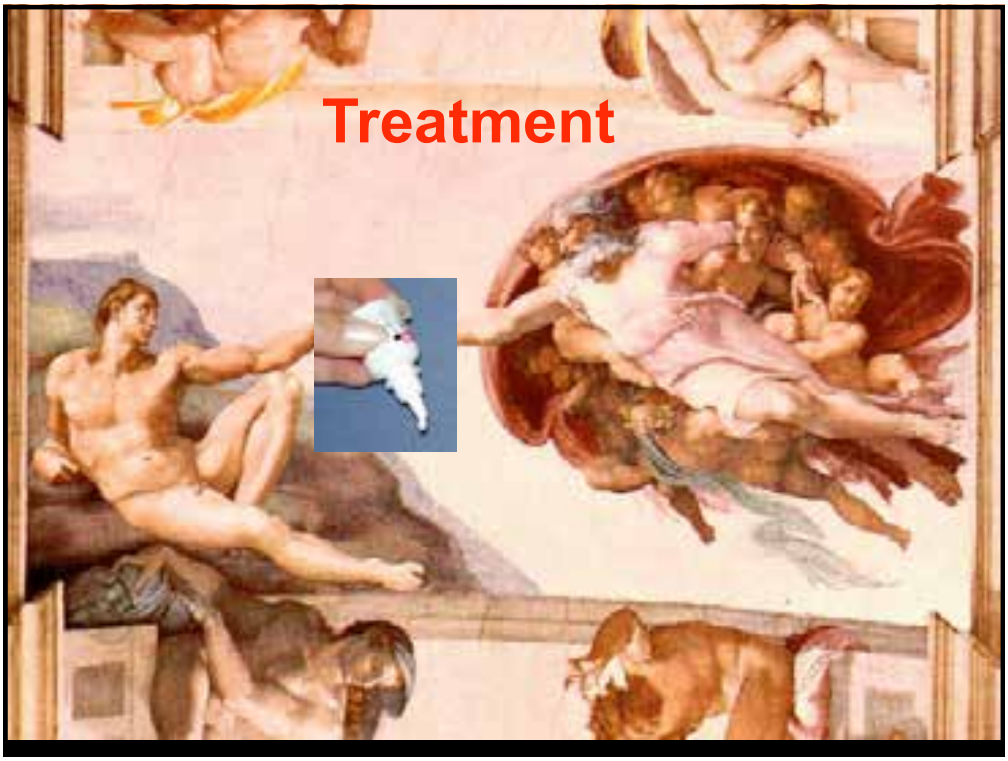
- Proteins ↓
- Growth factors ↓
- Soluble mucines ↓
- Proinflammatory Cytokines ↑ (IL-1, TNF, IL-6, IL-23, IL-17)
- MMP ↑
- Electrolytes ↑




Dry eye
Tear deficient dry eye
Sjogrens
1°
2°
Rheumatoid arthritis
Lupus erythematodes
Polyangitis (M. Wegener)
• Very common
• 5 Mio pts in Europe
• Lacrimal dysfunction
• decreased tear volume
• increased osmolarity


Dry eye
Evaporative dry eye
Sjogrens
Non Sjogrens
1°
2°
Lacrimal disease
Rh. arthritis
Lupus ery.
Polyangiitis
Ideopathic congenital
Sarcoidosis
Graft vs. host
Xerophthalmia


Dry eye
Evaporative dry eye
Sjogrens
Non Sjogrens
1°
2°
Lacrimal disease
Rh. arthritis
Lupus ery.
Polyangiitis
Ideopathic congenital
Sarcoidosis
Graft vs. host
Xerophthalmia
Pemphigoid
Trachoma
Stevens-Johnsen, Burn


Treatment

Dry eye

Treatment

- Artifical Tears
- Antiinflammatory Agents
- Autologous serum

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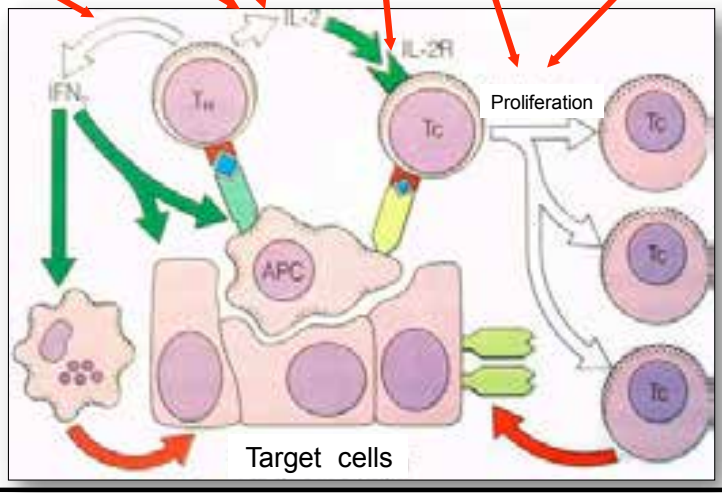
Dry eye

Immunomodulators

Steroids CsA FK506 Rapa MMF Everolimus

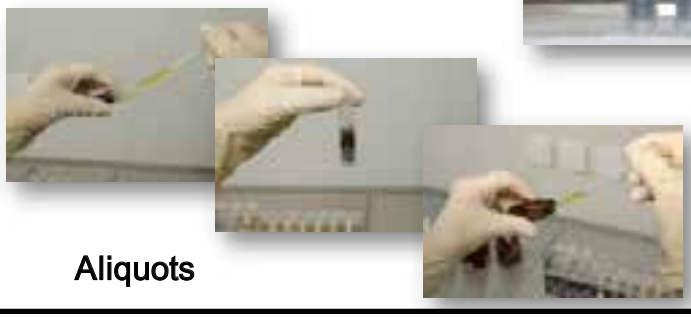


Dry eye

Autologous Serum Eye drops

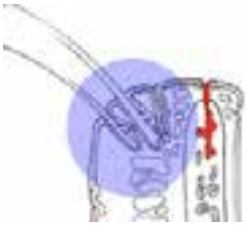
Clotting

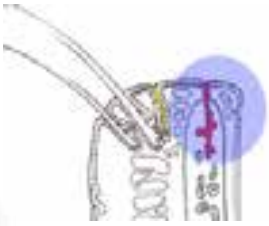
Centrifugation



Aliquots

Lipid dysfunction





Simple meibomian gland obstruction

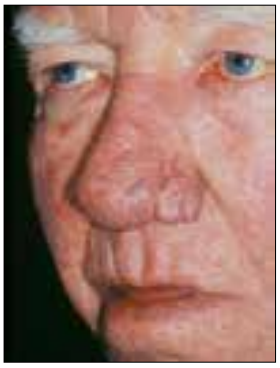
Rosacea

Cicatricial obstructive meibomian gland disease

Lipid dysfunction

Rosacea

- Chronic, recurrent disease
- Teleangiectasia, papula, pustula
- Erythema, rhinophyma
- Advanced age, women



- Eye can be involved prior to dermatological signs
- Severe symtoms

Dry eye

Tear deficient dry eye

Oil deficient

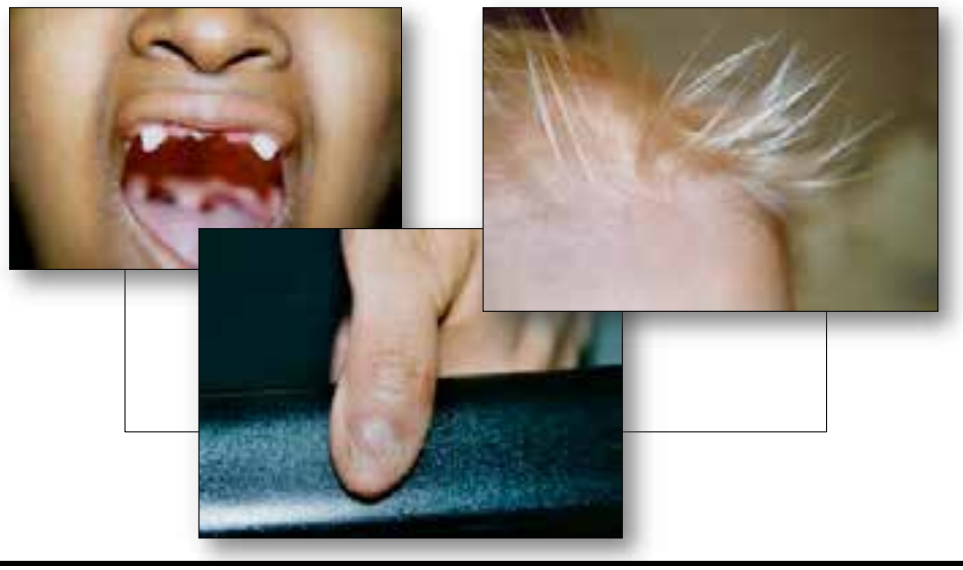
2°

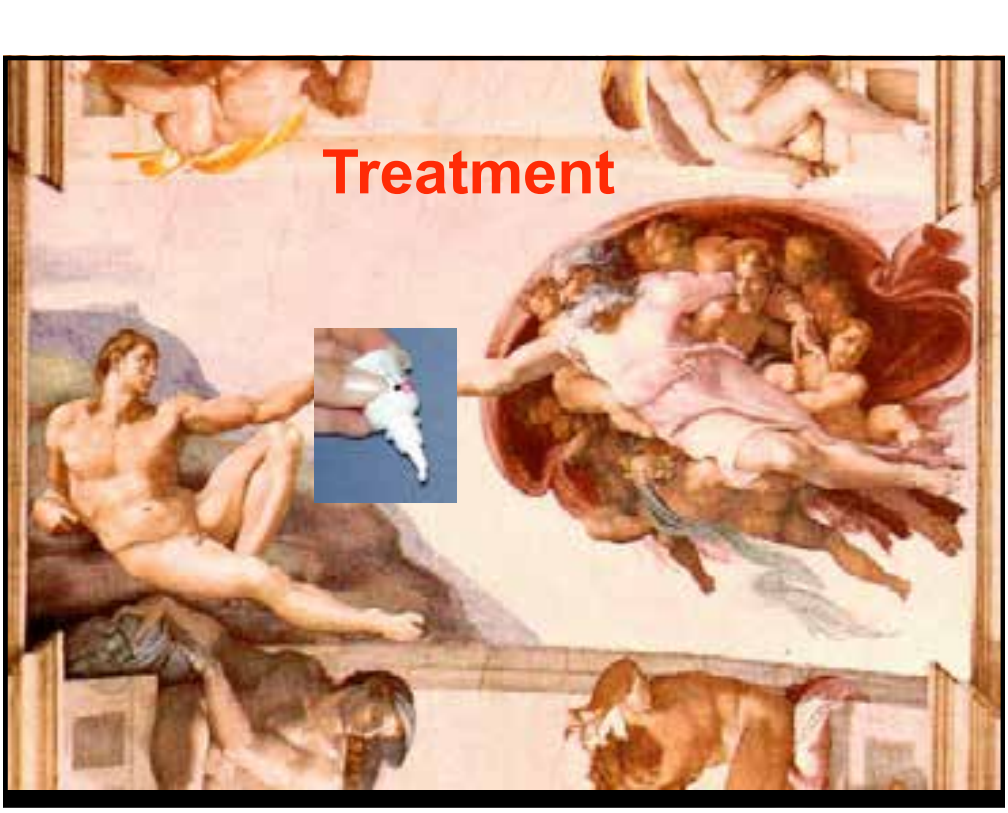
1°

Absence of glands

Ectodermal Dysplasia
Genetic disorder 7/10.000
Definition: 2 ectodermal tissues involved

Clinical Signs of Ectodermal Dysplasia
Teeth, Hair, Nails





Blepharitis: Lipid phase treatment

Causative treatment

- Lid hygiene
- Hot compresses (e.g. Blepha steam) } Baseline
- Lipid flow
- Topical antibiotics (Azythromycine)
- Systemic antibiotics
- Local steroids

Symptom. treatment

- Artifical tears
- Soft contact lens, Sceral lens
- Antiinflammatory treatment

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Blepharitis: Lipid phase treatment

Twice daily

- warm/hot compress applied to the lids for 5 minutes (reduces melting point of lipids)
- Treatment of the lid margin (Cotton-Tips)

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Blepharitis: Lipid phase treatment

Antibiotics

Rationale: Several antibiotics act antiinflammatory in blepharitis
(e.g. by inhibition of MMP´s and IL-1)

- **Tetracycline 1000 mg/d**
- **Erythromycine 250 mg/d**
- **Oraceya 40 mg/d**
- Therapy must be applied for at least 8 weeks!

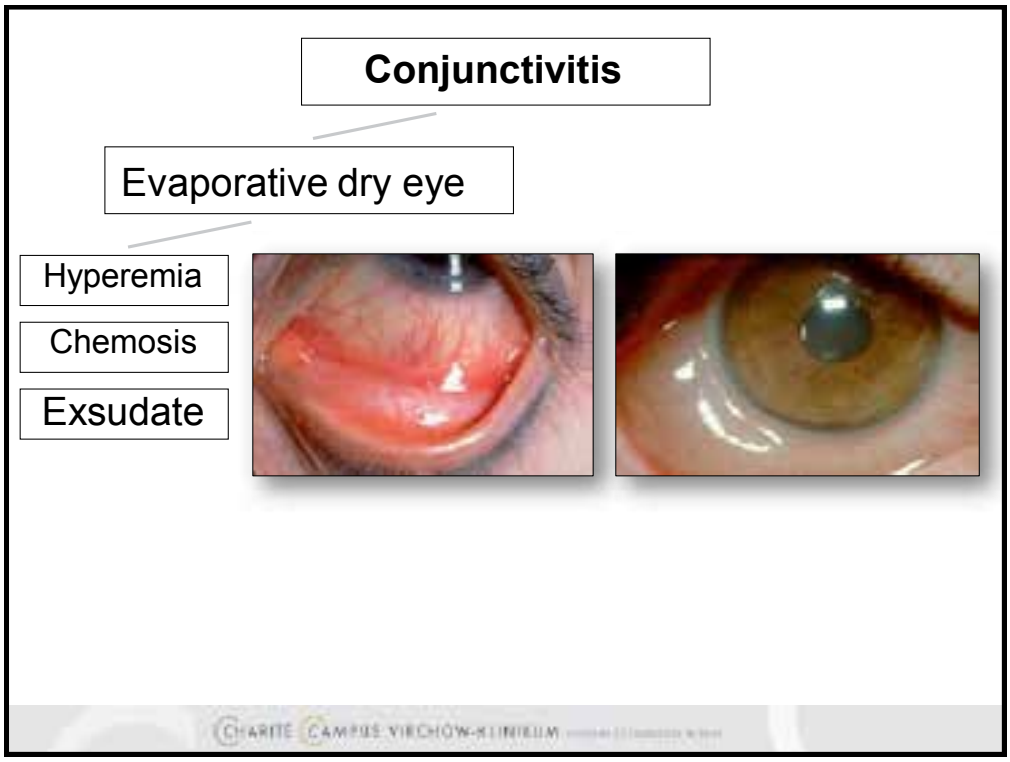
- **Topical Azythromycine!**

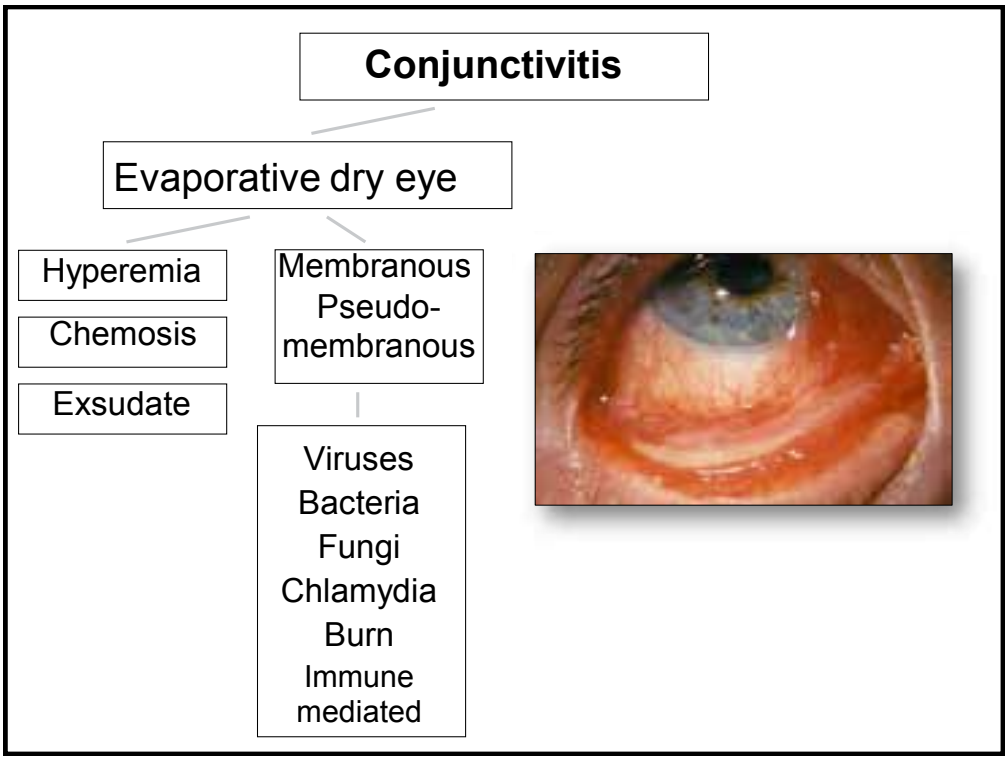
Blepharitis: antiinflammatory treatment

Steroids

Rational:
Steroids inhibit inflammatory mediators for ocular surface disease associated with blepharitis and meibomitis

- Unpreserved steroids
- Loteprednole (less steroid related side effects)
- Very effective in patients with rosacea


Conjunctivitis
Evaporative dry eye
Hyperemia
Chemosis
Exsudate


Conjunctivitis
Evaporative dry eye
Hyperemia
Chemosis
Exsudate
Membranous
Pseudo-
membranous
Viruses
Bacteria
Fungi
Chlamydia
Burn
Immune
mediated

Conjunctivitis

Evaporative dry eye

- Hyperemia
- Chemosis
- Exsudate

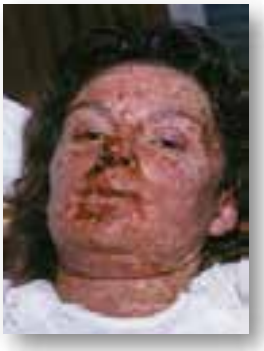
Membranous Pseudo-membranous

- Viruses
- Bacteria
- Fungi
- Chlamydia
- Burn
- Immunological

Ulcerating Necrotizing

- Viruses
- Immunological
- Burn
- Toxins
- **SJS**

Stevens-Johnson Syndrome



Yang MS et al. Incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. PLoS One (2016)

Conjunctivitis

Stevens-Johnson syndrome and toxic epidermal necrolysis

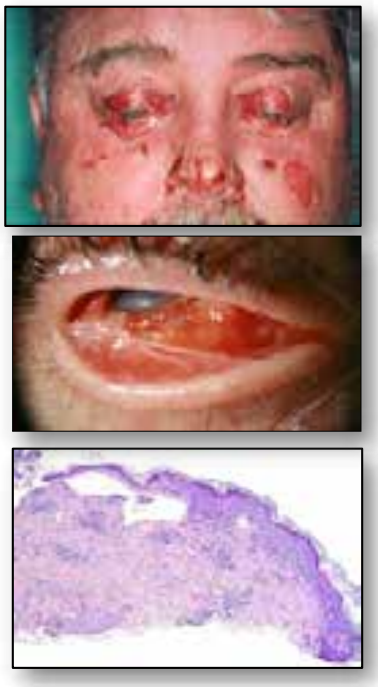
- Erythema with transition to more or less large-area bubble formation
- Fever and feeling sick
- Mucosal manifestations (erosions of the oral mucosa, bloody crusts in the lip area, blepharitis, balanitis, vulvitis or colpitis)

Acute phase

- Lid involvement
- Severe papillary conjunctivitis
- Severe membranous or pseudomembranous conjunctivitis

Late phase

- Scarring of the upper tarsus
- Conjunctival keratinization / fornix shortening
- Posterior blepharitis
- Symblephara
- Loss of goblet cells
- Sicca syndrome
- Corneal keratinization
- Entropion, trichiasis



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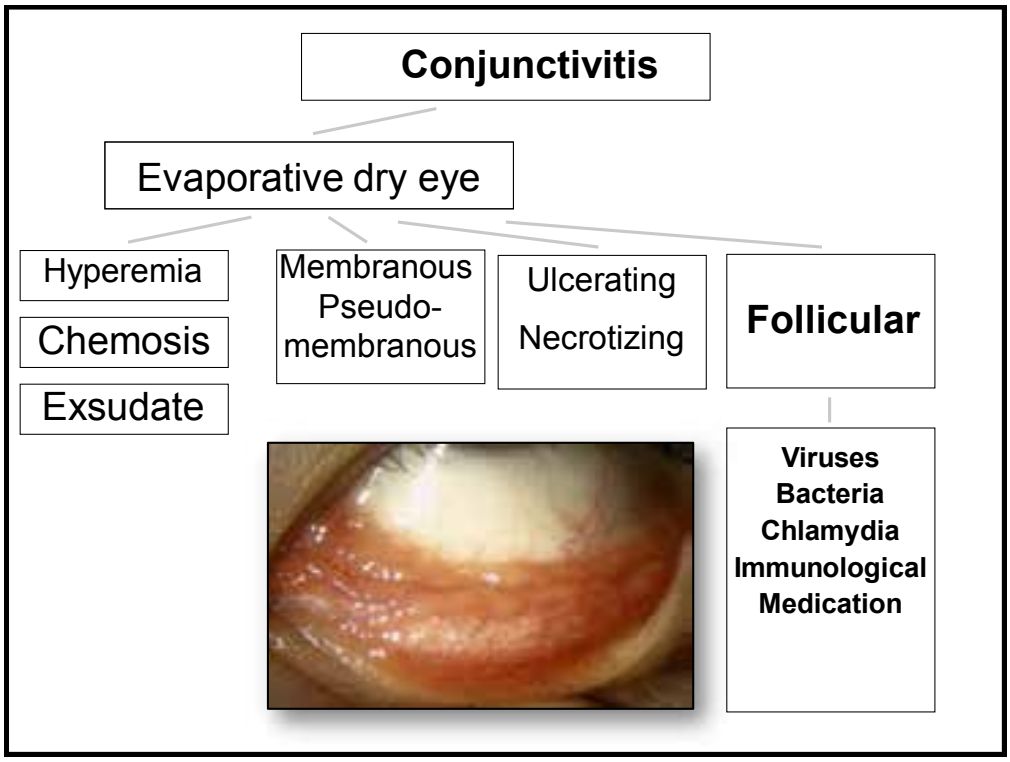
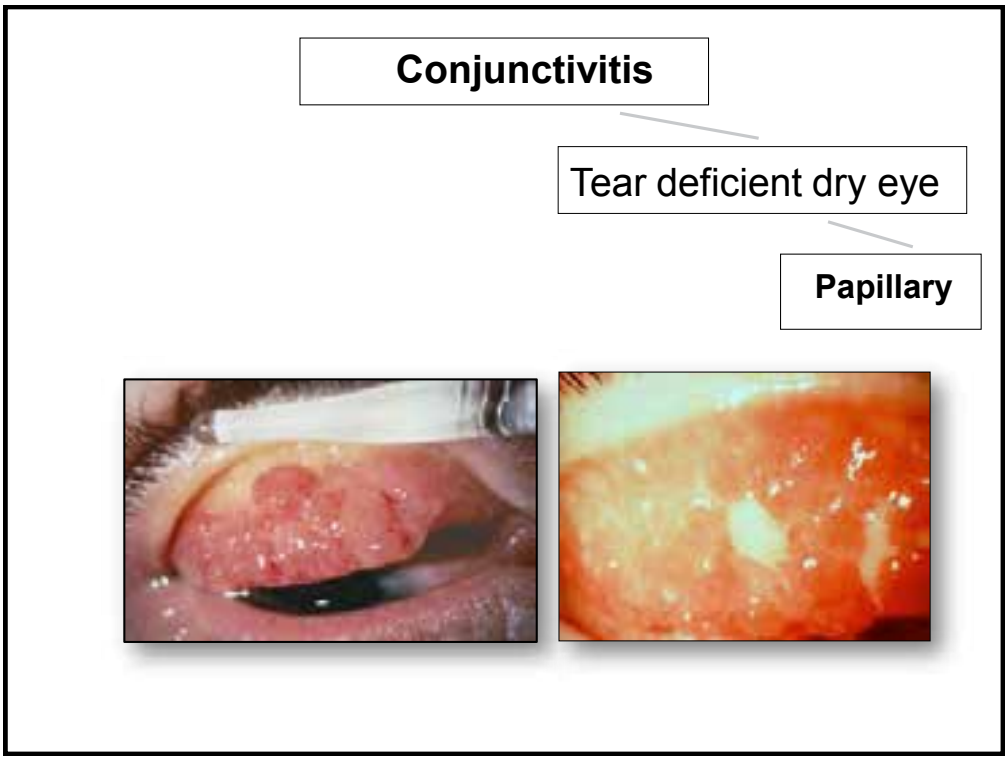
HLA-B Phenotype
Relation to drug associated manifestation (%)

Allel	*allo*	*carba*	*lamo*	*oxic*	*sulfa*	*SJS/TEN*
	n = 31	*n = 12*	*n = 19*	*n = 14*	*n = 30*	*n = 131*
B*15	3.2	**33.3**	**31.6**	-	16.7	9.2
B*1502	-	**33.3**	-	-	-	-
*other B*15*	-	-	**31.6**	-	-	9.2
B*35	16.1	25.0	10.5	21.4	**33.3**	**26.7**
B*38	-	8.3	**26.3**	7.1	**23.3**	**10.7**
B*51	12.9	8.3	**26.3**	**21.4**	10.0	**18.4**
B*58	**61.3**	-	-	-	3.3	**15.4**
***B*5801*61.3**	-	-	-	-	13.7	
*B*5802*	-	-	-	-	3.3	3.3
B*73	-	**8.3**	-	**14.3**	-	**2.3**

Yang MS et al. Incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. PLoS One (2016)

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

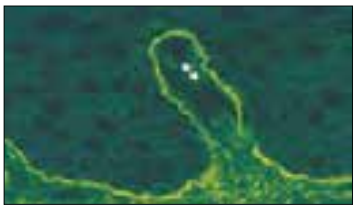

Conjunctivitis
Evaporative dry eye
Hyperemia
Chemosis
Exsudate
Membranous
Pseudo-
membranous
Ulcerating
Necrotizing
Follicular
Viruses
Bacteria
Chlamydia
Immunological
Medication


Conjunctivitis
Tear deficient dry eye
Papillary

Conjunctivitis

Ocular Pemphigoid

Tear deficient dry eye



Symblepharon

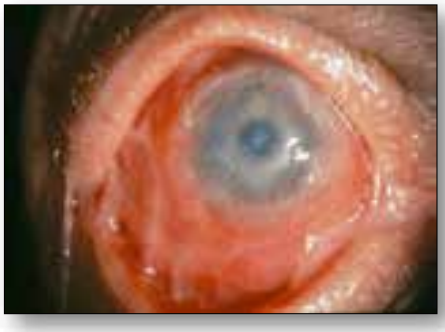
Papillary

Viruses
Bacteria
Chlamydial
Immunological
Burn
Injury
Drugs

Rübsam A, Stefaniak R, Pleyer U. Rituximab preserves vision in ocular mucous membrane pemphigoid. Expert Opin Biol Ther. (2015)

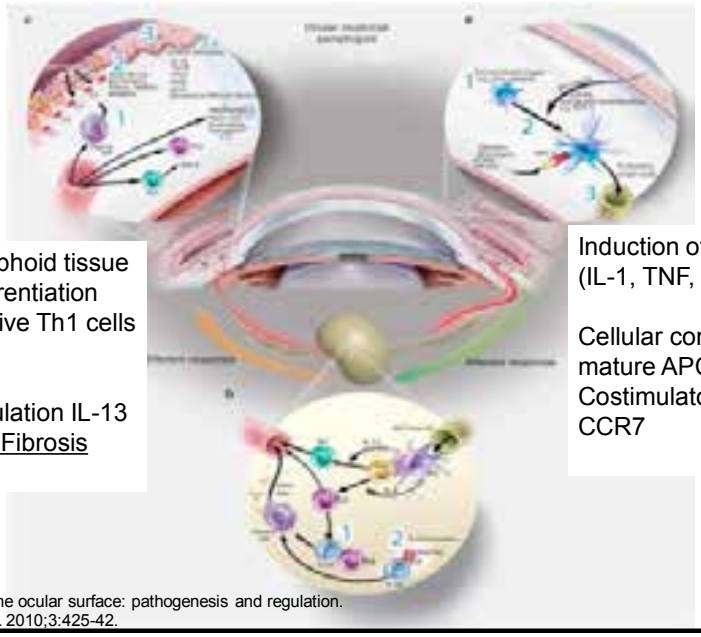
Ocular Pemphigoid

- **Slow onset, „chronic conjunctivitis“**
- **Initial change in the area of the caruncula**
- **Subepithelial fibrosis**
- **Therapy according to degree of inflammation !**



Rübsam A, Stefaniak R, Pleyer U. Rituximab preserves vision in ocular mucous membrane pemphigoid. Expert Opin Biol Ther. (2015)

Ocular Pemphigoid



Local lymphoid tissue
Tcell differentiation
Autoreactive Th1 cells
B cells

Overstimulation IL-13
TGF-ß -> Fibrosis

Induction of proinflam.
(IL-1, TNF, MMP)

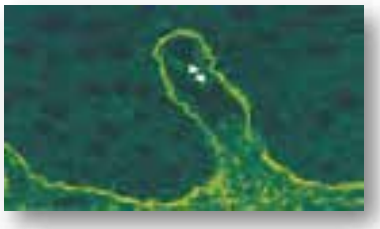
Cellular components
mature APC
Costimulatory CD80
CCR7

Stern ME et al.
Autoimmunity at the ocular surface: pathogenesis and regulation.
Mucosal Immunol. 2010;3:425-42.

Ocular Pemphigoid

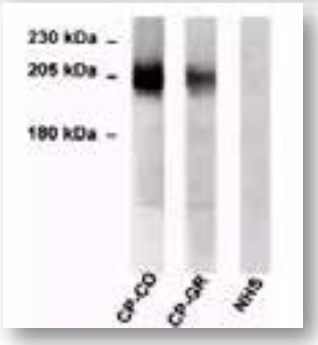
Diagnosis

Clinical !
Immune histology !



Autoantibodies

- **Increasing in importance !**
- **Target structure = ß4 Integrin**
- **May correlate with activity**
- **Several mucosa sites: BP180 AG**



Yasukochi A et al. Clinical and Immunological Studies of 332 patients. A Novel BP180 C-terminal Domain ELISA. Acta Derm Venereol. 96:762-7 (2016)

Ocular Pemphigoid

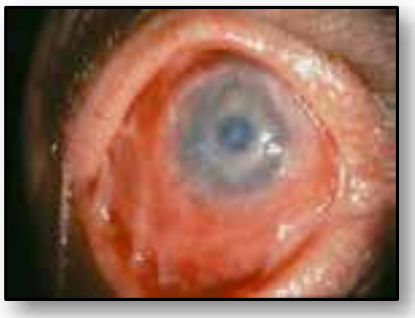
Follow up !?

Clinical Course
Varies - no correlation:

- **Age, Gender**
- **Immunhistology**
- **ß4 Integrin Antibodytiter !**

Progression associated:

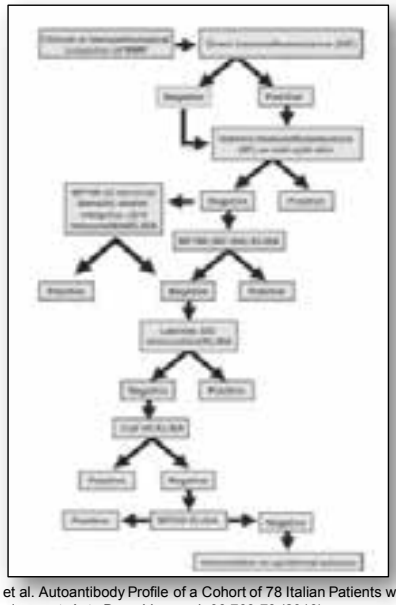
- **Stage of disease**
  - **I-II Risk -> IV 30%**
  - **III Risk -> IV 80%**

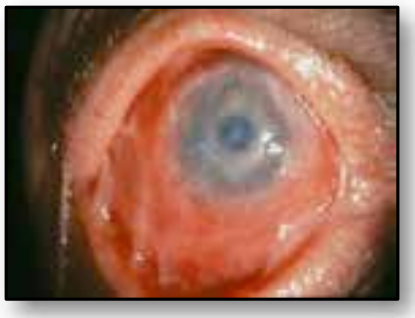


No EBM recommendations….

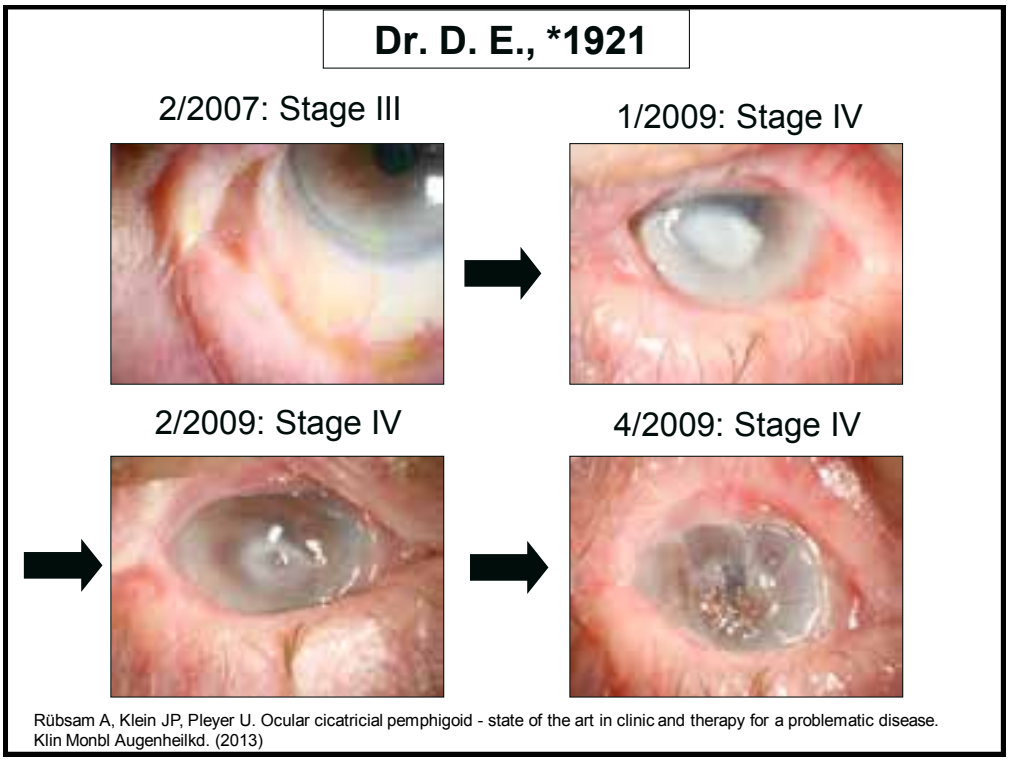
Cozzani E et al. Autoantibody Profile of a Cohort of 78 Italian Patients with Mucous Membrane Pemphigoid: Correlation Between Reactivity Profile and

Ocular Pemphigoid

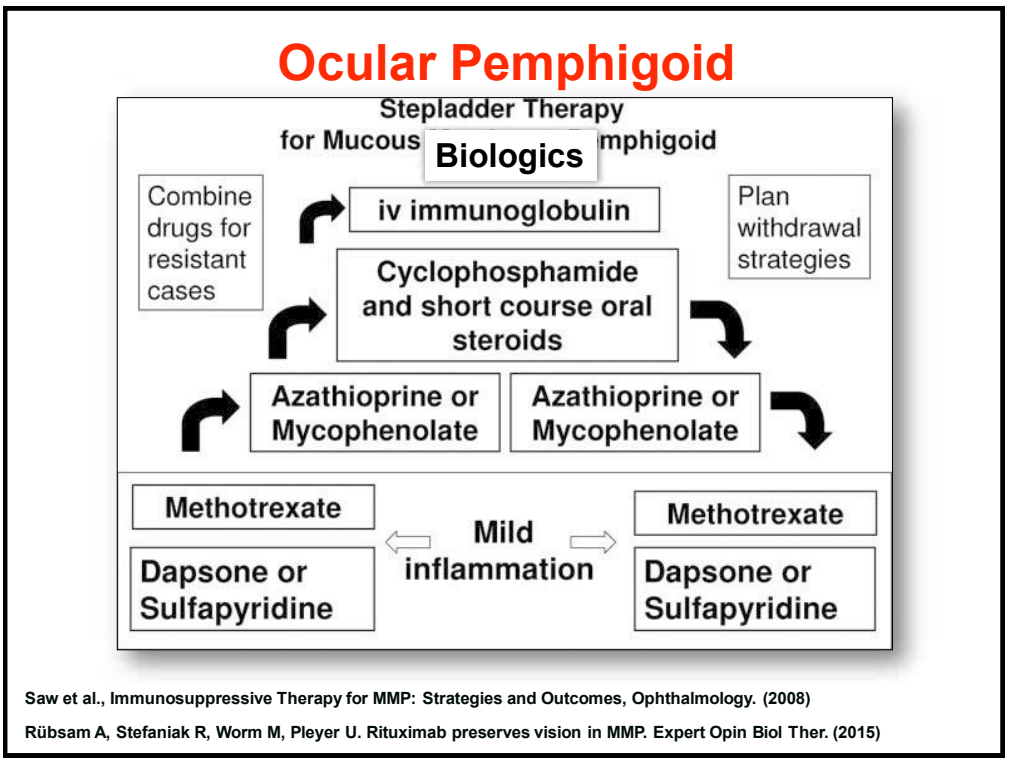




Cozzani E et al. Autoantibody Profile of a Cohort of 78 Italian Patients with Mucous Membrane Pemphigoid: Correlation Between Reactivity Profile and Clinical Involvement. Acta Derm Venereol. 96:768-73 (2016)



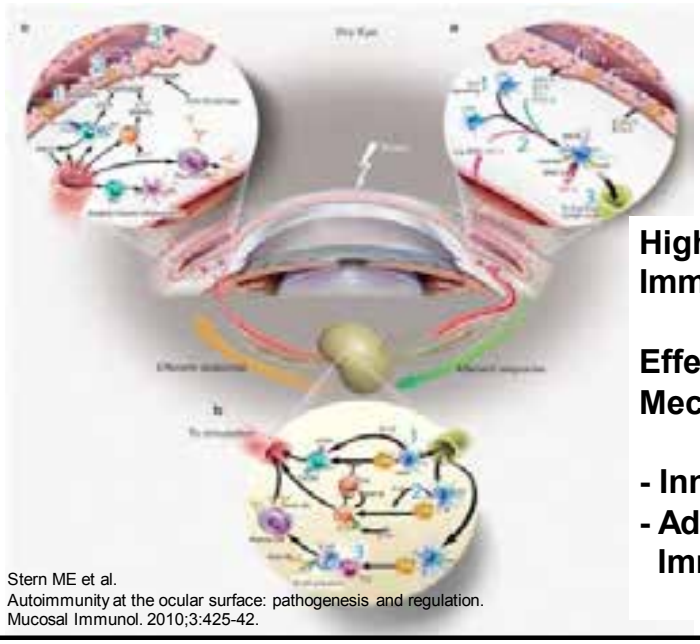
Rübsam A, Klein JP, Pleyer U. Ocular cicatricial pemphigoid - state of the art in clinic and therapy for a problematic disease. Klin Monbl Augenheilkd. (2013)



Saw et al., Immunosuppressive Therapy for MMP: Strategies and Outcomes, Ophthalmology. (2008)

Rübsam A, Stefaniak R, Worm M, Pleyer U. Rituximab preserves vision in MMP. Expert Opin Biol Ther. (2015)

SUMMARY: Ocular surface

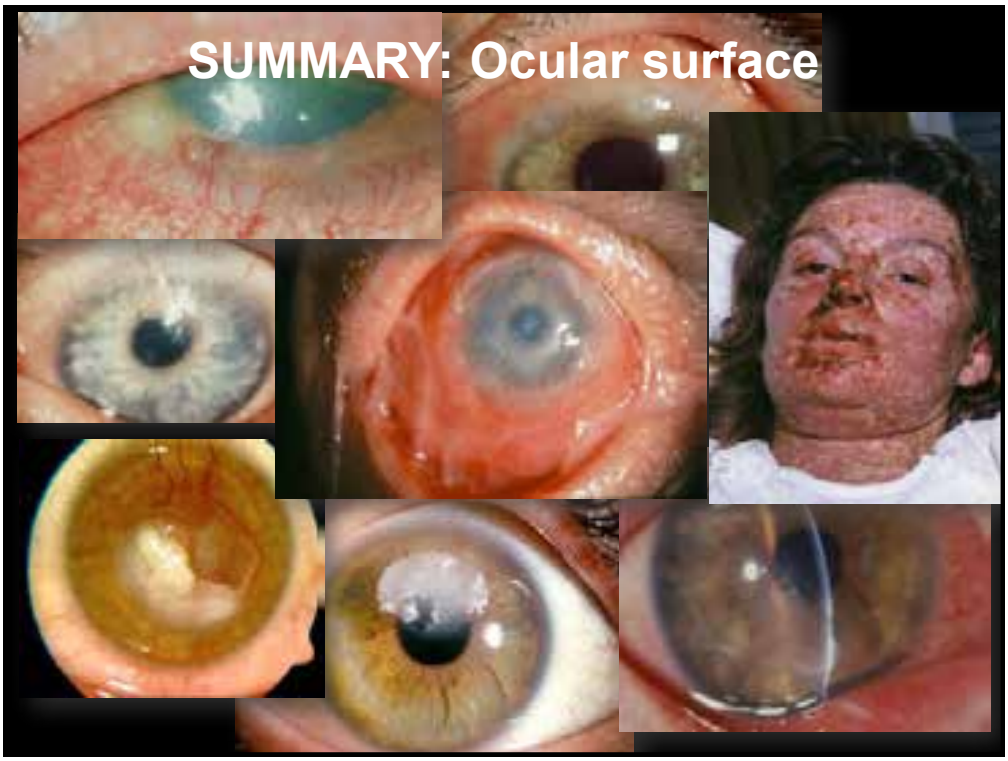


Stern ME et al.
Autoimmunity at the ocular surface: pathogenesis and regulation.
Mucosal Immunol. 2010;3:425-42.

