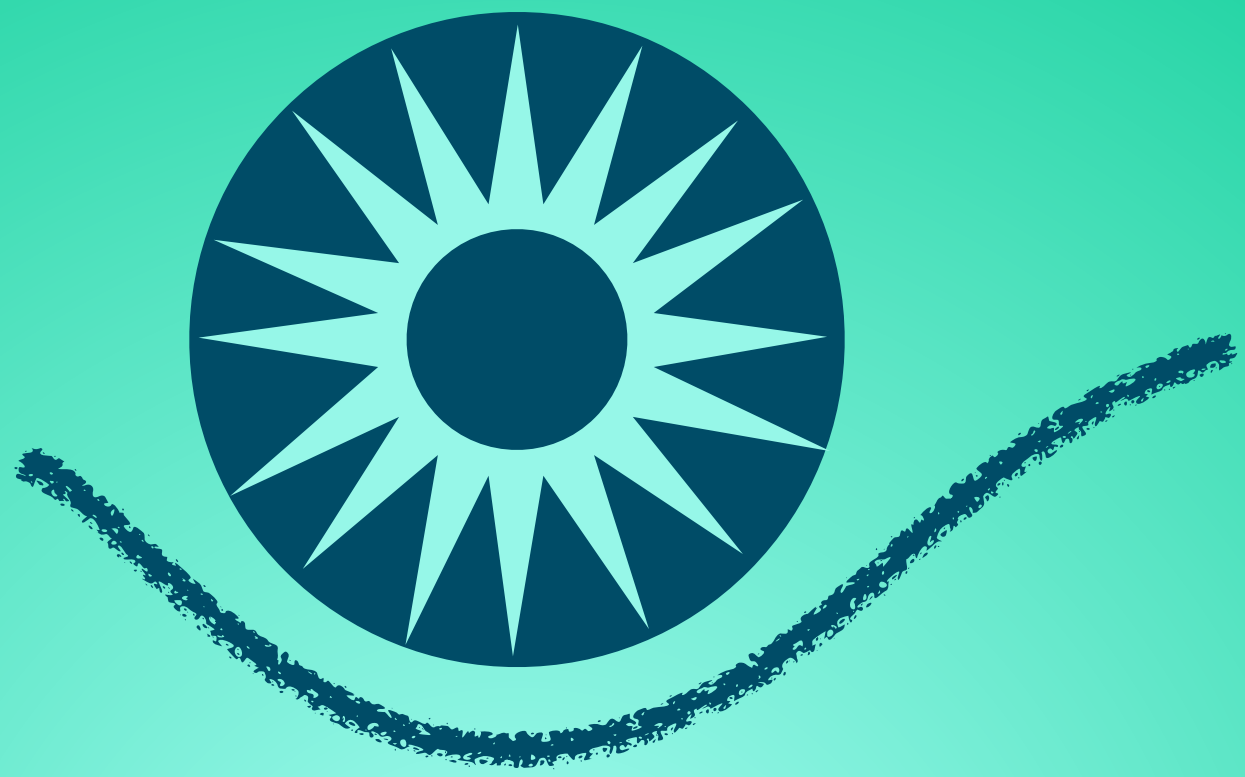
Ophthalmology PG Exam Notes



NOTES

2020

Cornea & Refractive

Dhaval Patel MD

I notes 2020

(Ophthalmology PG Exam Notes)

Dhaval Patel MD (AIIMS)

drdpatel87@gmail.com

by eye.sadbhaavclinic.com

1st edition, 14-02-2014

2nd edition, 10-10-2020

This is a compilation effort from my Post-graduation preparation notes and multiple other sources. Whole of the Manual is now revised from advices received from students from all over the world. Any contributions or comments are welcomed in the effort to improve this Manual.
This manual is made to serve the Exam purpose and as a Handy Reference tool only.

If you are reading this, just drop a comment or critic at:
drdpatel87@gmail.com

Dedication

To The **GOD**, the Almighty, for Giving me Imagination & Curiosity which keeps me always learning, for Giving me fine skills from which I can do my best for patients…

To My Grand-Mother; **Tejaben Patel**, for Training my childhood in such a disciplined way which has helped me to become what I am today…

To My Parents; **Bharat & Sudha Patel** and My Parents-In-Law; **Anil & Neela Patel**, for Trusting me, Motivating me and Helping me in my difficult times…

To My Wife; **Dr Dhara Patel**, for Believing in my strengths, Always supporting me in my all ventures, Bearing with me when I don't give her enough time while I am busy in my all ongoing projects and many more innumerable things which I always forget as usual…

To My Brother; **Dr Keyur Patel**, for helping me getting all the knowledge regarding Medical Science in the other continent…

To My Brother-In-Law; **Raj Patel**, for Bringing out Computer Science Kid within me and Teaching me in-numerous tips and tricks while dealing with computers…

To My Many **Friends and Relatives**; naming them all is not possible but they have helped me to Refine my life in one or the other way…

To All the **Ophthalmologists;** for pouring their knowledge and skills in this field which has now become one of the finest speciality in Medical field…

To **Patients;** for creating a demand which keeps all the ophthalmologists motivated to keep inventing and innovating methods, models and devices for their benefits…

I NOTES 2020

Ophthalmology PG Exam Notes

Cornea & Refractive

If I have seen further than others,
It is by standing upon the shoulders of giants.
-Isaac Newton

Thank you GOD !

When I compiled first edition of this **iNotes** Manual in 2014, It was simple collection of few notes (*very much incomplete!*) which I prepared for my Post-graduate Ophthalmology Exams at AIIMS, New Delhi. Since then I am regularly receiving emails and messages regarding usefulness of these notes as a study material for Post-graduate students all across the world.

For last few years, I am getting emails asking that if I am going to bring any updated version of my **iNotes** as ophthalmology has advanced a lot in last 10 years. Hence from last one year I have started reading newer edition of books, recent question papers, gathered notes and presenting to you as completely new version as **iNotes 2020**.

In this edition of iNotes, I have tried to include clinical, practical and surgical tips which is going to be used in your future practice also so that this manual can be a handy book for you as a future reference too.

Also Remember, this is a "**Manual**" and not a "Complete Book", and Just like most of others, it is also far from Complete. One of the best way to utilise this for your exam preparation is to use this as a reference and make your personal manual by adding your own notes and topics asked in your university.

My Best wishes and Good luck to you All !!

Dhaval Patel MD (AIIMS)
drdpatel87@gmail.com
10-10–2020

INDEX

Evaluation of the Cornea and External Eye

Examination of the Lids

- History of Patient
- Dermatologic Examination
- Eyelid Position: ectropion and entropion, Floppy Eyelid Syndrome
- Tear Meniscus and Puncta
- Anterior Eyelid: A ***collarette***, which forms in areas of inflammation or hyperkeratinization, is simply mucous debris, Lice, Demodex
- Posterior Eyelid
- **Meibomian Gland Expression**: normal diameter of each dome is **0.5–0.7 mm**, The volume of lipid is increased if any of the lipid domes are 0.8 mm or larger; this finding is sufficient to diagnose ***seborrheic meibomian gland dysfunction*** → viscosity and opacity of the expressed lipid are important signs
- After instilling lissamine green, rose Bengal or fluorescein onto the ocular surface, a visible line of demarcation, called the **Marx line**, is often apparent on the lid margin. This line is thought to represent the ***mucocutaneous junction***, and anterior displacement relative to the meibomian gland orifices may correlate with gland dysfunction.
- **Meibomian Gland Imagery**: The most obvious change seen with transillumination is gland dropout. Dropout is associated with obstructive meibomian gland dysfunction and is not associated with infectious blepharitis, allergic phenomenon, or seborrheic meibomian gland dysfunction.

Tear Film Evaluation

- **Indications**
  - Keratoconjunctivitis sicca
  - Evaluation of ocular discomfort
  - Evaluation of intermittent blurred vision
  - Neurotrophic keratopathy
  - Exposure keratopathy
  - Preoperative evaluation for refractive or cataract surgery
- General Inspection: Alterations in the eyelid structure
- **Inferior marginal tear strip**: normally about **0.5 mm** in width and has a concave upper aspect. If this strip is thin **(<0.25mm)** or discontinuous, it is evidence of deficient aqueous tear volume.
- **Tear Stability**:

- The interval between the last complete blink and the appearance of the first random dry spot is the break-up time (**BUT**). Normally **10–30 seconds**. Values of less than **10 seconds** are considered abnormal. Seen in aqueous tear deficient and in evaporative dry eye.
- **Noninvasive BUT** that employs reflective devices with a grid projected onto the corneal surface.
- **Video-recorded BUT**: Values below **7 seconds** are considered abnormal and reflective of the presence of dry eye disease.
- **Ocular Protection Index (OPI): OPI = BUT/IBI**. Values **below 1** are characteristic of tear film instability and dry eye disease. Blink rate, which is calculated by dividing 60 by the number of observed blinks per second. (IBI: Inter-Blink Interval)