Highly regulated Immune system

Effective protective Mechanisms

- Innate
- Adaptive Immune system



Gracias…

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Berliner
Immunologie Seminar
Samstag, 17. Juni 2017

Anmeldung

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MCQ answers page 30

MCQ's not yet received

MCQ's

MCQ's not yet received

05 - Dry eye and clinical disease of tear film, diagnosis and management, MERAYO-LLOVES J - Spain

Outline not yet received

MCQ answers page 56

MCQ's not yet received

MCQ's

1. Which of the following is <u>not</u> a primary corneal degeneration?

a. Cornea farinata
b. Posterior crocodile shagreen
c. Pinguecula
d. Arcus senilis

2. Which of the following is <u>not</u> a characteristic of Salzmann's nodular degeneration?

a. Regular astigmatism
b. Hyperopic refractive shift
c. Decreased vision
d. Glare

3. Which of the following is <u>not</u> true in Terrien's marginal degeneration?

a. Corneal gutter
b. Lipid deposition
c. Pseudo-pterygium development
d. Epithelial breakdown

NON-INFLAMMATORY CORNEAL PATHOLOGY

Prof. Dr. Murat Irkec, MD, FEBO

Director, Corneal Unit
Department of Ophthalmology
Hacettepe University Faculty of Medicine
Ankara - Turkey

EUPO Course, Barcelona, 2017

Disclosure Statement of Financial Interest

• Nothing to disclose

Degeneration : deterioration and decrease in *function*

Degenerations may be :

- Unilateral or bilateral
- Often asymmetric
- An inheritance pattern usually not found
- Many occur later in life (normal aging)
- Secondary to systemic or pathological process
- Often eccentric or peripheral
- Relation to vascularity

Classification of corneal degenerations

A. Primary

- Iron lines
- White limbal girdle of Vogt
- Cornea farinata
- Ant. and post. crocodile shagreen
- Corneal arcus (arcus senilis)
- Hassal-Henle bodies

Classification of corneal degenerations

B.Secondary

- Pinguecula
- Pterygium
- Spheroid degeneration
- Salzmann's nodular degeneration
- Terrien's marginal degeneration
- Corneal amyloid
- Lipid degeneration
- Coat's white ring
- Band keratopathy
- Neurotrophic keratopathy
- Exposure keratopathy
- Recurrent erosion syndrome

WHITE LIMBAL GIRDLE OF VOGT

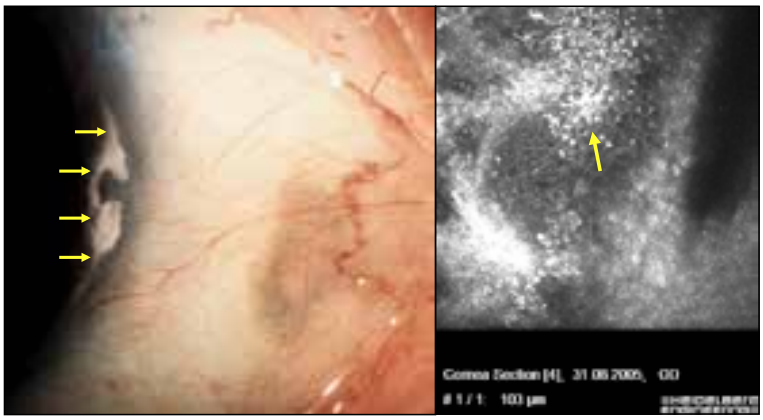
- White, cresentic, peripheral corneal opacities in the interpalpebral area
- Two clinical forms

  Type 1: rare, early band keratopathy, clear zone from limbus

  Type 2: common, 100% after 80 years of age, more common at the nasal limbus, no peripheral clear zone from limbus
- Histology: subepithelial hyaline and elastotic changes

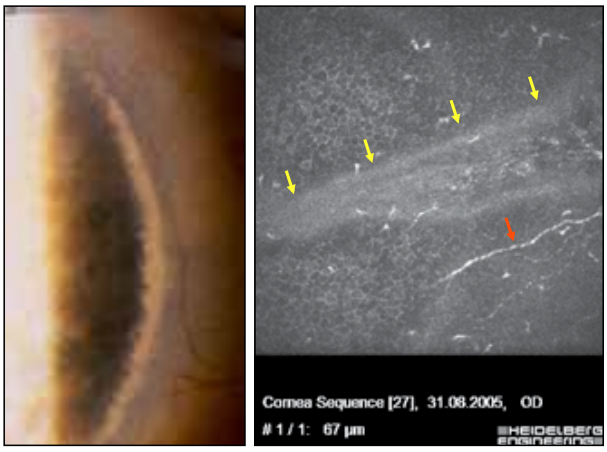
  Bowman's membrane and superficial stroma replaced by basophilic granular deposits

VOGT's LIMBAL GIRDLE TYPE 1

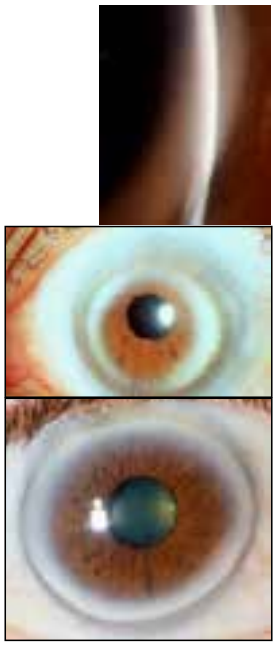


- Early calcific band keratopathy
- Narrow lucent area from the limbus
- White band contains holes (Swiss cheese)
- Destruction and calcification of Bowman's layer

VOGT's LIMBAL GIRDLE TYPE 2



- Asymptomatic and incidental
- Lesion is subepithelial
- Elastotic degeneration and calcium at the level of Bowman's layer

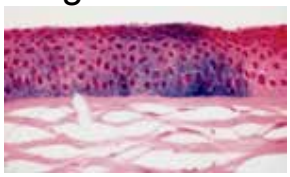


CORNEAL ARCUS

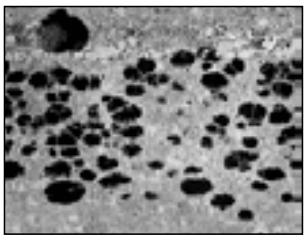
- Gerontoxon in the aged (Arcus senilis)
- Ant. embryotoxon in the young (A. juvenilis)
- Lipid deposition in the peripheral cornea
- Cholesterol, cholesterol esters, phospholipids,neutral glycerides
- Lipid is extracellular
- Lipids are of vascular origin
- Men affected more than women
- Increased risk of CAD (<40 years)
- Hyperlipoproteinemia type 2 and 3

IRON LINES

- Iron deposition in the epithelium
- Several types due to different causes
- Hudson-Stahli lines (Fleischer, Ferry & Stocker)
- Prevalence and intensity increase with age
- Source of iron unknown
- May be physiological (young people)
- No sex predilection
- Asymptomatic and require no treatment

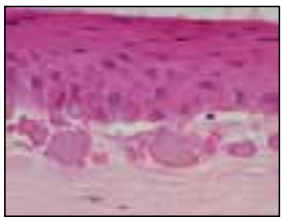
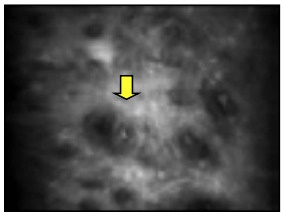






SPHEROID DEGENERATION

- Climatic droplet keratopathy
- More than one form
  - Primary age-related
  - Secondary form
    - Traumatic corneal scars
    - Herpetic keratitis
    - Chronic corneal edema
    - Lattice dystrophy
    - Chronic open-angle glaucoma
  - Conjunctival degeneration
    - Pinguecula

SPHEROID DEGENERATION

- Prevalence related to geography
- Males affected more than females
- Usually bilateral, may be unilateral
- Clinically yellow-gold subepithelial droplets
- Advance from periphery to the center
- Foreign body sensation,irritation, VA decrease possible
- EC proteinaceous material at Bowman's membrane level and anterior stroma
- Treatment: PTK, lamellar KP, lamellar keratectomy

BAND KERATOPATHY

- Common secondary degeneration
- Calcium phosphate deposition in the anterior cornea
- Caused by local or systemic factors
- Calcium deposition :
  - Intracellular in systemic Ca metabolism abnormalities
  - Extracellular in local ocular disease

BAND KERATOPATHY

Classification

Chronic ocular diseases

- Uveitis (juvenile chronic arthritis)
- Glaucoma
- Corneal edema
- Interstitial keratitis
- Phthisis

Ocular trauma

- Climatic exposure
- Mercurial containing preservatives

BAND KERATOPATHY

Classification

Systemic abnormalities

- Hypercalcemia
- Hyperphosphatemia

Heredity

- Norrie's disease
- Autosomal recessive band keratopathy

BAND KERATOPATHY

- Confined to the interpalpebral fissure
- Peripheral clear zone at the limbus
- Begins nasally and temporally
- 'Swiss cheese' appearance (corneal nerves)
- Histology:
  - Epithelial BM- basophilic staining
  - Bowman's layer /ant. stromal lamellae - Ca^{++} deposition and fragmentation
  - Subepithelial fibrous pannus
  - Scarring

BAND KERATOPATHY

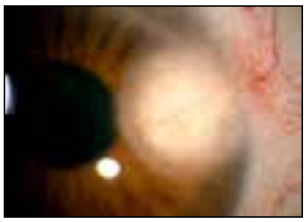
- Ulceration of the corneal epithelium ğdiscomfort
- Reduced vision (visual axial involvement)
- Treatment:

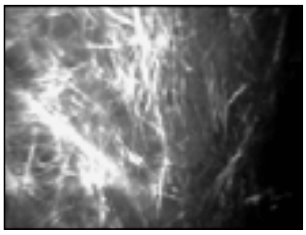
  Epithelial removal ğchelation with Na_2EDTA

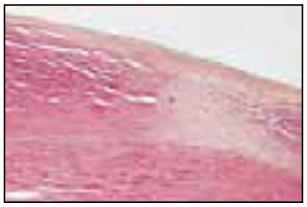
  ğmechanical debridement with a blade or burr

LIPID DEGENERATION

- Accumulation of cholesterol and fatty acid deposits
- **Primary form** - rare, usually bilateral
  no stromal vascularization
- **Secondary form** - more common, leakage from
  stromal vessels



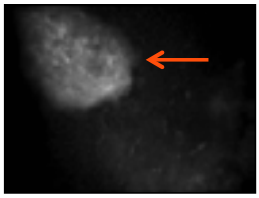




LIPID DEGENERATION

- Deposits around an area of vessels:
  - Crystalline or diffuse
  - Yellow or cream
  - Discrete or fan-like
- Sudden appearance from NV + VA ⇩
- Causes of corneal NV in lipid degeneration:
  - Corneal trauma
  - Infectious keratitis (HSV or HZV)
  - Interstitial keratitis
- Spontaneous regression (occasionally)
- Treatment:
  - Argon laser to the feeding vessel
  - Anti-VEGF therapy
  - Penetrating keratoplasty

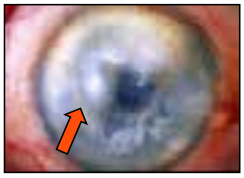
SALZMANN'S NODULAR DEGENERATION



- First reported in 1925
- Rare, noninflammatory, slowly progressive
- Degeneration characterized by bluish white nodules elevated above corneal surface (forming circular array)
- Irregular astigmatism
- Hyperopic refractive shift
- Foreign- body sensation
- Corneal scarring and decreased VA
- Glare

SALZMANN'S NODULAR DEGENERATION

Etiology

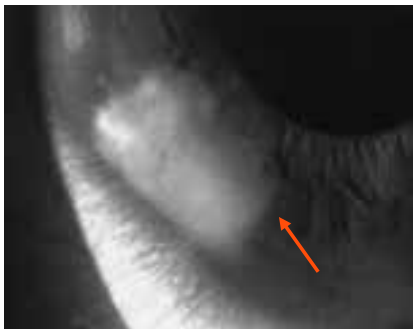


Late sequelae of previous corneal inflammation

- Phylectenular keratitis (common)
- Trachoma (common)
- Vernal disease (common)
- Exposure keratopathy
- Interstitial keratitis
- Chronic keratitis
- Idiopathic (rare)
- Following contact lens wear
- Postcorneal surgery
- Epithelial basement membrane dystrophy

SALZMANN'S NODULAR DEGENERATION

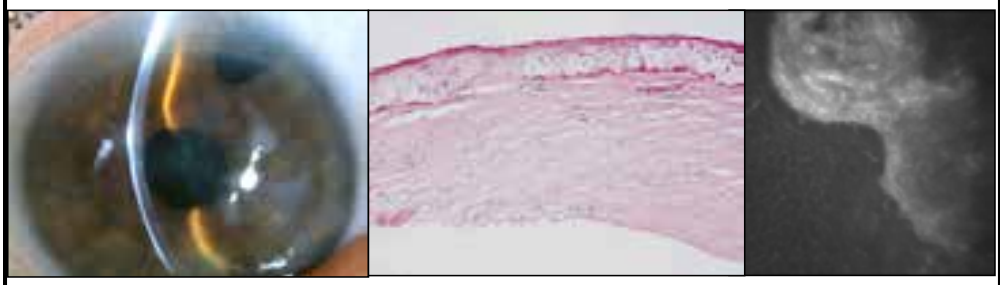
Etiology



- Myopic LASIK
- Correlation of normal or inverse Bell phenomenon to the location

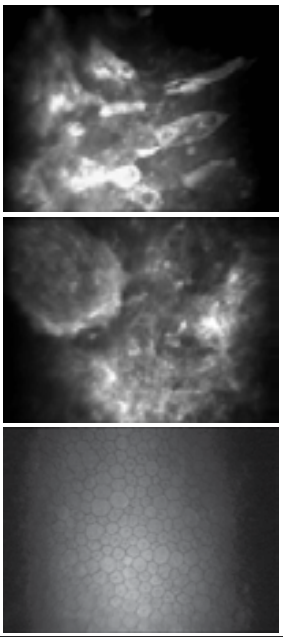
Lim, Chan *Cornea* 2009
Nissirios et al. *Cornea* 2013

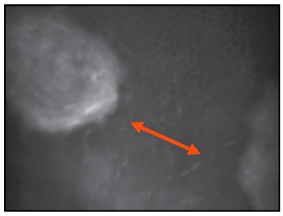
SALZMANN'S NODULAR DEGENERATION



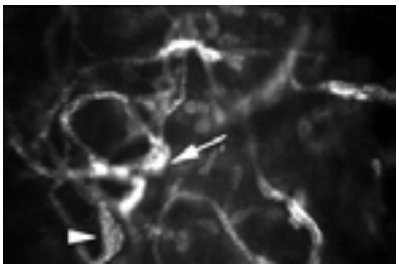
- A fibrillar, hyaline degeneration of collagen–cellular debris.
- The number of fibrocytes in the affected areas can vary (numerous cells that are active to scarce degenerating cells)

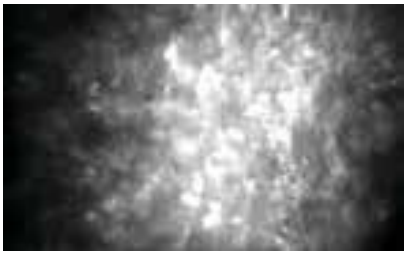
SALZMANN'S NODULAR DEGENERATION





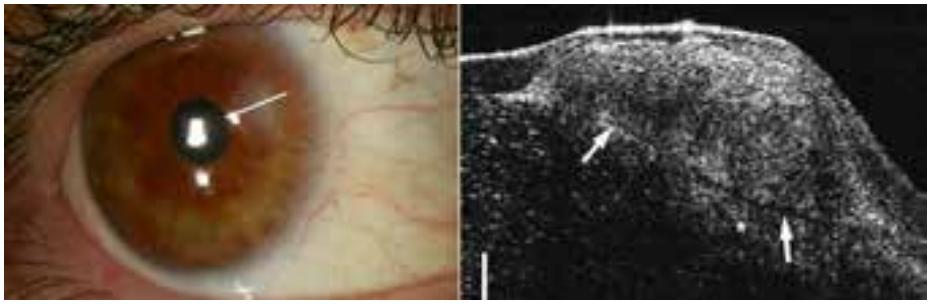
- Clear area between the nodules
- Thinning of the overlying epithelium
- Basal epithelial cell degeneration
- Replacement of Bowman's layer by (eosinophilic) material





- Confocal microscopic findings are associated with LM and TEM findings
- Epithelial changes are milder
- More pronounced changes of the BM and Bowman's layer
- Increased keratocyte activity
- Altered nerve pattern

From: Roszkowska et al. *IOVS* 2011



Slit-lamp photograph and ultra-high-resolution OCT images of Salzmann nodular degeneration:

- Significant epithelial thinning
- Surface elevation above the nodule
- Asterisk: stromal scarring
- White arrow: Bowman layer

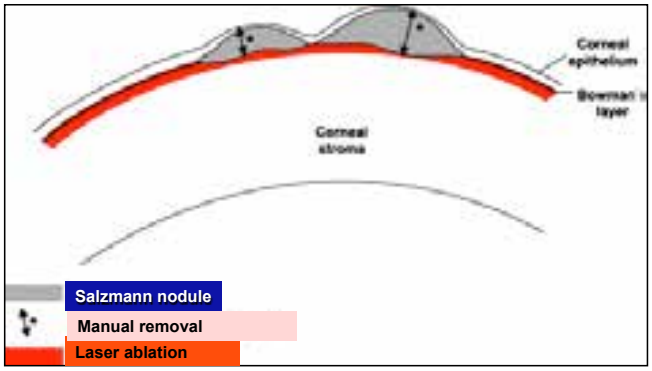
From: Hurmeric et al. *Am J Ophthalmol* 2011

SALZMANN'S NODULAR DEGENERATION

Treatment Modalities

- Manual removal
- PTK with or without MMC
- Lamellar/penetrating keratoplasty
  - All Salzmann cases are individual in their appearance and experience is needed to reach optimal surgical technique

Bowers Jr PJ et al. J Cataract Refract Surg 2003
Marcon AS, Rapuano CJ Cornea 2002

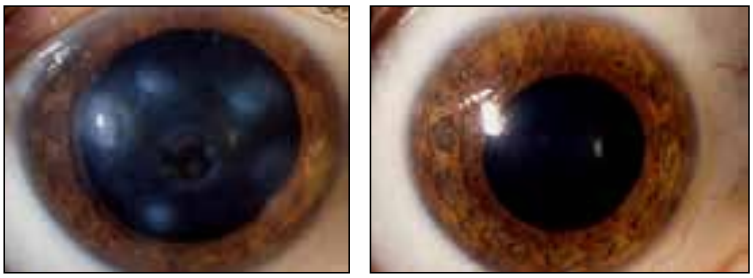


Schematic drawing of the surgical procedure

- Tissue removal with a surgical knife
- Laser ablation to smooth the surface
- Masking fluid employed several times

From: Sujata D et al. J Cataract Refract Surg 2005

SALZMANN'S NODULAR DEGENERATION



Before Treatment | After Treatment

PTK appears to be an effective and safe procedure for treatment of Salzmann's nodular degeneration

From: **Sujata D et al. J Cataract Refract Surg 2005**

SALZMANN'S NODULAR DEGENERATION

Please keep in mind

- Certain lesions cannot be removed by a blade only
- Lamellar or penetrating keratoplasty require donor material and are more invasive
- PK rarely recommended due to good endothelium
- Lamellar grafting is useful when PTK is not successful
- Interface haze is a problem in lamellar keratoplasty
- Mitomycine-C may prevent recurrence, but is toxic

TERRIEN'S MARGINAL DEGENERATION

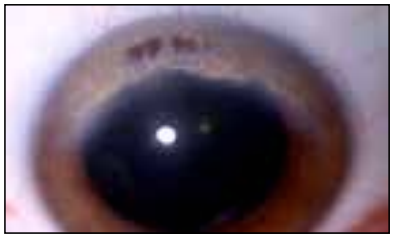
- Slowly progressive thinning of peripheral cornea
- Most common in men (3:1)
- Patient age: 10-70 years
- Most cases are bilateral (± asymmetry)
- Early stages generally asymptomatic
- Sometimes mild irritation in early stages
- Induced against- the -rule astigmatism (late stages)
- Spontaneous or traumatic corneal rupture (rare)

TERRIEN'S MARGINAL DEGENERATION

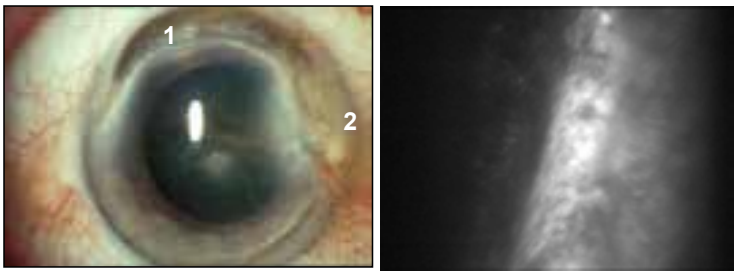
Deposition of refractile yellowish-white opacities (superiorly peripheral anterior stroma)

Development of gutter (parallel to the limbus)

Superior or more extensive corneal thinning



TERRIEN'S MARGINAL DEGENERATION



- Gutter is steep centrally, shallow peripherally (1)
- Gutter is 1-2 mm in width
- The epithelium remains intact
- Superficial vessels fill the gutter to the central edge
- Deposition of lipid at the central edge
- Pseudo-pterygium development (2)

TERRIEN'S MARGINAL DEGENERATION

- Most cases are non-inflammatory
- Rare cases with corneal and conjunctival vascular congestion (with moderate to severe pain)
- Mixed lymphocytic and neutrophil reaction (stroma)
- Relatively young patients

TERRIEN'S MARGINAL DEGENERATION

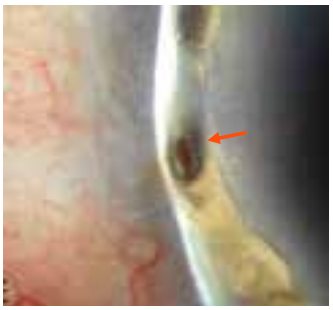
Pathology

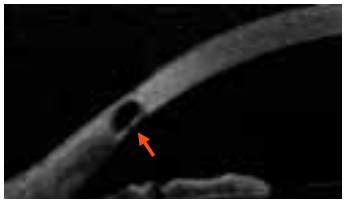
A. Limbal side B.Central

- Stromal thinning
- Thickened epithelium
- Loss of Bowman's layer
- <25% of the resident cells express MHC Class II antigens
- CD_4/CD_8 cell ratio≙1:1
- <5% of the infiltrating cells CD_{22}(+) (B cells)

Depiction of Cavity Formation in Terrien Marginal Degeneration by Anterior Segment Optical Coherence Tomography

Takaaki Hattori, MD, PhD, Shigeto Kumakura, MD, PhD, Hideki Mori, MD, PhD, and Hiroshi Goto, MD, PhD



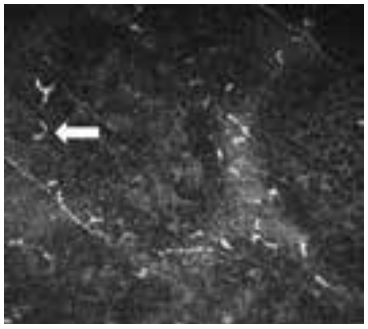


- Cavity formation may be one of the mechanisms of corneal thinning in TMD.

Cornea 2013;32:615–618

In Vivo Confocal Microscopy in Terrien Marginal Corneal Degeneration: A Case Report

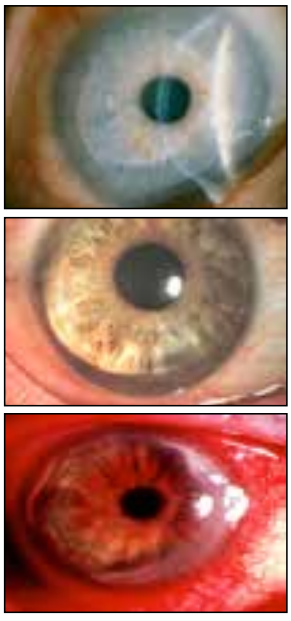
Gaia Ceresara, MD, Luca Migliavacca, MD, Nicola Orzalesi, MD, and Luca Rossetti, MD



- In vivo confocal microscopy can detect subtle corneal changes in an advanced case of TMD, which may be signs of subclinical inflammation.

Cornea 2011;30:820–824

TERRIEN'S MARGINAL DEGENERATION



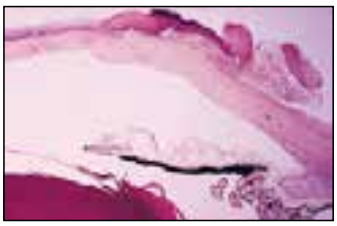
Differential Diagnosis

- Arcus senilis (early)
- Mooren's ulcer
- Furrow degeneration
- Marginal pellucid degeneration
- Inflammatory peripheral keratitis
- Peripheral corneal melting (autoimmune)
  - Rheumatoid arthritis
  - Wegener's granulomatosis
  - PAN

MOOREN'S ULCER

- Chronic, painful corneal ulceration
- Two different clinical types:
  - Benign- usually unilateral, older patients
  - Progressive type- 25% of all cases,young patients
- Starts in the peripheral cornea ğcircumferential spread
  sclera ⇦ centrally ↩
  (not involved)

MOOREN'S ULCER



- Inappropriate immunologic responses
- Cornea infiltrated by lymphocytes and plasma cells
- 75% to 100% of the resident cells express MHC class II antigens
- CD_4/CD_8 cell ratio ≙ 2.4:1
- 25% to 50% of the infiltrating cells CD_{22} (+) ğB cells

TERRIEN'S MARGINAL DEGENERATION

Treatment

- Observation
- Astigmatic control with spectacles or contact lenses
- Surgical treatment:
  - Excision of ectatic tissue and direct closure
  - Eccentric penetrating keratoplasty
  - Crescentic onlay lamellar keratoplasty

Compressive C-shaped lamellar keratoplasty

Cheng CL et al. Ophthalmology 2005

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MCQ answers page 59

1. **Answer: c**

2. **Answer: a**

3. **Answer: d**

MCQ's

1. In front of a residual significant leukoma after infectious keratitis we should consider:
What is false:

a. PTK if less than 100 microns deep
b. Penetrating keratoplasty if the endothelium is severly affected
c. Automated anterior keratoplasty (microkeratome) if there is a significantly high irregular astigmatism
d. Deep anterior keratoplasty if there is high distorsion and the endothelium is healthy

2. The more effective and safest approach in performing a big-buble dissection is:

a. Injecting air under high pressure
b. Injecting BSS under normal pressure
c. Injecting viscoelastic
d. Layer by layer manual dissetion

3. Automatic (microkeratome) anterior lamellar keratoplasty is indicated:

a. Irregular anterior superficial opacities
b. Postinfectous leukoma
c. Scar after perforating trauma
d. Post LASIK flap deformation

Whenever a corneal transplant is indicated either for visual or clinical reasons, and the posterior layers of the cornea, mostly the endothelium, is healthy, an anterior lamellar approach should be considered. More than 90% of the postoperative rejection episodes are related with the transplanted endothelium in full thickness grafts, chronic endothelial progressive loss is obviously more common also in full thickness techniques with a resultant higher number or possible regrafts throughout patient's life and a significantly more robust surgery from a biomechanical point of view in lamellar technique are their main advantages.

We will cover the main surgical strategies: automated anterior lamellar, deep anterior lamellar keratoplasty,.....focusing on the surgical technique, indications, complications as well as advantages and disadvantages of each strategy. A number of clinical cases also be presented.

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MCQ answers page 82

1. **Answer: c**

2. **Answer: c**

3. **Answer: d**

MCQ's

1. Where is the "niche" of the stem cells of the corneal epithelium?

a. bulbar conjunctiva
b. paracentral cornea
c. peripheral and central cornea
d. basal layer of the peripheral cornea

2. When the corneal limbus is damaged the conjunctiva migrates and the cornea becomes opaque and vascularized: what is the treatment?

a. full-thickenss corneal transplant
b. lamellar corneal transplant
c. limbal stem cell transplantation
d. anti-VEGF eyedrops

3. At present, ex-vivo expansion of stem cells can be the treatment of:

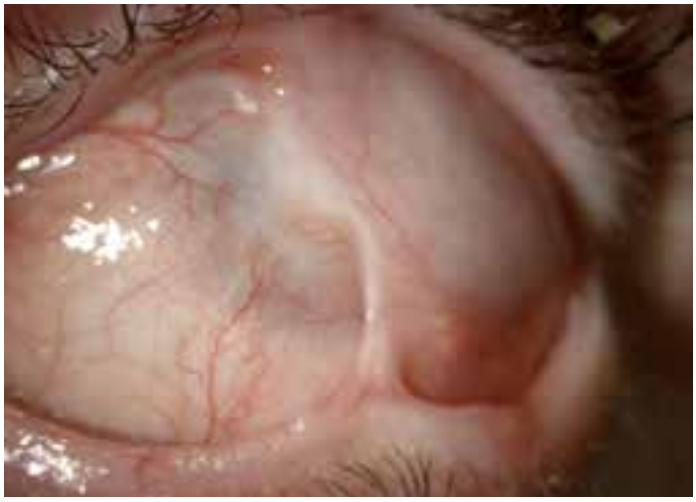
a. macular degeneration
b. corneal burns
c. optic nerve atrophy
d. retinitis pigmentosa

Limbal stem cell deficiency (LSCD) includes a group of heterogeneous diseases involving failure of the corneal epithelial stem cells caused by congenital abnormalities, acquired diseases such as chemical and thermal injuries, immunological diseases, toxicity and infections *(Dua et al. 2000; Shortt et al. 2007).*

Causes of LSCD

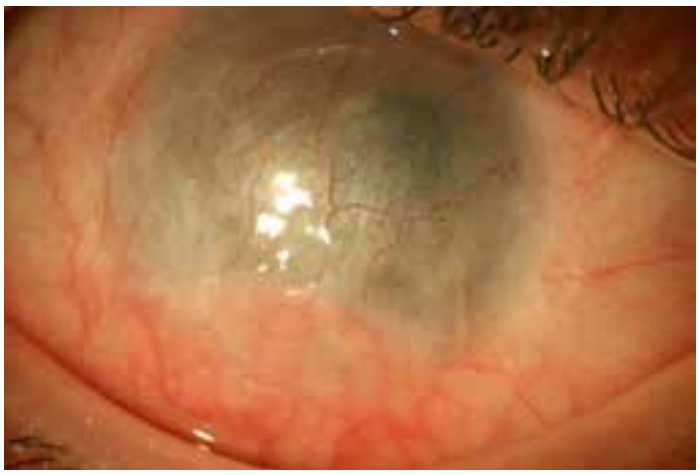
Congenital	**Acquired**
- Aniridia	- chemical/thermal injuries
- Dyskeratosis congenita	- radiation
- Autoimmune polyglandular syndr.	- contact lens abuse
- Ectodactyly ectodermal dysplasiaclefting syndr.	- drug-induced
- Endocrine deficiency	- extensive limbal surgery
- Xeroderma pigmentosum	- extensive corneo-limbal infections
	- Stevens-Johnson sindr.
	- Mucous membrane pemphigoid
	- Atopic keratoconjuntivitis
	- Graft-vs-host disease

Such diseases may not only damage the limbus, but eyelids, conjunctiva, corneal stroma, nerves and endothelium, immune and lacrimal systems can also be involved. Ocular surface disease is the most appropriate term for such a complex disorder.



Severe ocular burn with involvement of eyelids, conjunctiva, limbus, and cornea

Impairment of the limbal stem-cell compartment causes corneal epithelial turnover breakdown, resulting in damage to the corneal epithelium, which will ultimately repair due to conjunctiva migration on to the cornea *(Dua et al. 2000; Shortt et al. 2007)*.



Corneal "conjuctivalization" secondary to severe limbal stem cell deficiency

Conjunctival migration, or "conjuctivalization", is a compensatory repair mechanism that protects the cornea from infection, stromal ulceration, melting, and perforation. While it provides a stable and protective superficial layer to the cornea, it is often accompanied by persistent inflammation, severe visual impairment, and other symptoms.

Lamellar and/or penetrating keratoplasty cannot be used successfully in these cases as donor corneal epithelium is replaced by that of the recipient within months. In the presence of corneal epithelial stem-cell compartment deficiency, donor graft reepithelialisation will not take place, with subsequent epithelial defects and the ultimate recurrence of conjunctivalization, and the risk of rejection and failure.

Graft failure after penetrating keratoplasty with recurrence of conjunctivalization in limbal stem cell deficiency after chemical burn

Scrupulous step-by-step reconstruction should be planned, treating the structures involved separately, to prepare the best recipient bed for the reconstruction of the limbus and cornea.

Eyelid malposition and malocclusion should first be treated. Conjunctival symblepharon should be then addressed using the appropriate procedures. Once the eyelids and conjunctiva have been treated, tear film and inflammation should be carefully evaluated. The minimum of tear film, and the maximum inflammation allowing the successful long-term survival of the grafted stem cells is not clear. In our previous clinical trials *(Rama et al. 2001; Rama et al. 2010)* we excluded patients with Schirmer test below 5 mm/5 min, but this was arbitrarily chosen, and one might suggest that the quality of tears might be even more important than the quantity. Unfortunately, at present there is still no valid method for its assessment. We do not include in our clinical protocol for limbal transplantation patients showing severe active inflammation. As for tear film, we are still far from having reproducible clinical assessment and inflammation grading, with the exception of redness scoring. Limbal stem cell transplantation (LSCT) is the last step in the reconstruction of the ocular surface, while lamellar or penetrating corneal graft will finally restore corneal transparency, when the stroma and/or endothelium are involved, leading to the recovery of visual capacity.

Transplantation of cultivated limbal stem cells is the most recent and promising treatment to restore the integrity of the corneal surface, when LSCs have been destroyed *(Baylis et al. 2011)*.

Source of LSCs is typically classified in autologous (donor and recipient are the same subject) grafts and allogenic (donor and recipient are different subjects) transplantation.

Autologous Cultivated Limbal Epithelial Transplantation (CLET) has been granted approval from the European Medicine Agency (EMA) in February 2015 for the treatment of corneal burns (Holoclar®). A recent review summarizes the history of CLET, from discovery to clinical approval, including regulatory aspects *(Pellegrini et al.2016)*. Pre-requisite for CLET is the availability of a small area of preserved limbus (2-3 mm), which is biopsied, expanded in culture, and transplanted on the LSCD affected eye. The procedure of ex-vivo stem cells' expansion is complex, time consuming, and expensive but it has several advantages compared to the traditional limbal grafting: it has fewer risks for the donor eye, possibility to treat partial bilateral LSCD, and possibility of re-grafting in case of failure. This procedure has proven effective and safe in the majority of patients with a 76,6% of success and with stable results up to10 yrs *(Rama et al. 2010)*. Fasolo et al have recently reported a retrospective analysis of 65 patients treated with CLET. One year after surgery, 80% of surgeries were judged as successful or partially successful; the overall 3 year effectiveness of the procedure was 68%.

Cultivated allogenic limbal epithelial transplantation (CALET), on the other hand, could provide an option for patients where bilateral corneal damage has left no viable LSCs.

In CALET, cultivated cells from a living related donor or from a deceased not-related may be grafted on the recipient cornea. The major disadvantage of CALET is the risk of rejection and consequently the need of prolonged systemic immunosuppression, and risk of late failure. A recent publication *(Eslani et al.2017)* reported a case series of 6 eyes which showed graft rejection up to 8 years after limbal allograft. The authors suggest that prolonged and tailored systemic immunosuppression, guided by an organ transplant team, should be maintained, however they also reported that despite appropriate immunosuppressive treatment two third of their patients developed some degree of failure. Others *(Chen et al.2016)* performed DNA analysis on 19 samples of recipient coneal epithelium collected after CALET procedure, and found, as previously reported *(Henderson et al. 2001; Daya et al 2005)*, no persistence of donor DNA beyond 3 months from CALET. They raise provocative questions as to what may be the origin of regenerated epithelium and whether long term immunosuppression may be needed following CALET in the examined patients. Finally, Parihar et al compared allogenic limbal stem cell transplantation with cadaveric keratolimbal graft transplantation. One year later, they found the two procedures comparable in terms of improvement in visual acuity, corneal opacity, and other ocular surface clinical parameters.

We think that CLET is a promising technique to treat unilateral and partial-bilateral LCSDs. It is safe and provide good and stable long-term results. Holoclar® is the CLET product that has been approved by EMA and now available in Europe to treat corneal neovascularisation due to ocular burns. At present, limits are costs and expertise required to produce a GMP grade industrial product. CALET may represent an option for patients with bilateral total LSCD. Questions remain regarding the long-term efficacy, best regimen of systemic immunosuppression to prevent rejection, and the explanation how the cornea improved in some cases after CALET despite not-detectable donor DNA in the recipient epithelium.

Novel research has uncovered the potential of other sources of corneal epithelial cells. Mesenchymal stem cells from the bone marrow or adipose tissue might be a source, however their efficacy has not yet been confirmed . Other potential sources include hair follicle derived stem cells *(Meyer-Blazejewska et al. 2011)*, immature dental pulp cells (Monteiro et al. 2009), and umbilical cord stem cells *(Reza et al. 2011)*.

Induced pluripotent stem cells (iPSC) have also potential for limbal stem cell transplantation. It has been recently demonstrated that these cells can be successfully differentiated into corneal epithelial cells, and effectively recover function in animal models *(Hayashi et al. 2016)*. IPSC have great potential for clinical applications because they are not generated from embryos, which may be ethically challenging. In addition they could theoretically be generated from each single patient, which abolishes the risk of rejection. A recent study also showed that the process of reprogramming induced variants that were generally benign and unlikely to make the cells inappropriate for therapy *(Bhutani et al. 2016)*. The costs and expertise required to produce a GMP grade product as well as still concern of risk of cancers, however, pose a significant threat to full clinical development of iPSCs for limbal transplantation.

Conclusions

Autologous cultivated limbal stem-cell transplantation is an effective and safe procedure to treat limbal stem-cell deficiency when there is an undamaged, even small, portion (1-2 mm^2 are sufficient) of the limbus that will provide donor cells to be expanded in vitro. Unilateral and partial bilateral limbal deficiency can thus be successfully treated with long-term survival, and without the need for systemic immunusuppression.

Limbal stem-cell deficiency is part of the complex disorder known as Ocular Surface Disease, and scrupulous step-by-step reconstruction should be planned, treating the structures involved separately, to prepare the best recipient bed for the cultivated cells.

The procedure of ex-vivo stem-cell expansion is crucial and mandatory to demonstrate the presence, survival, and concentration of stem cells in culture and in the graft, and validate the procedure under GMP conditions. We are still dependent on the presence of animal-derived products, such as 3T3 feeder layer and fetal calf serum. Even though all these ingredients have been proven to be safe, and have been approved for human use by regulatory agencies, we hope to find a way to be free of them in the future.

We still lack a valid solution for total limbal stem-cell deficiency cases. Contrasting results have been reported on the use of allogeneic keratolimbal grafts, and in the absence of allogeneic cell survival we cannot rely on this treatment for long-term success in total bilateral diseases.

Future perspectives include: i) finding other sources of autologous stem cells able to function like the corneal epithelium to treat bilateral limbal stem-cell deficiency, ii) preparation of a "composite" graft with stem cells seeded with other cells, such as keratocytes, fibroblasts, melanocytes, and/or other cells, on a 3D scaffold that might reproduce the "niche" where stem cells normally reside, iii) improve tear substitutes and/or tissue engineering of the lacrimal gland to treat severe dry eye, iv) more accurate modulation of the inflammatory response before and after grafting.

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MCQ answers page 85

1. **Answer: d**

2. **Answer: c**

3. **Answer: b**

MCQ's

MCQ's not yet received

Outline not yet received

MCQ answers page 94

MCQ's not yet received

MCQ's

1. All are TRUE concerning the selection of the reference surface for displaying corneal elevation EXCEPT:

a. The appearance of the map will vary with different reference surfaces
b. The ability to visually diagnose pathology will vary with different reference surfaces.
c. Accuracy will vary with different reference surfaces
d. Maximum elevation values will vary with different reference surfaces

2. The following pairs are all CORRECT EXCEPT:

a. Specular Microscopy - Fuchs dystrophy
b. Confocal Microscopy - Bacterial keratitis
c. Scheimpflug Imaging - Subclinical keratoconus
d. OCT - Narrow angle glaucoma

3. Select the correct answer:

a. Computerized videokeratoscope (Placido topography) measures the anterior corneal surface
b. Placido topography measures the center of the cornea
c. Scheimpflug tomography directly measures corneal thickness
d. OCT can determine posterior corneal curvature

Corneal Examination Techniques:

Pachymetry, Endothelial Evaluation, Confocal, Topo/Tomography, & OCT

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Southern AZ VA Healthcare System

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Consultant OCULUS GmbH

Topics

- Pachymetry
- Specular
- Confocal
- Topography
- Tomography
- OCT

Topics

- How do they work?
- What are the clinical applications?
- Do you need them?




Introduction

- The different Imaging Modalities are not so much competitive as they are complimentary and/or different.




TECHNOLOGY	PRIMARY UTILIZATION	STRENGTHS	LIMITATIONS
PACHMETRY (Ultrasound)	Refractive screening, Glaucoma, Grafts	Inexpensive, portable, ease of use,	Single point reading, operator dependent
SPECULAR MICROSCOPE	Eye Banks, Pre-op Cataract	Quantitative & Qualitative evaluation	Small area of analysis, clear cornea
CONFOCAL	Specular microscope, Fungal & Acanthomoeba	Real time imaging, observation at the cellular level	Very limited coverage area
TOPO/ TOMOGRAPHY	Refractive screening, Post Refractive IOL,	Measuring, area of coverage, ease of operation	Influenced by scars, cannot fully image the angle
OCT	Angle, Iris tumors, IOL evaluation	Imaging, coverage > confocal < Scheimpflug	Not as good at measuring as Scheimpflug, pigmented tissue

Optical Pachymetry

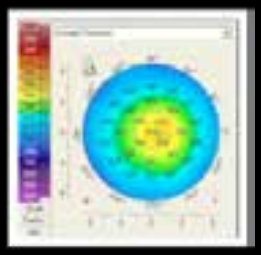
- One of the first devices for accurately measuring the corneal thickness
- Operator dependent
  - Usually required a physician
- Single point measurement
- Somewhat time consuming

Ultrasonic Pachymetry

- Easy, fast and often performed by a technician
- Single point measurement
- Not overly reproducible
- Still one of the most commonly used methods
- Potential for infective transmission

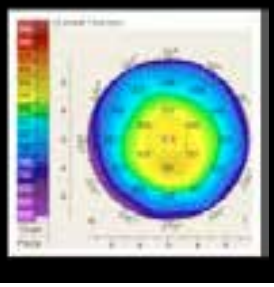
Rotating Scheimpflug / OCT

- Produce a near limbus to limbus corneal thickness map
  - Less susceptible to errors in abnormal corneas



Central Cornea Thickness

- For the most part, however, physicians (surgeons) still relied only on a single central measurement.
  - Pre-operative screening
  - Residual bed computation
- Variability in the thinnest point location was not utilized or appreciated



Apex v. Pupil v. Thinnest

	Apex	Pupil	Thinnest
Mean	539.3	538.8	536.3
Median	539.0	539.0	537.9
Mode	542.0	542.0	539.0
SD	36.8	36.9	37.12
Range	411-664	410-664	409-664

n = 1,436

Belin MW, Khachikian SS: New Devices & Clinical Implications for Measuring Corneal Thickness. Clin & Exp Ophthalmol 2006; 34: 729-731

Apex v. Pupil v. Thinnest Comparison

	Apex-Pupil	Apex-Thin	Pupil-Thin
Mean	1.06	2.99	1.94
Median	1.0	2.0	1.0
Mode	zero	1.0	1.0
SD	1.73	4.34	3.07
Range	**0 - 31**	**0 - 93**	**0 - 61**

n = 1,436

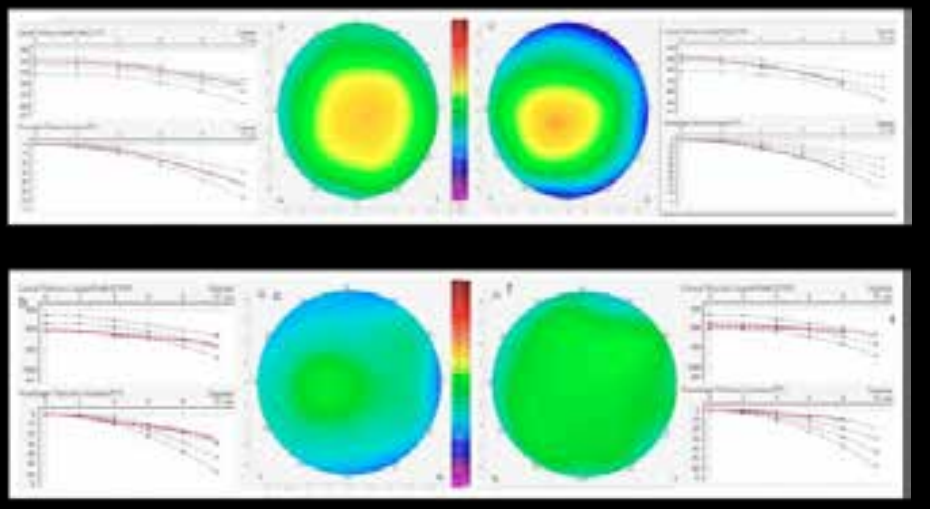
Ectasia and RBT

- It has been assumed that variability in flap thickness is the major confounding variable in cases of post LASIK ectasia without apparent cause.
- Pachymetry distribution variability may be a significant overlooked factor.
  - You cannot rely on a single "*central*" reading
  - Risk analysis involves "*worst case constructs*"

Limitations of CCT

- Renato Ambrosio got us to think beyond single point CCT values and moved us into two dimensions.
  - This helped separate eyes with the same CCT but differing rates of change.

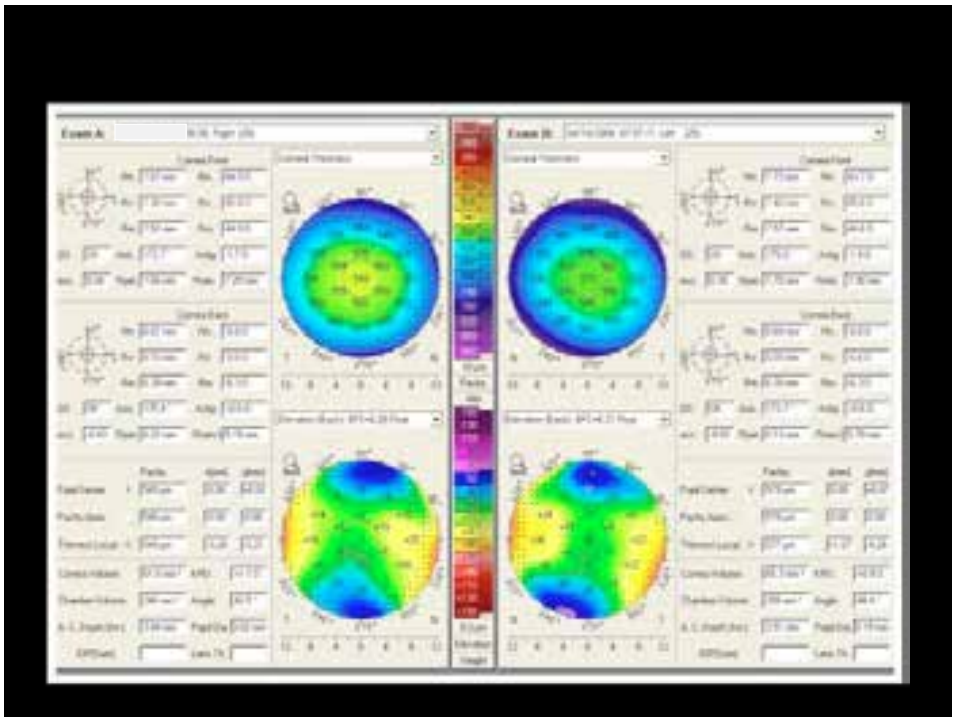
Pachymetric Progression

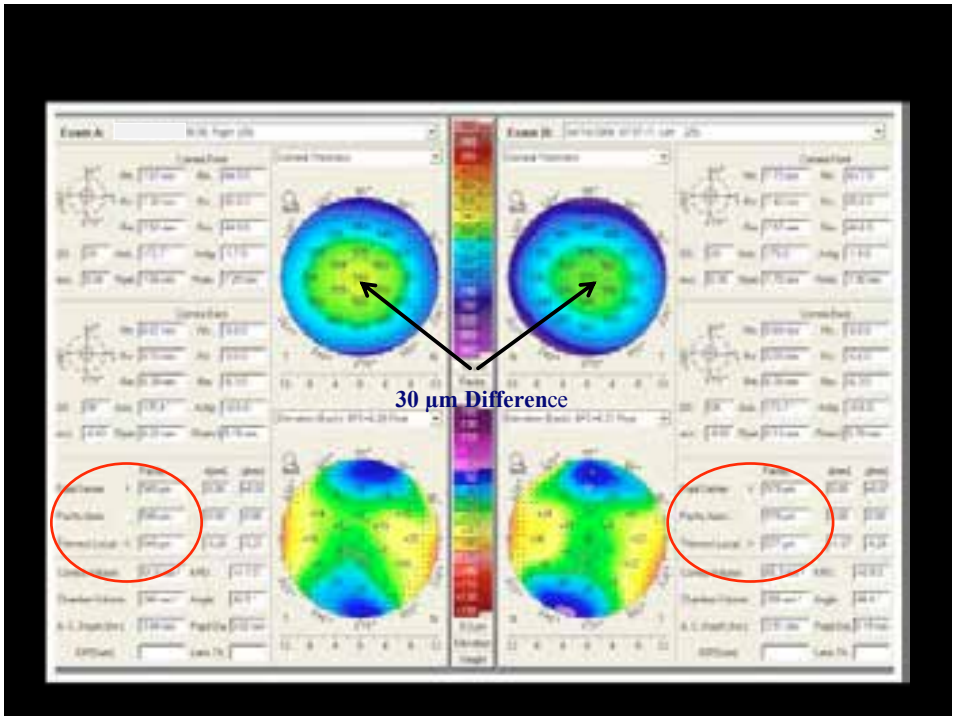


Ocular Symmetry

- We commonly consider "*normal*" parameters "*abnormal*" if there is a significant amount of asymmetry. (IOP, CDR, Refractive error)
- While normal values for corneal thickness are well established, little is known about the variation between an individuals' eyes

Khachikian SS, Belin MW, Ciiolino JB. Intrasubject Pachymetric Asymmetry Analysis. J Refract Surg, 2008; 24:606-609




30 µm Difference

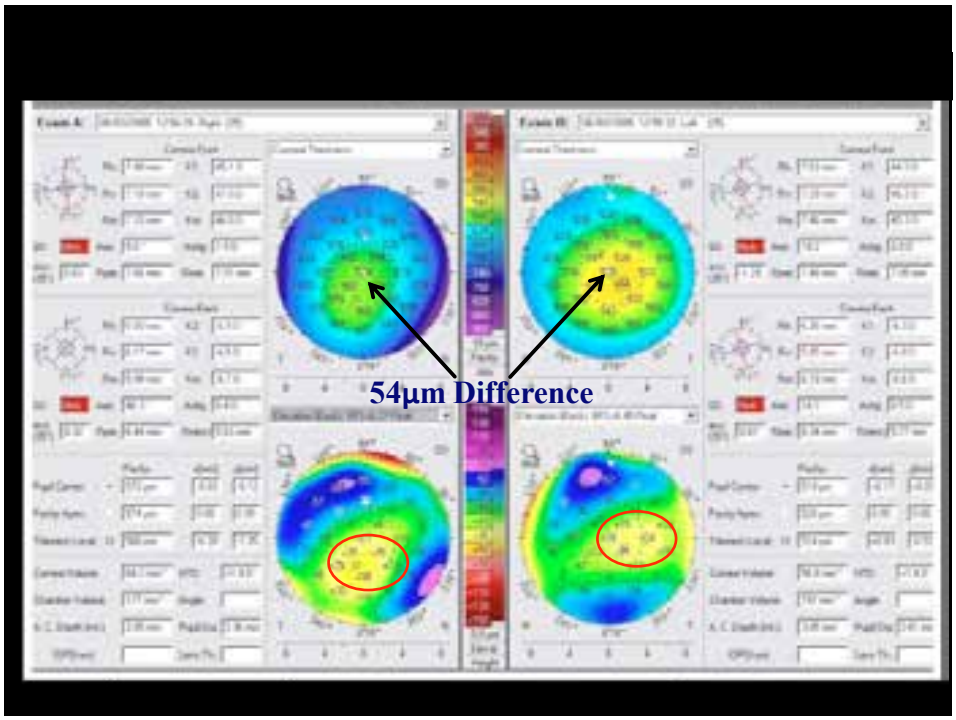
OD/OS Pachymetry Variance

	Thinnest Point	Corneal Apex	Pupil Center
Avg. OD/OS Difference	9.0µm (SD 8.3)	8.8µm (SD 7.2)	8.9µm (SD 8.3)
Range	0-105µm	0-59µm	0-105µm
2SD/3SD	25.6/33.9	23.2/30.4	25.5/33.8

N=724

Symmetry Values

- Individuals with a >25µm difference in CCT represent <5% of the population.
- Individuals with a >34µm difference in CCT represent <0.5% of the population.



Pachymetry / Corneal Thickness

- Do you need it
  - YES
- Applications
  - Refractive
    - Pre and Post
  - Glaucoma
  - Pre op Cataract
  - Corneal Transplant

Topics

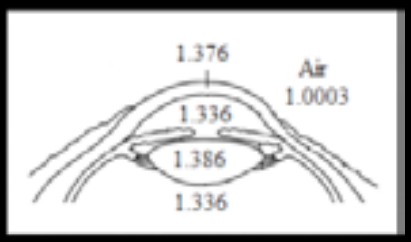
- Pachymetry
- Specular
- Confocal
- Topography
- Tomography
- OCT

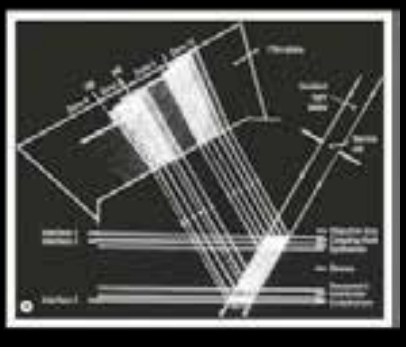
History of Endothelial Imaging

- 1918. Vogt A: direct visualization of the endothelium
- 1924. Graves B: description of Fuchs' endothelial dystrophy
- 1968. Maurice DM: first laboratory specular microscope
- 1975. Laing RA: in vivo photomicrography of the corneal endothelium in rabbits
- 1976. Bourne WM & Kaufman HE: specular microscopy of human corneal endothelium in vivo

Specular Reflection

- Light is reflected from the interfaces of materials with different indices of refraction.
- The greater the difference in index of refraction between the surfaces↑ the intensity of reflected light↑





Types of Specular Microscopes

Contact (CSM)

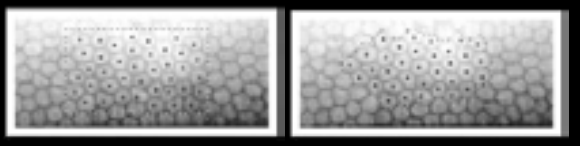
- Objective cone applanates the cornea
  - resulting in a flat surface (angle of incidence = angle of reflection)
- The cone may displace or compress the precorneal tear film → the light passes through only the corneal layers

Non-Contact (NCSM)

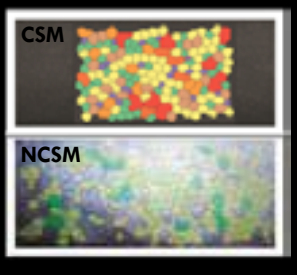
- Images the endothelium without changing the corneal surface
  - endothelial imaging is affected by the corneal curvature
- 2 additional refractive media (air and tear film) may affect the refraction and the image quality

Image Analysis

- Automated, Semiautomated, Manual
- Frame method
  - Fixed frame
  - Variable frame



- Different software options may not equally identify the cell borders
  - Poor agreement between automated image analysis programs
    - Not interchangeable



Specular Microscope

- Do you need it
  - NO
- Applications
  - Eye Banking
    - MANDATORY
  - Pre op Cataract
  - Corneal Transplant
    - Slit lamp examination typically adequate

Slit Lamp Specular Microscope

- Need 16 X oculars
  - 25.6 – 40 X total mag
- Slit lamp arm at 45 degrees
- High illumination / Narrow (not slit) beam
- Bring light source into filament reflection
- Look for bright (specular) reflection
  - monocular
- Easier with dilated pupil

Topics

- Pachymetry
- Specular
- **Confocal**
- Topography
- Tomography
- OCT

In Vivo Confocal Microscopy

- Light is focused onto a small area of the cornea
- Only reflected light in focus is visualized
  - eliminating light not in the focal plane
  - high resolution, thin optical sections are produced.