- **Tear Production**
- Whatman #41 filter paper strip (5 mm wide, 35 mm long) is placed across the lower lid at the outer 1/3 of the lid margin
  - **Schirmer's test**: ***Schirmer's II (with anesthesia)*** has been purported to measure '**basal'** tear secretion, i.e. nonstimulated tears. Values **below 5.5 mm** of wetting are diagnostic of aqueous tear deficiency.
  - A **Schirmer's I (without anesthesia)** has become the generally accepted method for assessing aqueous tear production.
  - Without anesthesia, wetting of less than 15 mm indicates dry eyes, and less than 5 mm indicates very severe dry eyes.
  - **The phenol red test**: phenol red impregnated cotton thread is inserted over the inferior lid margin into the temporal conjunctival sac. At the end of **15 seconds**, the dye, which is pH sensitive, turns color ***from yellow to orange***, indicating the length of the thread wetted by tears. This test has been reported to be less uncomfortable and more specific in the diagnosis of aqueous tear-deficient dry eye disease.
- **Tear Composition and Characteristics**
  - **tear lysozyme** levels are decreased in aqueous tear-deficient dry eye disease
  - **tear protein lactoferrin**: Touch MicroAssay,
  - **Tear ferning**: normally there is crystalline pattern of tear mucin. In aqueous tear deficiency, this pattern resembles ferns
    - **Ocular Ferning Test**: Crystallization of a drop of tear fluid on a glass slide at room temperature. (DES display type III and IV pattern)
  - **Tear osmolarity**: **single diagnostic test with the highest accuracy** in identifying patients with dry eye disease. **Cutoff 316mOsm** (DEWS Report)
- **Meibomian Gland Structure and Excreta**
  - Expression of Meibum
  - transillumination of the eyelid
- **Tear Clearance Tests**
  - **Dye dilution studies**: concentration of the dye is measured over time.
  - **Fluorescein Clearance Test [FCT]:**

- This **tear function index (TFI)** is the ratio of the value of the Schirmer's test over the tear clearance rate. The use of the TFI in the diagnosis of dry eye disease is reported to demonstrate a specificity of 91% and a sensitivity of 79%.

- **Staining of the Ocular Surface**
  - Fluorescein, which stains damaged epithelial cells, is best visualized on the corneal surface.
  - Staining of the conjunctiva is seen when there are disruptions in the protective mucin coating; RB and LG are used.
- **Tests of visual function**
  - **tear stability analysis system (TSAS)**, serial videokeratographic images are collected each second between blinks.
  - **functional visual acuity (FVA)** device has been developed which measures visual acuity by way of rapid presentation of optotypes.

Corneal Diagnostic Techniques

- **Corneal Staining**
  - **Fluorescein and rose Bengal:** both dyes can stain living cells, rose Bengal does so more effectively and is intrinsically toxic. healthy preocular tear film will block rose Bengal staining of healthy and damaged cells. Cell degeneration or death increases membrane permeability to both dyes, but rose Bengal diffusion into the stroma is limited. *Fluorescein stains BM of epithelial defect, while RB stains dead epithelial cells even without epithelial defect.*
  - **Lissamine green**: better tolerated than rose Bengal.
- **Pachymetry**
  - **thinnest** part of the cornea is usually located about ***1.5 mm temporal to the center*** of the cornea
  - Mean thickness is 515 µm in the central cornea.
  - cornea with a ***central thickness greater than the thickness in the midperipheral*** should be considered suspicious for endothelial dysfunction centrally or thinning in the midperiphery
  - If the intraocular pressure is normal, epithelial edema develops when the stroma has **swollen about 40%,** to a corneal **thickness greater than 700 *µ*m**.
  - corneal striae become visible at 4–8%, folds are seen at 11–12% swelling, and loss of transparency can occur at greater than 20% swelling.
  - Techniques for measuring CCT include optical pachymetry, ultrasound pachymetry, confocal microscopy, ultrasound biomicroscopy, optical ray path analysis or scanning slit corneal topography, and optical coherence tomography.
- **Aesthesiometry**
  - **cotton-tipped swab**

- **Cochet-Bonnet aesthesiometer**: **6.0 cm**-long adjustable **nylon monofilament**, Measurements are taken by advancing nylon filament smoothly and perpendicularly toward the center of the cornea. Contact is detected by the slightest bend of the nylon; ***sensitivity*** is measured as the length of the filament that gives a 50% positive response from a minimum of four stimuli. The **normal cutoff is 4.5 cm**, and measurements below this are compatible with decreased sensation.
- jet of warm saline
- noncontact air puff technique
- Ocular sensitivity is greatest in the central cornea except in elderly patients, in whom the peripheral cornea is the most sensitive.

Diagnostic techniques for Infectious diseases of cornea and conjunctiva

Specimen collection

- **Eyelid margin specimen**
  - Microbial cultures are obtained by swabbing the abnormal area with a sterile applicator moistened with thioglycollate broth followed by direct inoculation of appropriate culture media and slides
  - Viral eyelid vesicles or pustules can be opened with a sterile small-gauge needle or a sharp pointed surgical blade
  - Material for cytology is smeared onto a glass slide and fixed in methanol or acetone for immunofluorescent staining
  - Collected vesicular fluid can be inoculated into chilled viral transport medium for culture isolation or detection via polymerase chain reaction (PCR) amplification
- **Conjunctival specimen**
  - Sterile Dacron swabs moistened with thioglycollate broth are used to collect surface conjunctival cells
  - Swabbed material can be plated onto solid media, smeared on slides, and inoculated into the broth tube
  - Conjunctival biopsy may also be performed with forceps and scissors
- **Corneal specimen**
  - Corneal infiltrates can be scraped using a sterile spatula, e.g., Kimura platinum spatula, needle, jeweler's forceps, or surgical blade, or swabbed
  - Specimens may be immediately inoculated onto room temperature microbiologic media or placed into transport medium
  - Contamination and false positives must be avoided by not allowing the blade or swab to touch the eyelids
  - Viral specimen can be obtained with a swab, and then inoculated into chilled viral transport medium

- Corneal biopsy can be performed with a 2-3 mm trephine to create a partial-thickness incision; forceps and scissors can then be used to excise a lamellar piece of cornea

- **Contact Lenses**
  - Consider also swabbing/scraping contact lenses or contact lens cases if applicable
  - Fluid in the contact lens case may also be examined and cultured for micro-organisms
- **Tear Specimen:** Immunochromatography to detect Adenoviral infection

Isolation Technique

- Bacterial and fungal culture plates and broth are examined periodically to detect visible growth
- Microorganisms are identified by chemical staining and reactions, and may be tested for antimicrobial susceptibility
- Acanthamoeba may be identified by trophozoite trails on blood agar, but optimally on non-nutrient agar with an overlay of killed E. Coli that must be prepared in advance
- For viral and chlamydial infections, an appropriate tissue-culture cell line is selected for inoculation and examined for the development of cytopathic effects and cellular inclusions

Culture Media & Stains

Organisms	Culture Media	Stain/Test
Aerobic bacteria	Blood agar, chocolate agar, thioglycollate or thiol broth	Gram, acridine orange
Anaerobic bacteria	Anaerobic blood agar, phenyl ether alcohol agar in anaerobic chamber, thioglycollate or thiol broth	Gram, acridine orange
Mycobacteria	Blood agar, Lowenstein-Jensen agar, Middlebrook agar	Gram, acid-fast, lectin
Fungi	Blood agar (25oC), Sabouraud's agar with antibacterial agent (25oC), brain-heart infusion (25oC)	Gram, acridine orange, calcofluor white, Gomori's methenamine silver, wet mount (potassium hydroxide preparation)
Acanthameba	Non-nutrient agar with bacterial overlay, blood agar, buffered charcoal-yeast extract agar	Acridine orange, calcofluor white, Giemsa, PAS
Viruses	Cell culture	PCR, EIA, EM, Serology

Diagnostic techniques for Neoplasia

- **Techniques**
  - Exfoliative or impression cytology
  - Incisional biopsy to remove a representative portion of the lesion
  - Excisional biopsy to remove entire lesion

        - Superficial debridement to remove superficial lesion of the epithelium
        - Shave biopsy to remove superficial lesion of the epidermis
        - Complete excision of deeper lesion
- **Complications**
    - Structural alteration during healing, including distortion and scarring
    - Lesion recurrence
    - Inadequate quality or quantity of material for adequate histopathological evaluation
- **Histopathological features of Neoplasia**
    - Benign
    - Dysplastic
        - Abnormal or precancerous growth of cells
        - Cellular atypia is a set of histopathological features involving cellular polarity; number, size, and shape of nuclei; and number of mitoses
    - Malignant
        - Invasion of dysplastic cells beneath the basement membrane into adjacent tissue
        - Metastatic spread with secondary centers of neoplastic growth
- **Clinical correlations**
    - Gelatinous lesion may have acanthosis (thickening of epithelial layer with increased mitoses of basal epithelial cells)
    - Papilliform lesion may have hypertrophy (increased size of cells) and hyperplasia (increased number of cells)
    - Epidermalization and leukoplakia may have hyperkeratosis (excessive formation of keratin) and dyskeratosis (abnormal formation of keratin)

Keratometry and Topography

- 1619, **Father Christopher Scheiner** observed that shiny glass spheres of different radii produced reflected images of different sizes
- **Ramsden** later added a magnification system and also introduced the doubling device
- **1854**, **Helmholtz** extended this work and constructed a complex instrument that he called an **ophthalmometer**.
- **1881**, **Javal and Schiotz** introduced a simplified ophthalmometer → **keratometer**
- P = 0.3375/r
- **Principle**:

- Anterior corneal surface to behave like a convex mirror and reflect light. The optical design of the keratometer allows the examiner to measure the size of the reflected image and thereby determine the radius of curvature of the anterior corneal surface.

- **Limitations**:
  - assumes that the mires are measuring an area directly over the pupil.
  - assumption that the cornea has a sphero-cylindrical surface with a single radius of curvature in each meridian and a major and minor axis separated by 90 degrees.
  - no information about areas central or peripheral to the points measured
  - only analyzes approximately 6% of the corneal surface
- Series of instrument developments that began with the **keratoscope**, followed by the **photokeratoscope**, and finally the **videokeratoscope** → now called the **corneal topographer**.