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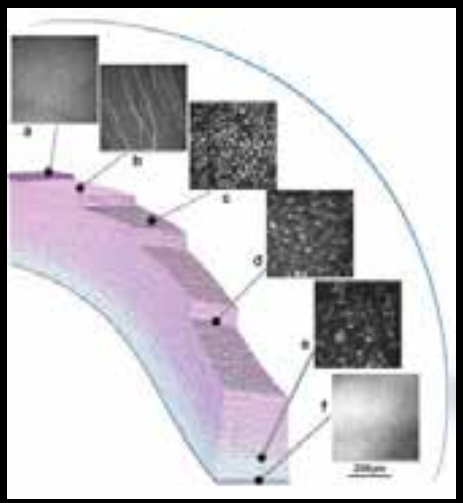
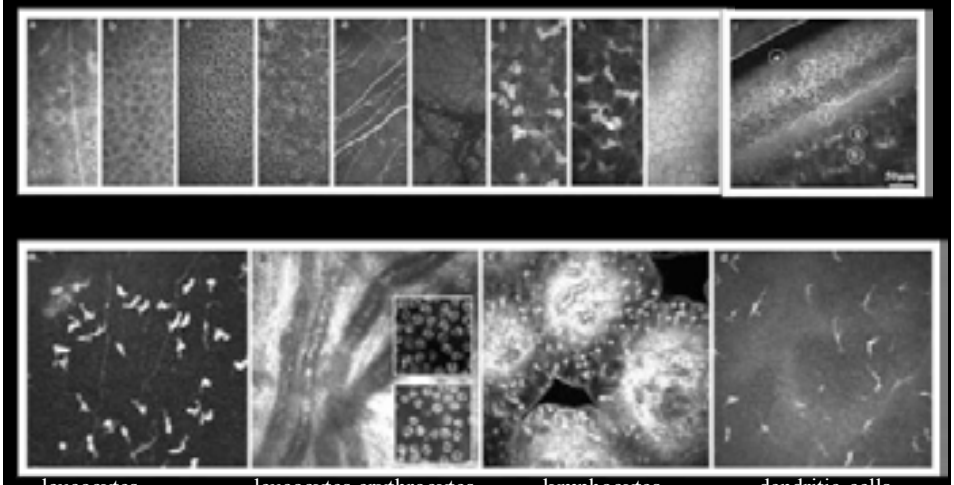


Visible Structures



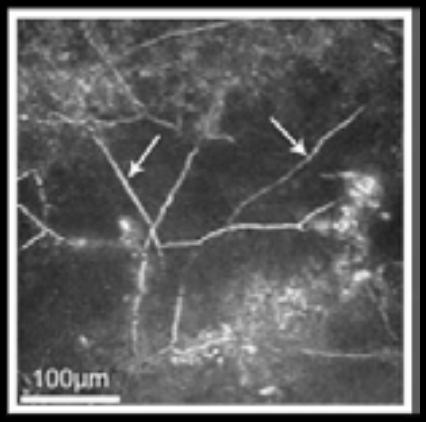
In Vivo Confocal Microscopy

- Slit scanning confocal microscope (SSCM) (Nidek Confoscan 4)
  - White, non-coherent light, conjugate slits
- Tandem scanning confocal microscope (TSCM)
  - White, non-coherent light, conjugate pinholes in rotating disc
- Heidelberg Retina Tomograph II Rostock Corneal Module (RCM)
  - Laser scanning using a 670nm red wavelength diode laser source.

No longer commercially available

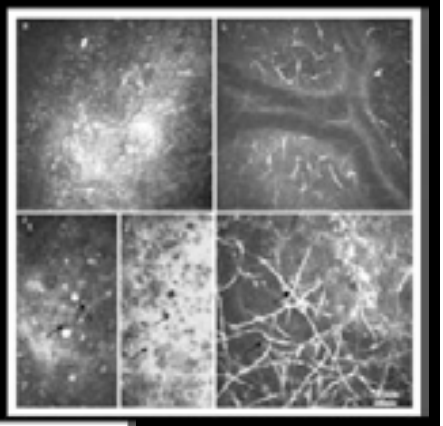
Clinical Applications

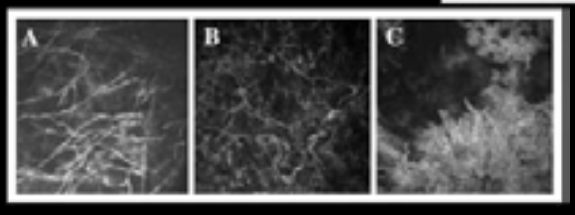
- Infective Keratitis
  - Adjunctive not diagnostic
    - Acanthamoeba keratitis
    - Fungal keratitis
      - Limited use for bacterial / viral due to resolution
- Endothelial morphology
    - Specular microscope
- Corneal nerves
    - Research applications



Keratitis

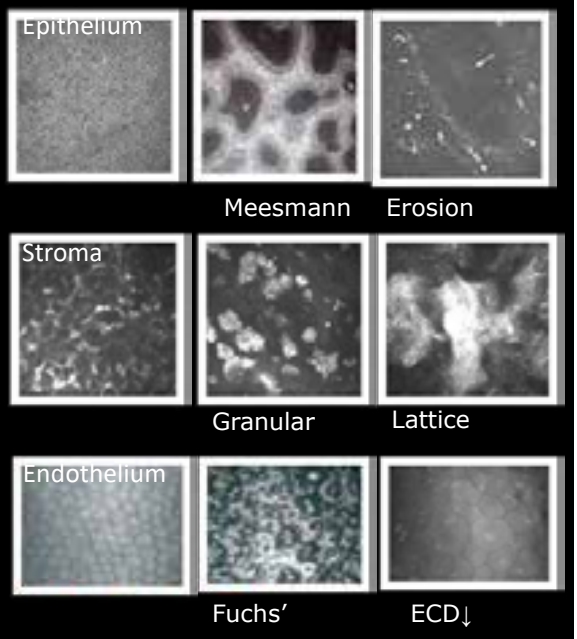
- Major clinical indication
  - Fungal Keratitis
  - Acanthamoeba Keratitis





Dystrophies

- Examination at the cellular level
- Differential diagnosis
- Measuring depth of the lesion (e.g. before ALK)
  - OCT, Slit Lamp, Scheimpflug



Confocal Microscope

- Do you need one
  - Probably NOT
  - More common in referral academic centers
  - Main use in infectious keratitis
- May be cost effective as opposed to specular microscope

Topics

- Pachymetry
- Specular
- Confocal
- Topography
- Tomography
- OCT



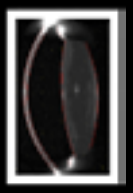

Terminology

Topography

- Limited to devices that only measure anterior corneal surface
  - Placido imaging
- Computerized Video-keratoscopy
  - More accurate term
- Measure Slope
  - Generates Curvature
    - First Derivative

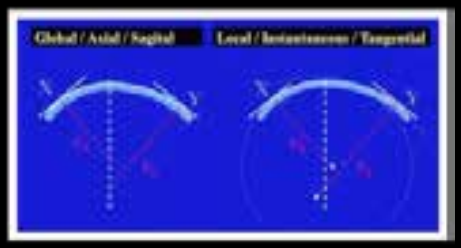

Tomography

- Limited to devices that recreate a 3-D image of the anterior segment / cornea
  - Scheimpflug
  - OCT
  - Optical cross-section
- Measures Elevation
  - Generates Curvature
    - Second Derivative



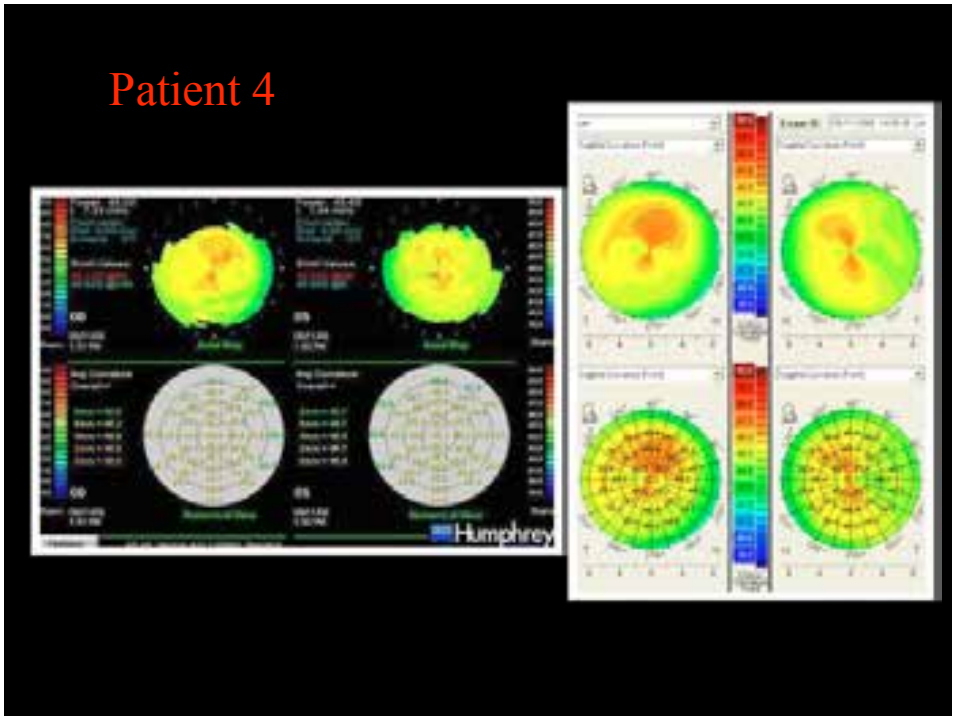

Curvature

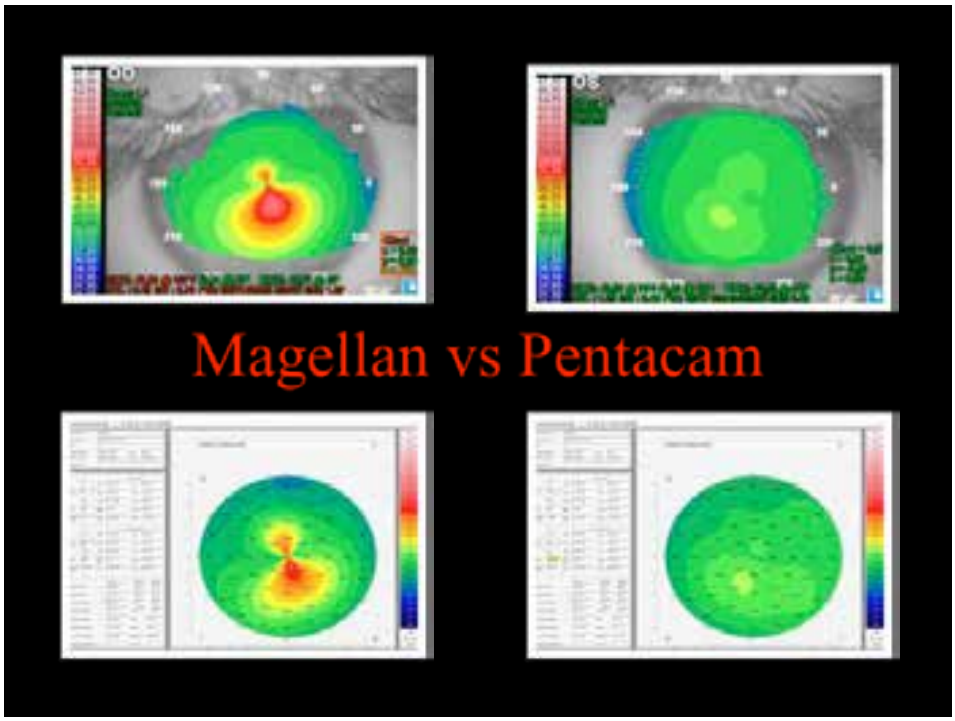
- Axial or Sagittal
  - All centers of rotation fall on the normal line
    - First order equation
    - Low noise
  - Most commonly used
- Tangential or Local
  - Centers of rotation not limited.
    - Second order equation
      - More representative of shape (but NOT shape)
    - High noise



Topography *vs* Tomography Curvature

- If your elevation is accurate then the Curvature maps from tomography should be the same as the curvature maps from topography
  - Tomography more coverage
  - Less susceptible to surface problems
    - Dry eye, MGD
- No significant difference in accuracy


Patient 4
Humphrey


Magellan vs Pentacam

Results

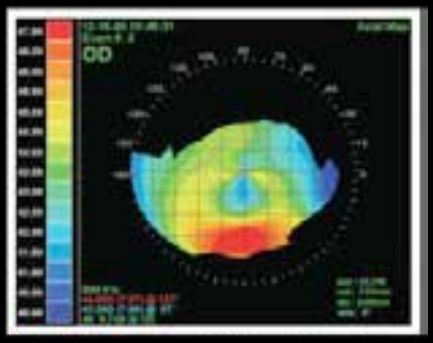
- Other than a significant difference in the corneal coverage (*Pentacam >> Atlas*) the curvature maps were almost identical

Results

- While Clinically Identical they will never be Absolutely Identical since Placido measures Tear Film & Scheimpflug the Corneal Surface

Topography

- Applications
  - Contact lens fitting
  - Screening for refractive surgery
    - Supplanted by Tomography
  - Toric IOL
    - Supplanted by Tomography
  - Dry eye Analysis
    - Useful as adjunct
- Do you need
  - Probably NOT



Topo / Tomography

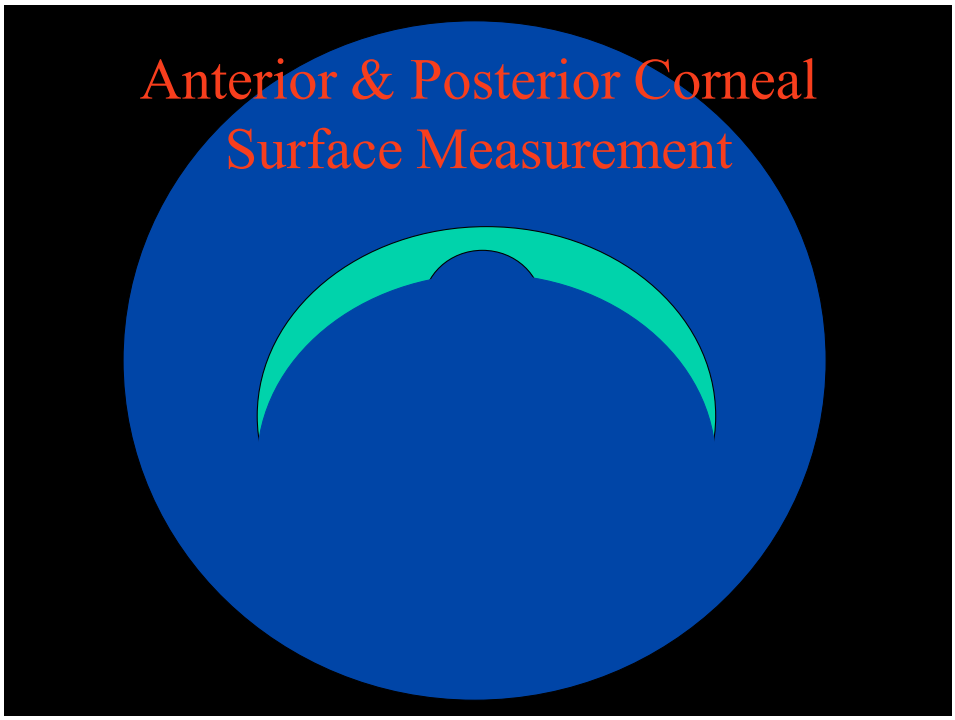
I have a strong preference (*bias*) against Curvature in favor of Elevation as the Primary Topo/Tomographic Measurement

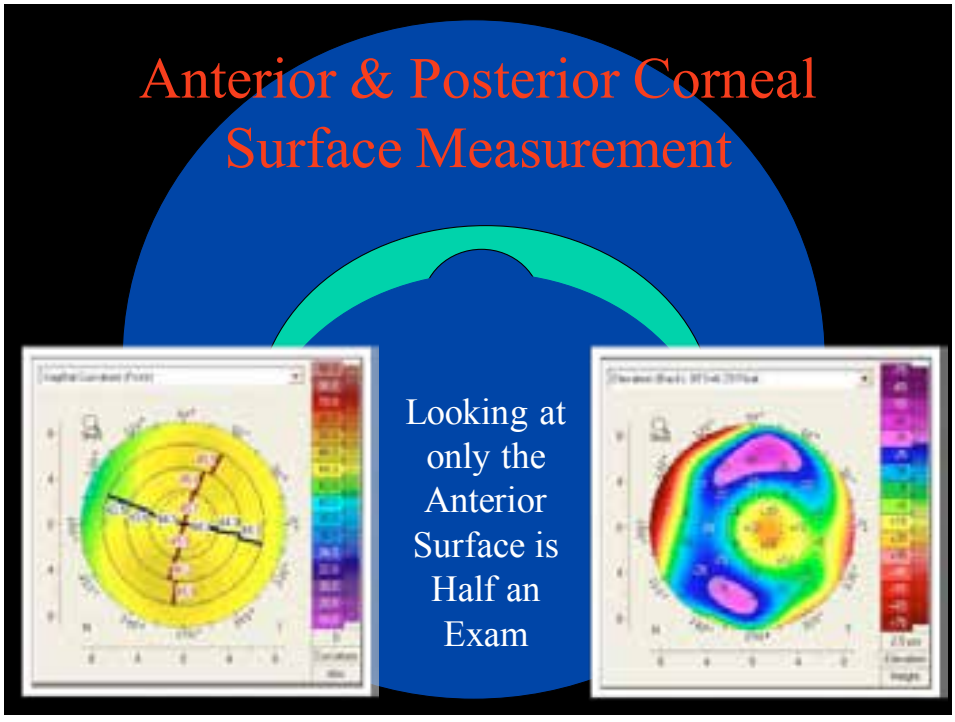
Posterior Surface

- In the past we were told not to pay much attention to the posterior surface because it is less important as a refractive surface and in the past, information about it was unreliable

Posterior Surface

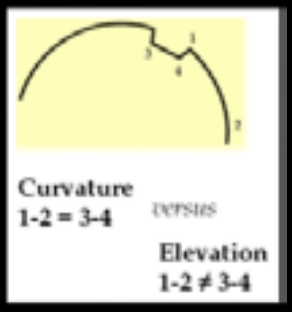
- The Posterior corneal surface is just as important as the anterior surface and serves as a more subtle or early indicator of potential pathology than any anterior surface parameter.


Anterior & Posterior Corneal
Surface Measurement


Anterior & Posterior Corneal
Surface Measurement
Looking at only the Anterior Surface is Half an Exam

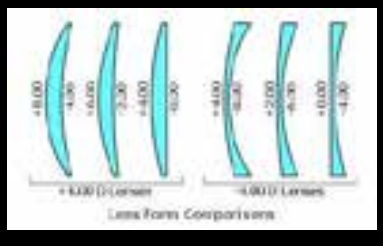
Elevation vs Curvature

We need to understand How Elevation and Curvature Differ

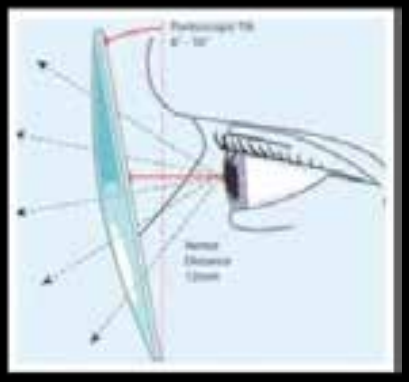


- Curvature is analogous to measuring spectacle lens power.
  - It may be accurate, but tells you nothing about the shape of the lens

- Curvature is analogous to measuring spectacle lens power.
  - It may be accurate, but tells you nothing about the shape of the lens
    - i.e. multiple spectacle lenses *(different shapes)* can have the same power



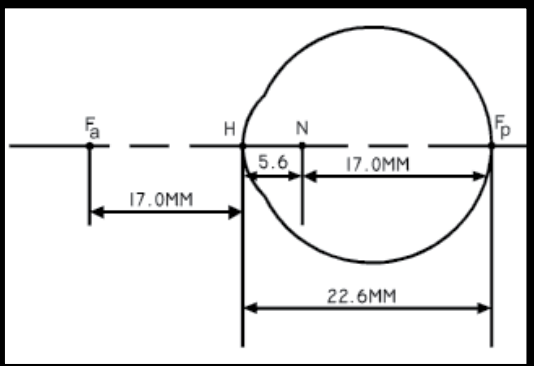
- Curvature & Power will change with orientation
  - Lens tilt and/or measurement axis
  - The same lens (shape) can have multiple powers



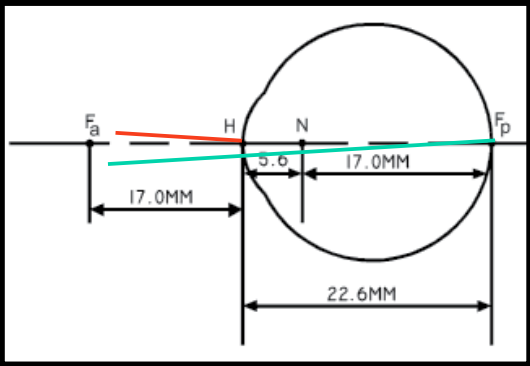
Elevation *vs* Curvature

- Elevation is analogous to a Geneva lens clock and caliper
  - It doesn't directly measure power but it give an accurate representation of the true shape of the lens
    - If the shape is known, lens power can then be calculated

Curvature Based Topography Treats the Eye as if its a Gullstrand Reduced Eye

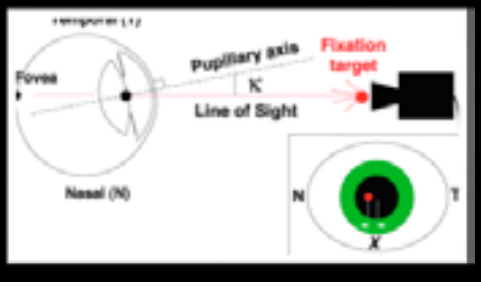


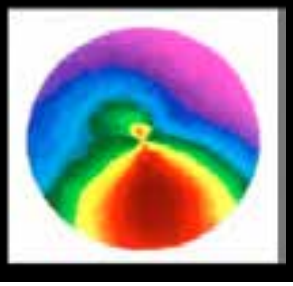
Normal Eyes are more commonly

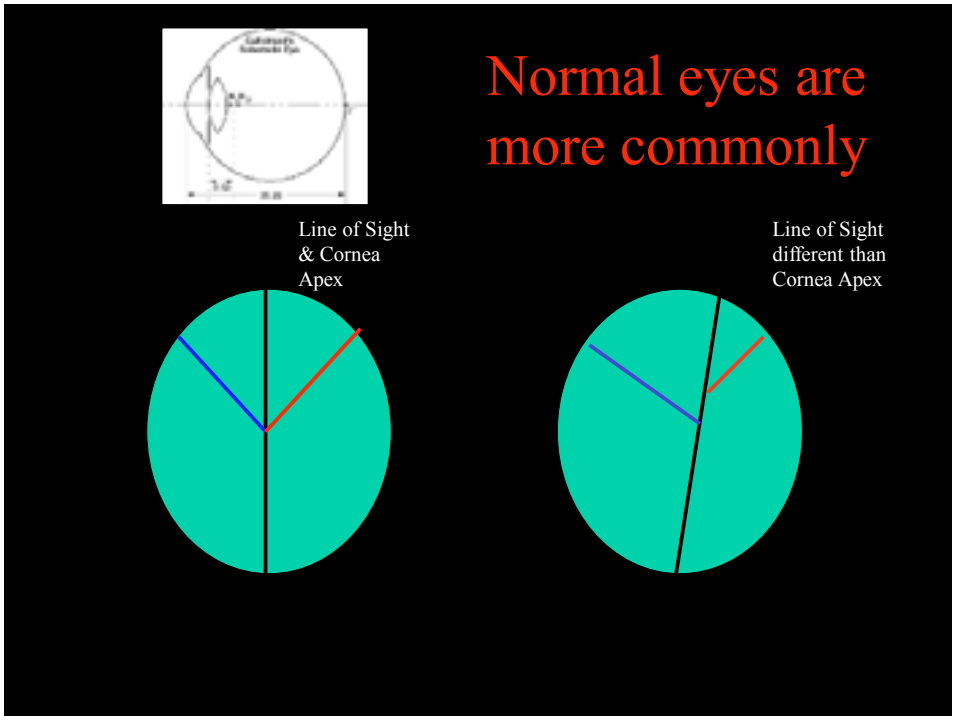


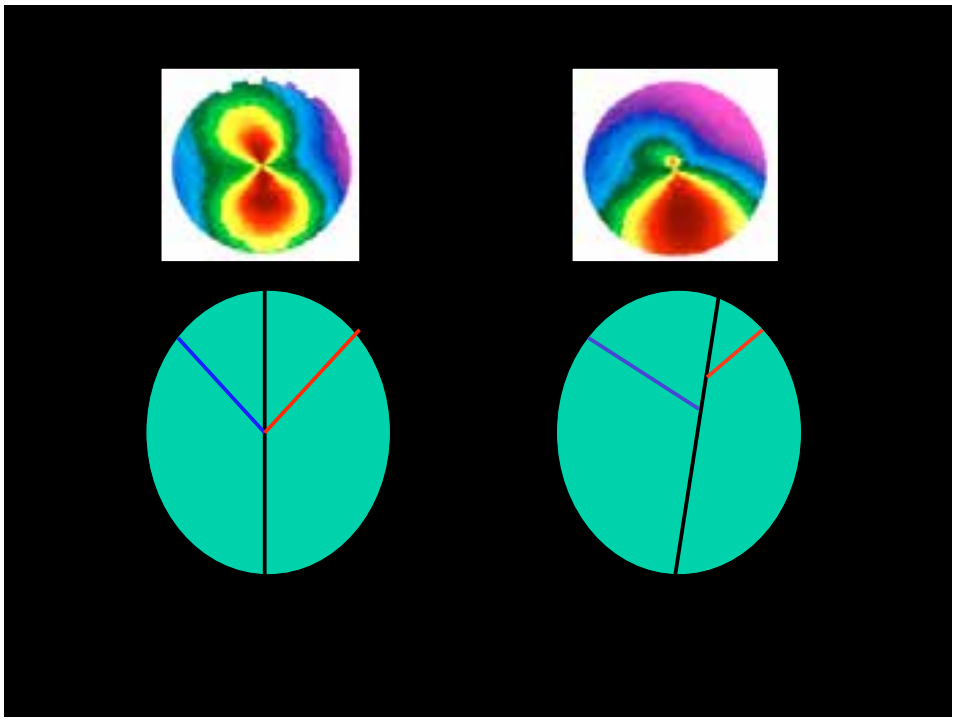
Angle Kappa

- Angle between the pupillary and visual axis
  - Displacement of up at 5 degrees is physiologic and considered normal
  - A "*normal*" angle kappa is enough to produce an "*abnormal*" curvature map

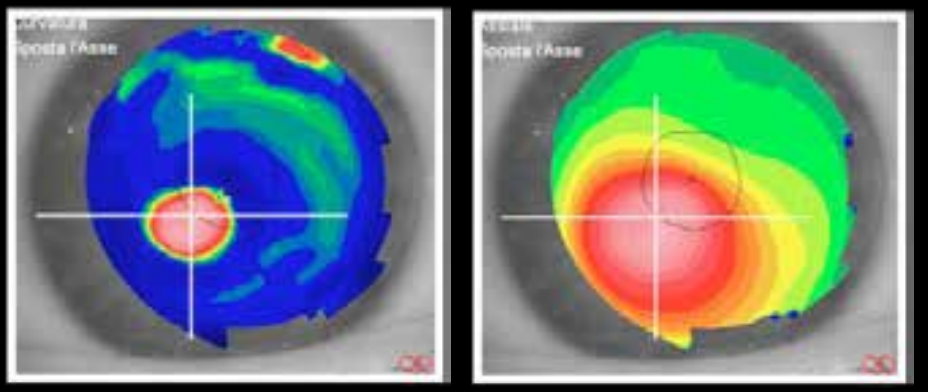





Normal eyes are more commonly
Line of Sight & Cornea Apex
Line of Sight different than Cornea Apex

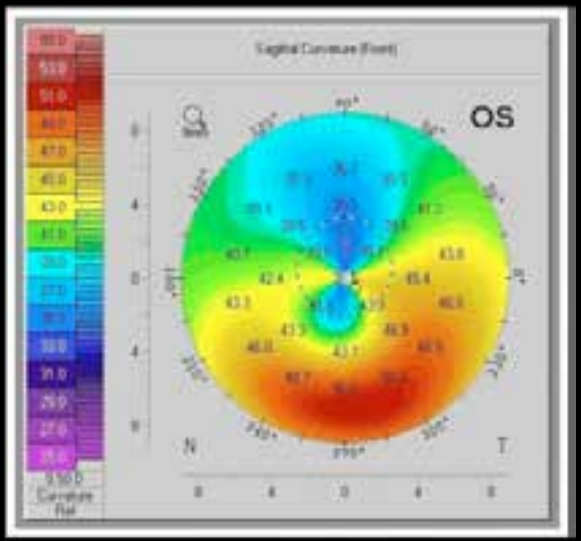


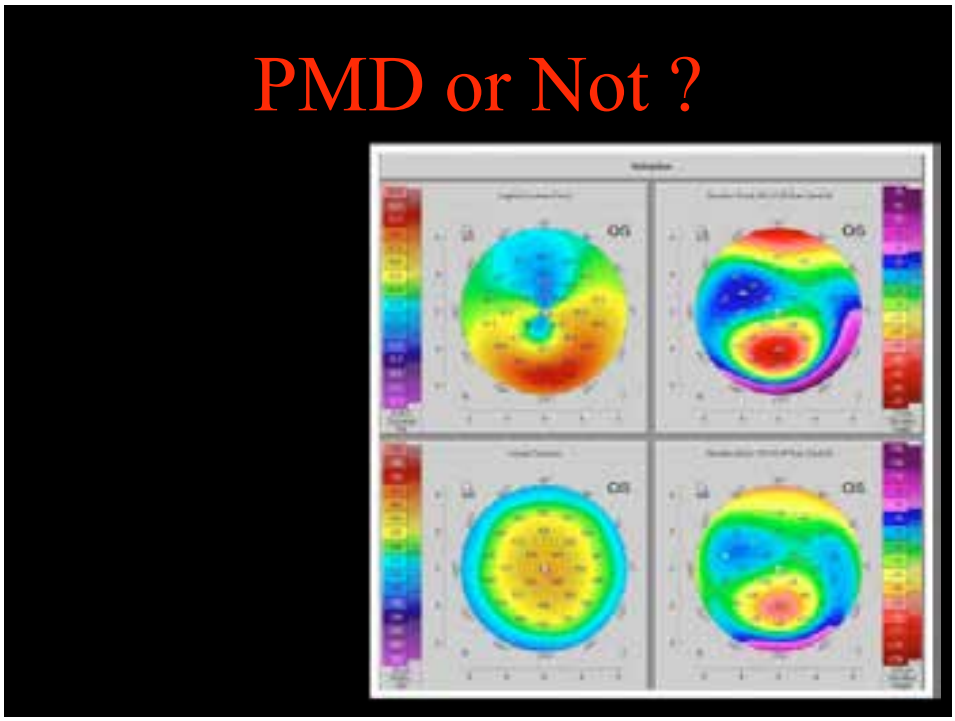
When the Apex is De-Centered the Axial Map Misplaces Cone Location and Underestimates Magnitude.

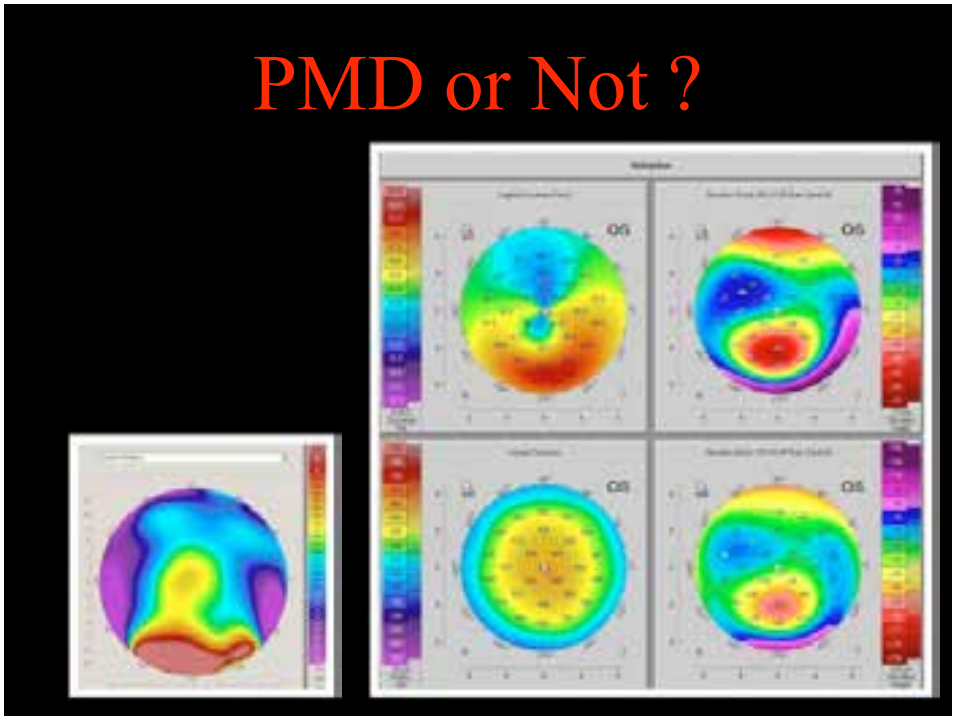


by: Renzo Mattioli PhD

PMD or Not ?



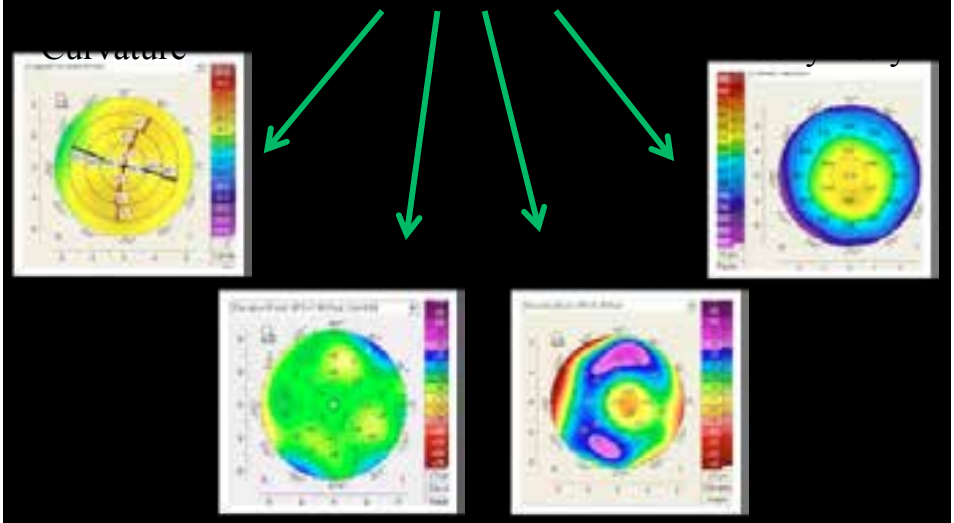

PMD or Not ?

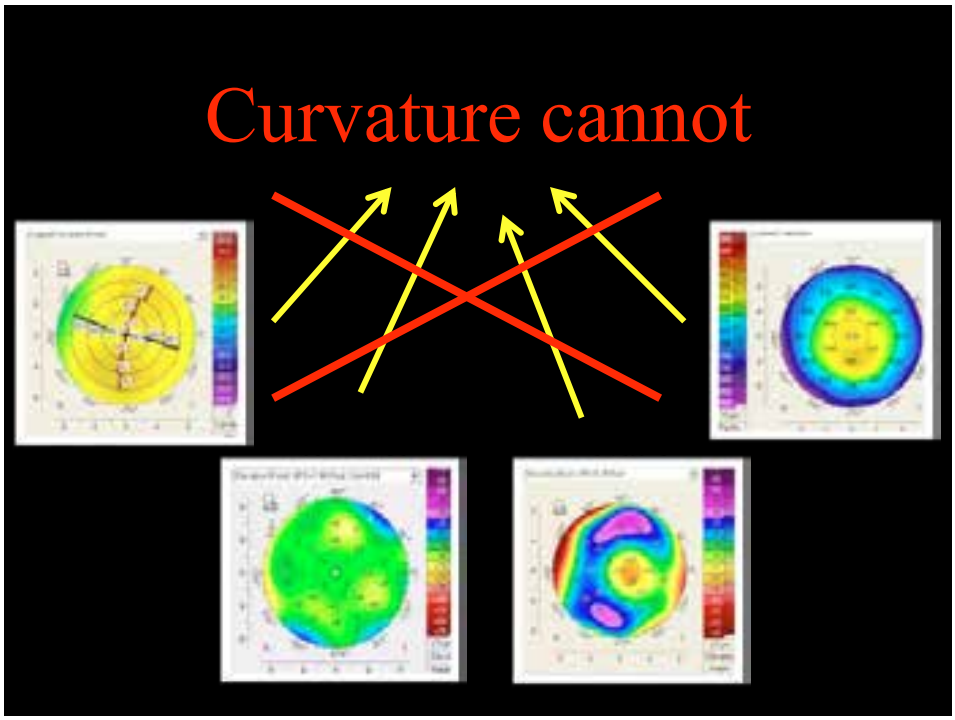

PMD or Not ?

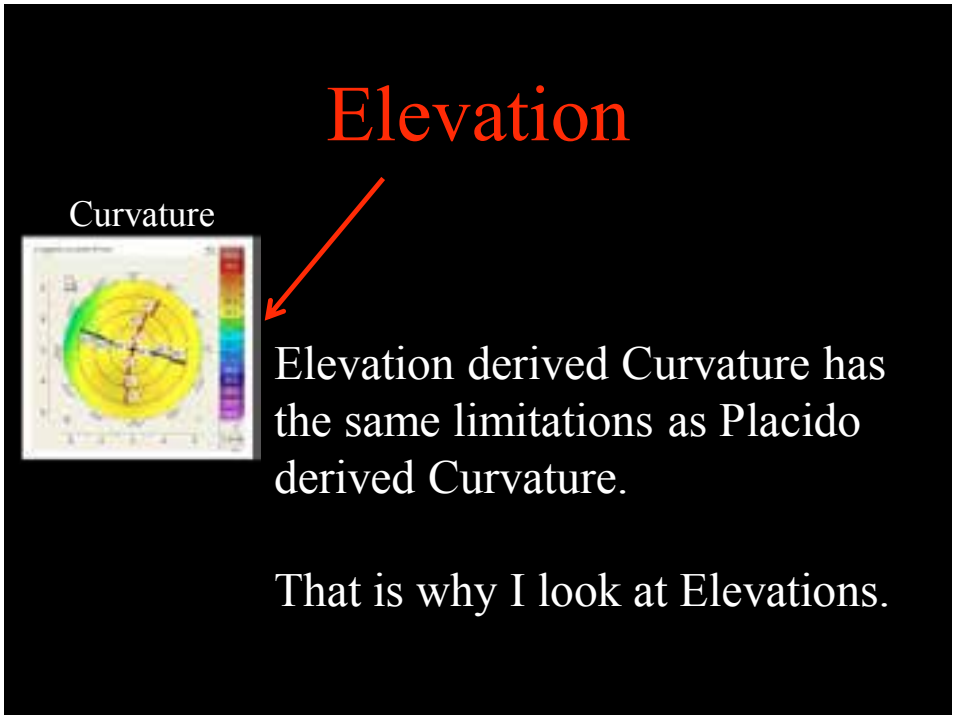
Elevation Data

- Elevation represents TRUE shape
  - It is independent of axis, orientation or positioning.
- All subsequent maps (curvature) can be derived from ACCURATE elevation data
  - Curvature is the second derivative of elevation

Elevation can derive




Curvature cannot

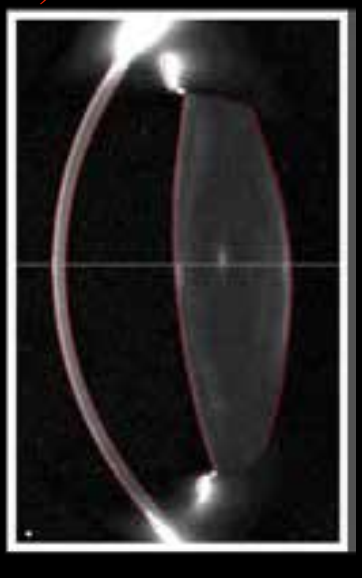

Elevation
Curvature
Elevation derived Curvature has the same limitations as Placido derived Curvature.
That is why I look at Elevations.

Tomo/Topographic Comparison

- Tomography
  - Anterior & Posterior Surfaces
  - Full Pachymetric Map
  - Limbus to limbus coverage
  - Less susceptible to false positives
- Placido Based
  - Anterior ONLY
  - No Measurement of Thinning
  - Coverage limited to < 9.0 mm
  - High incidence of False Positives

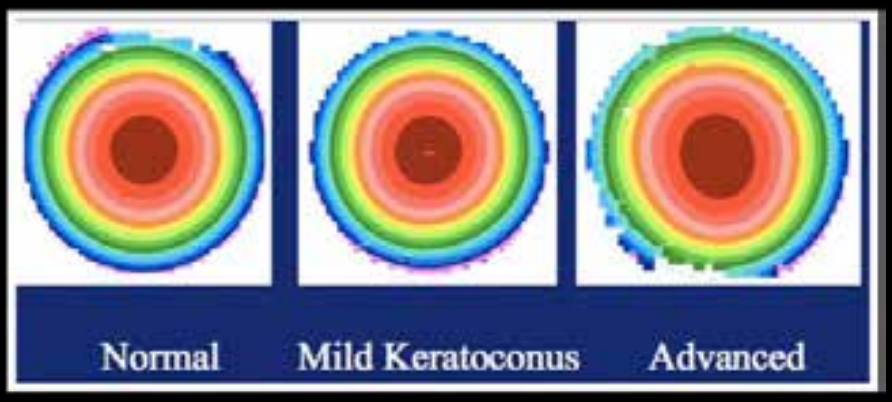
Scheimpflug Imaging (Elevation) (OCT similar)

- Scheimpflug Imaging
  - Image edge detection
    - Anterior Cornea
    - Posterior Cornea
    - Anterior Lens
    - Posterior Lens
    - Anterior Iris



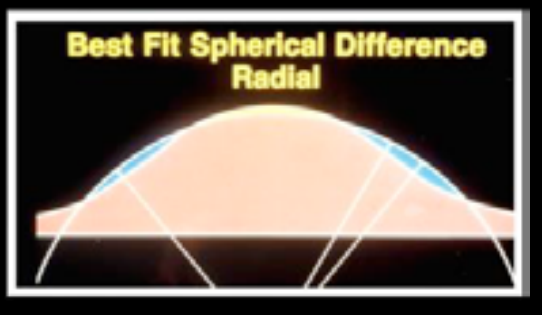
How is Elevation Data Displayed

- "RAW" elevation maps are rarely used



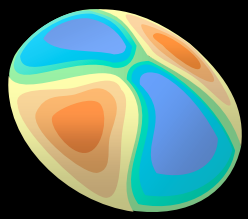
How is Elevation Data Displayed

- The most common method is to compare (*amplify*) the raw elevation data against some common shape
  - The most common shape used is the Best Fit Sphere (BFS)
    - Other shapes can also be used
      - Ellipse
      - Toric Ellipsoid

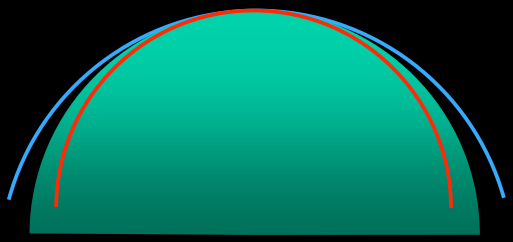


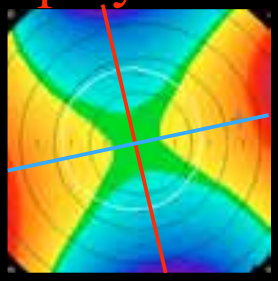
Why use a Best-Fit-Sphere ?

- A BFS (Sphere) conveys the most intuitive *qualitative* information about corneal shape
  - The differences are only qualitative as all maps are generated from the same raw elevation data.

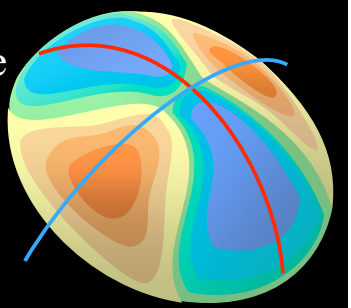


How Elevation is Displayed

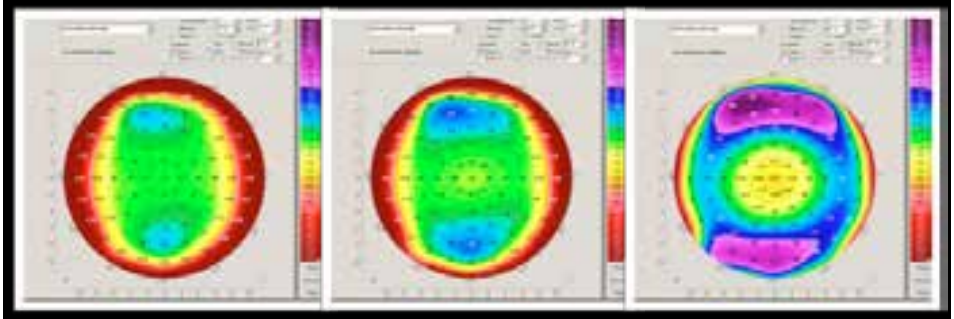




- The steep profile falls below the reference surface.
- The flat profile rises above the reference surface.