Keratoscopy

- **Cuignet** first described the technique of keratoscopy in the 1820
- **Henry Goode** described the first keratoscope in 1847
- **Antonio Placido** was the first to photograph the corneal reflections of a series of illuminated concentric rings in the 1880s.
- In 1896, **Gullstrand** was the first to quantitatively analyze photokeratoscopic images of the cornea.
- evaluate about 70% of the total corneal area (limited by the optics of the reflecting system itself)
- Types
  - **Flat-target keratoscope**: rings of the target are located in the same plane
  - **Collimating keratoscope**: rings in different planes along the interior of a column and in this way are able to maximize the amount of corneal surface that can reflect the target mires
- Limitation
  - To produce an obviously distorted image, the cornea must be quite distorted itself
  - Astigmatism of at least 3 diopters (D) must be present to be detected by traditional keratoscopy.

Videokeratoscopy = Topography

- **Klyce** in 1984: union of rapid computer analysis and digital video
- Two approaches are in general use currently: the Placido disk or reflection-based topographers, and the scanning slit-based tomographers.
  - **Placido disk-based topographers**:
    - vast majority of the older units

- Transilluminated cone acting as a modified Placido ring
- Most systems can be divided into 'near-design' and 'distant-design.'
- Sensitive to disruptions in the tear film

- **Slit scanning tomography**
  - Elevation of each surface can be measured directly with slit beam technology
  - The **PAR CTS** (PAR Technology, New Hartford, NY) was the first 'topography system' to produce a true topographic map, using elevation data from the corneal surface.
  - **Bausch & Lomb Orbscan**: Orbscan is a hybrid system – both a **topographer and a tomographer** – that uses Placido disk technology to display conventional corneal topography. Is is ***limited in its ability to reliably measure the postoperative posterior cornea***, the Oculus Pentacam had greater success in this area.
  - **Oculus Pentacam** uses a scanning slit but with ***Scheimpflug optics***, which increases the depth of focus. In doing so, simultaneous imaging of the cornea, lens, and iris is possible; this permits corneal, anterior chamber, and lens geometry to be imaged and analyzed.
  - **Zeimer Galilei**, also a ***Scheimpflug imaging*** device, has similar advantages with regard to image registration and measurement of the posterior corneal surface.

- **The main uses of corneal topography**
  - **Preoperative evaluation** to rule out certain corneal abnormalities, establish refractive stability, determine whether the patient's corneal shape will allow surgery to be performed safely, and determine whether the surgical outcome is likely to allow acceptable visual performance.
  - **Operative assessment** to determine surgical parameters, plan complicated 're-op' cases, and input data for customized ablations.
  - **Postoperative evaluation** to monitor the surgeon's and laser's performance.
  - **Aid in the calculation of IOLs** for patients who have undergone refractive surgery.
- **Presentation Methods**
  - **Color-coded maps**: The 'warmer' colors represent higher dioptric powers (steeper curvatures), while the 'cooler' colors are used to represent the lower dioptric powers (flatter curvatures). Similar color-coded maps can be used to present changes in elevation.
- Topographies of fellow eyes tend to be mirror images of each other: ***enantiomorphs***
- The Universal Standard Scale has been adopted by the ANSI standard on corneal topography.
- **Axial = sagital Curvature Maps**: The cornea has a prolate shape, so power is higher in the center than in the periphery.
- **Refractive Power Map**: normal cornea will have a higher calculated power peripherally than in the center. This is due to the natural residual spherical aberration of the cornea.

- **Instantaneous or Tangential Power Map**: not recommended for routine clinical use, extremely useful in the demonstration and measurement of the optical zone size in modern refractive surgery as they emphasize transition zone power changes
- **Difference Maps**: Progression of keratoconus
- **Elevation Maps**: Commonly, the best-fitting sphere or toroidal surface is subtracted from the elevation data. Posterior elevation values can be used to distinguish normal and keratoconic corneas, but posterior elevations are not sensitive enough a measure to separately classify forme fruste keratoconus and normal corneas.
- **Pachymetric Maps**: thinnest areas of the corneal stroma are generally inferotemporal to the fixation-reflex
  - Simulated Keratometry: power derived from the corneal topography.
  - Surface Regularity Index (SRI): irregularity of the corneal topography over the pupil, correlated to potential visual acuity
  - I-S index: introduced by Rabinowitz and McDonnell
  - Contact lens warpage can mimic mild keratoconus and needs to be ruled out