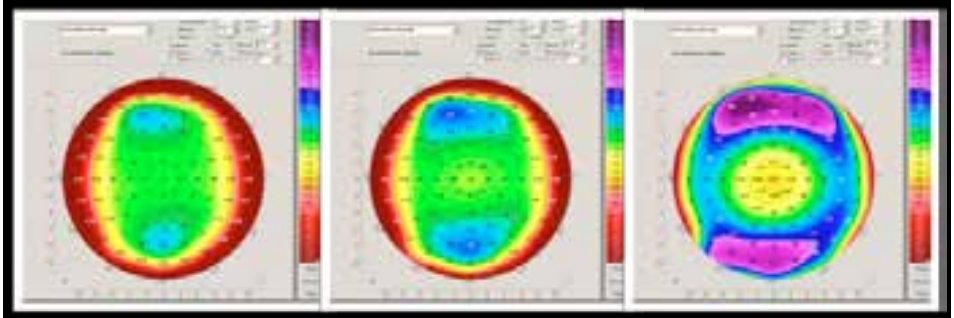


Effect of BFS Diameter on the Appearance of the Elevation map



Diameter = 7.0 mm | Diameter = 9.0 mm | Diameter = 11.94 mm

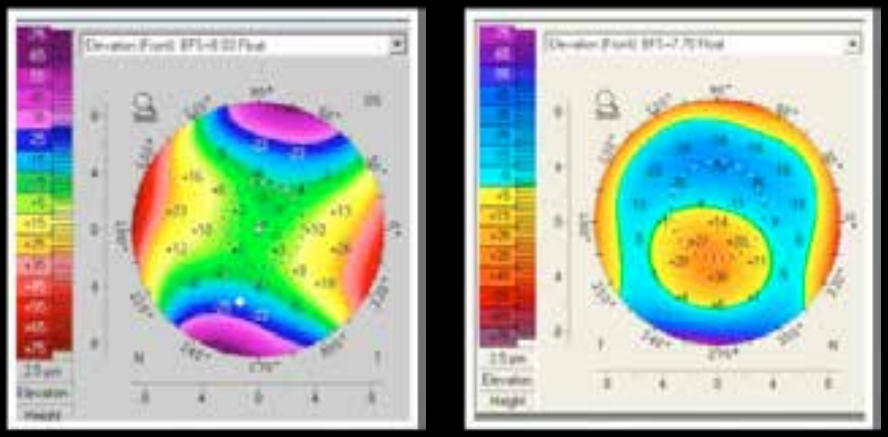
Effect of BFS Diameter on the Appearance of the Elevation map



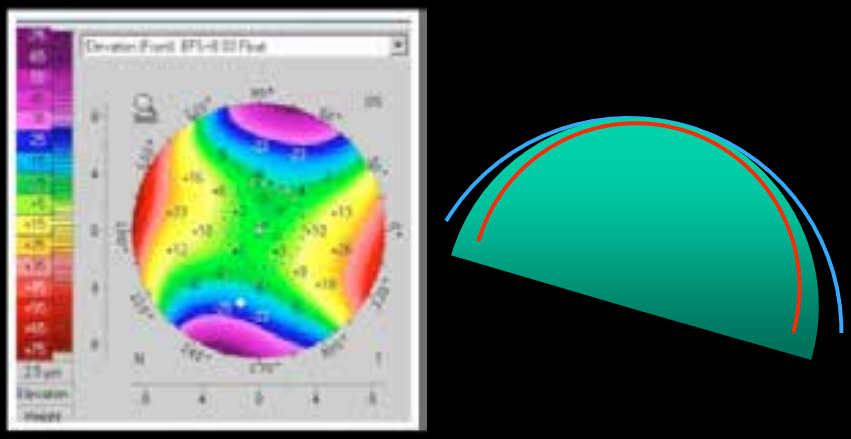
Diameter = 7.0 mm | Diameter = 9.0 mm | Diameter = 11.94 mm

Most systems default to using a central optical zone between 8.0 – 9.0 mm to define the BFS

Astigmatism vs. Keratoconus

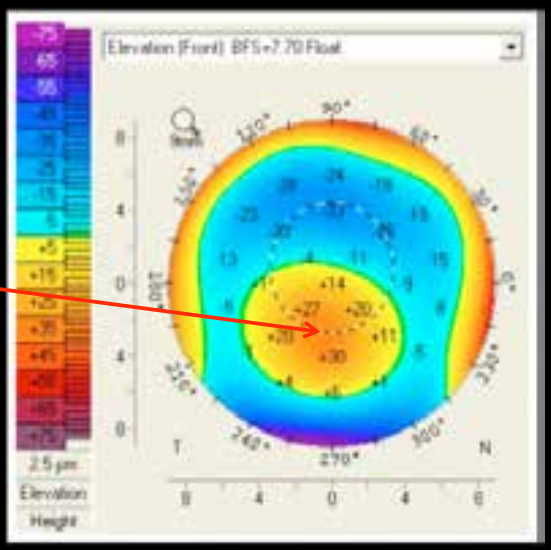


Astigmatism



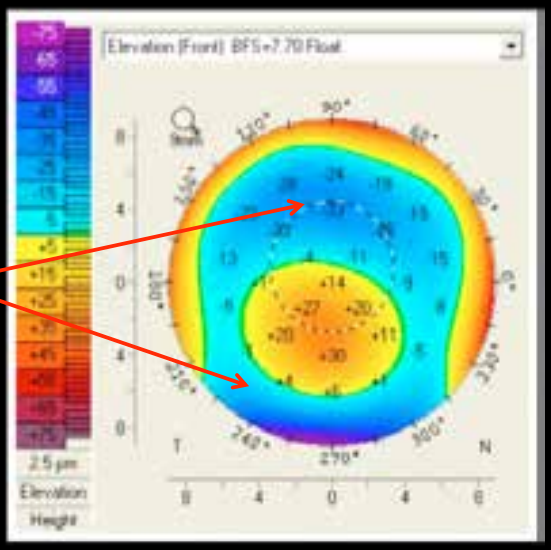
Keratoconus

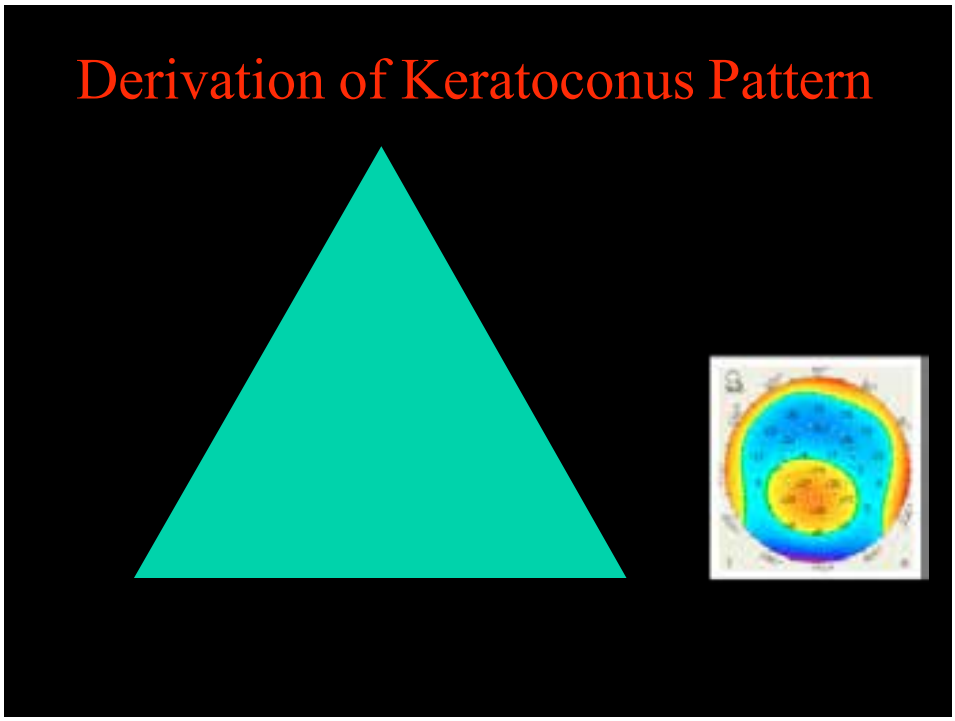
We look for central or para-central *"Positive Islands of Elevation"*

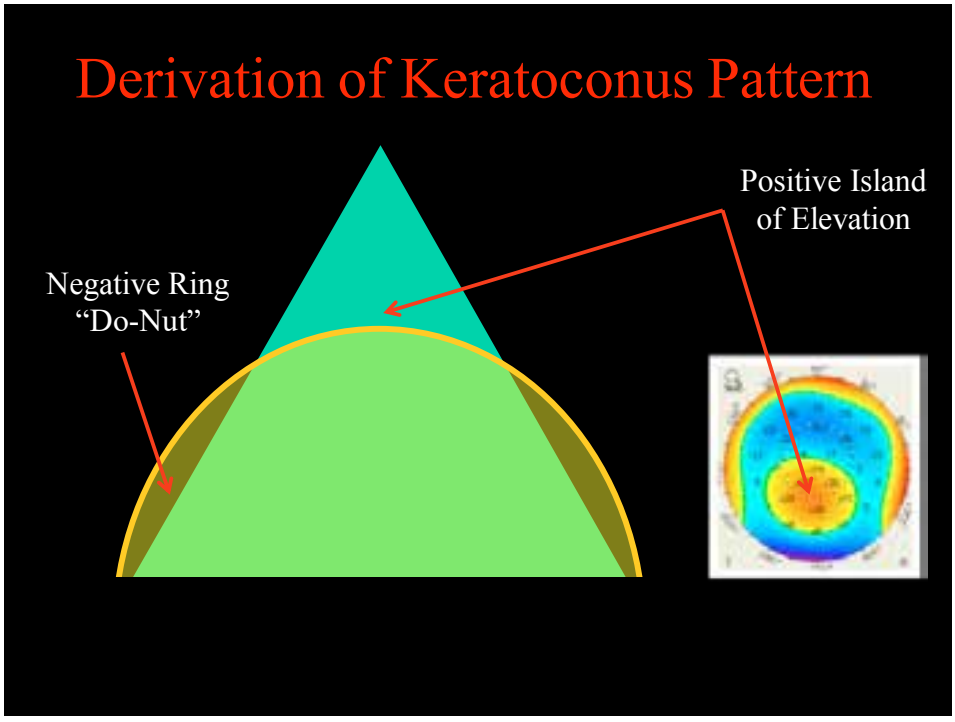


Keratoconus

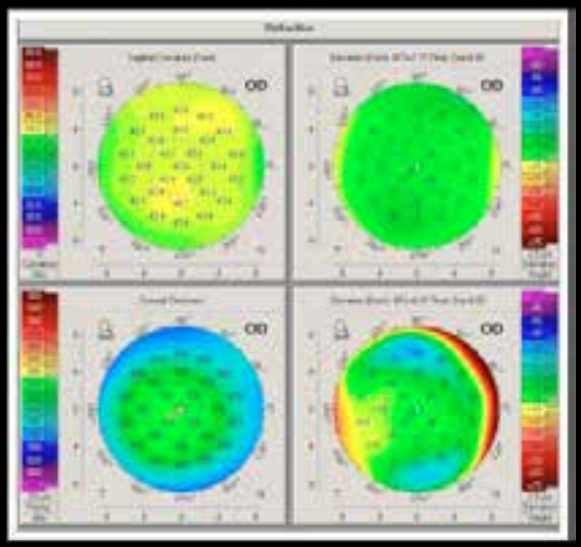
How would you describe the blue "ring" ??



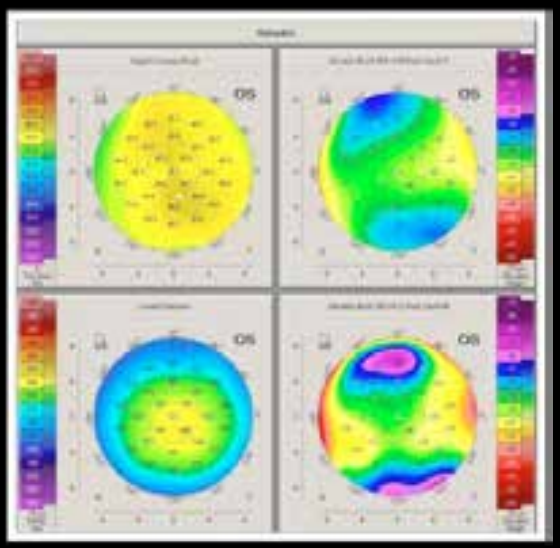

Derivation of Keratoconus Pattern


Derivation of Keratoconus Pattern
Positive Island of Elevation
Negative Ring "Do-Nut"

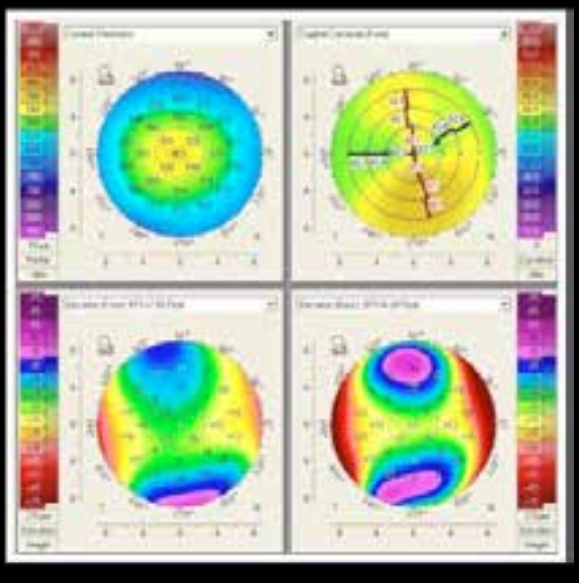
Normal Map



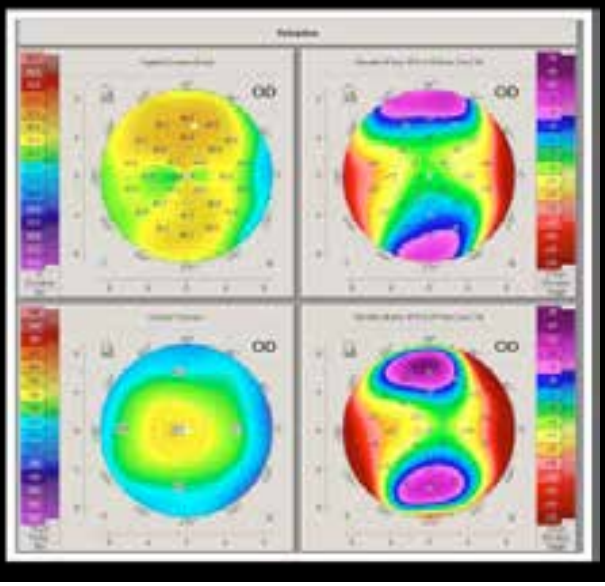
Mild Astigmatism



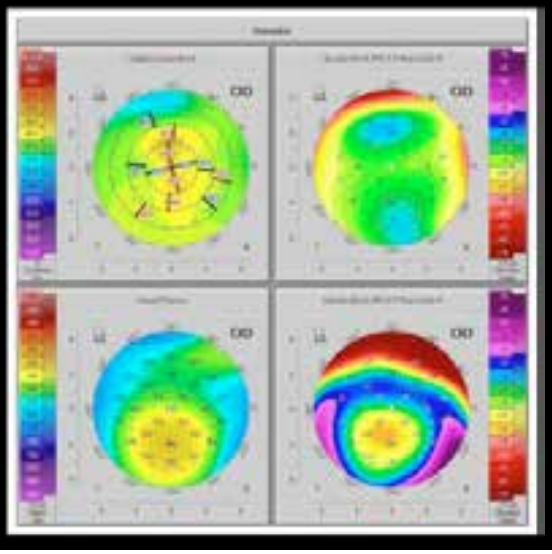
Displaced Apex



Displaced Apex

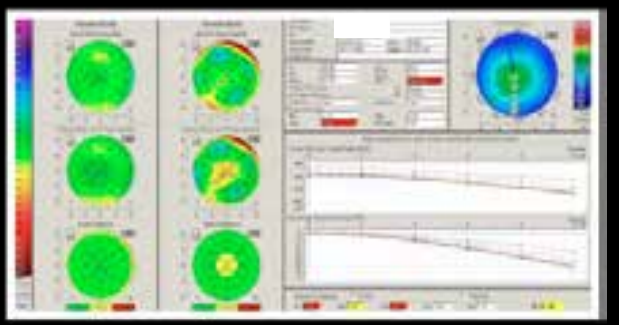


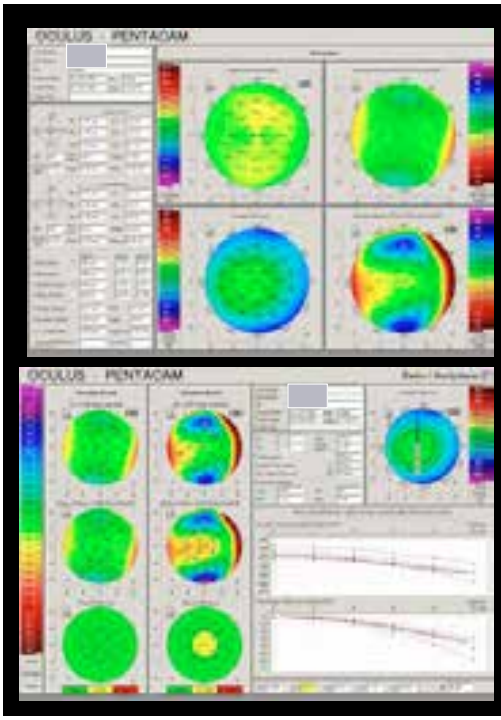
Isolated Posterior & Pachymetric Changes



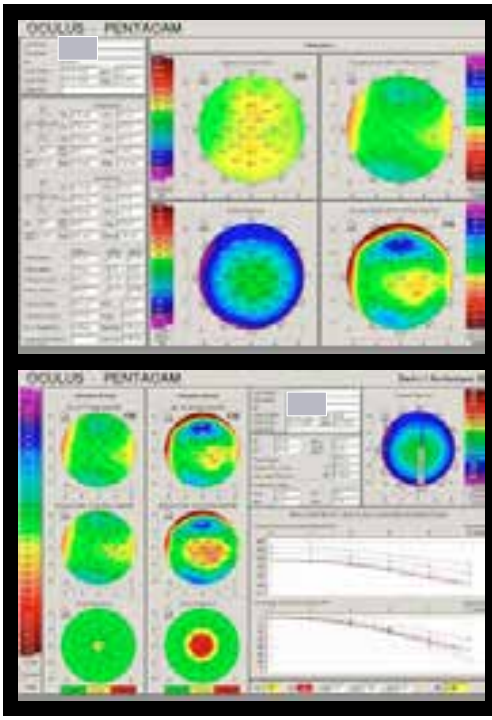
Belin/Ambrosio III

- Pre-Op Refractive Screening
  - Final "D" based on a regression analsysis
    - Change in Anterior & Posterior Elevation
    - Anterior & Posterior Elevation at thinnest point
    - Progression Index
    - Thinnest Pach
    - Kmax
    - ARTmax

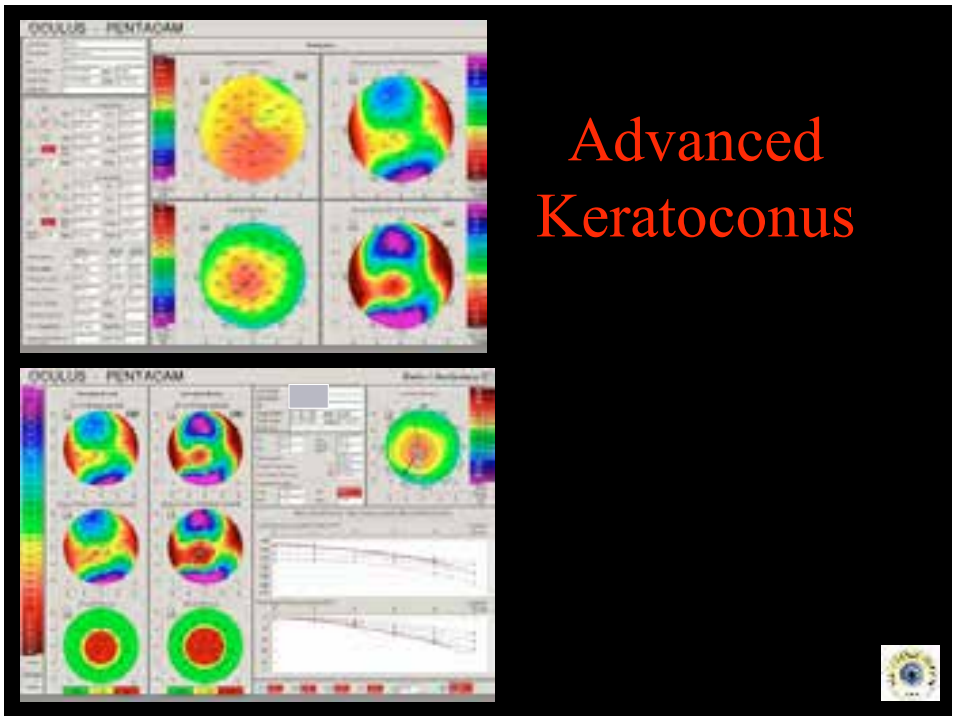


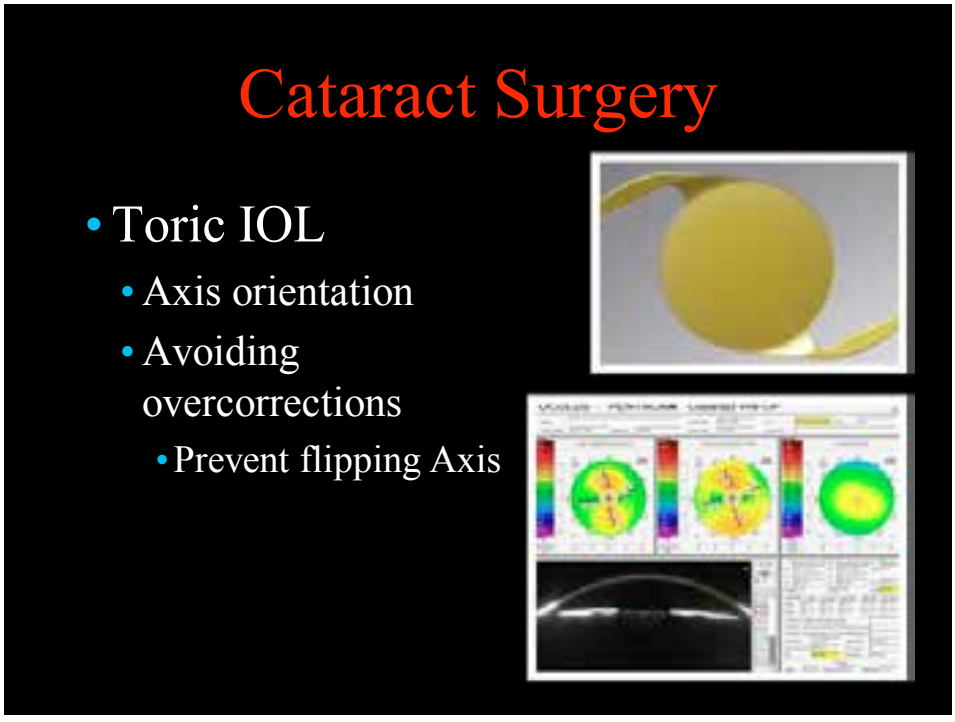


Borderline
Posterior
Elevation



Significant
Posterior
Elevation
Changes

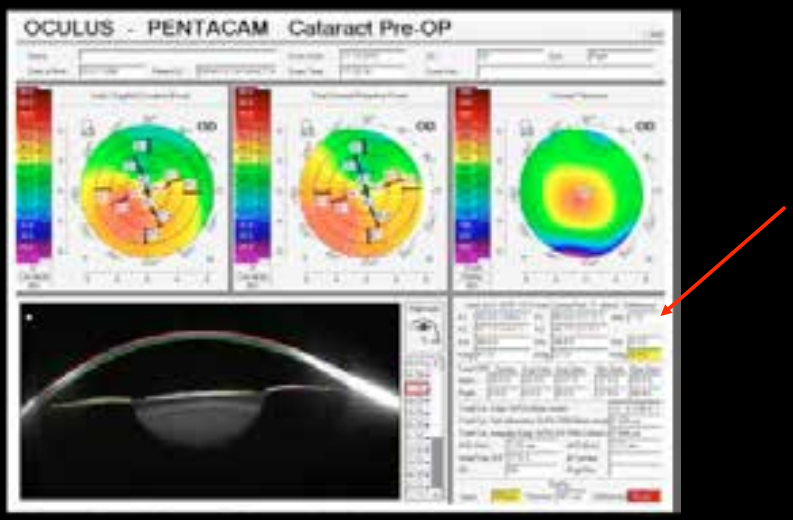

OCULUS PENTACAM
OCULUS PENTACAM
Advanced
Keratoconus


Cataract Surgery
• Toric IOL
• Axis orientation
• Avoiding overcorrections
• Prevent flipping Axis

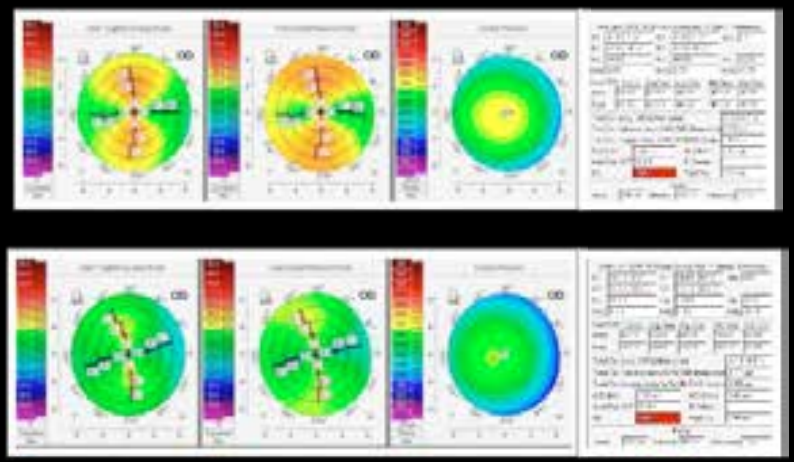
Magnitude vs Axis

- Most Toric IOL formulas attempt to compensate for not measuring the Posterior Cornea Surface
  - Unless there is a very large difference between the Anterior Corneal vs the Total Corneal Power Astigmatism I use Anterior Power
  - The Formulas cannot compensate for Axis Error and I use the Axis determined by the Total Corneal Power.

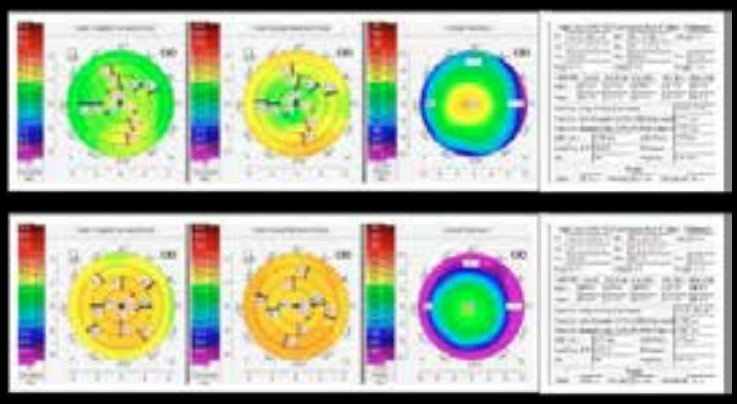
Cataract Pre-Op Display



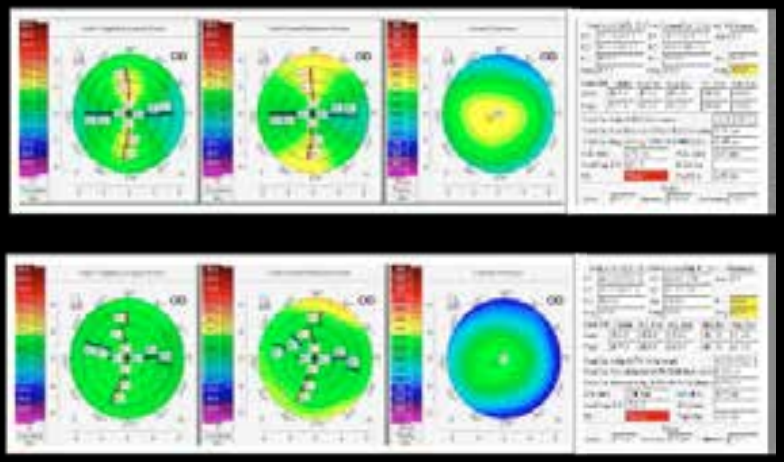
High Cylinder and Axis Match



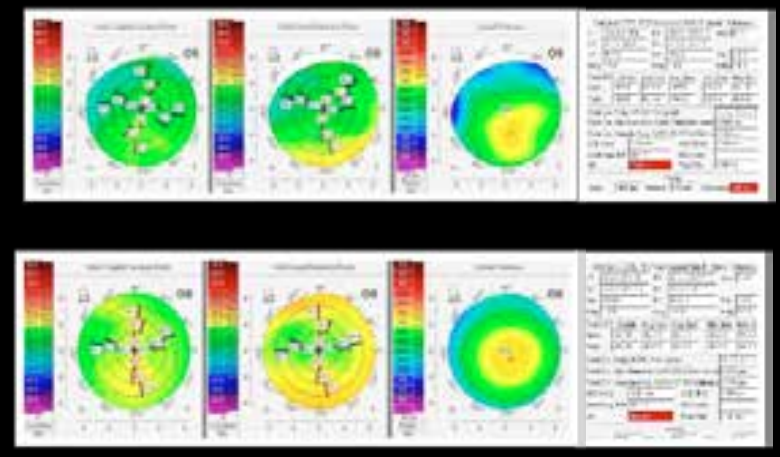
Axis Change but Low Magnitude



Clinically Significant Magnitude Change



Clinically Significant Axis Change

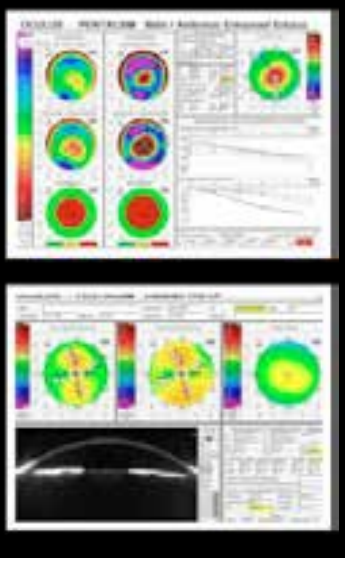


Clinically Significant Axis Change

- Axis alignment
  - 10% loss of effect with 3 degree misalignment
  - 33% loss with 10 degree misalignment
  - 50% loss with 15 degree misalignment
  - Increase in cylinder with 30 degree misalignment

Tomography

- Applications
  - Refractive Screening
  - Post Refractive
  - Pre-op Cataract
    - Toric IOL
    - Multi-focal IOL
  - Keratoconus
    - CXL
- Do you need one
  - For anterior segment surgeon
    - YES



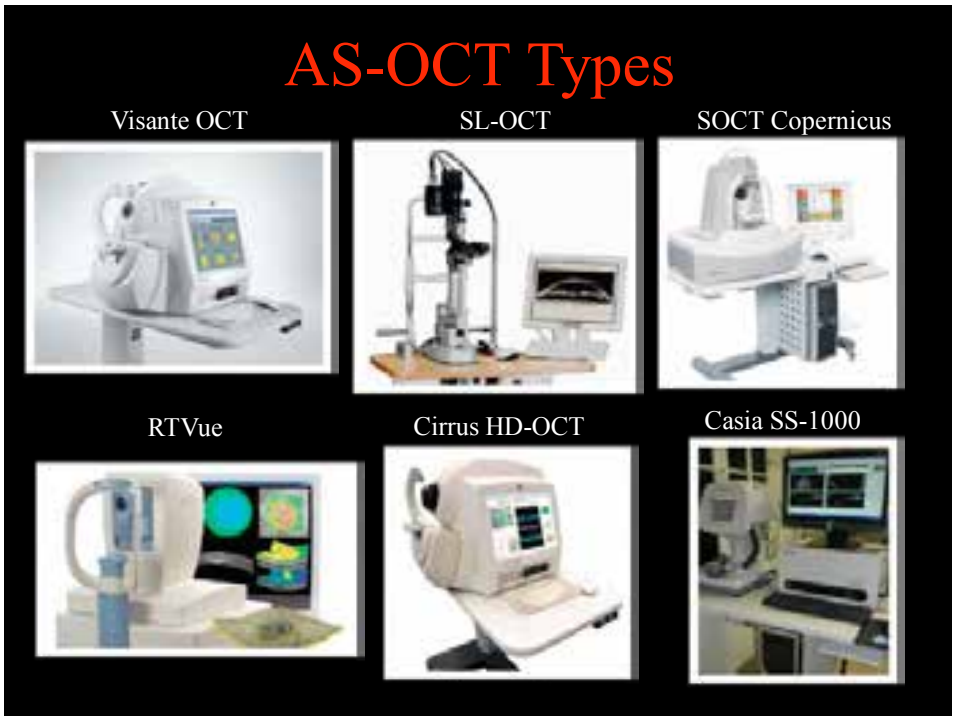
Topics

- Pachymetry
- Specular
- Confocal
- Topography
- Tomography
- OCT




Optical Coherence Tomography

- Non-contact, non-invasive, three-dimensional imaging technique used to measure the retina and anterior segment using reflected light
  - Similar to ultrasound except using non-visible (near infrared) light vs sound to create 3-D reconstruction
  - Higher spatial resolution than ultrasound
    - But, limited by dense opacities
      - E.g. cannot image CB tumors

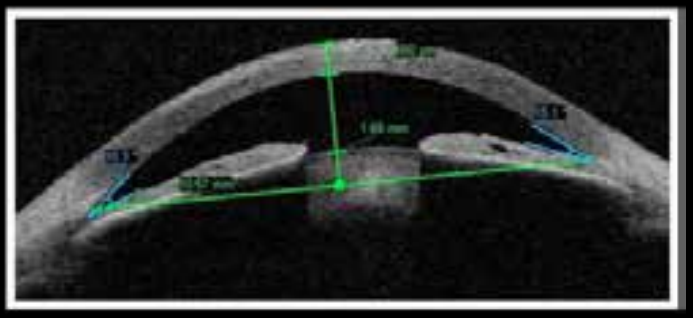


TD-OCT *vs* FD-OCT *vs* SS-OCT

	TD-OCT (Visante)	FD-OCT (RTVue)	SS-OCT (Casia)
Wavelength	1310 nm	830 nm	1310 nm
Scanning speed	2000 A-scans/sec	26 000 A-scans/sec	30 000 A-scans/sec
Scanned area	16x6 mm lines with 256 scans		16x16 mm with 256 B-scans
Penetration depth	6 mm	5 mm	6 mm
Scanning time	0.125 sec	0.04 sec per B-scan	0.0125 sec per B-scan
Optical resolution	18 - 60 µm	5 µm	10 - 40 µm

Optical Coherence Tomography

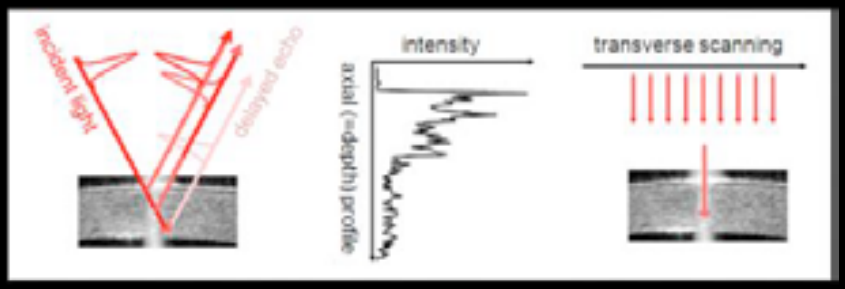
- Use is in Glaucoma, where OCT offers views of the angle / iris in-vivo without deformation of the cornea (non-contact)
  - Superior to Scheimpflug for angle imaging



OCT Gonioscopy

Swept source OCT

- also known as optical frequency domain imaging
- a narrowband tunable laser varies the wavelength

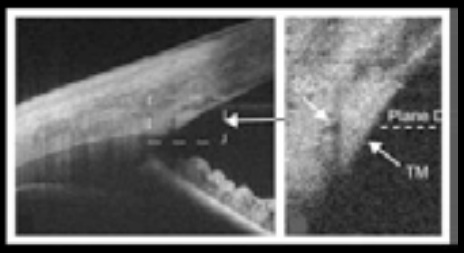


Specifications of Ant SS-OCT

- Swept laser source operating at λ=1310 nm
  - highly absorbed by water (safe)
  - 6x deeper penetration
- Provide 30 000 A-scans per second
- Achieve an axial resolution of $\leq$ 10 µm and a transverse resolution of $\leq$ 30 µm
- Image acquistion time of 0.3-4.8 seconds
- Deeper scleral penetration and more precise imaging of the irido-corneal angle structures

Ultra-high resolution OCT

- Swept-source OCT at 1050 nm
- 3 µm resolution
- 100 000 to 400 000 axial scans per second
- visualization of Schlemm's canal and the trabecular meshwork through the sclera



- Surface tumor evaluation

Swept source OCT vs. Scheimpflug

	Casia SS-1000		Pentacam HR
Scan type	Anterior segment	Corneal map	Scheimpflug
Light source	1310 nm tunable laser		475 nm UV-free blue light
Number of scans	512 per A/B-scan 128 per B/C-scan	512 per A/B-scan 16 per B/C-scan	25, 50 or 100
Acquisition time	0.2-4.8 sec	0.3 sec	2 sec
Penetration depth	6 mm	4 mm	14 mm

Optical Coherence Tomography

- Non-glaucoma applications in the anterior segment are similar to Scheimpflug
  - OCT a better IMAGING modality than Scheimpflug
    - Intraoperative OCT
      - Cannot image behind pigmented structures
  - Scheimpflug a better MEASURING modality than OCT
    - OCT more susceptible to motion artifact

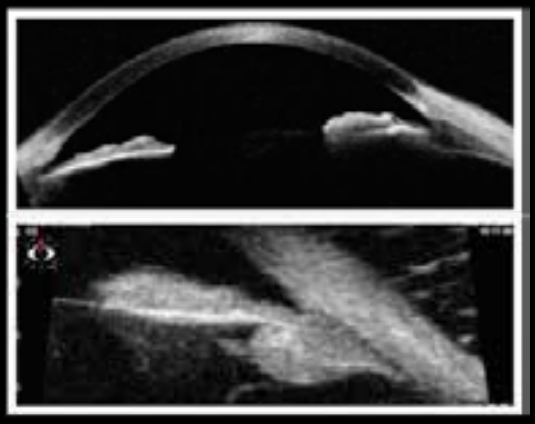


Scheimpflug vs OCT Imaging

- Scheimpflug cannot see behind opaque object
  - Iris, Limbus
- Scheimpflug does a better job at 3-D reconstruction of entire anterior segment
- OCT does a better job at looking at the angle, flap measurements and intra-operative
- UBM can image behind the iris
  - UBM cannot be used on a regular basis
    - Very time consuming and not useful for routine screening

Optical Coherence Tomography

- e.g. Cannot image CB tumors
  - UBM vs OCT



OCT

- Applications
  - Similar to Scheimpflug
    - More limited for refractive screening
  - DMEK
    - Intraoperative useful
  - Glaucoma evaluation
  - Surface tumor evaluation
    - Ultra high frequency
- Do you need one
  - YES if you don't have Scheimpflug
  - YES depending on practice needs

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Tucson, Arizona
USA
Email: mwbelin@aol.com

MCQ answers page 97

1. **Answer: b**

2. **Answer: b**

3. **Answer: d**

MCQ's

1. A keratoconus is suspected. Which factors may contribute to its pathogenesis?

a. Diabetes mellitus
b. Eye rubbing
c. Smoking
d. Prematurity

2. Which of the following topographic criteria suggests a keratoconus?

a. Inferior steepening
b. Keratometric value < 45 diopters
c. Corneal enantiomorphism
d. Symmetric bowtie

3. About contact lens fitting in keratoconus:

a. The main goal of fitting contact lenses is to slow down keratoconus progression
b. Corneal topography helps in getting a successful fitting with rigid gas permeable lens
c. An ideal fit will show a central touch
d. Contact lens fitting is contraindicated after corneal hydrops

Keratoconus:
What we have accomplished and what is still left to do

First and foremost it is important to mention that recent advances in keratoconus have been made possible thanks to a better knowledge of the innermost structure of this mysterious dystrophy. With this aim in view, the histological works, but also the combined advances of genetic and molecular biology have really brought about the "modern" keratoconus era.

The advance of para clinical exploration, have allowed to make more and more precise detection of its "forme fruste", which is a real nightmare for the refractive surgeon. Among these, most importantly the topography of the cornea, but also more recent technologies such as aberrometry, biomechanics, will undoubtedly cast a new light on this difficult diagnosis to the point of abnormality.

The treatment of this disease – a disease which nowadays remains the first indicated cause for corneal transplantation among young adults – is at the beginning of a major turning point in its evolution. Contactology has advanced, with increasingly better fitting lenses that can be adapted to the unusual curvatures of keratoconus. When rigid gaz permeable lenses are no longer tolerated, hybrid and scleral lenses offer remarkable quality of vision and comfort. It has allowed to postpone surgery still further for as long as possible. This surgery, which accouts for approximately 10% of these patients, is often dreaded by our young patients.

The surgical technique of transplantation has considerably evolved, thanks to the rapid expansion of lamellar transplantations which today allow to keep the patient's endothelium and thus lessen the risk of rejection as much as possible. New preserving strategies are developing, such as intracorneal rings and corneal collagen cross linking which is becoming a precious tool in the fight against this dystrophy.

Keratoconus is now an ailment which is the target of many new kinds of diagnostic and therapeutic techniques, which create wonderful prospects for all our patients. However, keratoconus remains a mysterious disease, and the goal in the future will be to better understand the pathophysiology of this disease in order to propose an etiological treatment.

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France
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MCQ answers page 158

1. **Answer: b**

2. **Answer: a**

3. **Answer: b**

MCQ's

1. A corneal dystrophy is caused by

a. Environmental effects such as UVA and diet
b. Ageing and degeneration of the cornea
c. A abnormal change in the genetic code of the individual
d. Premature birth

2. Which of the following can be associated with secondary glaucoma

a. Granular corneal dystrophy
b. Posterior polymorphous dystrophy
c. Reis-Buckler dystrophy
d. All of the above

3. Which corneal dystrophy primarily affects the corneal epithelium

a. Fuchs corneal dystrophy
b. Lattice corneal dystrophy
c. Amiodarone vortex keratopathy
d. Meesmann dystrophy

UCL

The impact of genetics on the clinical management of patients with monogenic corneal diseases

2017

Stephen Tuft
Moorfields Eye Hospital

FIGHT FOR SIGHT
The Eye Research Charity

moorfields eye charity

Moorfields Eye Hospital NHS
NHS Foundation Trust

UCL

What has been the impact?

- Revision of classification and identified gaps in our knowledge
- Insight into disease mechanisms
- Genetic diagnosis
- Identify masquerade (phenocopies) cases that require medical management

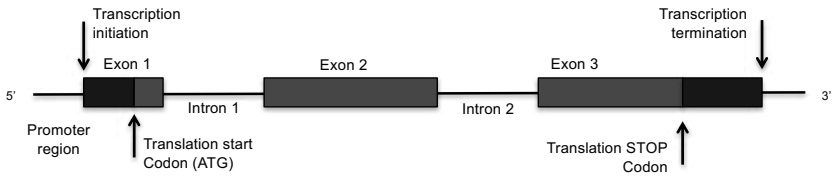
IC3D Classification of Corneal Dystrophies—Edition 2

(Cornea **2015;34:117–159)**

UCL

Monogenic corneal disease

- A single defective gene
- Dominant, recessive or x-linked
- Can be many different mutations in a gene (e.g. CHST6 and TGFBI)
- Site of mutation in a gene can affect the phenotype



UCL

Monogenic corneal disease

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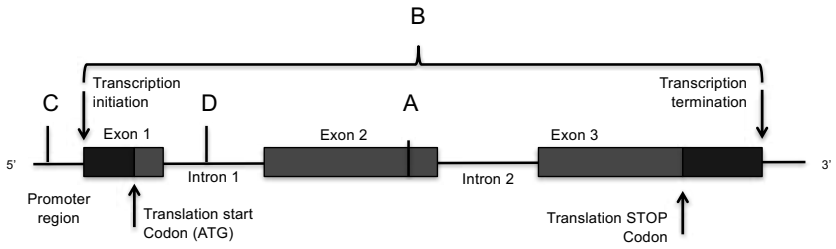
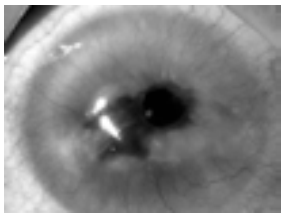


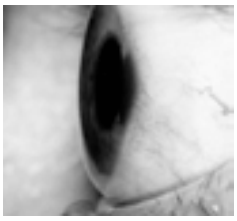
UCL

Types of monogenic disease

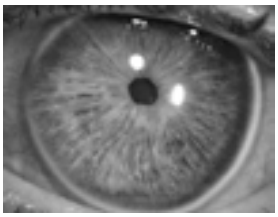
- Developmental disorder
- Abnormal protein products
- Functional disease



Aniridia



Cornea plana

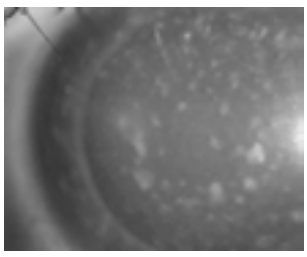


Megalocornea

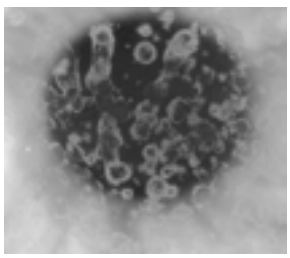
UCL

Types of monogenic disease

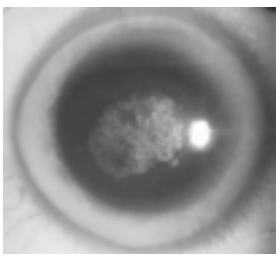
- Developmental disorder
- Abnormal protein products
- Functional disease



Macular



Granular Type II

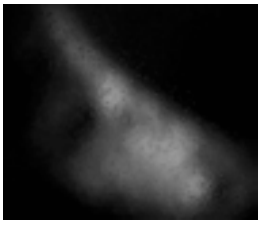


Schnyder

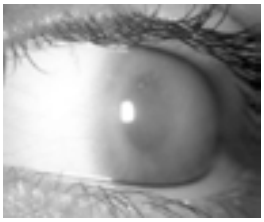
UCL

Types of monogenic disease

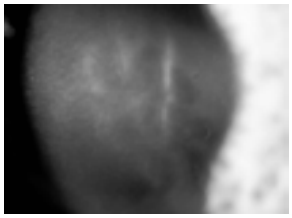
- Developmental disorder
- Abnormal protein products
- Functional disease



Meesmann



CHED Type II

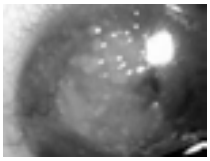


Fuchs

UCL

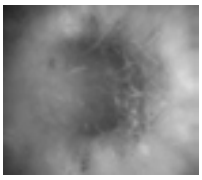
Classification

- Anterior layer
- Stroma
- Posterior layer



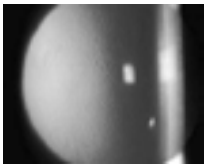
Gelatinous

A



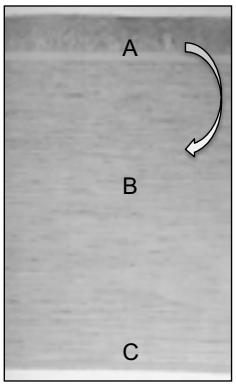
Lattice

B



Fuchs

C



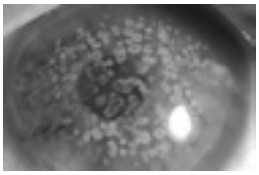
UCL

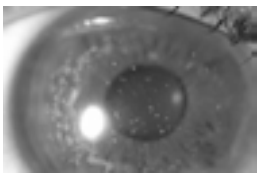
Management

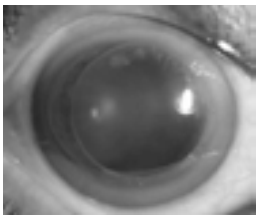
- Observation
- Ablate (PTK)
- Surgical excision (keratoplasty)

'Problem solved'
'Too rare to research'

Femto-assisted lamellar keratoplasty (FALK)



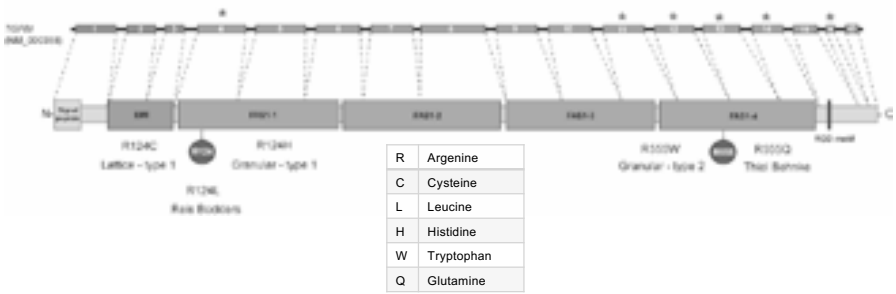




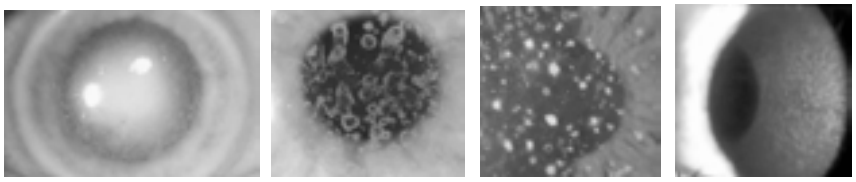
UCL

TGFBI – one gene gives different phenotypes

'mutation hot spots'



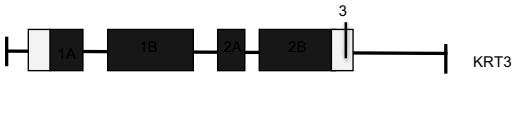
R	Argenine
C	Cysteine
L	Leucine
H	Histidine
W	Tryptophan
Q	Glutamine

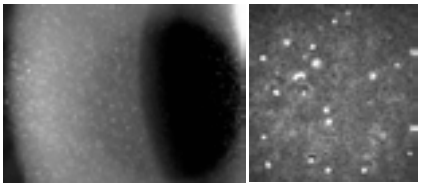


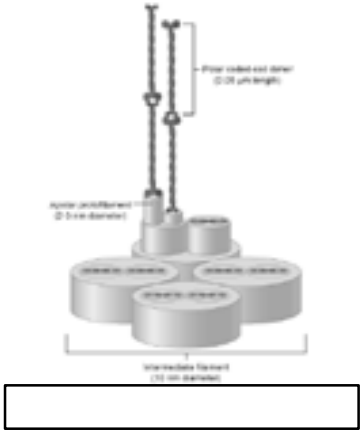
UCL

Meesmann dystrophy – different genes

= KRT helix initiation/termination domain







http://www.invoiceconnection.com/steve/phenotypic_Plush.html

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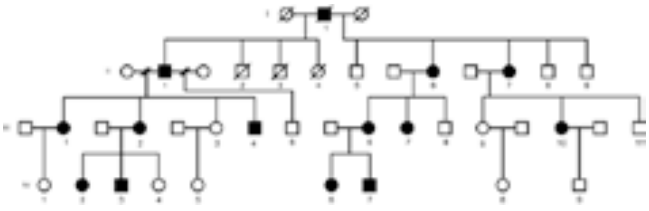
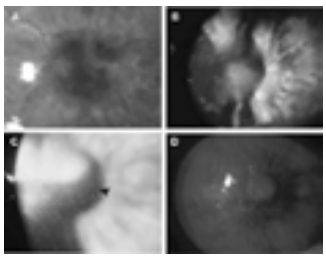
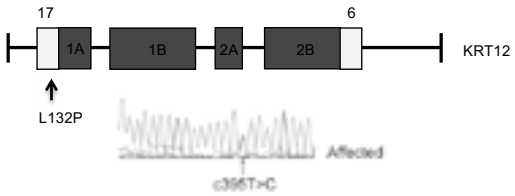
Meesmann dystrophy – different phenotypes





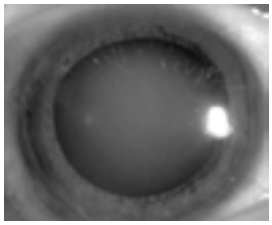


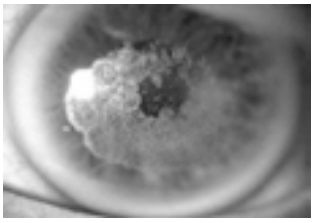
Amblyopia and blindness

UCL

Phenotypic confusion
Schnyder dystrophy (UBIAD1)

Description as new dystrophy





Central Discoid Corneal Dystrophy

Anthony J. Aldave, M.D., Deepak P. Edward, M.D., Anna J. Park, M.D., Irving M. Raber, M.D., and Ralph C. Eagle, Jr., M.D.

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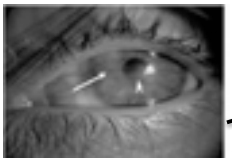
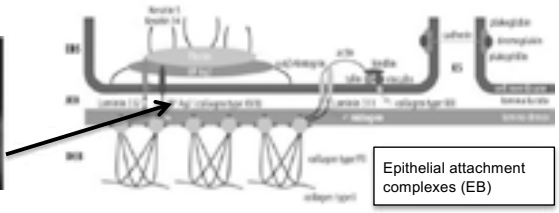
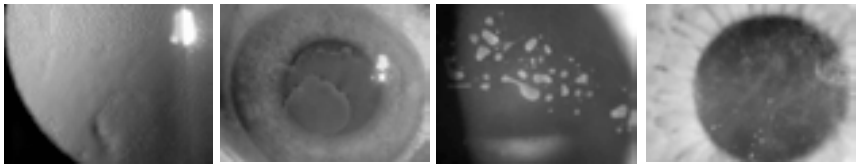
Epithelial Recurrent Erosion Dystrophy
(ERED – Col17a1)





Jonsson F *et al.* 2015

http://dx.doi.org/10.1590/S0365-05962013000200001



A reappraisal of the recurrent erosion/EBMD diseases is warranted

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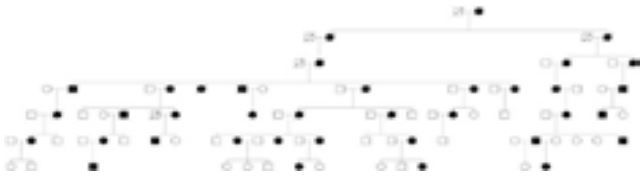
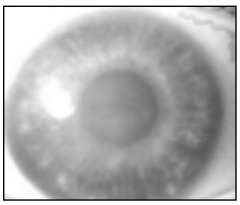
Posterior polymorphous dystrophy 1/CHED1
linking to Chr20p

Corneal dystrophy is a 'trivial disease'





All living individuals have had keratoplasty/keratoprosthesis and all severely visually impaired

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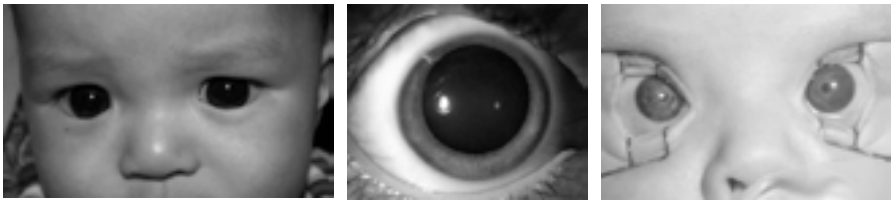
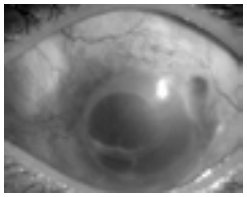
Mutations in *CHRDL1* Cause X-linked Megalocornea (MGC1)

Does this child with large corneal diameters have congenital glaucoma?





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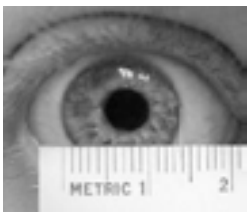
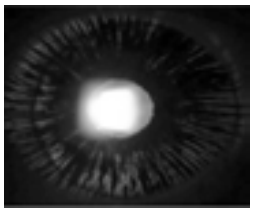
Identifying the genetic cause of X-linked Megalocornea

- **Corneal diameter ≥ 13 mm**
- **Reduced central corneal thickness** (average CCT=418 µm; n=30)
- **Very deep anterior chamber**
- No increase in intraocular pressure
- No breaks in Descemet's membrane
- No corneal edema






Webb TR *et al.* 2012

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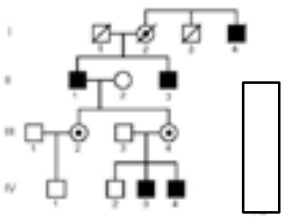
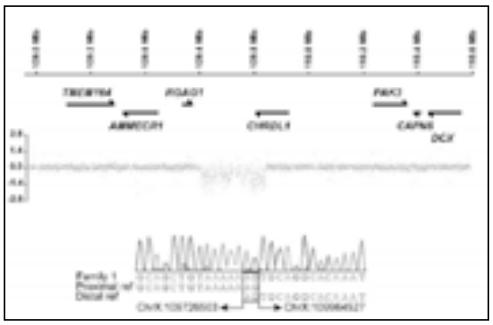
Identifying the genetic cause of X-linked Megalocornea



X-linked inheritance pattern



Comparative genomic hybridization (CGH) array analysis on X chromosome

Webb TR *et al.* 2012

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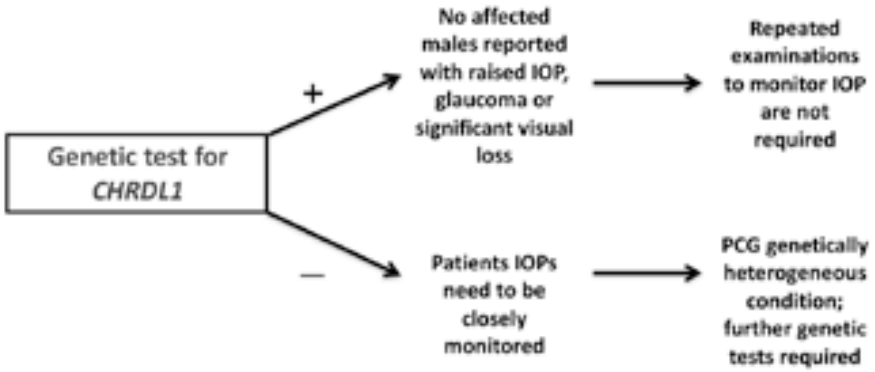
Distinguishing megalocornea (MGC1) from primary congenital glaucoma (PCG) in infants can be clinically challenging due to overlapping phenotypic features.



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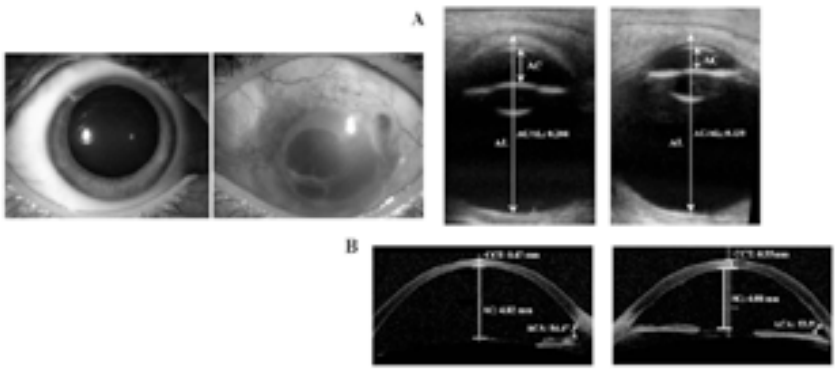
Clinical applications

X-linked megalocornea vs congenital glaucoma



Ultrasound is highly suggestive
- Deep anterior chamber -

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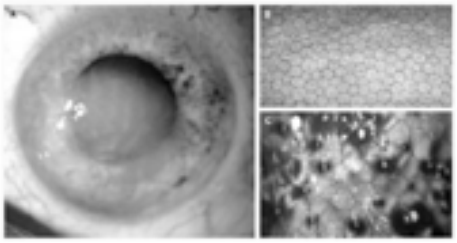
Fuchs Endothelial Corneal Dystrophy

- Fuchs is a progressive, bilateral corneal endothelial dystrophy



(Baratz KH, *et al.* 2010)

- Late onset and common condition
  - 2nd most common indication for corneal transplants in the UK
  - Age of onset: typically 4-5th decade
- Genetically complex disorder
  - Rare variants account for a small proportion of cases (e.g. *COL8A2*, *AGBL1*, *LOXHD1*, *ZEB1*)

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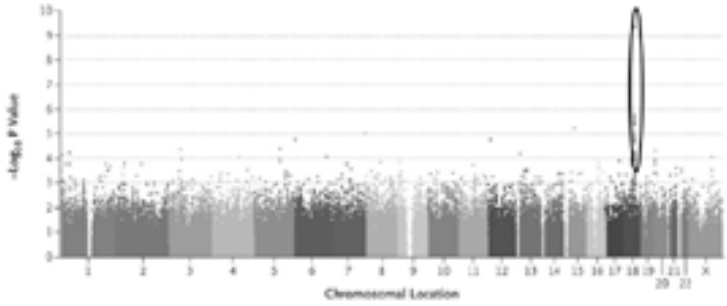
Common variants in *TCF4* are associated with Fuchs

A Genome Wide Association Study (GWAS) identified highly significant ($p=2.3\times10^{-26}$) association with common variants in the *TCF4* gene and Fuchs



Odds ratio (OR) = 5.5 (1 risk allele); 30 (2 risk alleles)

- **Suggestive of useful predictive clinical test may be on the horizon?**

Baratz KH, *et al.* 2010

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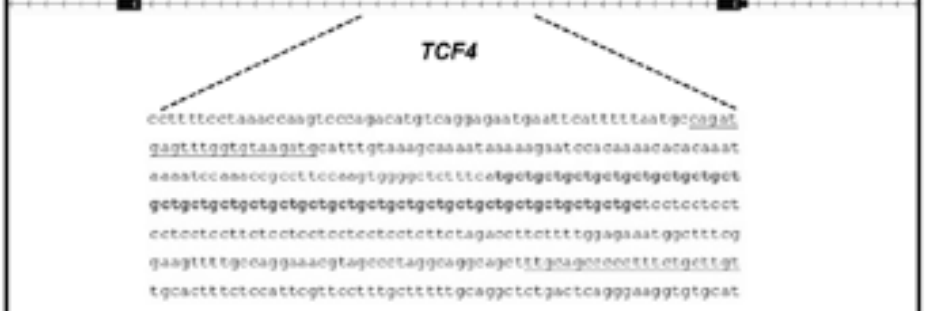
Fuchs is predominantly a trinucleotide repeat disorder



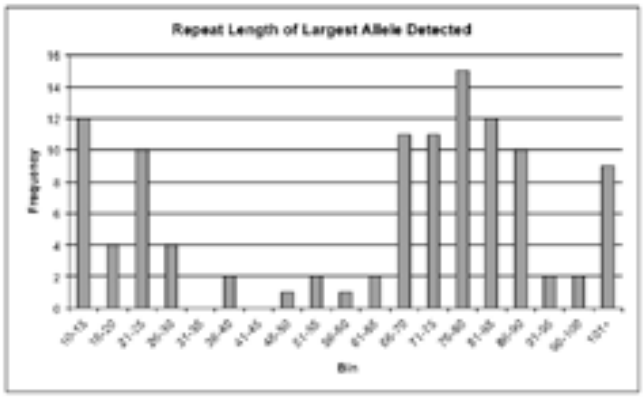
An unstable intronic tri-nucleotide CTG repeat expansion within the *TCF4* gene has been associated with Fuchs.

Also: Myotonic dystrophy type 1, Friedreich's ataxia

(Wieben *et al.* 2012)

UCL

Fuchs is predominantly a trinucleotide repeat disorder
repeat expansion in the non coding region of the *TCF4* gene



Although considered a complex disease, an unstable intronic tri-nucleotide CTG repeat within the *TCF4* gene has recently been identified as a major cause of FECD. In our MEH cohort, 71% (78/110) of FECD patients have one or more expanded CTG18.1 alleles (> 50 copies on at least one allele) (unpublished data)

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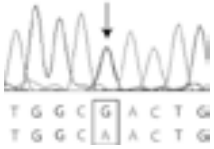
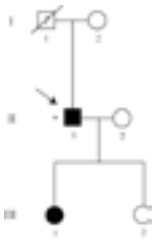
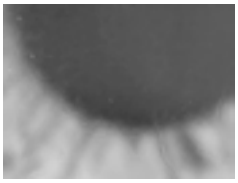
Missed diagnosis
Meretoja syndrome (GSN) – 4 cases

Mimics Lattice dystrophy

- facial nerve palsy
- renal amyloidosis







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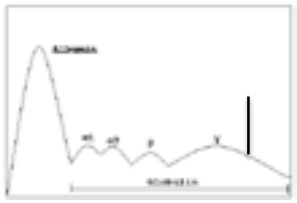
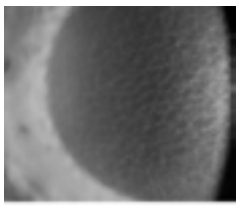
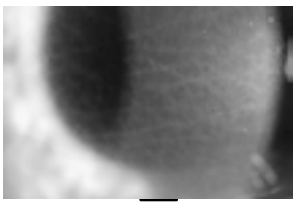
Paraproteimaemia keratopathy – 3 cases

Paraproteinemic Keratopathy

The Expanding Diversity of Clinical and Pathologic Manifestations







Review by haematologist

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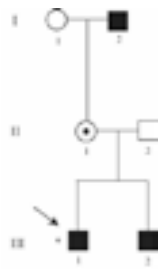
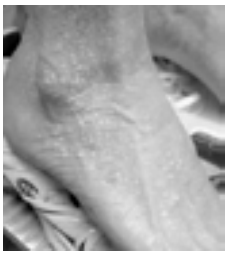
X- linked ichthyosis – 1 family
'Pre-Descemet dystrophy' - STS deficiency





Pre-Descemet Corneal Dystrophy and X-linked Ichthyosis Associated with Deletion of Xp22.31 Containing the STS Gene

Crystal Rung, M.D., Reed I. Ayres, B.A., Cynthia Wang, Ricardo F. Frausto, B.A., and Anthony J. Aldave, M.D.

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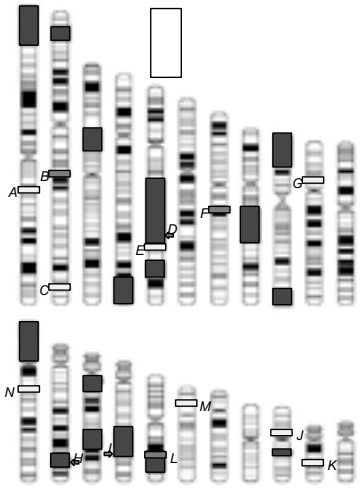
Polygenic (complex) disease
Keratoconus



Linkage region

Linkage with gene identified

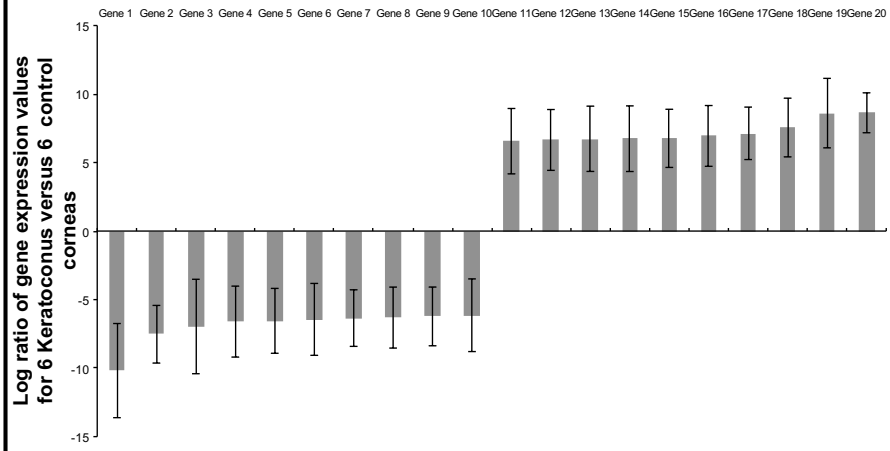
Gene identified by GWAS

Candidate Gene

A FLG
B RAB3GAP1
C COL4A3/A4
D LOX
E TGFBI
F HGF
G ZEB1
H DOCK9
I miR-184
J VSX1
K SOD1
L ZNF469
M AILP1
N AQP5

UCL

Keratoconus – transcriptome of diseased verses control tissue by RNA-sequencing



RNA-Seq analysis reveals up- and downregulated genes in diseased versus control corneal tissue.

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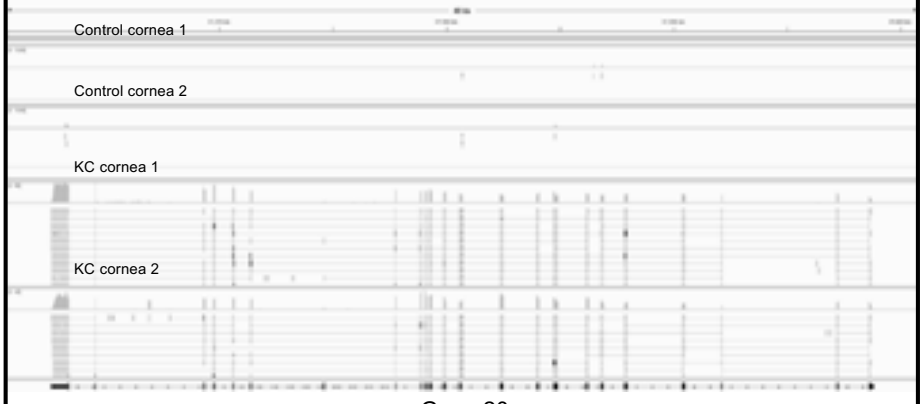

Gene 20

Example of RNA-seq data showing up-regulation of gene 20 in keratoconus tissue Gene 20 is not expressed that is not in control corneas

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What has been the impact?

- Revision of classification and identified gaps in our knowledge
- Insight into disease mechanisms
- Genetic diagnosis
- Identify phenocopies that require medical management
- Springboard for future research and therapies

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MCQ answers page 161

1. **Answer: c**

2. **Answer: b**

3. **Answer: d**

MCQ's

1. What is correct regarding topical quinolones

a. Compared to 2nd generation, the 4th generation of quinolones are better choice for treatment against gram positive and negative bacteria
b. Systemic or topical quinolones are the treatment of choice for microbial keratitis
c. Microbial resistance against topical quinolones did not change in the last 15 years
d. 4th generation of quinolones have good efficacy against staphylococcal microbial keratitis

2. Contact lenses have greater risk for microbial keratitis due to

a. Corneal anesthesia
b. Corneal abrasions
c. Decrease of normal flora
d. a and b and c are correct

3. What can be true regarding the adjunctive use of topical steroids in microbial keratitis

a. Topical steroids significantly reduce corneal scaring and improve the best corrected visual acuity
b. Increase the risk of recurrent infection in severe pseudomonas keratitis
c. It is safer to start topical steroids after the identification of the bacteria
d. Should be routinely used in every case of non-vision threatening microbial keratitis
e. b and c are correct

4. The accepted initial treatment for mild microbial keratitis is,

a. Laboratory investigation and combination of topical fortified antibiotics against gram positive and gram negative bacteria
b. Taking cultures and starting topical fortified antibiotics against gram positive and gram negative bacteria, after the cultures are positive
c. Systemic antibiotics are the drugs of choice
d. Topical quinolones Q2h and evaluation after 24 to 48 hours

5. A 27 year-old mail showed with red painful and photophobic eye. In the center of the RE cornea there was a 4.0 x 5.2 mm epithelial defect with deep stromal infiltrate. The correct approach is:

a. Immediate hospitalization
b. Treatment with topical quinolones and observation every other day by an ophthalmologist, in his clinic.
c. Laboratory investigation and immediate massive treatment with topical broad spectrum fortified antibiotics
d. 24 hours observation prior to starting topical fortified antibiotics and steroids
e. a and c are correct

The incidence of microbial keratitis varies in different parts of the world. In the USA the incidence is 11 to 30 cases per 100,000 people [1]. The most frequent causative organisms in bacterial keratitis in developed countries are Staphylococcus spp. ~ 30%-60%, Pseudomonas spp. ~15%-30% and Streptococcus spp. ~15%.

Bacterial Keratitis rarely occurs in normal eyes because of the human cornea's natural resistance to infection. Intact epithelium is the most important barrier to microbial invasion, while epithelial defect is a major risk factor for infection. Although in the developed countries contact lens wear and ocular surface diseases are the most common reasons for infections [~25-50% each], trauma is the most common reason in the developing countries [2]. Systemic disorders such as immunosuppression [HIV, etc.] DM, chronic alcoholism or long hospitalization are also risk factors for microbial keratitis.

The major factors influencing the final outcome of the infection are the virulence of the bacteria: their ability to invade or resist host defense and to produce tissue damage, and the tissue response including non-cellular [cytokines, antibody, enzymes] or cellular [T-cell lymphocytes polymorphonuclear neutrophils, macrophages] responses.

The infection may rapidly progress such as in pseudomonas or gonococcal infections and cause corneal perforation and endophthalmitis within 24 hours. It can also take an indolent course as in mycobacterial infections. It may end with minimal or significant corneal scarring and significant loss of vision when the visual axis is involved.

Clinical assessment at the first examination must be properly done. Detailed corneal evaluation and clinical drawing are important and should include the size of the epithelial defect, the size and depth of the infiltrate, the stromal edema intensity and size, and the stromal loss. AC inflammation has to be recorded as well as secondary glaucoma if it exists.

The non-severe ulcers are small [less than 2 mm in diameter], located in the superficial cornea; they progress slowly and the risk of perforation is minimal. The severe ulcers are large [>6 mm] involving the inner third of the cornea; they may progress very rapidly and cause corneal perforation. The differential diagnoses of bacterial keratitis includes: HSK, neurotrophic keratitis, marginal ulcerative/infiltrative keratitis, mycotic keratitis and others. It is a good practice to take smears and cultures in order to identify the pathogen. However, only in two-thirds of cases is the culture yield positive. It is extremely important to take cultures when the infection is severe and involving visual axis or non-responding to treatment or when non-bacterial infections are considered. The majority of community-acquired infections are successfully treated empirically without smears [3, 4]. Once the clinical diagnosis is made, the immediate goal is to treat aggressively with frequent topical antibiotics in order to eliminate the pathogen(s) and to prevent host tissue destruction, scarring and neovascularization and to preserve corneal transparency and function. The gold standard treatment of microbial keratitis include a combined use of fortified antibiotics or alternatively monotherapy using topical fluoroquinolones.

It is suggested to hospitalize the patients with severe and moderate corneal ulcers and to treat aggressively with intensive broad spectrum antibiotics. Once hospitalized, the initial treatment is usually empiric [before the type of bacteria is identified]. Broad-spectrum fortified antibiotics such as fortified Cefazolin 50mg/ml and Tobramycin 14mg/ml [or Gentamicin] are used to cover gram positive and negative bacteria. Other combinations may also include Vancomycin, Ceftazidime or Fluoroquinolone. Initial loading of topical fortified antibiotics is done by 5 applications of 1 drop of each drug every 2 min. During the first 24-48 hours the drugs are applied hourly, day and night. After 2 days the dose of medications may be decreased slowly, depending upon initial clinical findings and clinical judgment. The use of monotherapy with 4th generation of fluoroquinolones may be as effective as combined broad spectrum therapy for corneal ulcers [5,6]. However, there is a trend in the literature of emerging resistance to fluoroquinolones [7], and treating streptococcal or pneumococcal keratitis with fluoroquinolones monotherapy has a greater risk of corneal perforations [8].

In mild corneal ulcers commercial fluoroquinolones such as drops of gatifloxacin 0.3% or moxifloxacin 0.5% can be applied X 2h, and the patients examined in the clinic every other day.

Within the first 48-76 hours of treatment the pain decreases, the infiltrate consolidates, and the epithelialization begins. One can stop antibiotics after complete epithelialization has occurred and the infiltrate significantly decreased. However, in some bacteria such as P. aeruginosa, longer treatment may be required.

In cases of clinical improvement with initial antibiotics there is no need for alternative drugs regardless if bacteria were isolated or not. Modification of therapy is considered when after a few days of initial treatment there is a progression of stromal infiltration or progression of intraocular inflammation. One should consider drug resistance, multibacterial infection and rare pathogens such as mycobacteria, fungi or acanthamoeba. In these cases one should reevaluate the case including cessation of therapy, re-culturing and treating according to cultures outcome. Recently, some reports suggested the adjunctive use of crosslinking in antibiotic-resistant cases.

Adjunctive therapy with topical corticosteroids is still controversial [9, 10]. When the clinical improvement is obvious there is no need to add steroids. However, when the infiltrate is central or inflammation is significant, some will add topical steroids. Steroids are safer to apply in gram+ vs gram- infections. It is important always to use steroids under the cover of antibiotics. The comprehensive ophthalmologist should only occasionally use topical steroids, preferably when the bacteria were identified as sensitive to the treating antibiotics.

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MCQ answers page 179

1. **Answer: d**

2. **Answer: d**

3. **Answer: e**

4. **Answer: d**

5. **Answer: e**

MCQ's

1. Which statement is correct concerning trachoma

a. Trachoma is the most important cause of blindness in the world
b. Men are more often affected by blinding trachoma than women
c. Mass distribution of antibiotics should start when the proportion of children aged 1 - 9 years with active trachoma is greater than 10%
d. Mass distribution should continue until the prevalence of active trachoma in children falls below 0.5%

2. Which statement is correct concerning inclusion conjunctivitis

a. Adult inclusion conjunctivitis always presents as a bilateral disease
b. Adult inclusion conjunctivitis is most often transmitted by direct contact of infected genitourinary secretions
c. Prominent conjunctival scarring is a common complication of adult inclusion conjunctivitis
d. Symptoms of conjunctivitis of the newborn tend to occur earlier after birth in inclusion conjunctivitis than in neonatal gonococcal disease

3. Which statement is correct concerning fungal keratitis

a. Trauma with vegetable material is the most common risk factor for fungal ulcers in the industrialized societies
b. Ocular surface disease especially in a patient having received penetrating keratoplasty, is a major risk factor for mycotic ulcers
c. The major limitation of PCR tests for fungal ulcers is a lack of sensitivity
d. The main reason to use intrastromal voriconazole is to avoid the liver toxicity associated with systemic administration

Suggested readings

1) Recent advances in diagnosis and management of Mycotic Keratitis. *Prafulla K Maharana, Namrata Sharma, Ritu Nagpal, Vishal Jhanji, Sujata Das, Rasik B Vajpayee. Indian J Ophthalmol. 2016;64:346-57.*

2) Chlamydial ocular diseases. Bonnie B An and Anthony P Adamis. Int Ophthalmol Clin. 1998 Winter;38(1):221-30. Review

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Fungal keratitis

Introduction

Fungal keratitis is caused by yeast *(e.g. Candida)* or molds (filamentary fungi). Yeasts grow as creamy, opaque pasty colonies on culture media. Molds exhibit feathery or powdery growth on the surface of culture media *(Aspergillus, Fusarium).*

Epidemiology

Fungal keratitis was first described by Leber in 1879, a case of *Aspergillus*. In the industrialized world fungal keratitis is rather uncommon, but is one of the major causes of keratitis in tropical areas of the world. The incidence varies according to the geographical location: in temperate regions yeasts will prevail, whereas in the tropics *Aspergillus* and *Fusarium* are more common. The incidence of fungal keratitis is on the rise over the past 30 years for several reasons: widespread use of antibiotics; increased prevalence of immune suppressed patients; better isolation techniques; and use of multipurpose no-rub contact lens solutions. A recent outbreak of Fusarium keratitis was reported in the USA, in Singapore, and in Europe (U.K., Belgium, and France), probably related to the use of no-rub multipurpose products (BL ReNu Moisture Lock).

Pathophysiology

Fungi gain access into the corneal stroma through a defect in the epithelium. The organisms can penetrate intact descemet membrane, proliferate in the anterior chamber and spread to the posterior segment causing fungal endophthalmitis.

Risk factors

- corneal trauma with vegetable material (plant or soil matter)
- corneal trauma related to contact lens wear
  - – therapeutic lenses (candida)
  - – refractive lens wear (fusarium)
- topical steroids (but also systemic steroids)
- corneal surgery (PKP, RK)
- chronic keratitis (HSV, HZV, VKC)
- immunosuppressive disease

Clinical presentation

A fungal keratitis shows fewer inflammatory signs and symptoms during the initial period than a bacterial keratitis. As the keratitis progresses, intense suppuration may develop and the lesions may resemble bacterial keratitis. At this point rapidly progressive hypopion and anterior chamber inflammatory membranes will appear. If untreated extension in to the anterior chamber will occur and the fungus may invade the iris or the posterior chamber!

The clinical picture is different according to the causative organism. Filamentous fungal keratitis often follows corneal trauma. The lesion presents as a gray-white, dry-appearing infiltrate that may appear elevated. It has irregular feathery of filamentous margins with occasionally multifocal or satellite infiltrates. The initial break in the epithelium may have healed so that a deep stromal infiltrate is observed in the presence of an intact epithelium. Endothelial plaque and/or hypopion formation may also occur if the infiltrates are sufficiently deep or large.

The picture is somewhat different in yeast fungal keratitis. Here the normal microflora invades a preexisting epithelial defect. Most cases tend to remain superficial and present as superficial white raised colonies in a structurally altered eye. Occasionally deep invasion may occur with suppuration resembling bacterial keratitis.

In summary the most important clues to the diagnosis of fungal keratitis are the protracted time course, the discrepancy between the infiltrate and the level of inflammation, the presence of a plaque against the endothelium, the shape of the hypopion, and the association of intact epithelium over a deep infiltrate. When in doubt, confocal microscopy may be a useful technique. Confocal microscopy is a non-invasive, high resolution technique which allows rapid detection of fungal hyphae in the cornea long before laboratory cultures give conclusive results. If performed by an experienced observer a sensitivity of 50% and a somewhat higher specificity are obtained.

Laboratory examinations

Smears, culture, histopathology and PCR are all potential techniques to consolidate the clinical suspicion. Smears with conventional staining have a sensitivity of about 50% to 80%.

Drawbacks of conventional stains include the frequent presence of background artifacts with potassium hydroxide (KOH), the weak staining (yeast) and interference with background staining for the Gram stain, and the need for an expensive fluorescence microscope for calcofluor white staining. Therefor there is a need for a new staining technique that is rapid, easy to perform, highly sensitive and specific, and that can be done with a routine microscope.

[chlorazol black E mounts? very rapid (30 secs), not as sensitive as gram or lactophenol staining, more specific].

Culture is performed on Sabouraud and blood agar at 25°C. Most fungi can be isolated within 48-96h of incubation, but at least 25% require an incubation period of up to three weeks.

Histopathology a corneal biopsy can be considered when corneal smears and cultures are negative at 48-72 hours, in a patient who is strongly suspected of having a fungal infection or who is not improving on the initial, broad-spectrum antibacterial therapy. PAS and Grocott are classic stains for histopathology specimens. Fungal specific antibodies may be used as well.

PCR detects microbial DNA in the majority of fungal corneal ulcers and identifies potentially pathogenic organisms in a high proportion of culture-negative cases. The yield and concordance with culture are higher for fungal than bacterial ulcers. Unfortunately, there is a very high rate of false positives for apparently nonpathogenic organisms.

Treatment

The most important antifungal agents are the polyene and the azole components:

- polyenes
  - amphotericine B 0,15% (Candida)
  - natamycine 5% (only commercially available drop)
- azoles
  - econazole 2%
  - voriconazole 1% (Fusarium)

Different routes of administration have been tried:

- topical
  - hourly
  - with frequent (every other day) debridement of the epithelial layer
- intracamerular
- subconjunctival
- intrastromal injection

Surgical therapy is an option when medical treatment fails. If the infection extends into the anterior chamber under therapy, debulk with early PKP (use of UBM/visante OCT), remove and culture or perform pathology of all infected tissue. Rinse the anterior chamber and clean the instruments. Interrupted sutures are recommended. The postoperative management should include topical and systemic antifungals, cyclosporin A and no steroids in the immediate postoperative period, until adequate control of infection is assured.

Adult inclusion conjunctivitis

Introduction

The chlamydiae are nonmotile, gram-negative bacteria that are metabolically deficient in their ability to synthesize ATP. Their dependency on an exogenous source of energy explains their obligate intracellular life cycle. Chlamydiae undergo a biphasic development cycle, forming distinctive intracellular inclusions that permit identification by light or fluorescence microscopy.

The genus Chlamydia is composed of four species: *Chlamydia trachomatis, Chlamydia pneumoniae, Chlamydia psittaci,* and *Chlamydia pecorum*. The different serovariants or "serovars" of Chlamydia trachomatis are responsible for the following diseases: serovars A, B, Ba, and C cause trachoma, a chronic and potentially blinding keratoconjunctivitis endemic in many developing countries where poverty goes along with deficient sanitation and poor hygiene; serovars D to K are the cause of one of the most common sexually transmitted diseases worldwide and both adult and neonatal inclusion conjunctivitis arise from transfer of bacteria from the genitalia to the eye; serovars L1, L2, and L3 are the etiological agent in venereal lymphogranulomatosis. The observation under the microscope of inclusion bodies in conjunctival cells infected with Chlamydiae explains the term inclusion conjunctivitis (18, 19).

Epidemiology

Adult inclusion conjunctivitis is due to *Chlamydia trachomatis* serovars D, E, F, G, H, I, J, and K. The bacterial reservoir is the genital tract of the sexually active adult. Urogenital chlamydiosis is the most common STD in the developed world and accounts for approximately 3 million new cases each year in the United States (4). The highest prevalence is found in young, sexually active adults. The disease accounts for 40% to 50% of all cases of non-gonococcal urethritis in men (10).According to the WHO chlamydial prevalence rates in pregnant women range from 2.7% to 8% in Europe (24).

Fifty to 70% of genital infections are asymptomatic and less than 10% of prevalent cases are diagnosed (20,21). The genital infection causes urethritis, cervicitis, endometritis, salpingitis, and perihepatitis in women and is a major cause of sterility. In men it causes balanitis, urethritis, prostatitis, and epididymitis (3). The rising prevalence of chlamydial infection and its association with an increased risk of cervical cancer, sterility and acquisition of HIV brings up the question whether a comprehensive European-wide screening policy is needed (16).

Transmission to the eye occurs in the vast majority by autoinoculation with infected genital secretions from either the patient or his partner. Direct infection from the eye of one patient to the eye of another is possible but uncommon and could account for the small number of affected patients without concomitant genital disease. Indirect infection from inadequately disinfected swimming pools and from contact with contaminated inert surfaces has been described but is rare (23, 11, 13).

Clinical picture

The incubation period of adult inclusion conjunctivitis varies from 2 days to 3 weeks. It starts as a unilateral, papillary conjunctivitis with mucopurulent secretions and a swelling of the ipsilateral premandibular lymph glands. Later on typical follicules will develop on the upper and the lower tarsal plate. Swelling and infiltration of the subconjunctival tissue may obscure the vertical vessels of the upper tarsal plate mimicking the classic picture of inflammatory trachoma at this stage (1, 6). Pseudomembrane formation seen in neonatal inclusion conjunctivitis is not seen in the adult form. Involvement of the second eye may ensue, but is not always present.

Corneal involvement includes discrete pannus formation, superficial punctate keratopathy, and more seldom marginal infiltrates (7). Frank corneal neo-vascularisation and conjunctival scarring typical of trachomatous keratoconjunctivitis are not observed in adult inclusion conjunctivitis.

The initial phase of acute infection is often missed and most patients will present with a chronic red eye. They will complain of mucopurulent secretions and sticky eyes in the morning, a foreign body sensation and photophobia. Inspection at this stage will show a papillary and follicular conjunctival reaction, eventually discrete corneal changes, but the inflammatory swelling of the subconjunctival tissue will no longer be present (8).

The differential diagnosis of adult inclusion conjunctivitis is in the first place the differential diagnosis of chronic follicular conjunctivitis and should include the following entities: classic trachoma, adenoviral epidemic keratoconjunctivitis, herpes, Newcastle disease virus conjunctivitis, chronic allergic conjunctivitis, acnea rosacea and chronic blepharitis, and even floppy eyelid syndrome (15).

Laboratory diagnosis

The clinical diagnosis of adult inclusion conjunctivitis may be difficult and therefore identifying chlamydiae in conjunctival scrapings or direct diagnosis may be very useful. Because chlamydiae are obligate intracellular pathogen, the scraping should include infected cells. Therefore, specimens that contain only exudate or secretions but no cells are unsatisfactory. For conjunctival specimens any purulent exudate should be removed before collecting epithelial cells by vigorously rubbing a dry swab over the everted palpebral conjunctiva. The specimen is then transferred to a transport medium that makes it possible to perform both culture and DNA amplification techniques from a single swab. The lilelyhood of isolation is optimized if specimens are refrigerated immediately after collection at 2 to 8° Celsius and kept at this temperature during transport. The delay between collection and laboratory processing should be less than 48 hours. Specimens that cannot be processed within 48 hours may be frozen at – 70° Celsius, but this is likely to result in a 20% loss of viability. Freezing at – 20° Celsius should be avoided altogether (2).

The following laboratory methods are available to identify chlamydial infection:

1. Culture methods
2. Nonculture methods
    a. Direct cytologic examinaton to identify inclusion bodies by staining methods
    b. Identification of chlamydial antigen
    c. nucleic acid amplification techniques (NAATs)
3. Serologic tests.

Culture methods

Culture methods on viable cells used to be the gold standard for the diagnosis of chlamydial infection. They have lost this status with the advent of nuclear acid amplification techniques or NAATs during the last decade because of their relative insensitivity: culture methods have a specificity that approaches 100% , but their sensitivity is only 70 to 85% in comparison with NAAT's (cfr. infra). Other disadvantages of culture techniques include the requirement for a stringent cold chain for transportation of specimens, high cost, high level of technical expertise and a time delay to obtain results from 3 to 7 days.

Nonculture methods

a) Staining of conjunctival scrapings with Giemsa to demonstrate typical chlamydial inclusion bodies is not recommended for the diagnosis of adult inclusion conjunctivitis due to its lack of sensitivity (17). Moreover, recognition of chlamydial inclusions requires considerable expertise.

b) Antigen detection methods include the DFA test based on direct visualization of the chlamydial organism by staining with fluorescein-labeled specific antibody, the EIA test based on immunochemical detection of antigen, and the DNA hybridization probe to detect chlamydial rRNA. All these tests are commercially available and commonly used (Microtrak DFA, Behring Diagnostics; Chlamydiazyme, Abbott Diagnostics; Microtrak EIA, Behring; PACE 2, Gen-Probe).

c) The development of NAATs has been the major advance in the field of chlamydial diagnosis in the last decade. A number of commercial tests are available: polymerase chain reaction or PCR tests (Amplicor, Roche Diagnosts), strand displacement amplification (SDA, Becton Dickinson), and ligase chain reaction (LCR, Abbott Laboratories). They all combine exquisite sensitivity with very high specificity and are considered the new gold standard in the diagnosis of chlamydial disease (12).

Serologic tests

Serologic tests are general not useful in the diagnosis of genital tract infection caused by *Chlamydia trachomatis*. Antibodies elicited by infection are long lived and a positive titer will not distinguish a previous from a current infection. The presence of IgM is an unreliable marker of acute infection since it is often not present. The presence of antichlamydial IgG in tears might be helpful for diagnosis in patients with suspected chlamydial conjunctivitis, since IgG seems to be absent in tears from patients with only urethritis (9).

Treatment

Since adult inclusion conjunctivitis results from autoinfection in patients with genital disease in the vast majority of cases, systemic treatment is mandatory to prevent extraocular morbidity and ocular reinfection. The classic treatment includes oral doxycycline, 100 mg twice a day for one week; or in pregnant women erythromycin, 500 mg four times a day for one week. Azythromycin, 1 g as a single dose is equally effective, more patient friendly, but more expensive (14). Oral fluoroquinolones are also effective agents against C. trachomatis. Screening and treatment of infected sexual partners of the patients as well as counseling about safe sex should be part of the comprehensive care (5).

The CDC does not recommend routine test-of-cure visits during the post treatment period. If for some reason a test-of-cure seems indicated, only culture methods should be used. NAATs are less useful for this indication as they may pick up residual DNA in the early post treatment period in patients whose infection has been cured (2).

Summary for the clinician

- urogenital chlamydiosis due to C. trachomatis serovars D-K is the most frequent STD in the industrialized world
- although often asymptomatic, it is responsible for significant morbidity
- adult inclusion conjunctivitis arises from transfer of bacteria from the genitalia to the eye (autoinoculation)
- the prevailing clinical presentation is that of a chronic red eye with a moderate amount of mucopurulent secretions
- the differential diagnosis includes the different causes of follicular and chronic conjunctivitis, uni- or bilateral
- the clinical suspicion is confirmed by laboratory methods
- nucleic acid amplification tests have the highest sensitivity and specificity and have supplanted culture methods as the gold standard
- systemic administration of doxycycline, erythromycin, azythromycin or fluoroquinolones is the treatment of choice
- sexual partners of the patient should be screened as well
- counseling about safe sex should be provided to the patient and his partners

Trachoma

Trachoma is the second or the third most important cause of blindness in the world (either before or after glaucoma). According to WHO estimates 150 million people are infected and 5.5 million people are blinded by this disease. Blinding trachoma is the end result of repetitive infections that cause scarring of the tarsal plate and trichiasis which predisposes the corneal surface to micro-erosions and subsequent bacterial superinfections.

• Risk factors for the disease:
  - lack of personal hygiene
  - absence of pit latrines
  - keeping cattle in the immediate vicinity of the house
  - crowding
  - presence of waste and feces in the open air

All these factors will attract flies that feed on the nasal secretions and the tears of children and carry the infection from one person to the other. Children will get the infection at an early age and will reinfect the adults taking care of them, mainly women (mother, grandmother, elder sister). Reinfection of the adults creates a cycle of repetitive infections leading to chronic inflammation of the tarsal plate. This chronic

inflammation will cause scarring and contraction of the inner lamellae of the tarsal plate. Inward bowing of the upper eyelid causes trichiasis: the cilia of the upper eyelid will rub against the corneal surface. Chronic rubbing of the cilia will cause micro-erosions and subsequent bacterial superinfections. The cornea will gradually become opaque and vascularized as a result of the repetitive infections.

• Simplified WHO classification of trachoma

The WHO has proposed a simplified classification of trachoma that is useful for the diagnosis and the staging of the individual patient. Moreover it is a useful tool to assess the importance and the dynamics of the disease in the community.

TF	Trachomatous Inflammation Follicular (TF)
	Tat least 5 follicles on the flat surface of the upper tarsal plate
TI	Trachomatous Inflammation Intense (TI)
	Inflammatory thickening of the tarsal conjunctiva that obscures at least half of the normal deep tarsal vessels
TS	Trachomatous Scarring Scarring
	Citracial trachoma, presence of fine white lines in the tarsal conjunctiva
TT	Trachomatous Trichiasis
	At least one eyelash rubs on the eyeball
CO	Corneal Opacity
	Opacity of the cornea extending over part of the pupil

Screening of a population for trachoma with the aid of this grading system allows the following conclusions:

- the number of individuals with TF is a measure for the incidence (early infection = new cases)
- the number of individuals with TI is a measure for the prevalence of active disease; both TF and TI individuals need antibiotic treatment
- the number of individuals with TT is a measure for the magnitude of the population at risk of becoming blind; trichiasis surgery should be made available to this group
- the number of individuals with CO is a measure for the importance of trachoma as a blinding disease in that particular community

Differential diagnosis:

- with vernal keratoconjunctivitis
- with ocular pemphigoid

• Medical treatment (TF and TI)

- Tetracycline ointment BID for 6 weeks
- Azythromycine eyedrops BID for 3 days
- Doxycycline 100 mg per day for 3 weeks
- Tetracycline 250 mg QID for 3 weeks
- Azythromycine 1G as a single dose treatment

• Surgical treatment

- Epilation
- Electrolysis
- Cryoablation
- Trichiasis surgery (bilamelllar tarsal rotation procedure)

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MCQ answers page 185

1. **Answer: c**

2. **Answer: b**

3. **Answer: b**

MCQ's

1. In Acanthamoeba keratitis, the most common misdiagnosis is

a. Lattice corneal dystrophy
b. Recurrent corneal erosion syndrome
c. Herpetic keratitis
d. Keratomycosis

2. Acathamoeba keratitis cannot be diagnosed by ...?

a. PCR
b. In vitro culture
c. Histology
d. Conjunctival swap

3. Which of the following is not a typical sign of Acanthamoeba keratitis?

a. Hypopyon
b. Pain
c. Ring infiltrate
d. Keratoneuritis

4. Which of the following topical agents is not appropriate in the early course of Acanthamoeba keratitis?

a. Antibiotics
b. Costicosteroids
c. Propamidin-Isioethionat
d. Polyhexamethylenbiguanid

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Seitz B [1], Daas L [1], Laurik L[1], Langenbucher A [2], Szentmáry N [1]

[1] Department of Ophthalmology, Saarland University Medical Center UKS, Homburg/Saar, Germany
[2] Experimental Ophthalmology, Saarland University, Homburg/Saar, Germany

Saarland University Medical Center *UKS*
Department of Ophthalmology, Homburg/Saar, Germany
Chairman: Prof. Dr. Berthold Seitz ML, FEBO

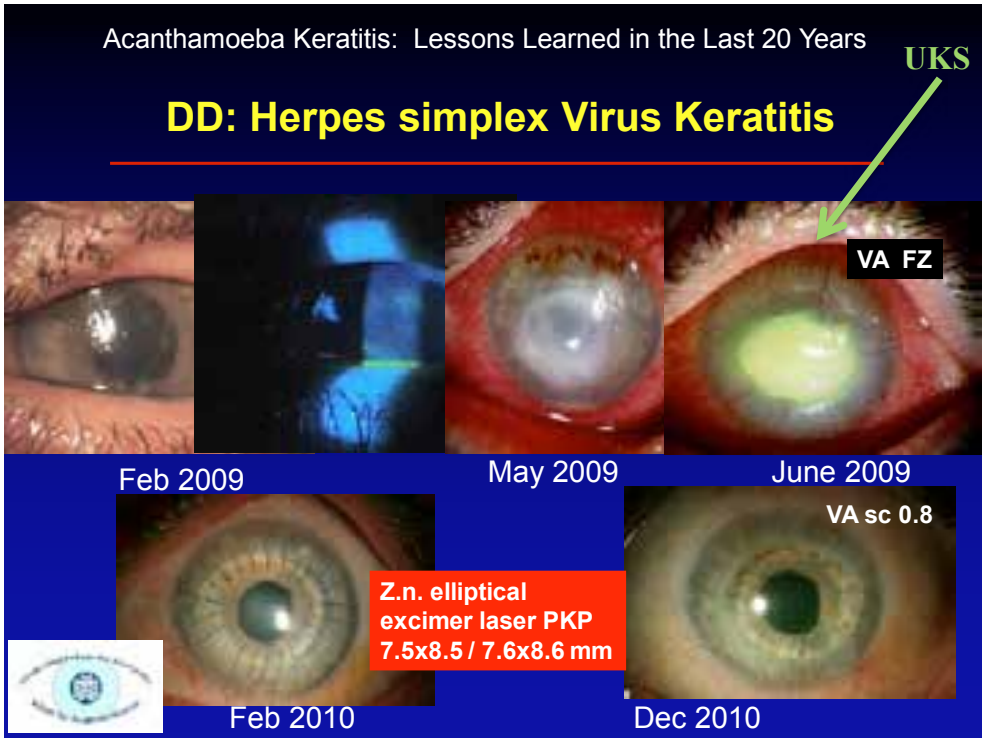
Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

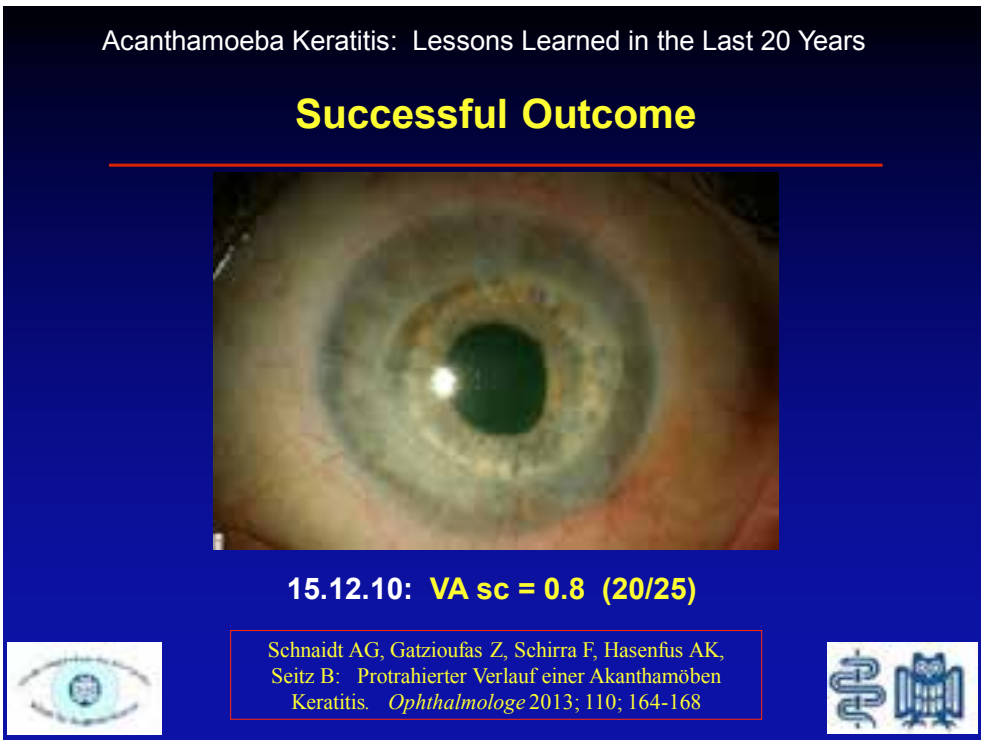
Background – Acanthamoeba Keratitis

- Worldwide increasing prevalence
- Diagnostic challenge
- Severe sight-threatening complications
- No absolute consent regarding therapeutic approach (medical and surgical)

„Saar Lope“

Lorenzo-Morales J et al. *An update on acanthamoeba keratitis: diagnosis, pathogenesis and treatment.* *Parasite* 2015; 22:10


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
UKS
DD: Herpes simplex Virus Keratitis
VA FZ
Feb 2009
May 2009
June 2009
VA sc 0.8
Z.n. elliptical
excimer laser PKP
7.5x8.5 / 7.6x8.6 mm
Feb 2010
Dec 2010


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
Successful Outcome
15.12.10: VA sc = 0.8 (20/25)
Schnaidt AG, Gatzioufas Z, Schirra F, Hasenfus AK, Seitz B: Protrahierter Verlauf einer Akanthamöben Keratitis. Ophthalmologe 2013; 110; 164-168

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

„Successful Outcome“

Graft Melting

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

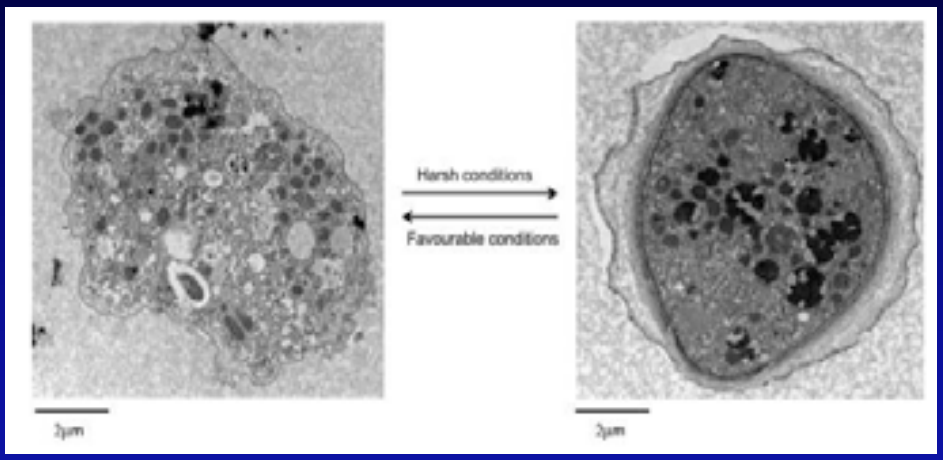
Classification of Acanthamoeba

- **Vegetative Form / Trophozoit**
  - Size 25-40 µm
  - Lives on bacteria (esp. Enterobacteriae), algae and yeast
- **Permanent Form /** double-wall **cyst**
  - Size 13-20 µm
  - Resistant against chlorine and antibiotics, low temperature (e.g. 15 months at -15 °C), high doses of UV- und γ-irradiation

Szentmáry N, Goebels S, Matoula P, Schirra F, Seitz B: Die Akanthamöbenkeratitis – ein seltenes und oft spät diagnostiziertes Chamäleon. *Klin Monatsbl Augenheilkd* 2012; 229: 521-528.