Specular Microscopy

- Images light reflected from an optical interface.
- Confocal or nonconfocal /contact or noncontact.
- First direct visualization of the endothelium was demonstrated by **Vogt** in 1918
- In 1968, **David Maurice** described the first laboratory specular microscope that could be used to study excised living corneas
- **Optical Principles:**
  - Light striking a surface can be **reflected, transmitted, or absorbed** or Combination of 3
  - Primary importance in clinical specular microscopy is the light that is reflected specularly
  - Four zones of reflection can be seen → **Zone 3 is the endothelial region**
- **Instrumentation**
  - Konan NonCon Robo Series (Torrance, CA)
  - Sequential images (Tomey, Inc., Phoenix, AZ)
  - Live view (HAI Labs, Inc., Lexington, MA)
- **Qualitative Specular Microscopy**
  - Epithelium:
  - Endothelium (miscellaneous bright and dark structures) → Guttae are excrescences of Descemet's membrane. Guttae, however, can also be seen in the far periphery of young individuals. In this case, they are called **Hassall-Henle warts.**
  - Endothelium: morphometry

- **Quantitative Specular Microscopy**
  - Endothelial cell density (**ECD**) (measured as cells/mm2), **mean cell area** (measured as µm2/cell), coefficient of variation (**CV**) (standard deviation of cell areas/mean cell area), and **pleomorphism** (usually measured as a percentage of 6, <6 or >6-sided cells).
  - The variable-frame analysis is more accurate than fixed-frame analysis because only whole cells are counted and it is not necessary to include portions of cells located on the frame boundary.
  - Cell density alone is not the most sensitive measure of endothelial health, as the endothelium functions even at low ECDs (under 500 cells/mm2).
  - **Polymegathism** (variation in cell area as determined by the CV) and **pleomorphism** (variation in cell shape as represented by the percentage of hexagonal cells) are a more ***sensitive measure of the endothelium under stress***.
  - The corners method
  - The Center method (Konan Medical USA)
  - The center-flex method
- **Clinical Applications**
  - The ECD at which corneal edema occurs is quite variable, but has been estimated to be between **300 and 700 cells** per mm2.
  - Difference between two eyes: greater than **280** cells per mm2 is abnormal
  - A cornea with a **CV greater than 0.40 or the presence of less than 50% hexagonal cells** should be considered abnormal and at increased risk for postoperative edema.
  - Age-related cell loss is approximately **0.5% per year**.
  - Combined surgery is considered **if CCT>600 and Specular <1000**
  - The most striking abnormality in keratoconus, however, is elongation of endothelial cells
  - FDA-approved Artisan/Verisyse phakic intraocular lens (IOL) has found acceptable mean cell loss rates of **1.8% per year** after insertion to correct high myopia.
  - **Cell loss after PKP:** *10% after 2 week, 33% at 3 months, 50 % at 1 year*
  - ***Cell loss after EK:*** *34% cell loss after 6 months, and 38% at 1 year*
  - Vitreous contact mechanically injures the endothelium and interferes with its physiologic function.
- **Interpretation**
- Image quality is Dependent upon: Degree of corneal opacification (Unable to visualize endothelium in cases of corneal opacification)
- Image interpretation
  - Dependent upon: Reader experience less than confocal microscopy
  - Corneal endothelial cell imaging
    - Mode

- Automated appropriate when endothelial mosaic well-visualized
- Manual appropriate when endothelial cell borders not well visualized or endothelial mosaic interrupted by guttae

- Endothelial cell density: Normal adult endothelial cell density is 2000-3000 cells/mm^2
- Endothelial cell morphology cell shape and size
  - Coefficient of variation Average cell size divided by the standard deviation of the average cell size
    - ✓ Normally < 0.30
    - ✓ Polymegathism increased variation in cell size, which is an indication of poor cell function
- Percentage of hexagonal cells
    - ✓ Should approach 100%
    - ✓ Polymorphism (Pleomorphism) increased variability in cell shape. Less than 50% hexagonal cells may be an indication of poor cell function

Confocal Microscopy

- The optical sectioning ability of confocal microscopy allows images to be obtained from different depths within a thick tissue specimen, thereby eliminating the need for processing and sectioning procedures.
- **Principle of Lukosz**, which states that resolution may be improved at the expense of field of view.
- In 1955, **Marvin Minsky** developed the first confocal microscope for studying neural networks in the living brain
- Because both condenser and objective lenses had the same focal point, the microscope was termed '**confocal**.'
- Because the illumination and detection of light through conjugate pinholes occurs in tandem, this microscope was named the ***tandem scanning confocal microscope (TSCM).***
- There are three main confocal imaging systems used clinically:
  - **TSCM** Tandem scanning-based confocal microscopy
    - Simple design, but low intensity of illumination
    - Inefficient illumination causes it to appear bright to the patient and causes patient discomfort.
  - **HRT III** (Laser scanning confocal microscopy (LSCM)
    - Provides faster scanning of the tissue plane via laser technology