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

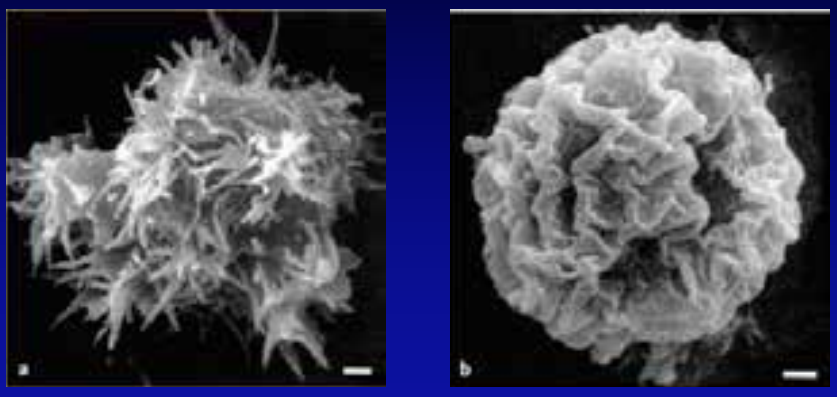
Two Appearances



Siddiqui R & Khan NA. Biology and pathogenesis of Acanthamoeba. *Parasit Vectors* 2012; 5:6

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Trophozoit and Cyst



Meltendorf C & Duncker G: Akanthamöben-Keratitis. *Klin Monatsbl Augenheilkd* 2011; 228: R29-R43.

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Epidemiology

- Risk factors: soft contact lenses
- 5% of contact lens associated microbial keratitis cases
- 83-93% are contact lens wearers
- 30% more often in case of orthokeratology contact lenses than in case of soft contact lenses
- Only contact lens cleaning solutions with hydrogene peroxide are desinfective against acanthamoeba

Szentmáry N, Goebels S, Matoula P, Schirra F, Seitz B: Die Akanthamöbenkeratitis – ein seltenes und oft spät diagnostiziertes Chamäleon. *Klin Monatsbl Augenheilkd* 2012; 229: 521-528.

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Patients

- Double peak age distribution (16-25 vs 65 years)
- Mostly only one eye involved
- Severe pain, often discrepancy with clinical picture
- **Injuries in agriculture** **OR**
- **Wrong contact lens „hygiene“**
  (e.g. cleaning of soft contact lenses with tap water or saliva, Swimming in pool or even „pond“ with contact lenses - **please ask patient carefully!**)

Ross J, Roy SL, Mathers WD et al: Clinical characteristics of Acanthamoeba keratitis infections in 28 states, 2008-2011. *Cornea* 2014; 33:161-168

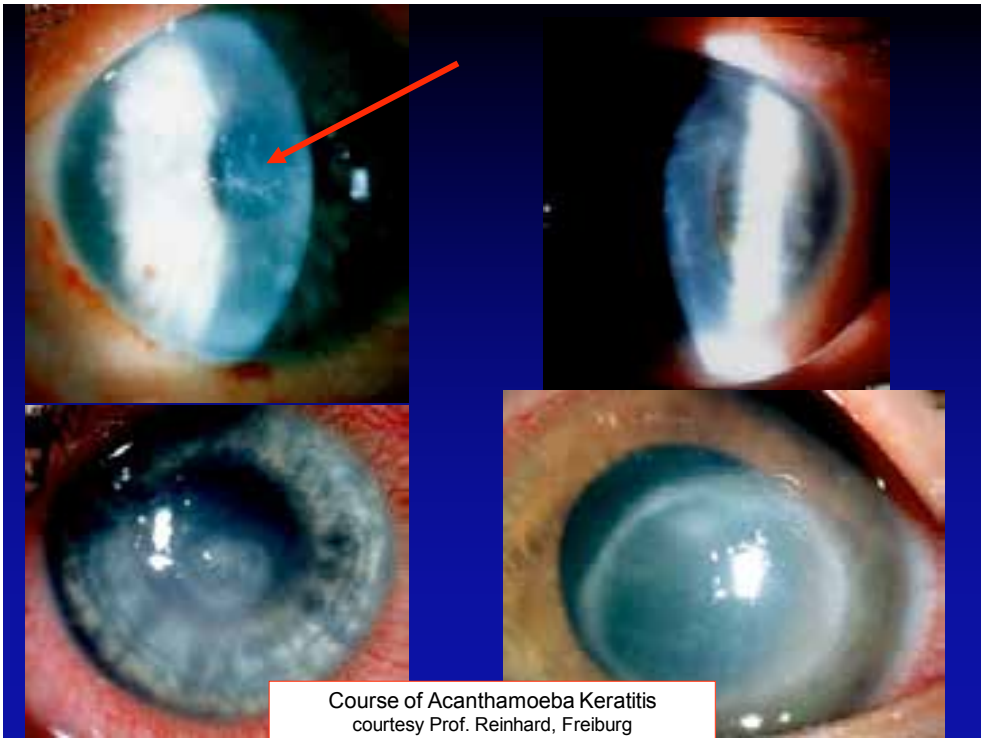
Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Clinical Picture - Chameleon!!!!

- „Pseudodendritiformic epitheliopathy“ = „dirty epithelium”
- Perineural infiltrates = „Radial keratoneuritis“ (early !)
- Ring infiltrate (late!) = „Wessely immune ring“
- (Multifocal) stromal infiltrates
- Nummularis-type subepithelial infiltrates (rare)
- Broad-based peripheral anterior synechia & mature cataract
- (Very rare: sterile anterior uveitis, scleritis, chorioretinitis)

Patel DV & McGhee CNJ: Acanthamoeba keratitis: a comprehensive photographic reference of common and uncommon signs. *Clin Exp Ophthalmol* 2009; 37:232-238

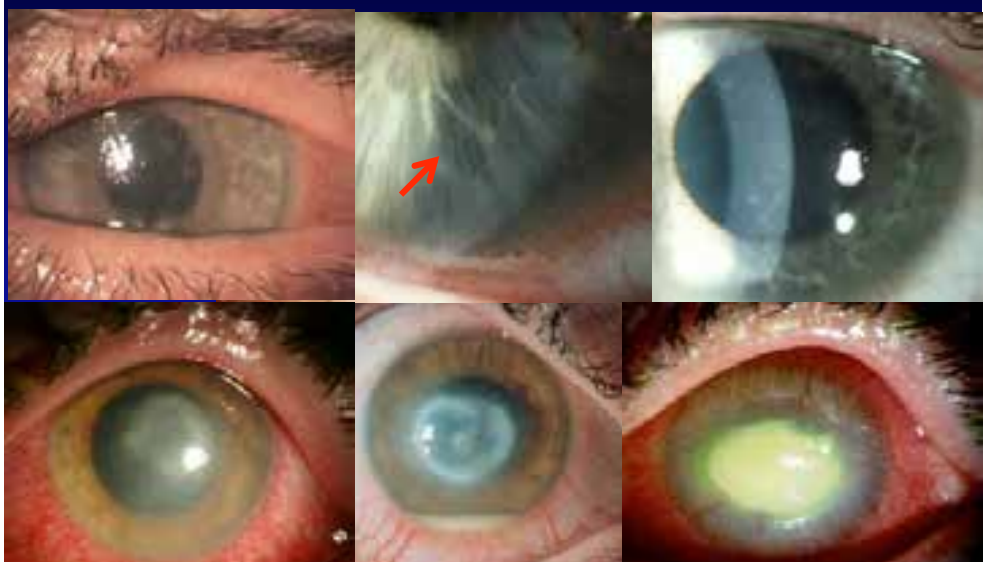
Reinhard T, Schilgen G, Steinert M et al: Nummular infiltrates in Acanthamoeba keratitis. *Acta Ophthalmol Scand* 2003; 81:541-543



Course of Acanthamoeba Keratitis
courtesy Prof. Reinhard, Freiburg

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Clinical Picture



Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

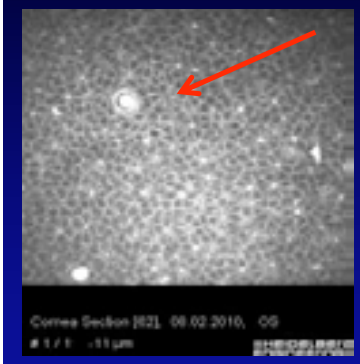
Apparative Diagnostics - *Literature*

- Confocal biomicroscopy 90% ????
- In-vitro culture 0-77%
- Histopathology 31-65%
- Polymerase Chain Reaction (PCR) 84-100%

Szentmáry N, Goebels S, Matoula P, Schirra F, Seitz B: Die Akanthamöbenkeratitis – ein seltenes und oft spät diagnostiziertes Chamäleon. *Klin Monatsbl Augenheilkd* 2012; 229: 521-528.

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Confocal Biomicroscopy



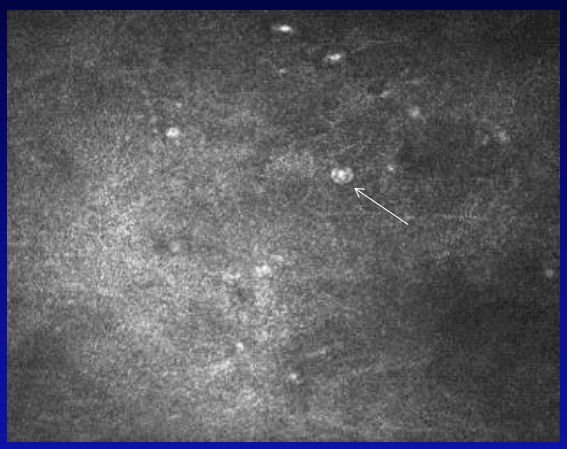
- „Prove“ of causative agent
- Extent of infestation
- Course of disease = Efficacy of therapy ?

Dr. Nölle: Univ.-Augenklinik Kiel:
Confocal corneal biomicroscopy (Rostock Cornea Modul am HRT II) shows intraepithelial double-wall cyst in acanthamoeba keratitis.

Page MA & Mathers WD: Acanthamoeba keratitis: A 12-year experience covering a wide spectrum of presentations, diagnoses, and outcomes. *Journal of Ophthalmology* 2013; 2013:670242

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Confocal Biomicroscopy

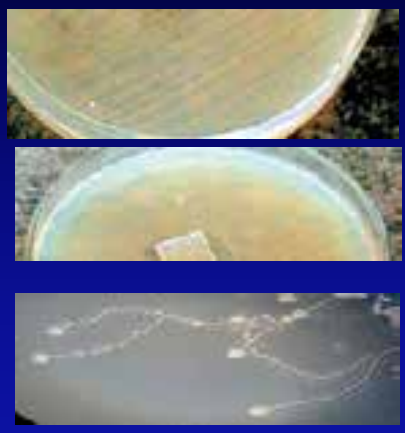


Seitz B, Geerling G, Maier P: Die infektiöse Keratitis: Herpes im Griff, Akanthamöben und Fusarien auf dem Vormarsch (Editorial). *Klin Monatsbl Augenheilkd* 2015; 232:735-737

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

In-vitro Culture

Scraping biopsy is transferred to an agar plate, which is overgrown by Gram-negative bacteria (e.g., *Escherichia coli*)

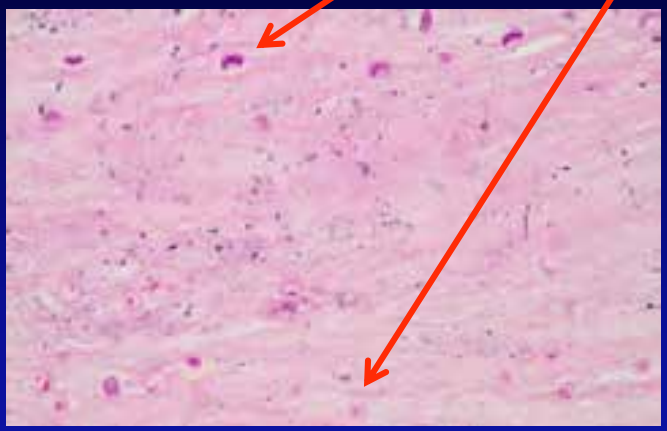


Gram-negative bacteria serve as food for acanthamoeba
-> moving trophozoits leave visibel tracks behind on the agar plate

Dart JKG, Saw VP, Kilvington S: Acanthamoeba keratitis: Diagnosis amd treatment update 2009. *Am J Ophthalmol* 2009; 148:487-499

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

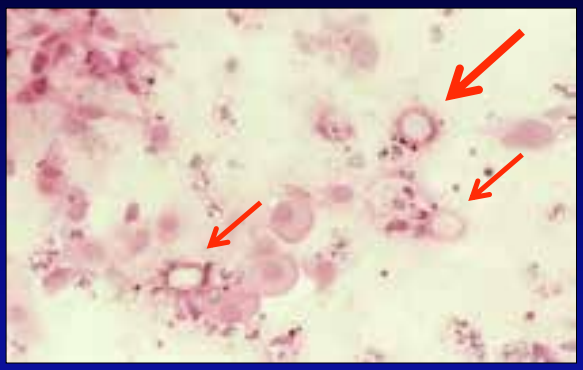
Histopathology - Trophozoits and Cysts



43-year-old patient, corneal midstroma, **PAS**, x40

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

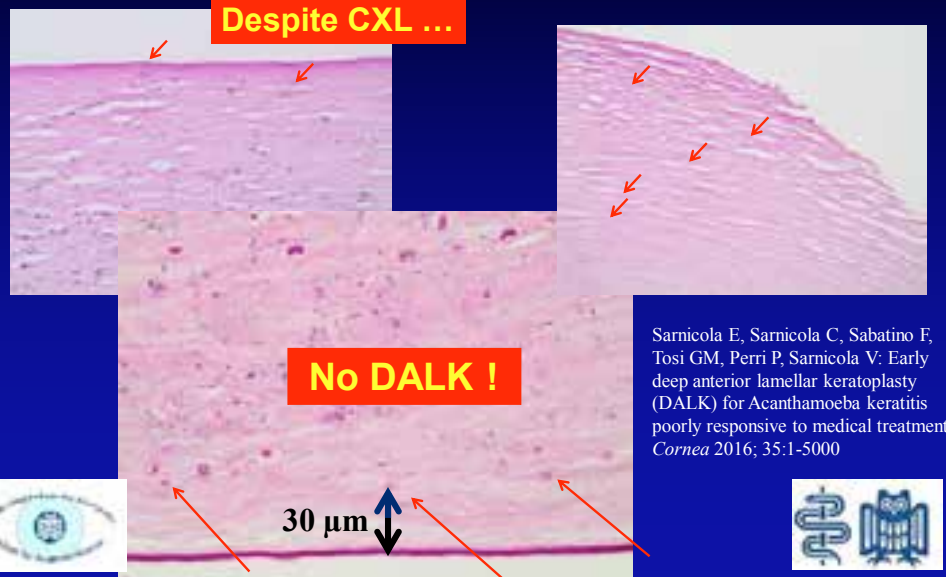
Histopathology - Epithelial Abrasion



Dr. Nölle, Univ.-Augenklinik Kiel:
Corneal epithelial abrasion in a 24-year-old CL wearer,
HE-stain: Three acanthamoeba cysts at 2, 4, 8 o´clock

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Histopathology - superficial / peripheral / deep



Sarnicola E, Sarnicola C, Sabatino F, Tosi GM, Perri P, Sarnicola V: Early deep anterior lamellar keratoplasty (DALK) for Acanthamoeba keratitis poorly responsive to medical treatment *Cornea* 2016; 35:1-5000

Hager T, Hasenfus A, Stachon T, Seitz B, Szentmáry N: **Crosslinking and corneal cryotherapy** in acanthamoeba keratitis -- a histological study. *Graefes Arch Clin Exp Ophthalmol*. 2016; 254:149-153

Patients	Crosslinking (CXL)	Central corneal thickness before CXL (µm)	Trophozoites	Cysts	Gram	CD34
1	-	n.a.	-	-	-	+
2	-	532	+	+	-	+
3	+	515	-	-	-	+
4	+	529	-	+	-	-
5	+	985	+	+	-	-
6	+	598	-	+	-	+
7	+	742	-	+	+	-
8	+	595	+	+	-	+
9	+	n.a.	-	+	-	-

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Molecular Diagnostics PCR

- Today method of first choice
- High sensitivity ~ 84%
- High specificity ~ 100%
- Quick results
- Especially in pretreated patients much better detection of causative agents than with culture
- No commercially available Kits
  -> In-house-PCR in reference labs
  (e.g., Univ.-Klinikum Regensburg, Prof. Reischl)

Walochnik J, Scheikl U, Haller-Schober EM: Twenty years of Acanthamoeba diagnostics in Austria. *Journal of Eukaryotic Microbiology* 2015; 62:3-11

Lehmann OJ, Green SM, Morlet N et al: Polymerase chain reaction analysis of corneal epithelial and tear samples in the diagnosis of Acanthamoeba keratitis. *IOVS* 1998; 39:1261-1265

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Diagnostics

ALWAYS:

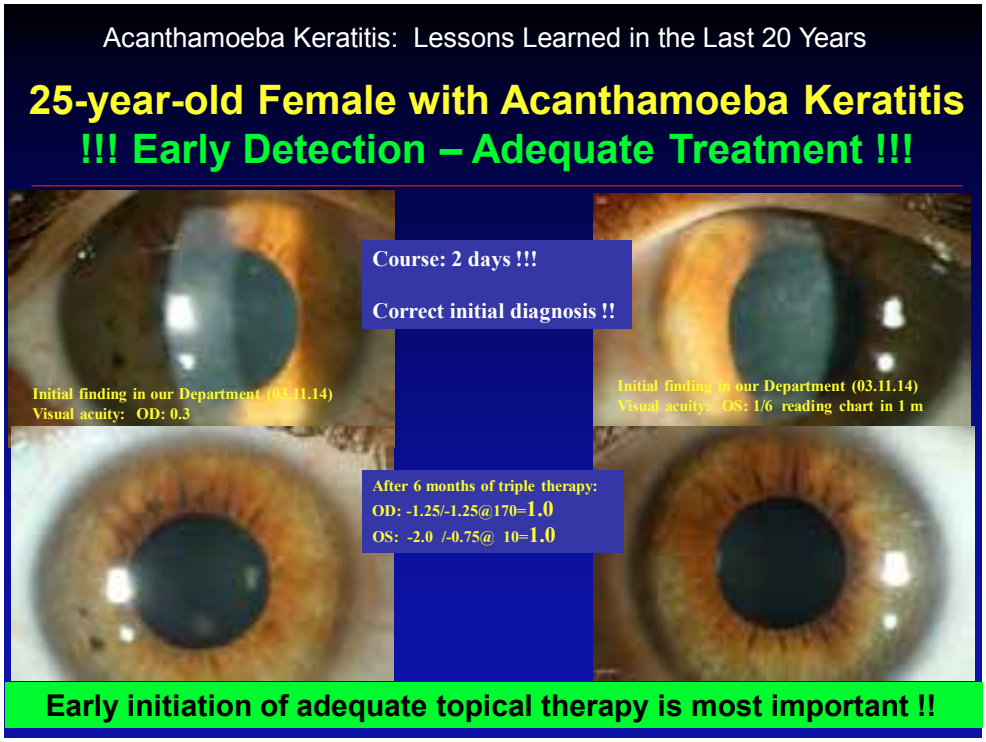
Submit contact lens,
contact lens fluid and
contact lens container
in special lab for PCR !!!!

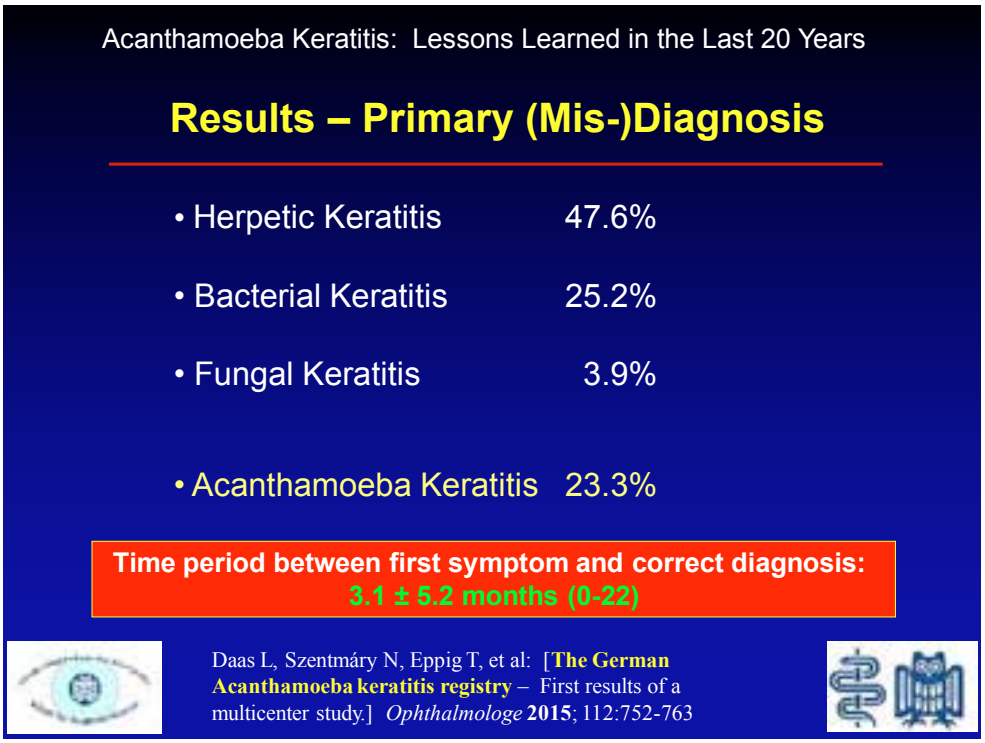
Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Topical Therapy

DIAMIDINES (Membrane disruption)	BIGUANIDES (Inhibition of oxygen supply)	ANTIBIOTICS
Propamidin Isethionat 0,1% (Brolene ®)	PHMB (Polyhexamethylen Biguanid) 0,02% (Lavasept ®)	Neomycin (Polyspektran ®)
Hexamidin Di-Isethionat 0,1% (Hexacyl ®)	Chlorhexidin 0,02% (Curasept ®)	„Surprise Attack“
Dibromopropamidin Isethionat 0,15% (Golden Eye ®)	… against trophozoits and cysts !!!	for 6 to 12 months !!

Szentmáry N, Daas L, Matoula P, Goebels S, Seitz B:
[**Acanthamoeba keratitis.**]
Ophthalmologe 2013; 110:1203-1211


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
25-year-old Female with Acanthamoeba Keratitis
!!! Early Detection – Adequate Treatment !!!
Course: 2 days !!!
Correct initial diagnosis !!
Initial finding in our Department (03.11.14)
Visual acuity: OD: 0.3
Initial finding in our Department (03.11.14)
Visual acuity: OS: 1/6 reading chart in 1 m
After 6 months of triple therapy:
OD: -1.25/-1.25@170=1.0
OS: -2.0 /-0.75@ 10=1.0
Early initiation of adequate topical therapy is most important !!


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
Results – Primary (Mis-)Diagnosis
• Herpetic Keratitis 47.6%
• Bacterial Keratitis 25.2%
• Fungal Keratitis 3.9%
• Acanthamoeba Keratitis 23.3%
Time period between first symptom and correct diagnosis:
3.1 ± 5.2 months (0-22)
Daas L, Szentmáry N, Eppig T, et al: [The German Acanthamoeba keratitis registry – First results of a multicenter study.] Ophthalmologe 2015; 112:752-763

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

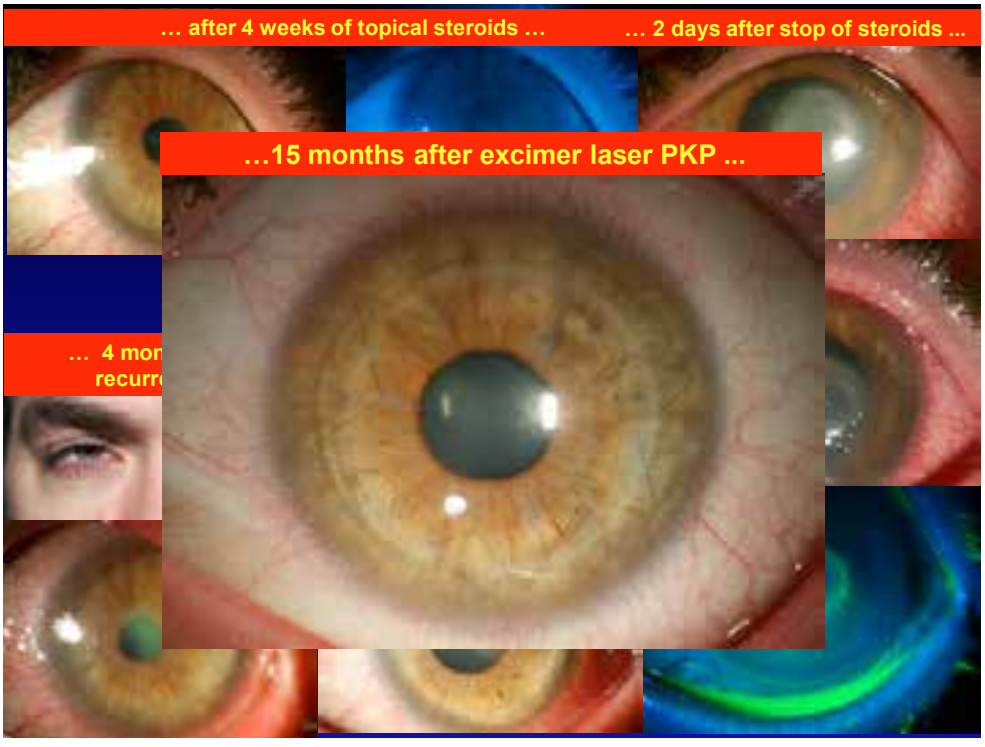
Topical Therapy

Early topical steroids ???

Masquerade of clinical picture
Late diagnosis
Higher rate of keratoplasty
Worse Prognosis !!!!

Robaei D, Carnt N, Minassian D, **Dart JKG**: The impact of topical corticosteroid use before diagnosis on the outcome of Acanthamoeba keratitis. *Ophthalmology* 2014; 121:1383-1388

Dart JKG, Saw VPJ, Kilvinngton S: Acanthamoebe keratits: Diagnosis and treatment update 2009. *Am J Ophthalmol* 2009; 148:487-499



Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Conservative Therapy

Role of Miltefosin unclear.

- 100 mg/day orally
- 65 µg/ml in eye drops

Natamycin 5% ????

Povidon-Jodine 1% ????

Sunada A, Kimura K, Nishi I, et al: **In vitro** evaluations of topical agents to treat Acanthamoeba keratitis. *Ophthalmology* 2014; 121:2059-2065

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Avoid Phosphate Containing Eye Drops

Course: 3 months

Initial misdiagnosis: Herpetic keratitis

Visual Acuity: -0.75/-2.0@160 =0.6
15 months after PKP

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Surgical Therapy

- Epithelial abrasion (Diagnosis, pathogen removal, pharmacokinetics)
- Photodynamic therapy (Riboflavin-UVA-Crosslinking) ?
- Cryotherapy (Cave: Limbus) ?
- Penetrating Keratoplasty (elliptical, DALK????)
- Simultaneous or sequential cataract surgery
- Amniotic membrane transplantation (AMT) – Patch, Graft, Sandwich
- [enucleation]

Seitz B, Resch M, Schlötzer-Schrehardt U, Hofmann-Rummelt C, Sauer R, Kruse FE: Histopathology and ultrastructure of human corneas after amniotic membrane transplantation. *Arch Ophthalmol* 2006; 124:1487-1490

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Cryotherapy

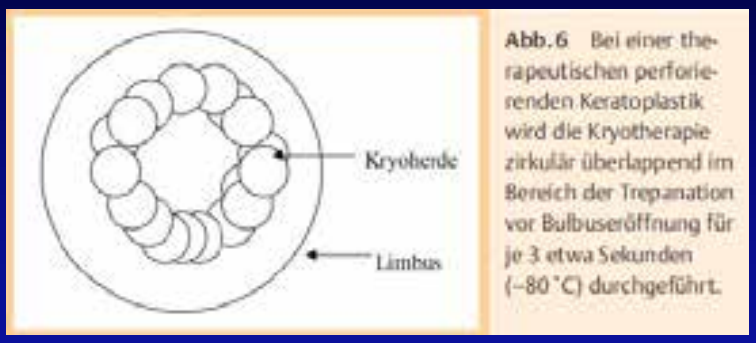
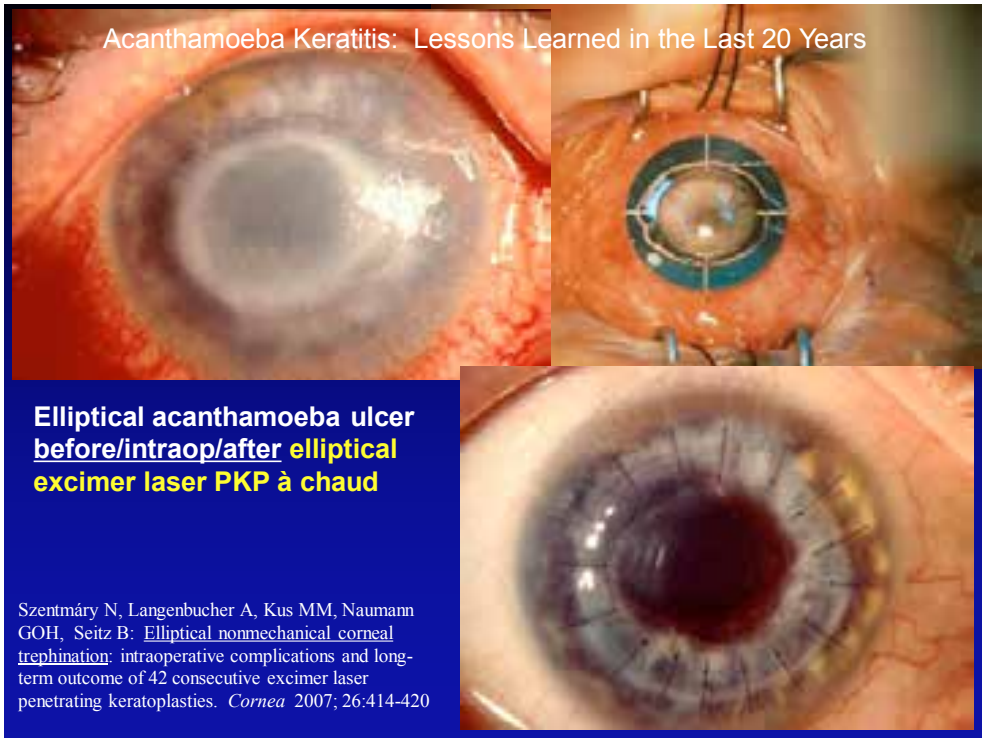


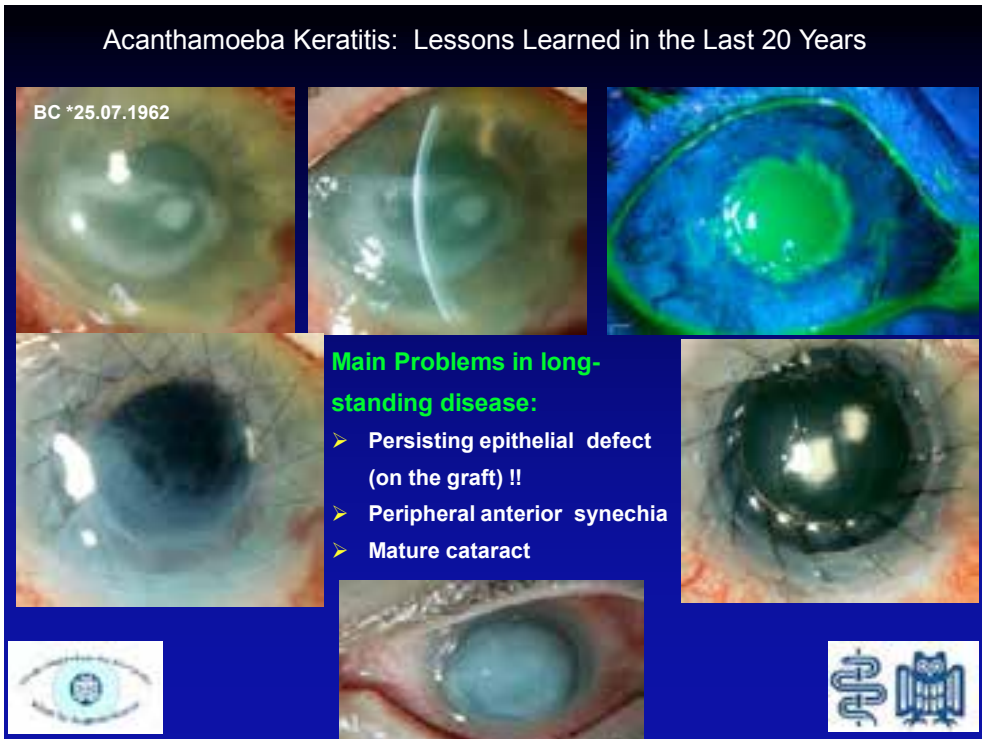
Abb. 6 Bei einer therapeutischen perforierenden Keratoplastik wird die Kryotherapie zirkulär überlappend im Bereich der Trepanation vor Bulbuseröffnung für je 3 etwa Sekunden (–80 °C) durchgeführt.

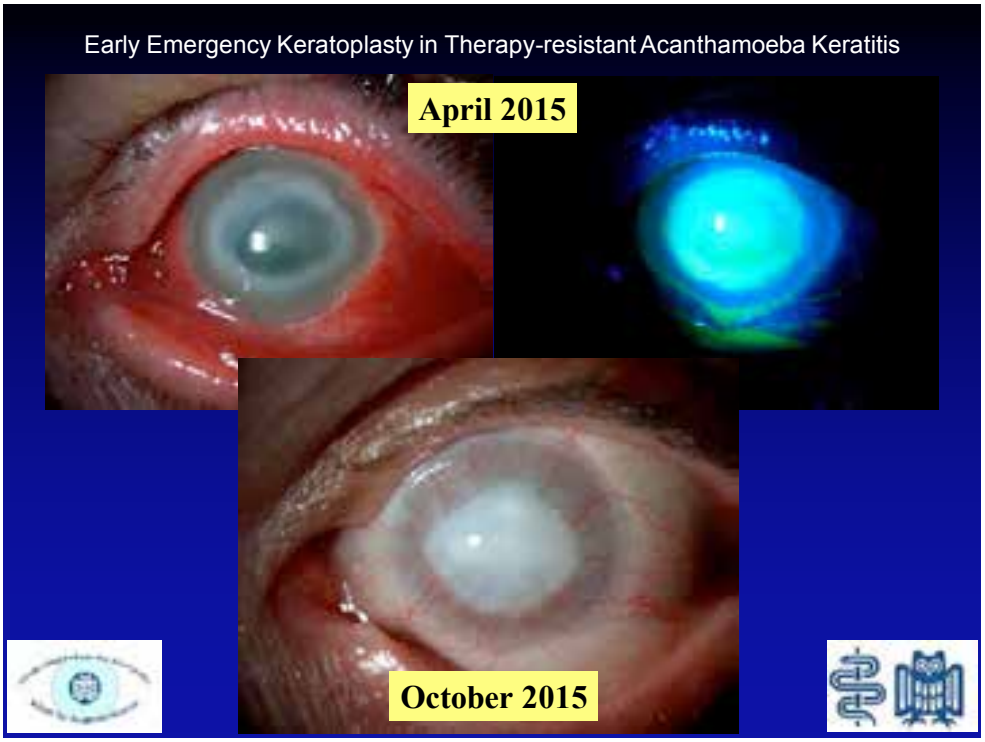
Szentmáry N, Goebels S, Matoula P, Schirra F, Seitz B: Die Akanthamöbenkeratitis – ein seltenes und oft spät diagnostiziertes Chamäleon. *Klin Monatsbl Augenheilkd* 2012; 229: 521-528.

Klüppel M, Reinhard T, Sundmacher R, Daicker B: Therapie der fortgeschrittenen Amöbenkeratitis mit Keratoplastik á chaud und adjuvanter Kryoapplikation. *Ophthalmologe* 1997 ; 94: 99-103.


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
Elliptical acanthamoeba ulcer
before/intraop/after elliptical
excimer laser PKP à chaud
Szentmáry N, Langenbucher A, Kus MM, Naumann GOH, Seitz B: Elliptical nonmechanical corneal trephination: intraoperative complications and long-term outcome of 42 consecutive excimer laser penetrating keratoplasties. Cornea 2007; 26:414-420


Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis
Excimer Laser PKP + Corneal Cryotherapy
Our standard surgical approach


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years
BC *25.07.1962
Main Problems in long-standing disease:
Persisting epithelial defect (on the graft) !!
Peripheral anterior synechia
Mature cataract


Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis
April 2015
October 2015

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Previous Literature

- Penetrating keratoplasty should, whenever possible, only be performed in an uninflamed eye after a medical cure.
- Elective penetrating keratoplasties in acanthamoeba keratitis should be postponed at least 3 months after completion of the medical treatment.

Unbearable long interval for patients and ophthalmologists

Robaei D et al. Therapeutic and optical keratoplasty in the management of Acanthamoeba keratitis. *Ophthalmology* 2015; 122:17-24

Khan YA et al. Riboflavin and ultraviolet light a therapy as an adjuvant treatment for medically refractive Acanthamoeben keratitis: report of 3 cases. *Ophthalmology* 2011; 118:324–331

Cohen EJ et al. Medical and surgical treatment of Acanthamoeba keratitis. Am J Ophthalmol 1987; 103: 615–625.

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Purpose of the Study

- Results of penetrating keratoplasty à chaud in therapy-resistant acanthamoeba keratitis
- Influence of preoperative disease duration on the success rate.

Schnaidt AG, Gatzioufas Z, Schirra F, Seitz B: [Delayed course of Acanthamoeba keratitis.] *Ophthalmologe* 2013; 110:164-168

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Patients with Acanthamoeba Keratitis at the UKS

Patients treated at the UKS between January 2006 – November 2015

- 28 eyes of 27 patients
- 12 female and 11 male
- average age at the time of the diagnosis: 39,6 ± 13,3 (13 - 63) years

UKS = Universitätsklinikum des Saarlandes
= Saarland University Medical Center

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Patients and Methods

- 23 eyes of 23 patients underwent penetrating keratoplasty (PKP) in the acute phase of the disease
  - overall 30 PKPs
  - 6 as triple procedure
  - 2 weeks (median) after the first examination at the UKS
- Preoperative disease duration
  - 2 weeks to 3 years
  - median **5.3 months**
- In 13 eyes Riboflavin-UVA-Crosslinking as PDT
  - 11.2 ± 9.4 days prior to PKP

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Follow-up

- Average follow-up 22.7 ± 18.5 (3 - 60) months
- Conservative postoperative therapy for > 6 months
  - Brolene® 5x/d
  - Lavasept® 5x/d
  - Polyspektran® 5x/d
  - Prednisolone acetate 5x/d
  - Hylogel® 5x/d

Reduction by 1 drop/day every 6 weeks

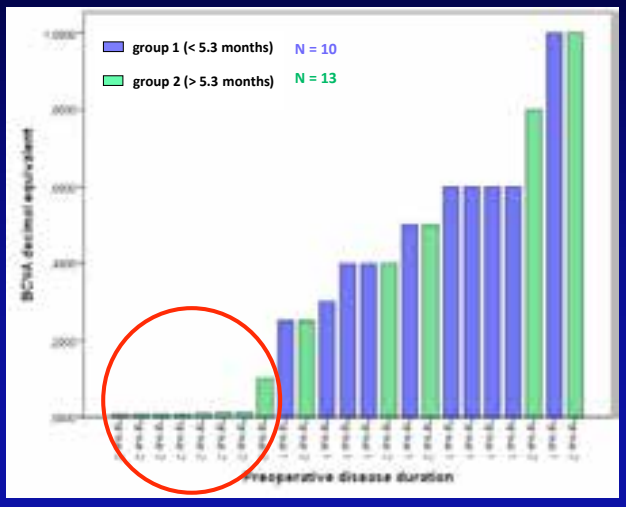
Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Results

- 18 (= 78.3%) clear corneal grafts
  - 13 after single keratoplasty, 4 after repeat keratoplasties
- Average BCVA for all 23 patients
  0.36 ± 0.32 (Median 0.40, Min: NLP – Max: 1.0)
- In case of preoperative disease duration **less than 5.3 months** all transplants remained clear, there were no persistant epithelial surface defects and the average BCVA was **0.52 ± 0.20** (**Median 0.55**)
- In case of preoperative disease duration **over 5.3 months** significantly worse results (BCVA **0.24 ± 0.32** (**Median FC**)

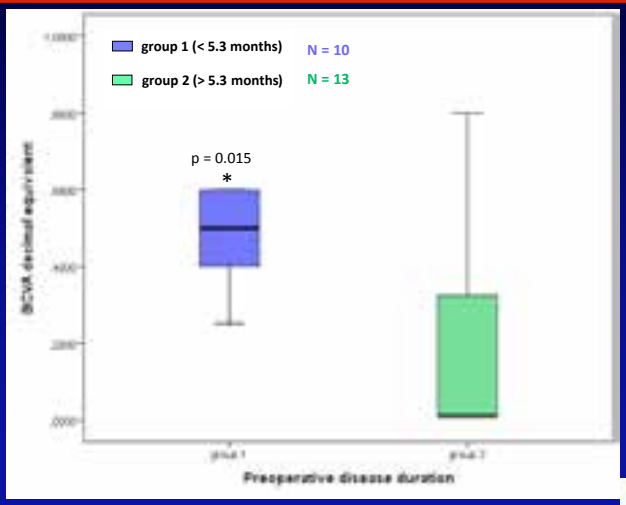
Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

BCVA at the End of Follow-up



Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Comparison of BCVA in Early and Late PKP



Mann-Whitney-U-Test

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Graft Survival after First Penetrating Keratoplasty

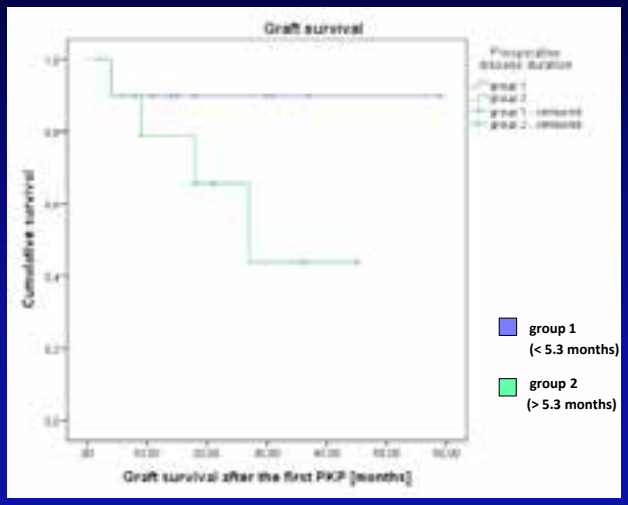
Graft Survival after 3 years:

Overall: 78.3%

Group 1: 90.0%
Group 2: 43.8%

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

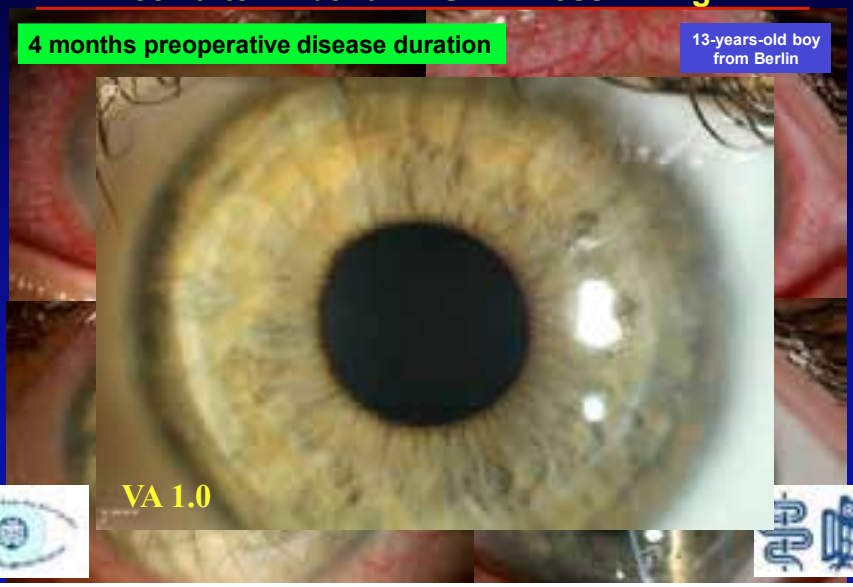
Graft Survival after First Penetrating Keratoplasty



Kaplan-Meier Analysis

Early Emergency Keratoplasty in Therapy-resistant Acanthamoeba Keratitis

Excimer PKP with simultaneous cryotherapy 1 week after Riboflavin UVA Crosslinking PDT

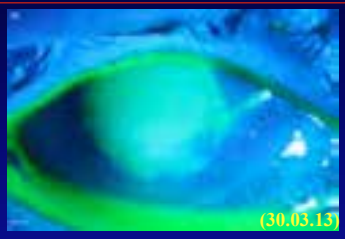


Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

27-year-old Female with Acanthamoeba Keratitis Before and After PKP à chaud with Cryotherapy

Course: 3 months

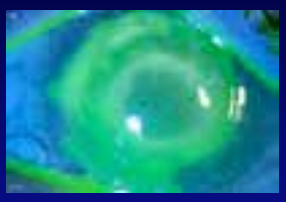
Initial misdiagnosis: Herpetic keratitis



Visual Acuity: -5.25/-2.5@25=0.8
1 year after PKP

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

40-years-old Patient before and after Triple à chaud with simultaneous cryotherapy



… 3 years preoperative disease duration … !!!!!

16 months after Triple Procedure - VA: NLP

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

VIDEO: Triple Procedure à chaud after 3-year course of acanthamoeba keratitis mit mature cataract - 7 days after UVA-CLX incl. Intraoperative corneal cryotherapy and simultaneous AMT (Patch)

Seitz B, Das S, Sauer R, Hofmann-Rummelt C, Beckmann MW, Kruse F: Simultaneous amnotic membrane patch in high-risk keratoplasty. *Cornea* 2011; 30:269-272

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Summary

- Most prevalent clinical signs and symptoms: „dirty epithelium“, *ring infiltrate,* pain
- 3/4 primary misdiagnosis (mostly HSV) !
- Correct diagnosis on average not before a 3 month course !
- Early detection and adequate therapy is essential for prognosis !
- For safe diagnosis, a combination of techniques is recommended: preliminary: Confocal Biomicroscopy, definitively: histology + PCR).
- **Triple therapy** as „surprise attack“ !
- No early application of topical steroids !
- **Early emergency keratoplasty** in therapy-resistant Acanthamoeba keratitis

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Conclusions I

In each case of unclear and/or therapy resistant corneal finding we should consider acanthamoeba keratitis timely !!

Acanthamoeba keratitis is a challenge for patient and doctor - **between hope and anxiety …**

Involvement of a psychotherapist fom the beginning may be a good option.

Acanthamoeba Keratitis: Lessons Learned in the Last 20 Years

Conclusions II

Adaequate topical therapy **+** microsurgery may result in very favorable results (VA 20/20) – but may end up with enucleation!

Based on our personal experience, we advocate early PKP à chaud (c/o previous CXL) and intraop cryotherapy to prevent further extension of the deleterious process.

Topical therapy for up to one year!!

Prof. Dr. Berthold SEITZ
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Email: berthold.seitz@uks.eu

MCQ answers page 197

1. **Answer: c**

2. **Answer: d**

3. **Answer: a**

4. **Answer: b**

MCQ's

1. With regard to the anatomy and physiology of the meibomian glands, which of the following is true?

a. The Meibomian glands lie anterior to the grey line of the lid
b. The Meibomian glands produce secretions rich in mucins
c. The predominant lipid present in meibum is cholesterol
d. Release of meibum into the tear film occurs with muscular contraction during blinking

2. Which of the following statements regarding the assessment of patients with MGD is correct?

a. A Schirmer type 1 test measuring < 12 mm is abnormal
b. A TBUT of <15 seconds is diagnostic of evaporative dry eye disease
c. The Oxford and Van Bijsterveld systems are used to evaluate ocular surface fluorescein staining
d. Hypo-osmolarity of the tear film is consistent with dry eye disease

3. A 38 year old woman presents with a 1 year history of ocular irritation and soreness on a background history of a dry mouth, generalised aches and pains and fatigue increasing over the last 2 years. Assessment reveals the following: mild lid margin erythema with clear Meibomian gland secretions, Oxford score +3 OU, Schirmer's test score 2mm OD and 0mm OS, TBUT 5 seconds OD, 2 seconds OS. The principle cause of disruption of the lacrimal functional unit in this cases is which of the following?

a. Aqueous tear deficiency
b. Mucin deficiency
c. Abnormal lid function and excessive ocular surface exposure
d. Meibomian gland dysfunction

Meibomian gland dysfunction (MGD) is a common chronic disorder and a leading cause of evaporative dry eye disease. The 2011 International Workshop on MGD, a consensus group of over 50 international experts in the field, provided the current and most widely accepted definition of MGD, which is as follows: *MGD is a chronic, diffuse abnormality of the Meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease*. This complex definition alludes to the physical and biochemical features of the disease and its importance as a cause of ocular surface inflammation and dry eye disease.

The meibomian glands have a key role in the stabilisation of the tear film and the prevention of tear evaporation through the production of lipid-rich meibum. MGD can be classified as a low or high delivery type, depending on the volume of meibum produced. The former may be a primary or secondary hyposecretory problem or, more commonly, is due to obstruction of the Meibomian gland orifices as an idiopathic phenomenon or as a result of a variety of conditions including atopy and acne rosacea. High delivery MGD is also common and characterised by over production of meibum with a typical frothy appearance to the lid margin and tear meniscus. Irrespective of the cause, MGD leads to ocular surface and eye lid inflammation, disturbance of tear function due to tear evaporation and hyperosmolarity, increased growth of bacteria on the lid margin, and symptoms of ocular irritation.

The diagnosis of MGD requires a comprehensive clinical evaluation including a detailed history, the use of self-assessment patient questionnaires, lid and external eye examination and some simple yet highly informative clinical assessments of the lacrimal functional unit. The medical history (e.g. acne rosacea), past ophthalmic history (e.g. contact lens wear), medication use including topical ocular agents, and the severity symptoms and their impact on patient quality of life must be evaluated. Clinical examination of the meibomian glands including their morphology and quality and volume of meibum expressed with digital pressure should be performed, along with more general ocular surface and tear film assessments like blink rate/ blink interval, the Schirmer's test, TBUT, fluorescein +/- lissamine green staining, tear meniscus height and tear osmolarity (if available). This clinical assessment enables the differentiation of MGD from the many other causes of dry eye disease (e.g. aqueous deficiency which commonly coexists with MGD) and the identification of the precise aetiology of the MGD. Many newer techniques for evaluating meibomian gland function are currently under evaluation.

The real advantage of the International Workshop 2011 classification of MGD is that it enables a more targeted and scientific approach to the management of the disease. The mainstay of treatment remains regular warm lid massage and lid hygiene. Modification of environmental factors that exacerbate symptoms is important. Antibiotic ointments to reduce bacterial overgrowth and short courses of corticosteroid ointments to reduce associated inflammation are very beneficial. The role of nutritional supplements and oral tetracycline antibiotics is well established,

as is the use of the topical immune modifying agent cyclosporine. A range of newer treatments are currently under evaluation.

A copy of my PowerPoint presentation is available in PDF for course attendees. Please contact cathyfox@rcsi.ie to receive a copy.

Recommended reading

Milner MS et al. Dysfunctional tear syndrome: dry eye disease and associated tear film disorders – new strategies for diagnosis and treatment. Current Opinion in Ophthalmology, epub ahead of print, March 2017.

Geerling G, Baudouin C, et al. Ocular Surface, epub ahead of print, January 2017.

Nichols KK. The international workshop on meibomian gland dysfunction: introduction. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1917-21. PMID:21450912

Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, Lemp MA, Sullivan DA. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1922-9. PMID:21450913

Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Knop E, Knop N, Millar T, Obata H, Sullivan DA. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1938-78. PMID:21450915

Green-Church KB, Butovich I, Willcox M, Borchman D, Paulsen F, Barabino S, Glasgow BJ. The international workshop on meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid-protein interactions in health and disease. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1979-93. PMID:21450916

Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, Foulks GN. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):1930-7. PMID: 21450914

Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, Yee R, Yokoi N, Arita R, Dogru M. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):2006-49 PMID:21450918

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Asbell PA, Stapleton FJ, Wickström K, Akpek EK, Aragona P, Dana R, Lemp MA, Nichols KK. The international workshop on meibomian gland dysfunction: report of the clinical trials subcommittee. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):2065-85. PMID:21450920

Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. I

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MCQ answers page 227

1. **Answer: d**

2. **Answer: c**

3. **Answer: a**

MCQ's

1. Immunological changes in atopic keratoconjunctivitis include

a. infiltration of neutrophils in conjunctiva
b. infiltration of B-lymphocytes
c. infiltration of T-lymphocytes
d. elevated serum IgA concentration

2. Vernal keratoconjunctivitis is

a. significantly more common in girls
b. significantly more common in boys
c. characterised by elevated serum IgA concentration
d. associated with a family history of vernal keratoconjunctivitis

3. Which of the following clinical abnormalities are not found in allergy?

a. conjunctival papillae
b. conjunctival follicles
c. reticulate conjunctival fibrosis
d. pseudogerontoxon

ASSESSMENT AND STEP-BY-STEP MANAGEMENT OF ALLERGIC EYE DISEASE

Frank Larkin

Cornea & External Diseases Service
Moorfields Eye Hospital, London

Allergic conjunctivitis classification

Disorders	Clinical Features	Treatment
Seasonal allergic conjunctivitis Perennial allergic conjunctivitis		Steroid not required
Giant papillary conjunctivitis	Loss of CL tolerance	
Vernal conjunctivitis ± keratitis	Limbal / Palpebral 85% male onset <10y in 85%	Steroid Calcineurin antagonists
Atopic keratoconjunctivitis	HSV, keratoconus, corneal vascularisation, cataract	

Atopic keratoconjunctivitis (AKC)

Correlation with systemic atopic disorders

95% atopic dermatitis
87% asthma

25% atopic patients get AKC

Calder et al. Curr Opin Ophthalmol 2010

Allergic conjunctivitis

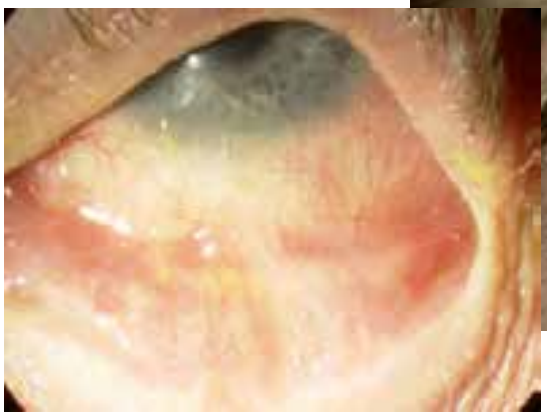
Investigation

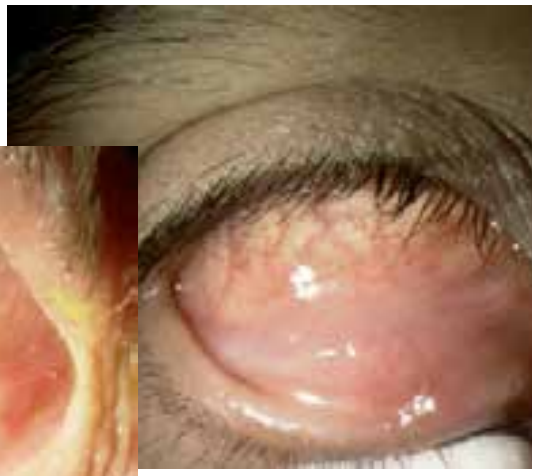
Serum [IgE]
Conjunctival cytology
Tarsal conjunctival biopsy *(off steroid 2 weeks)*
Eosinophil + mast cell infiltration
Epithelial hyperplasia, ↑ goblet cells

Skin test results do not correlate with specific IgE in tears, unhelpful in guiding management

Conjunctival signs in allergic disease

Papillae
Reticulate scarring
Fornix shortening

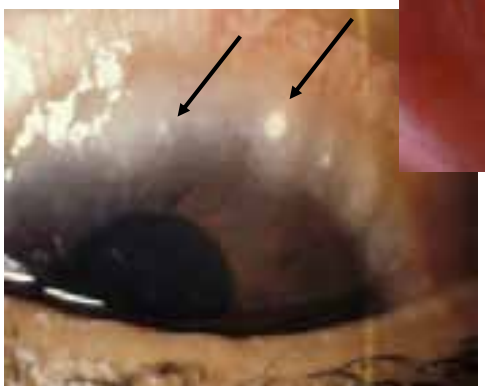


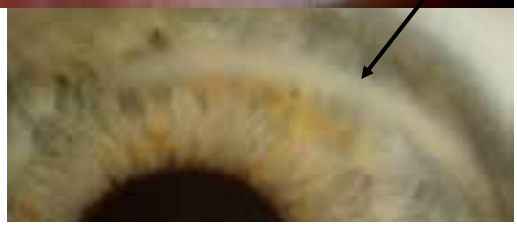


Atopic keratoconjunctivitis

Limbal signs in allergic disease

Swelling
Trantas' dots
Pseudogerontoxon



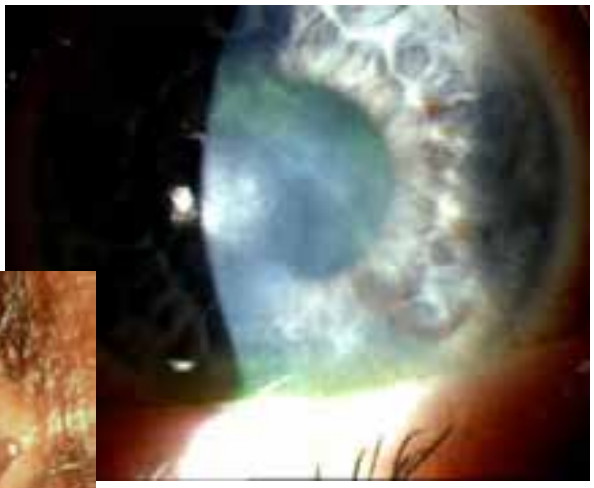


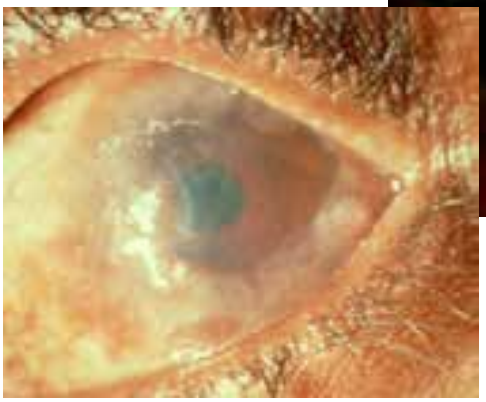
Corneal signs in allergic disease

Acute punctate epitheliopathy
Macroerosion± plaque

Stromal vascularisation

Surface scarring





Keratopathy in allergic conjunctivitis: pathogenesis

ACUTE PUNCTATE EPITHELIOPATHY → EROSION → PLAQUE

Inflammation (mast cell + eosinophil degranulation)

↓

epitheliotoxic cationic proteins

↓

erosion → plaque

Significant T-lymphocyte component in VKC, AKC

Allergic conjunctivitis: maintenance treatment

1. Antihistamine
   G. sodium cromoglycate (or whatever mast cell stabiliser works best)
   ↓
2. G. olopatadine
3. G.fluorometholone available to parents for use in exacerbation
   ↓
4. G.fluorometholone 1-3 times/day
   ↓
5. G.dexamethasone 1/day in exacerbations
   ↓
6. If dexa required more than 2-3 months / year
   ↓
   Trial G.ciclosporin 0.2%, or 0.05% ('Restasis')
   or 'Optimmune' 0.2% ointment

   Introduce when inactive inflammation

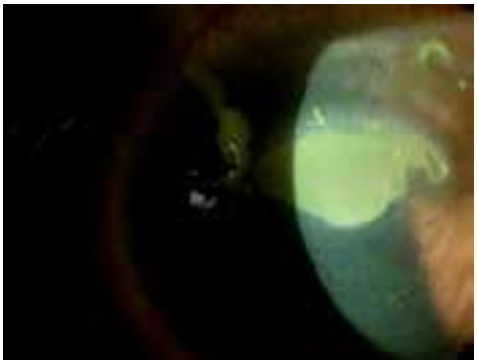
   tacrolimus 0.03% ointment to lids
7. Maintenance oral anti T-cell agent in most severe AKC cases
   Minimum dose for symptom control

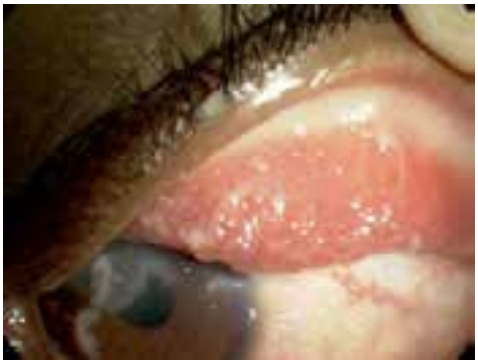
Keratopathy in allergic conjunctivitis: treatment

ACUTE PUNCTATE EPITHELIOPATHY → EROSION

Plaque can appear quickly →

dexamethasone q1h
chloramphenicol prophylaxis
acetylcysteine can be helpful





Keratopathy in allergic conjunctivitis: treatment

ACUTE PUNCTATE EPITHELIOPATHY → EROSION

↓

PLAQUE

If plaque does not spontaneously dehisce or respond to G.acetylcysteine PF 5% or 10%

↓

Remove plaque at slit-lamp or superficial keratectomy to avoid vascularisation, infection

Keratectomy after first control inflammation

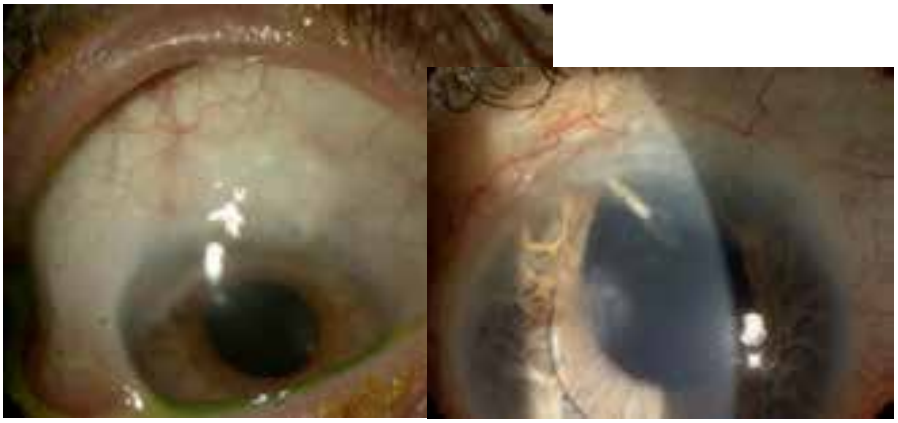
Atopic allergic eye disease

Sight threatening complications

HSV, fungal, Gram-positive bacterial keratitis

Atopic allergic eye disease

Sight threatening complications
- HSV, fungal keratitis
- Glaucoma induced by steroid → optic neuropathy
  → scarring post-trabeculectomy



Secondary glaucoma in atopic allergic eye disease

Features

- Steroid-dependent allergy symptoms (periocular skin steroid !)
- Fast progressing glaucoma
- Glaucoma drops tolerated *

Management problems

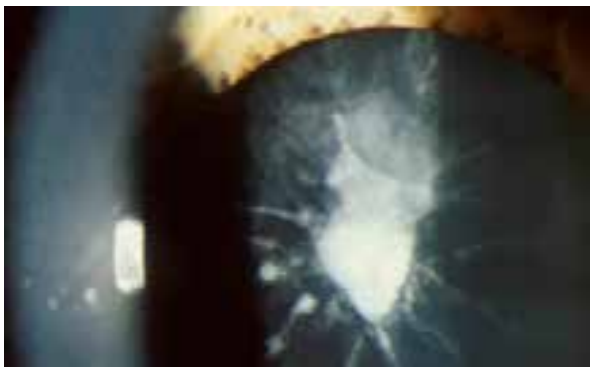
- Topical / laser glaucoma management only for short term
- Assessing IOP, fields in young children
- Conjunctival scarring post-trabeculectomy

Recommend

- Once IOP ↑ Baseline glaucoma assessment
  Reassess steroid treatment
- Early surgery

Atopic allergic eye disease

Sight threatening complications
- HSV, fungal, Gram-positive bacterial keratitis
- Glaucoma induced by steroid → scarring post-trabeculectomy
  → optic neuropathy
- Cataract



Atopic allergic eye disease

Sight threatening complications
- HSV, fungal, Gram-positive bacterial keratitis
- Glaucoma induced by steroid → scarring post-trabeculectomy
  → optic neuropathy
- Cataract
- Keratoconus, corneal transplantation → oral steroid pre-/post-graft

ALLERGIC EYE DISEASE Practice points

Realistic management goals

Maintenance treatment, then increase step-by-step

In severe exacerbations: → rapid patient access
→ intensive steroids

Treat plaque aggressively

Watch for HSV and steroid-induced glaucoma

ALLERGIC EYE DISEASE Further reading

Guglielmetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2010;10:478-85

Manzouri B, Flynn TH, Larkin F, Ono SJ, Wyse R. Pharmacotherapy of allergic eye disease. *Expert Opin Pharmacother* 2006;7:1191-200.

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MCQ answers page 232

1. **Answer: c**

2. **Answer: b**

3. **Answer: b**

MCQ's

1. Bandage lenses in dry eyes:

a. Are completely contra-indicated
b. Can only be applied in a daily wear modality
c. Soft and scleral lenses can be used
d. Topical use of antibiotics is mandatory

2. Soft bandage lenses:

a. One type of soft lens can be used for all cases
b. Siliconehydrogel materials are first choice
c. Lenses should be fitted flatter than normal to allow for extra oxygen exchange
d. Lens wear should always be combined with antibiotic drops

3. Therapeutic lenses for recurrent erosion

a. Are first choice in treatment of this disorder
b. Can be stopped after one week without pain upon awakening
c. Should be applied for at least 2 to 3 months
d. Are indicated only after PTK has failed

Bandage lenses are essential to the therapeutic armamentarium in the treatment of ocular surface conditions. All ophthalmologists need to have a basic knowledge about the use of these lenses which provide a very effective and simple approach to a number of eye diseases. In most cases we can apply soft lenses that are readily available and can be fitted immediately.

These therapeutic lenses do not only protect the cornea from the outside world, but they also counter the abrasive effect of the eyelids which delays re-epithelialization and induces pain. Tissue repair is facilitated while the pain is be treated at the same time and visual acuity is unhindered. For a small group of patients, there is a specific indication for scleral lenses. The fitting of these lenses, however, requires a qualified ophthalmologist or optometrist.

Indications for soft bandage contact lenses

• Protection. An obvious indication is protection of the cornea, in cases of entropion, trichiasis and exposed suture knots. In these cases bandage lenses are a temporary measure pending a structural solution.

Recurrent erosion after trauma or spontaneous erosion in the context of an epithelial dystrophy, is a frequent pathology in the everyday practice. The first-line treatment consists of hypertonic drops and / or ointment applied before going to sleep. If this treatment fails, the application of a bandage lens is the next measure in the stepwise approach of this pathology - before the application of phototherapeutic keratectomy. It is crucial that the bandage lens is used sufficiently long to give the epithelial adhesion complex sufficient time (minimum 2 months) to fully recover. An additional advantage of the bandage lens is that small irregularities of the ocular surface may be masked so that the patient can benefit from an improvement of visual acuity.

• Pain relief. Situations of intense pain due to corneal erosion, bullous and filamentous keratitis often show an immediate and favorable response to the application of a soft bandage lens.

A corneal erosion as a result of trauma is not a primary indication for the adaptation of a bandage lens, since the wound could, in fact, be infected. Corneal abrasions of iatrogenic origin (eg after laser or cross-linking treatment), however, are sterile lesions. In these circumstances, many eye surgeons choose to adapt a bandage lens, on the one hand to treat the pain, on the other hand in order to accelerate wound healing by neutralizing the abrasive effect of the eye lids on the epithelium.

In bullous keratopathy the use of a lens can limit the acute pain caused by the rupture of a bulla. Pending a corneal transplant, quality of life of a patient can be significantly increased by day-and-night wear of a bandage lens, which will be renewed by the ophthalmologist on a regular basis.

• Healing. Typical examples of epithelial healing problems are persistent epithelial defect and neurotrophic keratitis. Other situations in which we need to actively encourage epithelial repair are in chemical burns and after penetrating keratoplasty.

Neurotrophic keratitis is generally a very challenging problem in which all kinds of measures can be combined, including autologous serum, whether or not in combination with a bandage lens. In contrast to a botox-induced ptosis or a tarsorrhaphy, a bandage lens has the advantage that the visual acuity and the visual field of the eye as well as the binocular vision are preserved. The therapeutic effect of a bandage lens has become increasingly versatile: in the eye conditions described above the lens will protect the cornea from the abrasive effect of the upper eye lid and will also provide a splint for growth and protection of the epithelial cells.

• Protection against dehydration. The use of soft contact lenses for dry eye patients is controversial because of the risk of infectious complications. Typical patients in this category suffer from sicca or lagophtalmos. In both cases, no long term structural solution is possible, so these patients will want to wear bandage contact lenses on a chronic basis. The lenses protect the cornea from drying but will themselves lose water content as well. In addition to this, the surface of these lenses will spoil faster under these conditions. Most indications of bandage lenses require a day-and-night wear, for chronic use in dry eye patients daily wear is the preferred modality of wear in order to reduce the risk of infectious keratitis.

• Sealing. Bandage lenses have an important function in tamponating leaking wounds on a temporary basis eg after cataract surgery or for plugging small perforations. In the context of small perforations adapting a bandage lens in itself may be sufficiently effective to reshape the anterior chamber. If not effective, glue and / or amnion can be used; in such cases the bandage lens continues to be a supportive measure in order to prevent dislocation of the glue and / or amnion. For hyperfiltrating blebs after glaucoma surgery large-diameter bandage lenses are available which can be used for temporary tamponade.

Fitting of soft bandage contact lenses

The materials used for soft lenses are divisible into two groups: the lenses based on hydroxyethyl methacrylate (HEMA), which have been available since the 1970s, and the lenses made from silicone hydrogel (SiHy) polymers, available since 2000. Because of their high oxygen permeability SiHy lenses respect the physiology of the cornea a lot more than their predecessors, so that hypoxia related complications have virtually disappeared. A number of these lenses are FDA-approved for day-and-night wear and are therefore the first choice for bandage lenses. Acuvue Oasys contact lenses have been approved for weekly continuous wear while other brands (AirOptix N&D, PureVision) have been approved for monthly wear. More recently soft lenses have been developed with a lower water content so that they are more resistant to dehydration. Another relevant material characteristic is the elastic modulus, a parameter indicating the stiffness of the material: lenses with a low modulus are typically very flexible and drape better over the cornea. Lenses with more stiffness may be less comfortable for some patients but are better at optically correcting irregularities. In terms of fit the idea prevails that a bandage lens should fit a bit more tightly and be less mobile in order to prevent the lens from moving over the cornea and causing epithelial trauma

itself. Typically one size fits all, but there are exceptions: post keratoplasty the corneal profile is generally oblate (centrally relatively flatter) and post hydrops in keratoconus the cornea is extremely steep. In both cases, a standard lens will not fit: either we will see a central bubble or a bad fit of the lens edge (fluting). In both cases a custom-made bandage lens can be fitted.

After applying the bandage lens, a first check-up is required after 15 – 30 minutes to assess the fitting of the lens and to obtain feedback from the patient. If both are positive, the patient will be checked again after a night's sleep with the lenses, and then again after a week and after a month. The most common complication is that the patient may lose the lens by rubbing the eye. If this occurs, a larger diameter custom-made soft lens can be used.

Unpreserved tear drops are part of the standard treatment of all patients with bandage lenses in order to rehydrate the lens on the eye surface. The use of the bandage lens as a depot for medication has been much discussed, but in practice it is uncertain how this medication will be set free by a lens in a consistent way. There is a need for more research on the absorption and release of ophthalmic drugs through specific lens materials and lens designs.

Complications

A bandage lens is usually fitted for day-and-night wear depending on the nature of the disease. We know that continuous wear constitutes risk factor no. 1 for infectious keratitis. In many situations, fortunately bandage lens wear is only temporary. When, however, the use of the lenses becomes chronic, a switch to daily wear should be considered. Specifically, patients with dry eye disease and lagophtalmos must learn how to handle their bandage lenses. It is preferable to switch to daily disposable lenses, so that risk factor no. 2 for infectious ulceration (i.e. poor compliance with maintenance regulations) is reduced. For daily disposables rules are simple: wash your hands before each manipulation and use a new lens every day. There is no hassle with lens cases – a breeding ground for infection - and neither with lens solutions - potential source of toxic complications in the long run.

As regards the use of topical antibiotics, there is unanimity about administering unpreserved antibiotic drops in case an epithelial defect is present. If the epithelium is intact, this choice is left to the discretion of the treating physician. In any case, the patient must be informed again and again about the alarm signs of keratitis: pain, photophobia, visual acuity reduction, increased redness, and possibly pus formation. The patient needs to consult his ophthalmologist in emergency when these symptoms occur. The compromised cornea in itself is a risk factor for the development of microbial keratitis.

Scleral lenses

Scleral lenses are rigid lenses with a large diameter : they vault the cornea and limbus and rest on the conjunctiva and sclera. Since they do not touch the cornea and

provide a reservoir of liquid behind the lens, they are extremely beneficial for corneal wound healing. At the same time the rigid nature of the lens ensures maximum correction of vision in irregular corneas. This perfect combination of therapeutic and optical properties has vastly increased use of these lenses in tertiary cornea clinics since 2010. Specifically for patients needing a long-term bandage lens (sicca whether or not in combination with graft-versus-host-disease, lagophtalmos in case of Facial paralysis), the scleral lens is a life-changer.

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MCQ answers page 243

1. **Answer: c**

2. **Answer: b**

3. **Answer: c**

MCQ's

1. Which kind of keratoprosthesis has the longest anatomical survival rate?

a. Boston KPro (type 1)
b. OOKP
c. Boston KPro (type 2)
d. Legeais KPro

2. A 45-year-old man with history of atopic dermatitis and multiple graft rejection is considered for Boston KPro type 1. Which finding would increase the chance of surgical failure less than others?

a. Shirmer test less than 5 mm
b. Deep stromal vascularization
c. Inferior fornix symblepharon
d. Upper lid notching defect

3. Buccal mucosal graft should be sutured to:

a. To the conjunctival rim of recipient eye
b. To rectus muscle insertions and sclera
c. To the limbus
d. To the tarsal plates

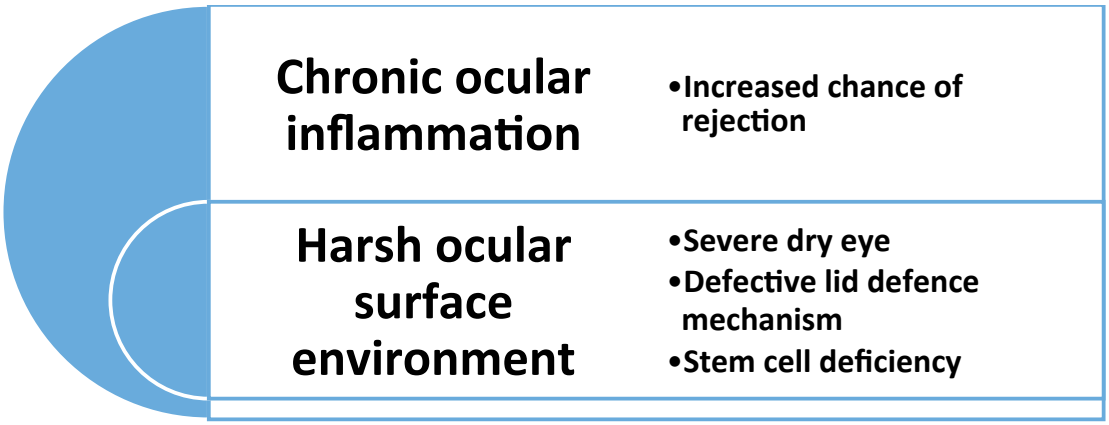
4. Which one is the most suitable medical and surgical options for treatment of glaucoma after osteo-odonto-keratoprosthesis?

a. Systemic acetazolamide - shunt valve surgery
b. Topical anti-glaucoma drops- shunt valve surgery
c. Systemic acetazolamide - endoscopic cyclophotocoagulation
d. Topical anti-glaucoma drops- endoscopic cyclophotocoagulation

Bypassing the ocular surface. Restoring sight with Keratoprostheses.

- Prevalence of Cornea Blindness

- Reasons for keratoplasty failure



- Indications and contraindications of KPro

Boston Type 1 KPro for wet blinking eyes

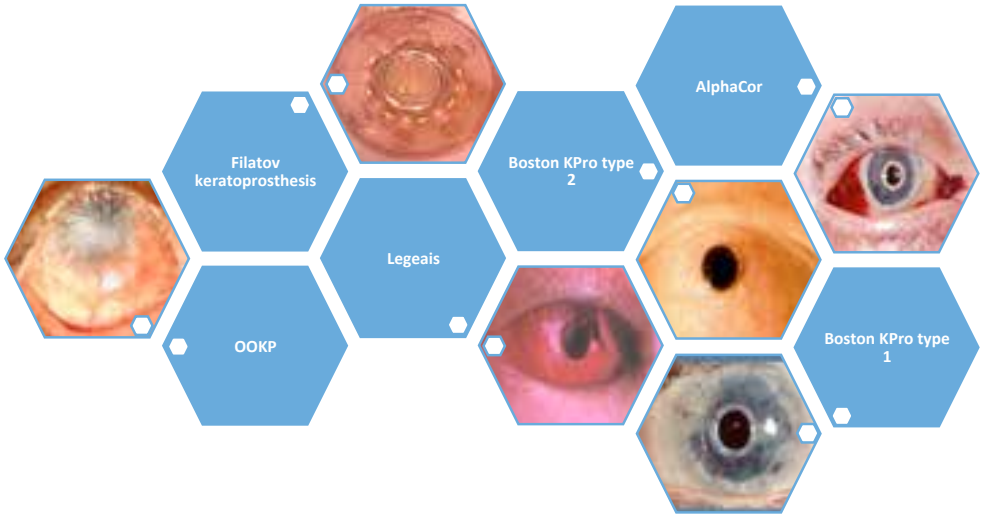
- Multigraft rejection
- Vascularised cornea
- Aniridia
- Vitrectomy with silicone oil

The OOKP for end stage ocular surface disease with dry keratinised ocular surface and or defective lid or blink

- Severe Stevens-Johnson syndrome
- Mucous membrane pemphigoid
- Trachoma
- Chemical and thermal injury

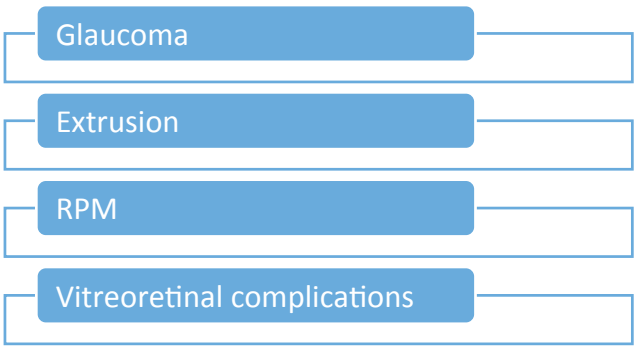
Bypassing the ocular surface. Restoring sight with Keratoprostheses.

- KPro types and selection

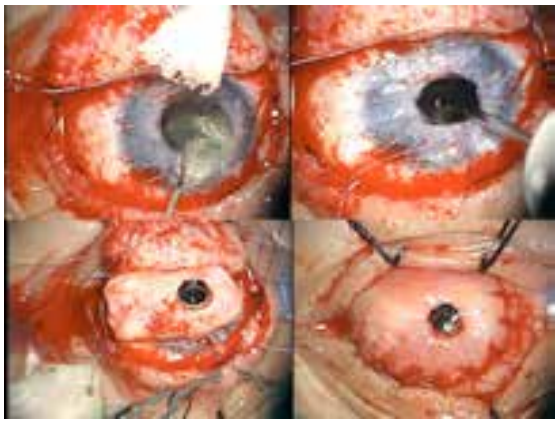


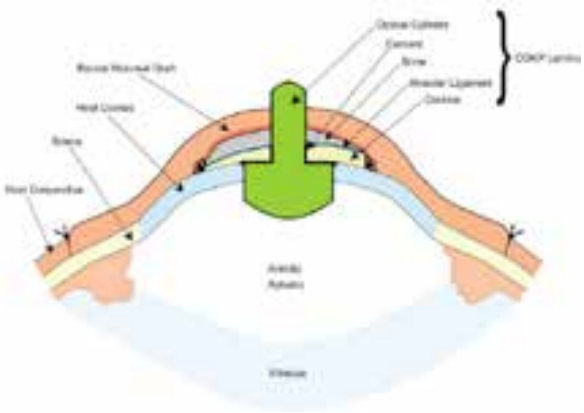
- Boston KPro technique

- Result and complications
    - o Long-term anatomical and visual outcomes
    - o Complications

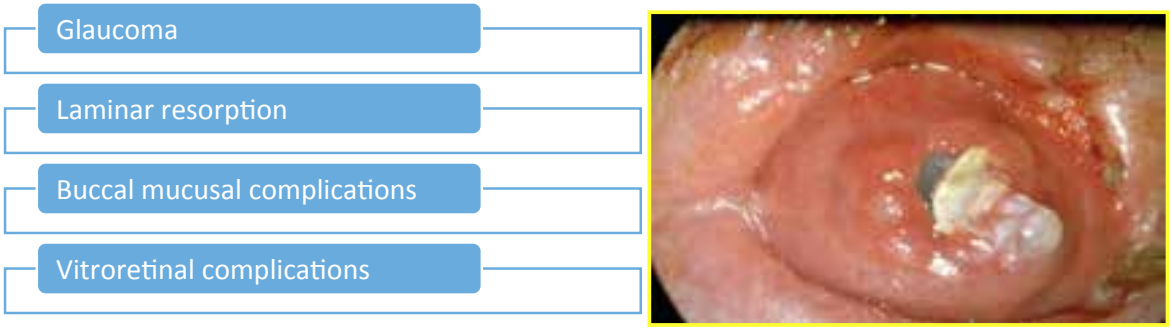


- OOKP technique

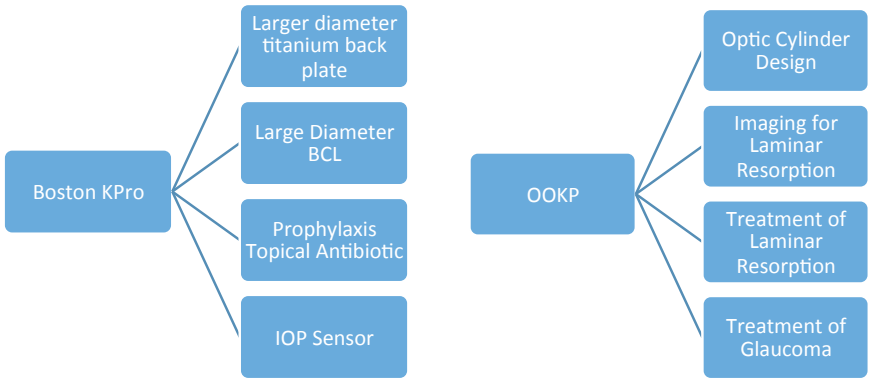




- Result and complications
    - o Long-term anatomical and visual outcomes
    - o Complications



- Recent Advancement



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MCQ answers page 249

1. **Answer: b**

2. **Answer: b**

3. **Answer: b**

4. **Answer: a**

MCQ's

1. Small incision lenticule extraction (SMILE) is performed using

a. A specially constructed excimer laser
b. A femtosecond laser
c. A femtosecond laser and an excimer laser
d. A microkeratome and an excimer laser

2. Compared with the LASIK procedure, corneal sensitivity is worse after a SMILE procedure during the first months after surgery

a. Correct
b. Wrong
c. Corneal sensitivity is similarly worsened
d. Corneal sensitivity is not changed by these surgeries

3. The SMILE procedure can be used to correct

a. Myopia
b. Hyperopia
c. Presbyopia
d. Irregular astigmatism

For more than two decades, evaporative photoablation by an excimer laser has been the preferred technique for refractive corneal tissue removal either as surface ablation techniques, such as PRK (Photorefractive Keratectomy), or after flap-creation in LASIK. The excimer laser uses radiation in the UV spectrum to photo-ablate tissue. Precision and patient satisfaction has been high. Many factors can, however, affect the ablation rate, amongst others corneal hydration, exposure time, parallax error, patient age, and laser fluency. These effects become more important as higher degrees of myopia are treated.

In 2001 the femtosecond laser (FS-laser) was introduced in refractive surgery. The FS laser is a solid state Nd:Glass laser source generating ultra fast (10-15) focused pulses at near infrared wavelengths. These impulses can create photo disruption at their focal point, in a process called laser-induced optical breakdown. The result is high precision tissue cleavage with very little collateral damage. The main application of the FS-lasers has been to replace the microkeratome in LASIK flap creation, offering increased precision. In a typical setup in modern refractive surgery, both a FS laser and an excimer laser are used.

With the introduction of the VisuMax (Carl Zeiss Meditec, Jena, Germany) FS laser in 2006, intrastromal keratomileusis became possible in the shape of refractive lenticule extraction, or ReLEx. A one laser, one-step surgical approach was now possible. Theoretically, a one-step FS laser refractive cut made before exposing the stroma to changes in humidity should therefore reduce changes in corneal hydration resulting in improved precision of the procedure.

Two new procedures, femtosecond lenticule extraction (FLEX) and small incision lenticule extraction (SMILE) (Figure 1), have been developed in which a lenticule is cut within the corneal stroma by the FS laser. Afterwards a surface cut allows manual dissection and removal of the lenticule. In FLEX, a LASIK-like flap approach is used to access the stromal lenticule. In SMILE, only one or two small incisions are made, thereby preserving a continuous Bowman's layer and intact stromal fibrils at the anterior corneal surface. Theoretically, this should reduce corneal denervation, postoperative dry eye, epithelial ingrowth, and enhance biomechanical stability as compared to flap-related procedures.

Since the VisuMax was first introduced, the laser firing frequency has been increased from the 200 kHz laser used in the first flex treatments, to 500 kHz used today. This permits lower energy pr. laser pulse, smaller spacing, faster treatment, and smoother corneal cuts. The procedure is CE (Conformité Européenne) marked, but still not FDA (U.S. Food and Drug Administration) approved, although such studies are currently ongoing in the U.S. The ReLEx software for treatment of myopia became commercially available in 2011 and the range for treatment of refractive errors with ReLEx (as described by the manufacturer) includes treatment of up to 10 diopters of myopia and 5 diopters of astigmatism.

The FLEX procedure is by many refractive surgeons described as an easy-to-learn, but also transitional procedure. From a biomechanical standpoint, most surgeons prefer

to move on to the less invasive SMILE procedure by gradually reducing the length of the corneal cut. The flap-free SMILE procedure seems to be truly different from FLEX, LASIK, and surface ablation techniques, but has accumulated many of their advantages, although it has been described as slightly more surgical challenging.

Up to now (January 2017), more than 20 clinical trials have been published on treatment of myopia and myopic astigmatism with SMILE. Overall, the efficacy, predictability, and safety have been similar to results obtained with the FS-LASIK technique and long-term results (3 and 5 year follow-up) document perfect refractive stability. Treatment of hyperopia by the SMILE technique is still not commercially available, but recent studies suggest this option will be available within the near future. Endokeratophakia, in which an autologous corneal lenticule is implanted in a stromal pocket have also been tested for treatment of hyperopia, but the predictability of the procedure is low.

In SMILE, the optimal way to perform enhancements has still to be determined. PRK with Mitomycin C, LASIK, a new SMILE procedure located deeper in the cornea, or laser-based opening of the cap with subsequent laser ablation, are possible re-treatment options.

Dry eye, decentration, microstriae, interface scatter, difficulties of removing the lenticule causing irregulaties, and abrasions are some of the most common complications responsible for loss of lines after smile. Longer-term systematic follow-up of 1,800 eyes treated with ReLEx smile at our clinic have documented, that although potential vision reducing complications may occur, no eyes had lost more than one line of CDVA at the latest follow-up visit. With the increasing use of the SMILE procedure, rare complications such as diffuse lamellar keratitis, bacterial keratitis, epithelial interface islands and corneal ectasia have been described, the latter, however, only in eyes with pre-existing abnormal corneal topography. Steroid-induced intraocular pressure rise, suction loss, opaque bubble layer formation, lenticule remnants, and perforation of the corneal cap during dissection have also been described, but may these complications may not result in loss of CDVA.

All types of keratorefractive surgery disrupt the integrity of corneal nerves and affect the tear film. Less reduction of corneal sensation and less denervation might be expected after smile as compared to flap-based techniques, due to the smaller cut size. In a prospective study, using Cochet-Bonnet esthesiometry, the decrease in corneal sensation after FS LASIK and FLEX was reported to be almost similar, because they both required flap-creation. This was in contrast to the flapless SMILE technique, in which significantly less reduction in corneal sensation was noted both 1 week, 1 month and 3 months after surgery. Similarly, studies by confocal microscopy has documented that the corneal sub-basal nerve morphology is better preserved in eyes treated with SMILE compared with eyes treated with FLEX or LASIK.

The future seems to point in the direction of ReLEx SMILE treatments as the new laser technique for treatment of myopia and today more than 450,000 SMILE procedures have been performed globally. As with any new technology, unexpected hurdles can

appear along the way. However, initial data, as presented here, seems to indicate that all femtosecond laser refractive surgery, using intrastromal keratomileusis, is complementary or perhaps even superior, to excimer laser based LASIK and surface ablation techniques.

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Three-Year Results of Small Incision Lenticule Extraction for High Myopia: Refractive Outcomes and Aberrations. Pedersen IB, Ivarsen A, Hjortdal J. J Refract Surg. 2015 Nov; 31(11): 719-24.

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Safety and complications of more than 1500 small-incision lenticule extraction procedures.
Ivarsen A, Asp S, Hjortdal J. Ophthalmology. 2014 Apr; 121(4): 822-8.

Subbasal nerve morphology, corneal sensation, and tear film evaluation after refractive femtosecond laser lenticule extraction. Vestergaard AH, Grønbech KT, Grauslund J, Ivarsen AR, Hjortdal JØ. Graefes Arch Clin Exp Ophthalmol. 2013 Nov;251(11):2591-600.

Predictors for the outcome of small-incision lenticule extraction for Myopia.
Hjortdal JØ, Vestergaard AH, Ivarsen A, Ragunathan S, Asp S.
J Refract Surg. 2012 Dec; 28(12): 865-71.

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MCQ answers page 255

1. **Answer: b**

2. **Answer: b**

3. **Answer: a**

MCQ's

1. Limitations of laser vision correction include the following except:

a. Inability to measure and render all higher order aberrations
b. Inability to predict surgically induced aberrations
c. Inability to treat surgically-induced astigmatism
d. Inability to perfectly position treatment on the corneal plane

2. Which of the following is not emphasized when calculating percent tissue altered (PTA) in laser vision correction?

a. Central corneal thickness
b. Residual Stromal Bed thickness
c. Flap thickness
d. Ablation depth

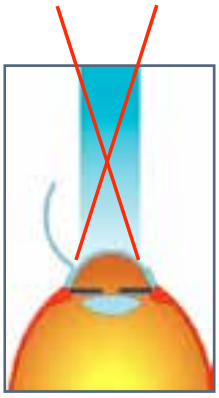
3. Which of the following may predispose for corneal ectasia after LASIK surgery?

a. Preexisting keratoconus
b. Deep flap
c. Deep laser ablation
d. All of the above

4. Visual outcomes after customized refractive surgery in the majority of patients are characterized by:

a. Worse uncorrected distance visual acuity after LASIK
b. Improved corrected distance visual acuity after LASIK
c. Postoperative uncorrected distance visual acuity within ± 1 Snellen line as compared to preoperative corrected distance visual acuity
d. Visual acuities approaching 20/8 after custom LASIK

Quality of Vision after Refractive Surgery



EUPO course 2017
June 9-10, 2017

Dimitri T. Azar, MD, MBA
Dean, College of Medicine,
B.A. Field Chair of Ophthalmologic Research,
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Non-Custom LASIK

1. Measurement of spherocylindrical error
2. Flap dissection with microkeratome/laser &
3. photoablation with excimer laser

Number of LASIK Procedures in US

1998	430,000
1999	800,000
2000-2015	1.5-2 mil./yr

Complication rate 0.5% - 2%

Mechanical complications relate to the flap
Optical complications relate to decentration, optical zone size, positive asphericity, and uncorrected HOA

VISX Laser Technology Advancements

Iris Registration
Multifocal Ablations

B&L Laser Technology Advancements

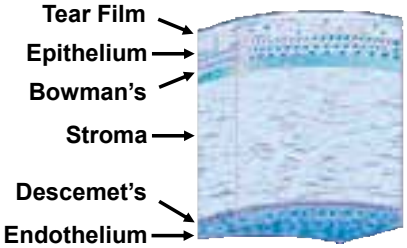
Multifocal Ablations

Allegretto Laser Technology Advancements

Mixed Astigmatism Approval
Instantaneous Pachymetric monitoring

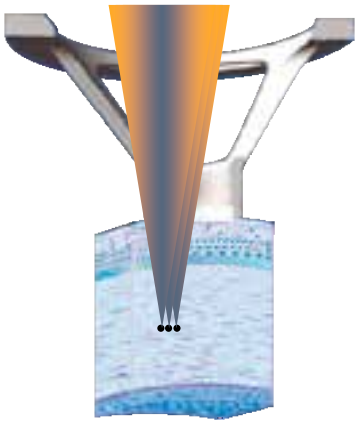
Femtosecond Optical Delivery System

- Glass Lens applanates cornea to flatten eye & maintain precise distance from laser head to focal point



Mechanical complications may be reduced with newer technologies

- Laser is set to desired depth
  - Defined distance from bottom of glass applanation surface
- Pulses delivered in a prescribed pattern creating a horizontal or vertical cleavage plane in the cornea

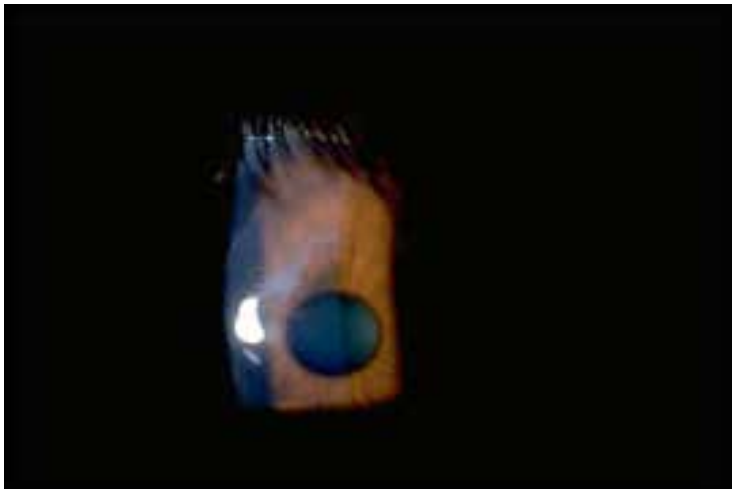


Optical complications may be reduced with custom LASIK and newer technologies of laser delivery

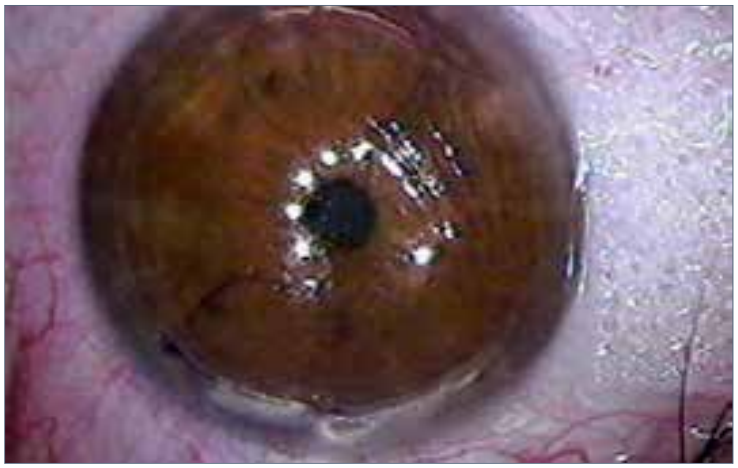
LASIK Limitations

- **Potential Flap-related Complications**
- **Custom corneal limitations**
- **Ectasia**

Epithelial Cysts



Striae

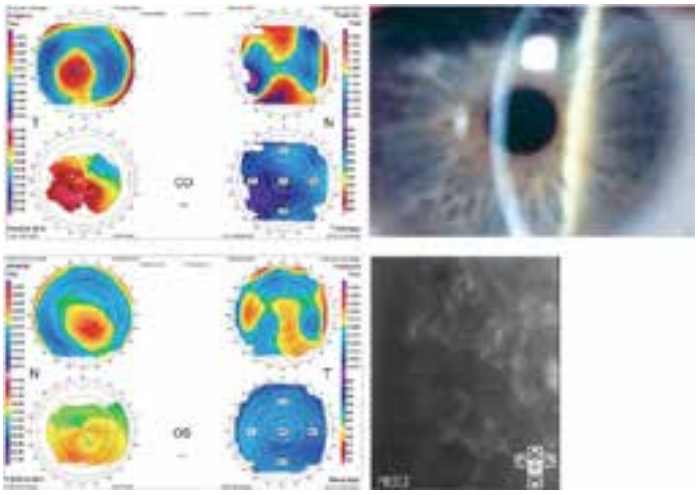


Corneal Ectasia in Myopia

Preexisting KC
Deep flap
High myopia
Deep laser ablation

(Ectasia is more likely to occur after LASIK)

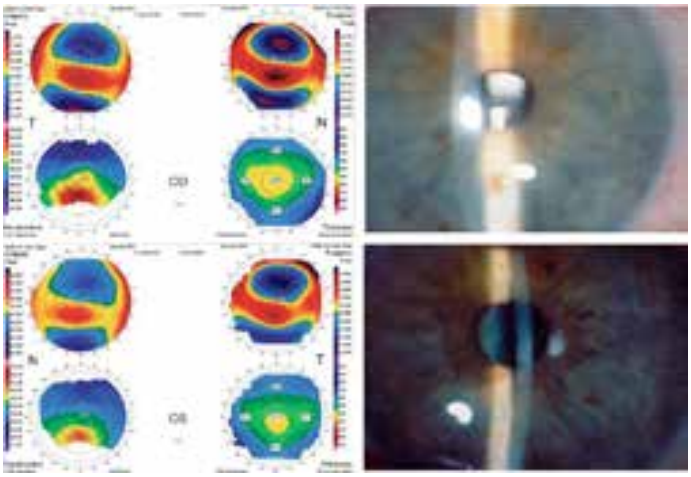
Potential Complications in Patients with Coexistent Keratoconus and Fuchs' Dystrophy



Case 1. Top, Orbscan topography showed advanced inferior steepening consistent with keratoconus changes on the right eye (OD), despite a diffusely thick cornea. Slit-lamp photography showed corneal guttae. Specular microscopy was unable to provide an image of the eye due to corneal edema. Bottom, Orbscan topography showed inferior steepening consistent with keratoconus. Specular microscopy of the left eye (OS) captured multiple guttae, with inability to perform cell counts. N = nasal; T = temporal.