        - High-depth resolution and high contrast allow for more detailed view of tissue vs. SSCM and TSCM
    - **Confoscan 4** (Slit-scanning confocal microscopy (SSCM)
        - Slit aperture allows increased light throughput, which improves field brightness and contrast vs. TSCM
        - Lower illumination is more comfortable for patients.
- **Indications**
    - Diagnosis of infectious keratitis
        - Fungal
        - Protozoal
    - Diagnosis of non-infectious keratitis
        - Corneal dystrophies
            - Fuchs endothelial dystrophy
            - Corneal stromal dystrophies
        - Interface opacities following lamellar corneal surgery
        - Corneal intraepithelial neoplasia
    - LASIK:
        - Corneal sub-basal nerve layer assessment
        - Corneal haze assessment
        - Flap healing
    - Cell density measurements
        - Analysis in LASIK/PRK
        - Analysis in Fuchs dystrophy
- **Complications**: Corneal epithelial abrasion
- **Interpretation**
    - Image quality: Dependent upon Operator experience, Patient cooperation, Degree of corneal opacification
    - Image interpretation:
        - Dependent upon Reader experience
        - Corneal endothelial cell imaging
            - Provides Endothelial cell density and Pachymetry
            - Some instruments (e.g. HRT 3) do not provide Coefficient of variation, Average cell size, % hexagonal cells

High-Resolution Ultrasound (UBM)

- University of Toronto: UBM

- Frequency range of 25–100 MHz
- Resolution ranging from 20 to 100 μm
- Penetration to the 4–15-mm range
- B-mode imaging system at 5-13 frames per second
- 23-50 micron axial resolution

- **For diagnosis of**: Corneal edema, DMD, IOL malposition, Imaging the anterior segment behind corneal opacities, Corneal dystrophies, Peripheral corneal degenerations, Keratoconus, Corneal Tumors, postKeratoplasty, Refractive surgery
- **Indications**
  - To provide an image of the anterior chamber (AC) angle when gonioscopy is not possible (e.g., with a cloudy cornea or hyphema)
  - To qualitatively and quantitatively image and assess up to 4-5 mm in depth the normal anatomy of the anterior segment
- **Interpretation**
  - Scleral invasion of conjunctival tumor may be difficult to ascertain
  - Resolution of tumor low compared with OCT
  - Accommodation, pupil position and patient fixation of the fellow eye may affect the angle anatomy.

ASOCT (Anterior Segment Optical Coherence Tomography)

- **Fujimoto, Huang**, and colleagues
- The ***optical delay of the reflected light is determined by interferometry*** to generate a ranging measurement called the axial scan (A-scan)
- The original OCT technology is now classified as time-domain OCT (**TD-OCT**), in which the **reference mirror is moved through a range of delay**, and the resulting inference patterns between the sample and reference beams are processed into an axial image.
- New technology called Fourier-domain OCT (**FD-OCT**) has been developed. In FD-OCT, the **reference mirror is stationary and the A-scan is generated by Fourier transformation of spectral interference** patterns between the sample and reference reflections.
- **Indications**
  - Assessment of cornea
    - Focal thinning/thickening of epithelium
    - Depth of corneal pathology to assist pre-operative planning of corneal surgery (ablative, lamellar, or full thickness)
    - Depth of intrastromal corneal ring segments (INTACS), providing accurate positioning and depth assessment
    - Position and thickness of endothelial grafts

        - Alignment and shape of donor-host junction in penetrating keratoplasty (e.g. top hat, mushroom, and zigzag-shaped incisions)
        - Depth of sutures in penetrating keratoplasty
        - Assessment of anterior segment tumors
        - Presence of iris cysts, iris nevi, and iris melanomas and angle configuration
        - Evaluation of ocular surface squamous neoplasia (OSSN)
        - Presence of cysts in pigmented lesions such as conjunctival nevi
    - Measurement of angle and central and peripheral anterior chamber depth
        - Population screening: non-contact exam, relatively quick procedure
        - Pre iridotomy and post iridotomy and/or iridoplasty
        - Possible new dark room provocative test for angle closure suspect eyes to evaluate the need for potential treatment
    - Assessment of conjunctival filtration blebs and glaucoma implants for function/ scarring or patency and assessment of non-penetrating glaucoma surgical procedures
    - Assessment of tear film

- ***Five pachymetric parameters for Keratoconus Screening:***
    1. Minimum – median thickness < –63 µm
    2. I – S < –31 µm
    3. IT – SN < –48 µm
    4. Minimum corneal thickness is less than 492 µm.
    5. The thinnest region of the cornea is outside of the central 2-mm area.
- **Advantages**
    - Non-contact, comfortable technique
    - Seated position of patient
    - Rapid image acquisition
    - Some devices provide image of scan localization
    - High resolution, cross sectional images are reproducible and accurate
    - Ability to image an eye immediately preoperatively and postoperatively without contact with the eye
    - Easy for technician to acquire skill in examination technique
    - Avoids potential mechanical distortion of the anterior segment of the eye and change in angle/iris anatomy
    - Can provide "optical biopsy" in some cases for differentiating OSSN from pterygia and other entities
    - Can follow tumor resolution when treating OSSN with medical therapies such as mitomycin, 5 fluorouracil, and interferon