Jurkunas U, Azar DT. Ophthalmology. 2006 Dec;113(12):2187-97.

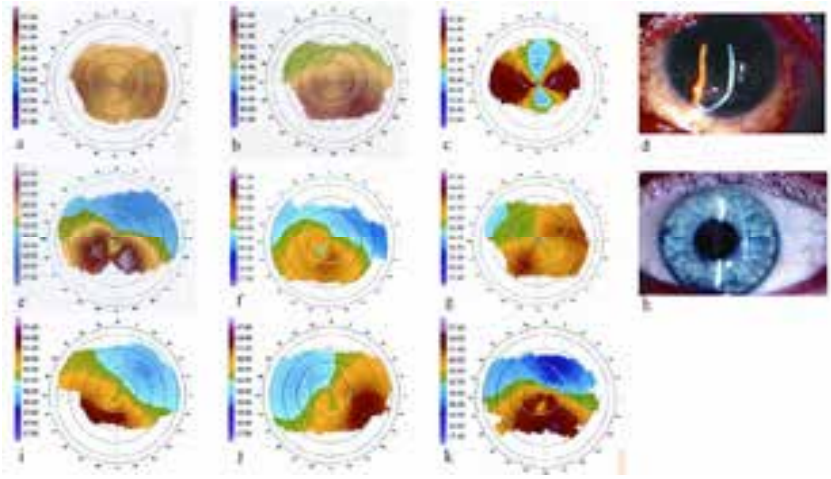
Potential Complications in Patients with Coexistent Keratoconus and Fuchs' Endothelial Dystrophy



Case 2. Top, Orbscan topography showed inferior steepening of the right eye (OD) consistent with keratoconus. Slit-lamp photography showed multiple guttae. Specular microscopy was unable to provide an image. Bottom, Orbscan topography showed inferior steepening of the left eye (OS). Corneal guttae were noted on slit-lamp photography. Specular microscopy was unable to provide an image of the eye. N = nasal; T = temporal.

Jurkunas U, Azar DT. Ophthalmology. 2006 Dec;113(12):2187-97.

Ectatic Disorders Associated with a Claw-Shaped Pattern on Corneal Topography



Lee BW, Jurkunas UV, Harissi-Dagher M, Poothullil AM, Tobaigy FM, Azar DT. Am J Ophthalmol. 2007 Jul;144(1):154-156.

Surface Ablation?

- **Potential Flap-related Complications**
- **Custom corneal limitations**
- **Ectasia**

Surface Ablation, Combined with MMC, May Overcome Several Limitations of Phakic IOLs

- **Shallow AC**
- **Low initial endothelial cell counts**
- **Progressive endothelial cell loss**
- **Cataract formation**
- **Serious intraoperative/postoperative complications**

Control-Matched Comparison of LASEK and LASIK

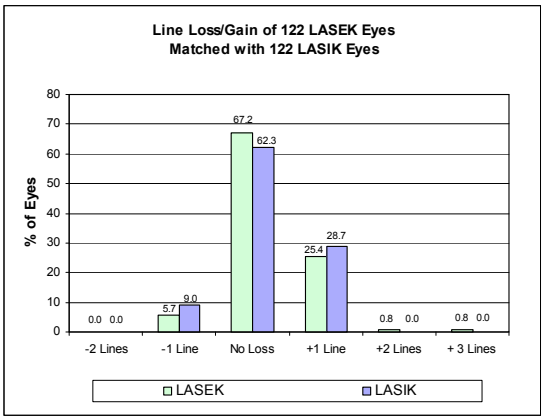
- Retrospective, nonrandomized, control-matched study
- The charts of 2257 eyes that underwent LASEK or LASIK treatment were reviewed.
- Inclusion criteria: patients who were 21 years of age or older having between −0.75 and −6.00 diopters (D) of myopia with up to −2.25 D of astigmatism.
- One hundred twenty-two LASEK-treated eyes were matched with 122 LASIK-treated eyes having preoperative spheres, cylinders, and SE within ±0.50 D.
- Both groups had similar preoperative best spectacle-corrected visual acuity (BSCVA), laser platform, and follow-up durations.

Tobaigy FM, Ghanem RC, Sayegh RR, Hallak JA, Azar DT. Am J Ophthalmol. 2006; 142(6): 901-8

Control-Matched Comparison of LASEK and LASIK

Postoperative results:

- Mean SE was −0.15 ± 0.40 D for LASEK and −0.37 ± 0.45 D for LASIK
- Mean logMAR of BSCVA was −0.03 ± 0.06 (20/19) for LASEK and −0.02 ± 0.05 (20/19) for LASIK.
- No eye lost 2 or more lines of BSCVA in both groups.



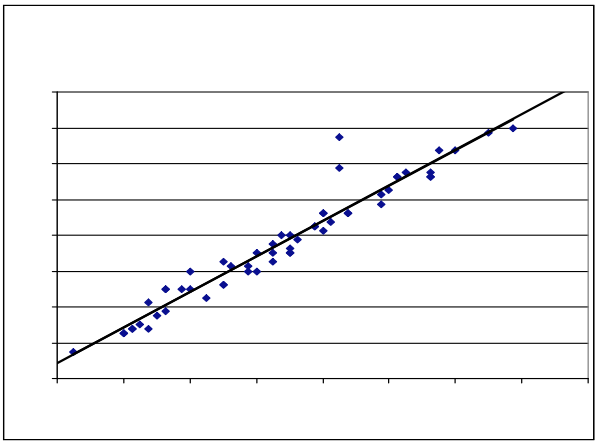
Tobaigy FM, Ghanem RC, Sayegh RR, Hallak JA,Azar DT. Am J Ophthalmol. 2006; 142(6): 901-8

Control-Matched Comparison of LASEK and LASK for LOW to Moderate Myopia

Conclusions:

- **Although there were some differences in the visual and refractive results favoring LASEK, they were not clinically significant.**
- **Both procedures seemed safe, effective, and predictable for the treatment of low and moderate myopia.**
- **Nomogram adjustment may be necessary for LASIK surgeons adopting surface ablation.**

Epi-LASIK Attempted versus achieved spherical equivalent correction



Surface Ablation

ADVANTAGES:

- **Surface ablation is a viable alternative to LASIK especially in young patients with thin pachymetry, steep K, and/or corneal irregularities.**
- **Microkeratome and flap-related complications are avoided.**
- **Surface ablation is a reasonable alternative to phakic IOLs in patients with low endothelial cell counts, shallow AC, early lens opacities, and/or high astigmatism.**

LIMITATIONS:

- **The long-term risks of prophylactic MMC are unknown.**

LASIK in the Presbyopic Age Group; Safety, Efficacy and Predictability in 40-69 Year Old Patients

Conclusions:

- **Despite a trend towards worse final BSCVA and higher retreatment rates in older patients, a greater risk of visual loss after LASIK was not observed with increasing age.**
- **LASIK for myopia and hyperopia has reasonable safety, efficacy and predictability profiles in the presbyopic age group.**

Ghanem Rc, de la Cruz, Tobaigy FM, Ang LP, Azar DT. Ophthalmology. 2007 Jul;114(7):1303-10.

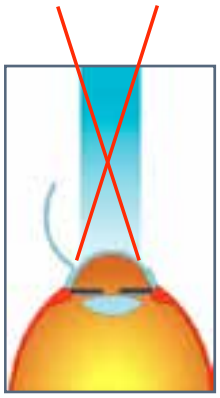
AFFERENT ARM **EFFERENT ARM**

Corneal Topography/
Wavefront Analyzer + Scanning Laser

=

Custom Ablation

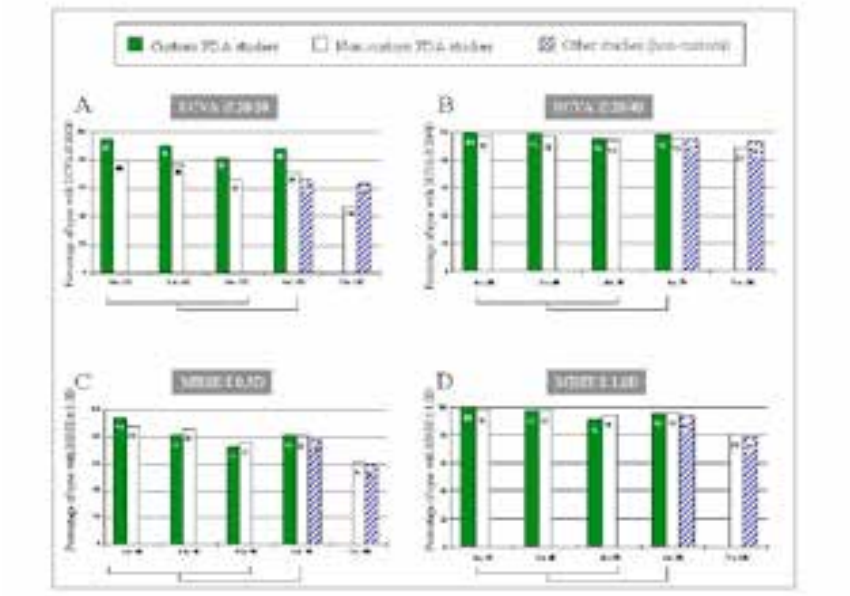
What are the Optical Limits to Corneal Refractive Surgery?

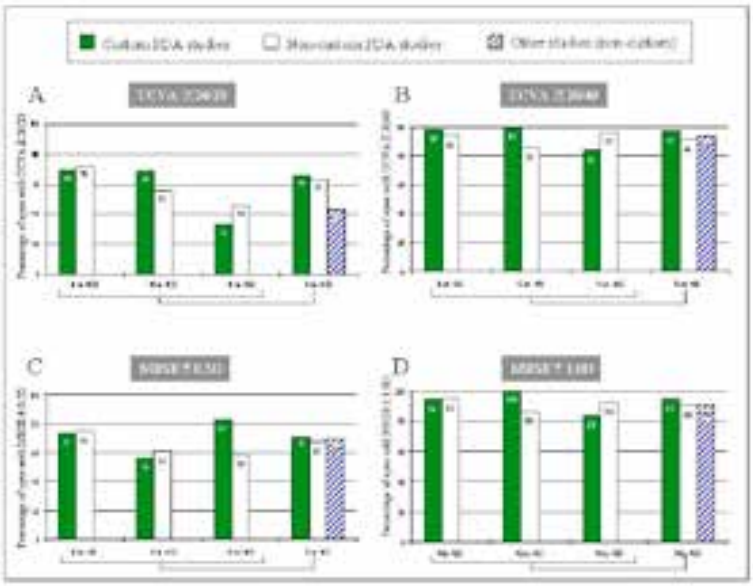


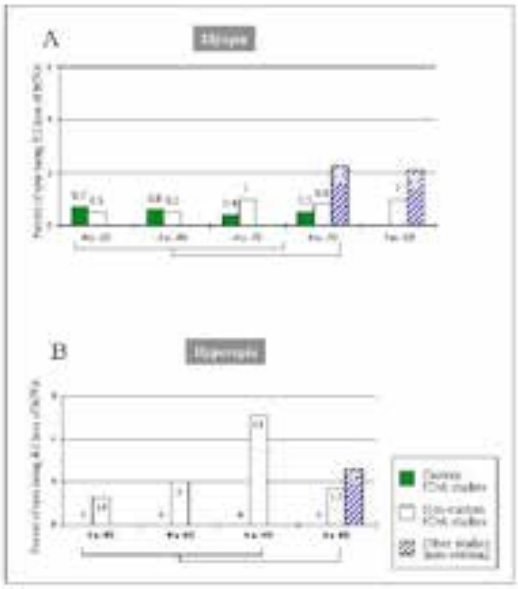
Comparison of Outcomes of Custom and Non-custom LASIK

- **FDA trials of LVC**
- **Subgroups: 0 to -2D, -2 to -4D, -4 to -7D, 0 to +2D, +2 to +4, & +4 to +6D**
- **Pooled data of approved lasers (3 custom and 5 non-custom) rather than head-to-head comparisons of individual lasers**
- **Literature Search (past 10 years); data pooled**
- **Outcomes: % ≥ 20/20; % ≥ 20/40; % ± 0.50D; %± 1D; % loss of ≥ 2 Snellen lines**

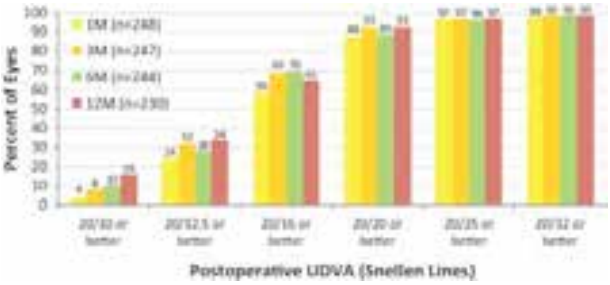
Sakimoto T, Rosenblatt MI, Azar DT - - Lancet 4/2006




A
B
C
D

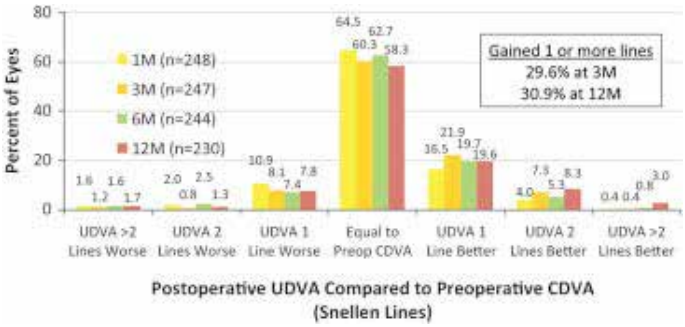

A
B

Visual outcomes after topography guided custom LASIK

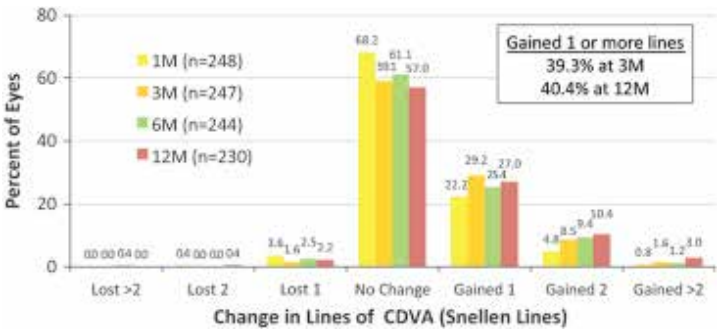


Cumulative postoperative UDVA

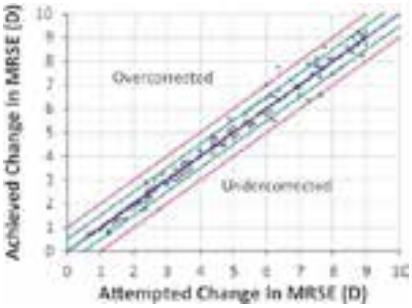
Stulting RD, fant BS. Results of topography-guided laser in situ keratomileusis custom ablation treatment with a refractive excimer laser. J Cataract Refract Surg. 2016; 42(1):11-18.



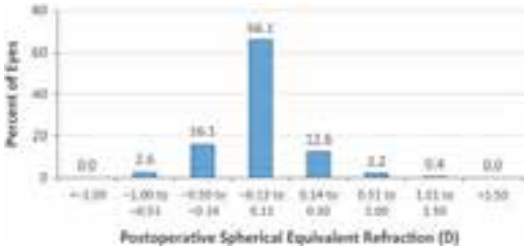
Postoperative UDVA compared with postoperative CDVA



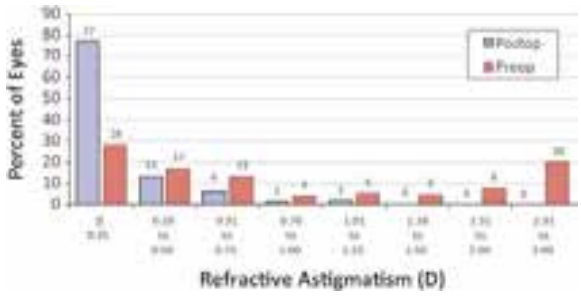
Postoperative CDVA compared with preoperative CDVA



Attempted versus achieved change in MRSE at 6 months



Accuracy of MRSE at 6 months



Accuracy of cylinder correction at 6 months

FDA reported visual outcomes of three latest platforms for LASIK: Wavefront guided Visx iDesign, topography guided Wavelight allegro Contoura, and topography guided Nidek EC-500 CATz

Table 1 Patient demographics

Surgery plan	Visx iDesign	Alcon Contoura	Nidek CATz	P-value*
Eyes (n)	234	249	135	
Gender, male/female (n)	93/77	93/119	64/69	0.027
Age, mean ± SD (years)	32.3±8.31	34.0±9.3	35.1±8.5	<0.016
Preoperative MSE (D)	−4.31±2.78	−4.61±2.43	−3.33±1.45	<0.0001

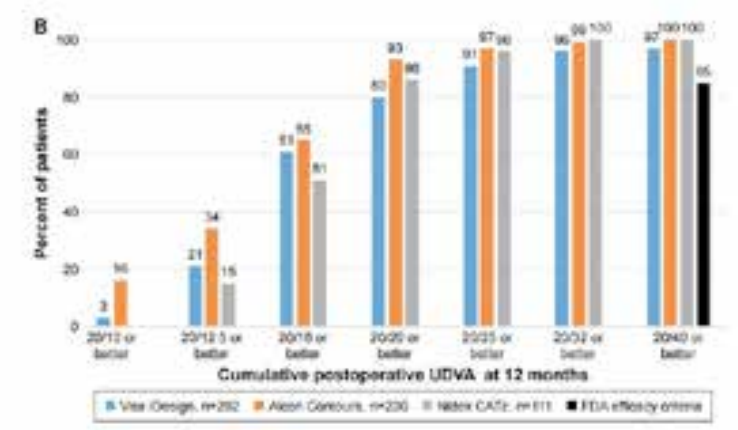
*Note: *P*-value calculated using one-way ANOVA at each time point.
Abbreviations: ANOVA, analysis of variance; MSE, mean spherical equivalent; D, diopter; SD, standard deviation.

Moshirfar M, Shah TJ, Skanchy DF, linn SH, Kang P, Durrie DS. Comparison and analysis of FDA reported visual outcomes of the three latest platforms for LASIK: wavefront guided Visx iDesign, topography guided WaveLight Allegro Controura, and topography guided Nidek EC-5000 CATz. Clin Ophthalmol. 2017; 11:135-147.

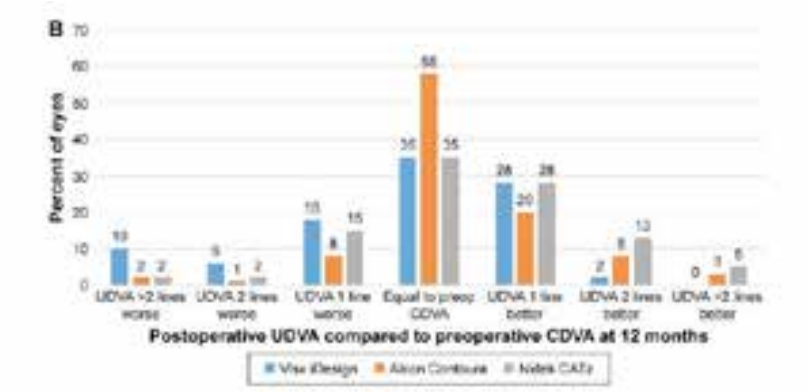
Table 1 FDA indications for use and range used in study

Refraction parameter	Visx iDesign	Alcon Contoura	Nidek CATz
Actual reported range			
Spherical equivalent	−0.01 to −12.0 D	−0.01 to −9.0 D	Not reported
Cylinder	0 to −8.0 D	0 to −6.0 D	−0.50 to −4 D
Sphere	Up to −12.0 D	Up to −9 D	Up to −6 D
Approved indication for use			
Spherical equivalent	Up to −11.0 D	Up to −7.0 D	−1.0 to −5.0 D
Cylinder	Up to −5.0 D	Up to −3.0 D	−0.5 to −2.0 D
Sphere	Not provided	Up to −8 D	−1.0 to −4.0 D

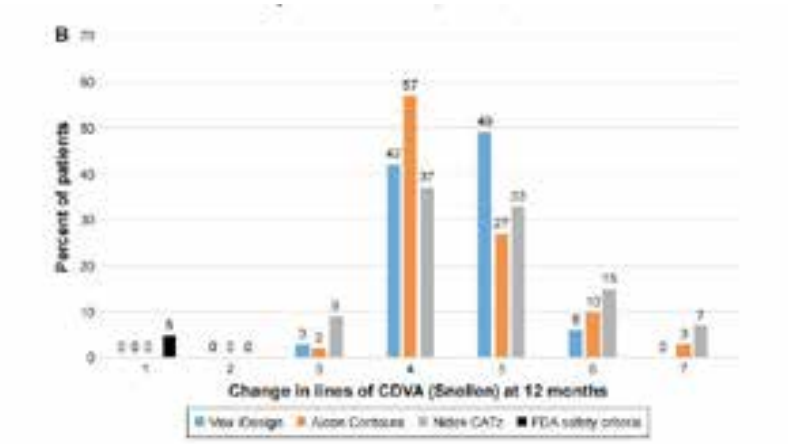
Abbreviations: D, diopter; FDA, US Food and Drug Administration.



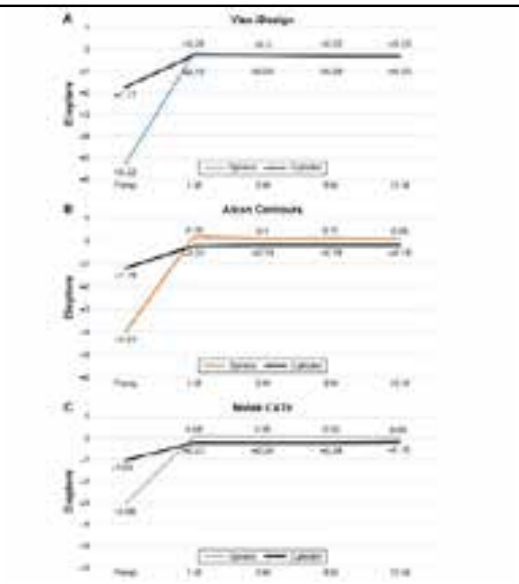
Cumulative postoperative UDVA at 12 months



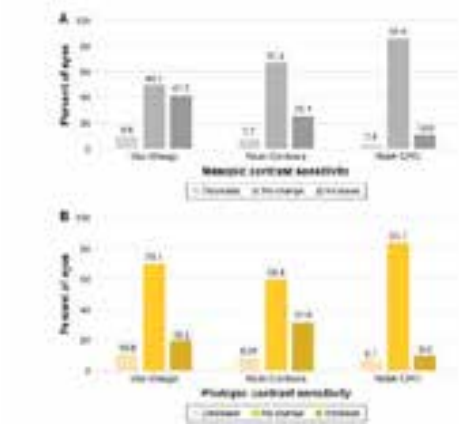
Postoperative UDVA compared to preoperative CDVA at 12 months



Change in lines of CDVA (Snellen) at 12 months



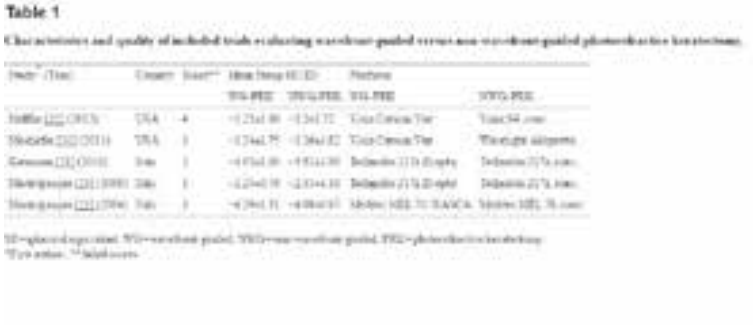
Illustrations of the change of mean MRS and cylinder over time for Visx iDesign, Alcon Contoura, and Nidek CATz, respectively.



(A) Clinically significant changes from preoperative to postoperative at 6 months in mesopic contrast sensitivity among the three platforms.
(B0 Clinically significant changes from preoperative to postoperative at 6 months for photopic contrast sensitivity among the three platforms.

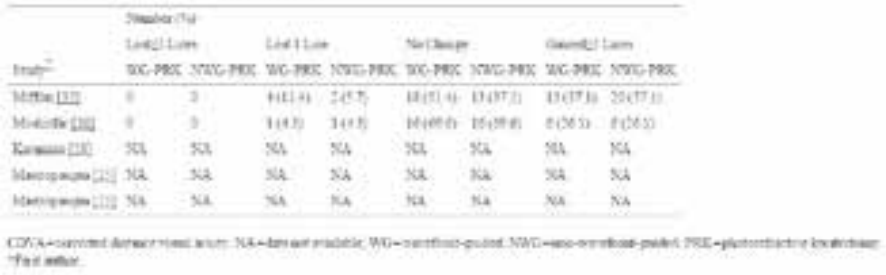
Comparison of visual outcomes between custom and non-custom PRK

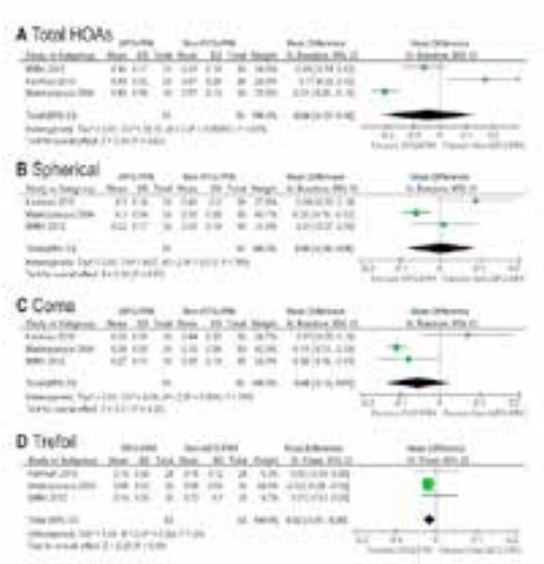
Table 1



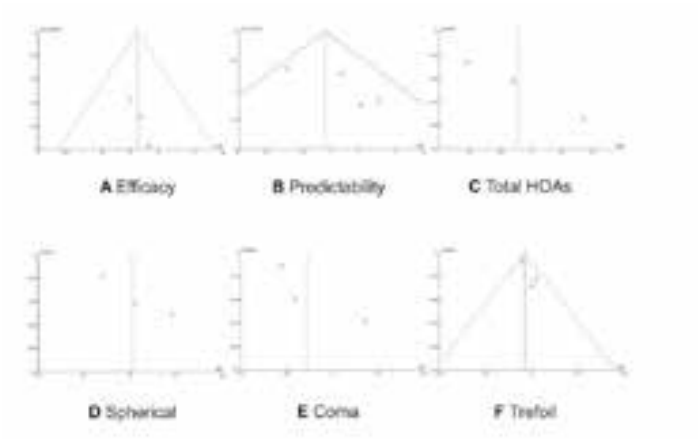
Kobashi H, Kamiya K, Hoshi K, Iagrashi A, Shimizu K. Wavefront-guided versus non-wavefront-guided photorefractive keratectomy for myopia: meta-analysis of randomized controlled trials. PLoS one/ 2014; 9(7): e 103605.

Eyes losing or gaining lines in Snellen CDVA





Forest plot comparing total HOAs outcomes after treatment with WFG-PRK and non-WFG-PRK in patients divided into 2 groups based on preoperative total HOAs.



Funnel plots showing the distribution between studies comparing each outcome. (A) Efficacy, (B) Predictability, (C) Total HOAs, (D) Spherical aberration, (E) Coma aberration, (F) trefoil aberration.

Limitations in Wavefront Analysis: Measurement Steps

- Wavefronts reconstructed/analyzed
  - higher order Zernike polynomial or Fourier representation of wavefront generated.
  - Effective clinical prescription generated and compared to phoropter.
  - Repeat measurements compared for consistency.

Scanning and Tracking Laser Technology Limitations

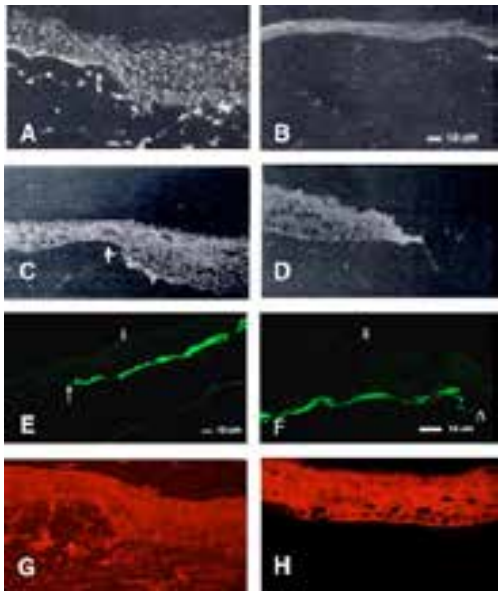
Avoidance of Eye drift during surgery

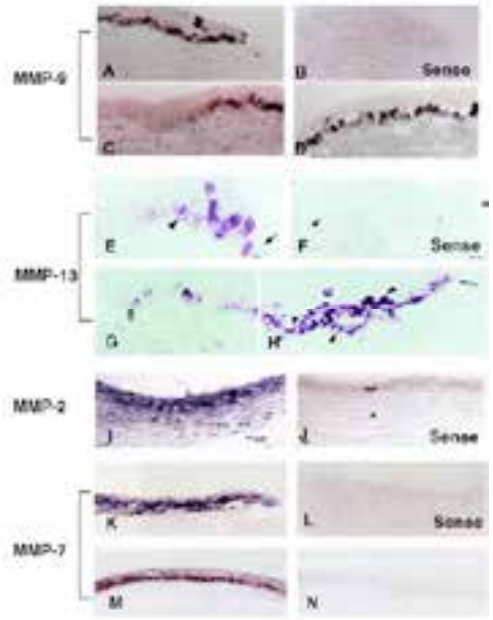
- **Tracking of cornea in 3 dimentions: x, y, and rotational**
- **Differentiation of rotational vs. translational movement (eye mvt vs head mvt)**

Additional Limitations of Wavefront-guided Excimer Laser Ablations

The refractive outcomes may be altered by surgically-induced HOA:

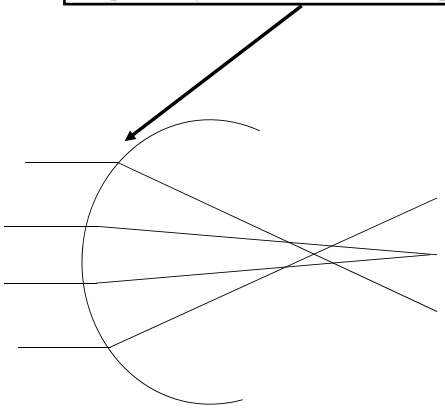
- **Wound healing**
- **Biomechanical changes after surgery (collagen relaxation, ectasia)**





Corneal Asphericity

Spherical surface (Shape factor: Q = 0);
or Oblate surface **(Shape factor: Q > 0) :**
Peripheral rays are bent more than the para-axial rays

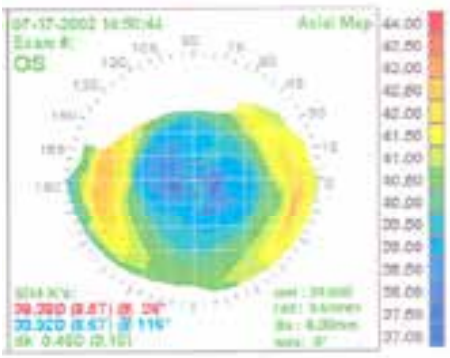


Q ≥ 0

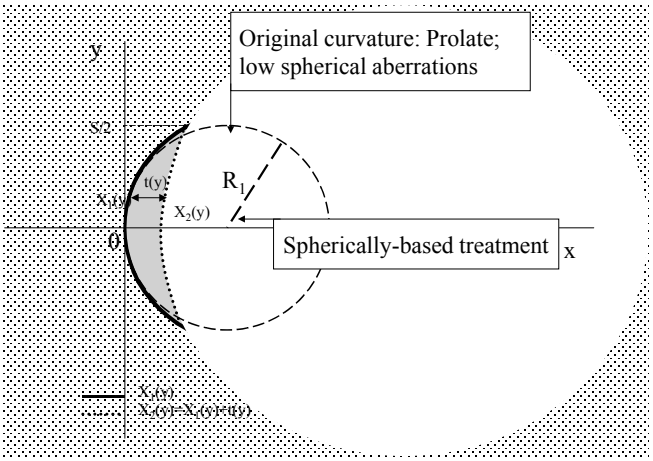
Myopic LASIK:

Central area flatter than Peripheral untreated zone

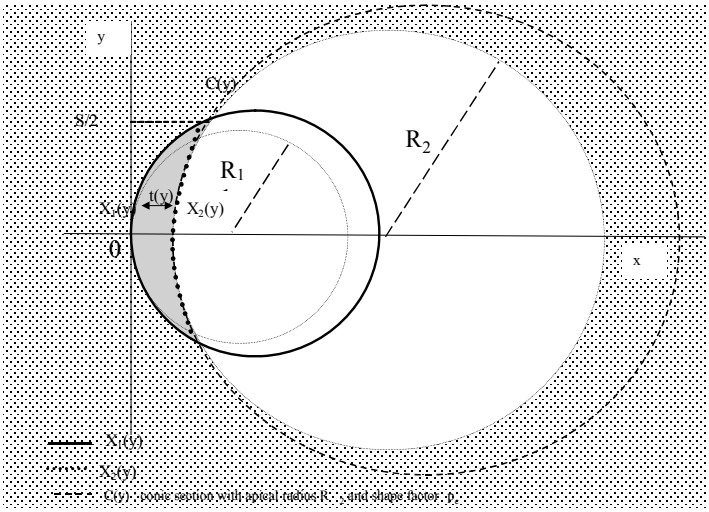
Is the treatment zone oblate?

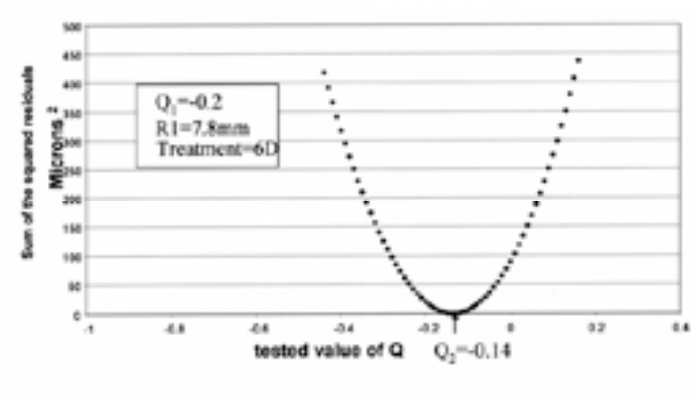


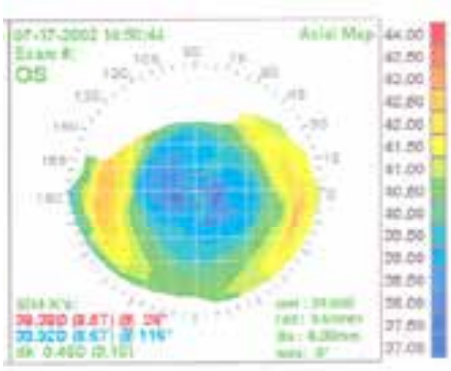
Preoperative Corneal Asphericity



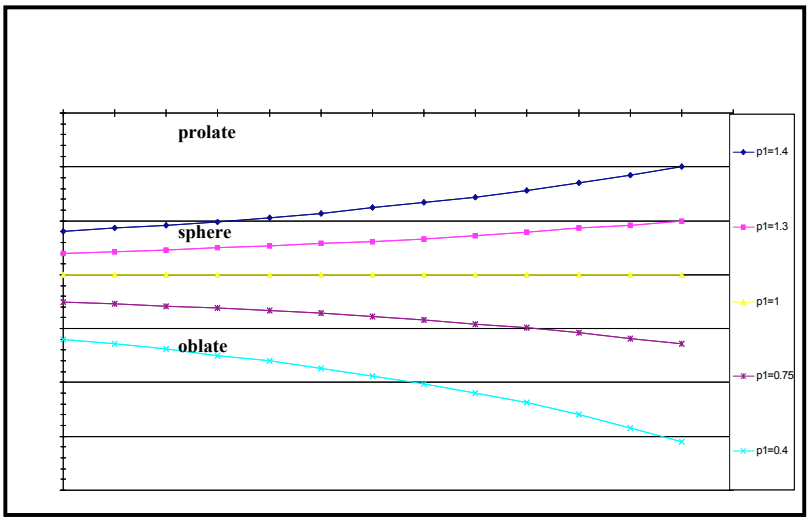
Preoperative Corneal Asphericity

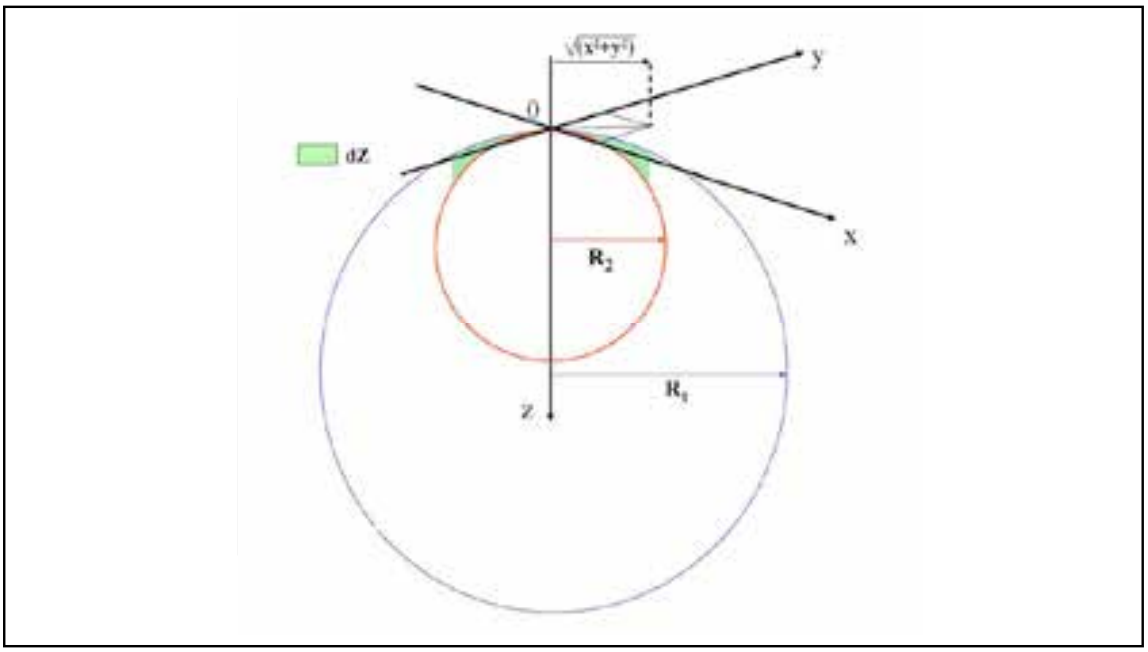


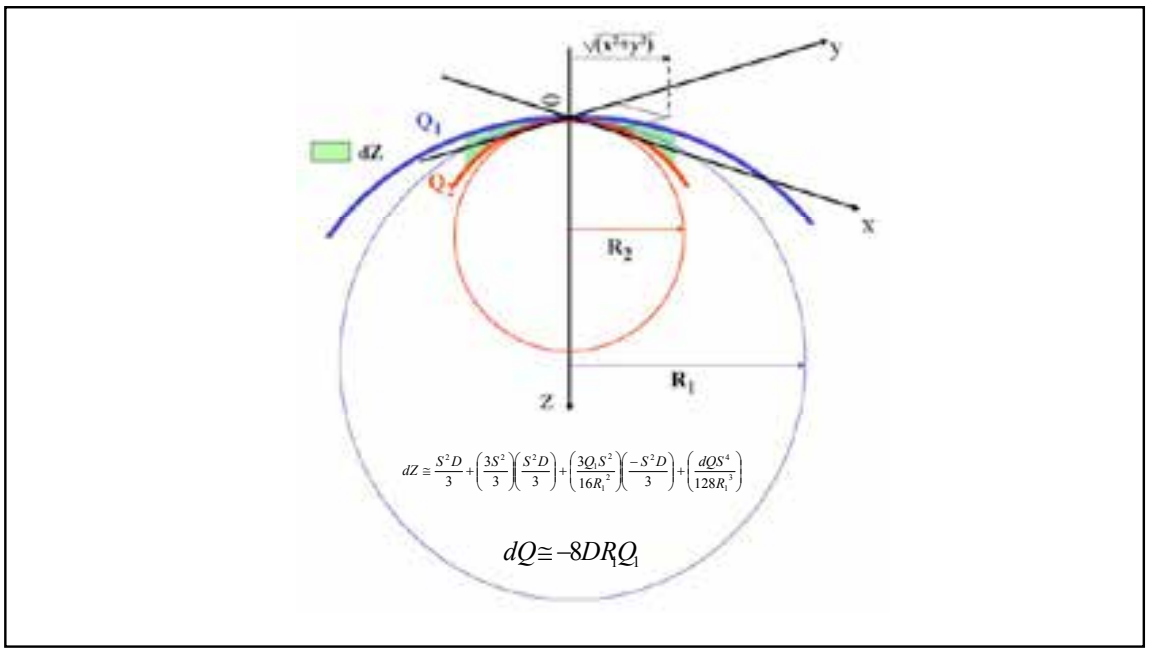


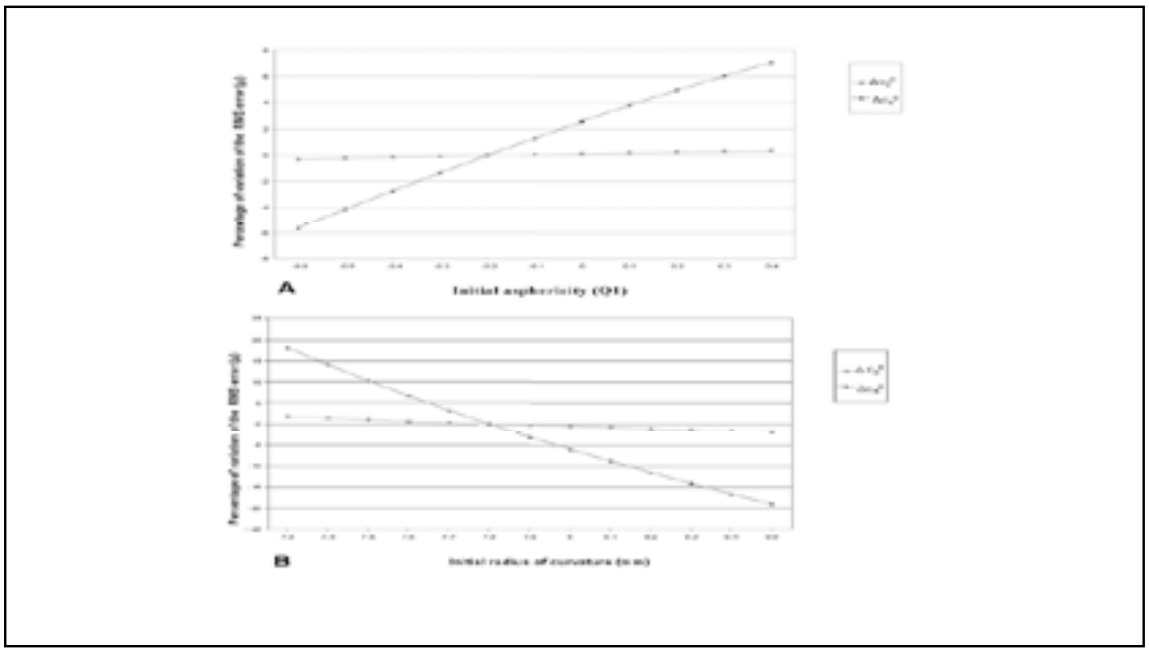


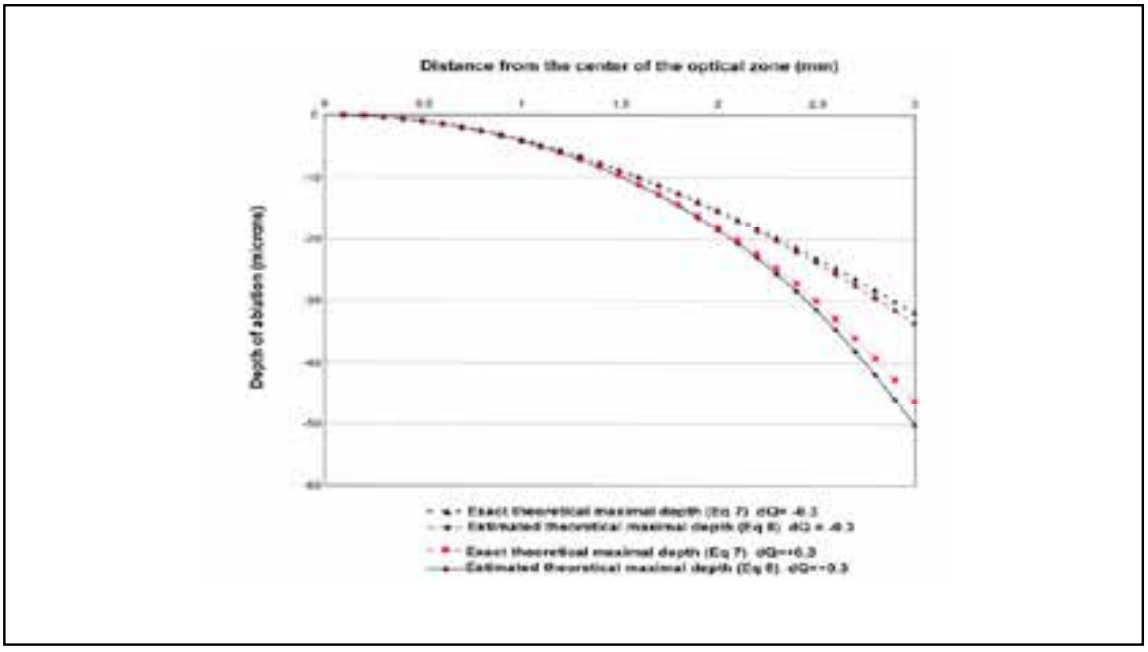
Prolate and Oblate Outcomes




√(x²+y²)
y
0
dZ
x
R2
R1
z


√(x²+y²)
y
Q
Q1
dZ
Q2
x
R2
R1
z
$dZ \cong \frac{S^2 D}{3} + \left(\frac{3S^2}{3}\right)\left(\frac{S^2 D}{3}\right) + \left(\frac{3Q_1 S^2}{16R_1^2}\right)\left(\frac{-S^2 D}{3}\right) + \left(\frac{dQS^4}{128R_1^3}\right)$
$dQ \cong -8DR_1Q_1$


A
B


Distance from the center of the optical zone (mm)
Depth of ablation (microns)

Percent tissue altered (PTA) to calculate ectasia risk in LASIK patients

Santhiago et al proposed a metric for calculating the ectasia risk in patients who are undergoing to undergo LASIK procedure. This metric can be expressed in terms of the following equation:

PTA = (FT + AD)/ CCT

where PTA = percent of tissue altered

FT = flap thickness

AD= ablation depth, and

CCT = central corneal thickness

Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro ML, Wilson SE, Randleman JB. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyed with normal preoperative topography. Am J Ophthalmol. 2014 Jul; 158 (1):87-95.e1

Santhiago's Receiver Operating Characteristic (ROC) Table for Percent tissue Altered (PTA) values related to post-LASIK ectasia risk for a study population of 30 eyes with bilateral normal preoperative Placido based corneal topography that developed ectasia after LASIK, and 174 eyes with uncomplicated LASIK and at least 3 years of postoperative follow-up

Cut-off Percent Tissue Altered Value (%)	Sensitivity (%)	Specificity (%)
48	27	100
47	33	100
46	33	98
45	53	97
44	63	96
43	77	94
42	87	91
41	90	91
40	97	89
39	97	87
38	97	83
37	97	82
36	97	79
35	100	72
34	100	64

The results of this table are derived from receiver operating characteristic (ROC) curve, and revealed a cut-off of 40% as the value with the maximized sum of sensitivity and specificity; PTA= Percent Tissue Altered (Flap Thickness + ablation Depth)/ Central Corneal Thickness.

CONCLUSIONS

- **Recent improvements in LVC include improved technology, patient selection, surface ablation, monovision, and asphericity-optimized/ wavefront-guided custom LASIK.**
- **Despite improved outcomes of custom LVC, limitations include inability to measure and render all HOA at all wavelengths, inability to predict the surgically-induced aberrations, and inability to perfectly position Rx on the corneal plane.**
- **Other important considerations include biomechanical changes and WH which interfere with customization and the ability to eliminate optical aberrations.**

Thank you for your attention

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MCQ answers page 260

1. **Answer: c**

2. **Answer: b**

3. **Answer: d**

4. **Answer: c**