- May help detect early recurrences of OSSN and map disease
- Can be used intra-operatively or post Descemet stripping and Descemet membrane endothelial keratoplasty to assess donor/host apposition
- Can assess potential depth of corneal pathology prior to phototherapeutic keratectomy, automated lamellar keratoplasty etc.
- Dynamic investigation of anatomical angle variation and occludability with changes in illumination intensity
- Potential for large scale, population screening at the primary care setting, in areas where angle closure glaucoma is highly prevalent

Disadvantages

- High cost of the device
- Limited depth of penetration (especially in spectral domain OCT)
- Shadowing often occurs due to keratinization, or depth > about 400um
- Cannot determine atypia as seen with histopathology
- Tumors in locations such as caruncle, inferior or superior fornix difficult to image
- Cannot image structures behind the iris such as the ciliary body, ciliary processes, lens equator, zonules, and lesions or tumors in these areas
- Inability to perform dynamic compression to discriminate appositional from synechial angle closure
- Potential for over diagnosis of angle closure by AS-OCT compared to under diagnosis by conventional gonioscopy

Corneal Pachymetry

Indications

- Diagnosis and management of glaucoma, glaucoma suspect, and ocular hypertension
- Preoperative planning for keratorefractive and anterior lamellar corneal surgery
- Corneal thinning disorders diagnosis, ongoing assessment
- Endothelial dysfunction ongoing assessment, preoperative planning for patients with visually significant cataract, following corneal transplantation

Methods

- Ultrasonic pachymetry
- Scheimpflug imaging (e.g., Pentacam, Galilei)
- Scanning-slit (e.g., Orbscan)
- Optical coherence tomography
- Optical pachymetry, focusing technique: Measure distance between focused images of anterior and posterior surfaces (e.g., specular microscopy)

Interpretation

- Falsely elevated readings if instrument is not perpendicular to cornea, or, for central corneal thickness (CCT), not centered properly
- Consistent pachymetry values (at least 3 measurement values): A wider range of variability is greater in abnormal corneas
- Compensating for intraocular pressure readings based on CCT
- Evaluation for corneal refractive surgery candidacy based on corneal thickness
- Corneal thickness should be compared with the appearance of the corneal endothelium
- Variability between instruments
  - Instruments are not interchangeable
  - Anterior segment OCT has better agreement with ultrasound although it may underestimate the measurement
  - Slit scanning pachymetry is particularly problematic in assessing corneal thickness after laser vision correction

Corneal Esthesiometry

- **Indications**
  - Determine the presence of abnormal corneal sensation in the presence of suspected disease
  - Monitor return of corneal nerve function
  - Estimate potential for complications prior to contact lens wear or corneal surgery
- **Instruments**
  - Cotton tipped swab
    - Qualitative, gross assessment
    - No topical anesthetics for 24 hours prior to testing
    - Wisp of cotton fiber from tip of swab brought in from side to avoid startle reflex
    - After touching central cornea of each eye, patient responds as to which eye is more sensitive, and examiner observes the interocular difference in blink reflex and verbal response
  - Dental floss
    - Can be used to check sensation in each quadrant
    - Waxed, unflavored dental floss
    - Held 1-3 cm from tip
  - Cochet-Bonnet esthesiometer
    - More objective, quantitative
    - No topical anesthetics for 24 hours prior to testing
    - Handheld "mechanical pencil" like device with 6 cm long adjustable nylon monofilament for testing

- Longest extension of filament (6 cm) exerts 11 mg/mm^2 pressure, shortest extension (1 cm) exerts 200 mg/mm^2 pressure when applied perpendicularly to cornea
- Perception of touch at full extension (6 cm) indicates normal corneal sensation
- Tip progressively shortened in 0.5 cm increments until patient can feel corneal touch
- Record length at which filament is first felt to quantify level of corneal sensation

- **Complication**: Corneal abrasion
- **Interpretation**
  - Accuracy depends on consistency in testing same area of cornea each time
  - Ocular sensitivity greatest in central cornea, except in elderly where peripheral cornea can be more sensitive
  - Esthesiometer
    - Confirm values by increasing and decreasing filament length by 0.5 cm from recorded measurement
    - Insure tip of monofilament is perpendicular to corneal surface
- **Differential of decreased corneal sensation**
  - Long term contact lens wearers
  - Topical medications (e.g. glaucoma medications)
  - Herpetic keratitis
  - Diabetics
  - Penetrating keratoplasty grafts are anesthetic initially and never recover full sensation
  - Endothelial keratoplasty corneas will have reduced corneal sensation only at the area of the limbal incisions, similar to cataract surgery patients
  - Radial keratotomy
  - Laser refractive surgery such as photorefractive keratectomy (PRK) and LASIK

Differential Diagnosis in Cornea

Congenital Corneal Opacities

- 3-6 per 100000
- **STUMPED classification (Waring)**
  - Sclerocornea
  - Tears in Descemet's membrane: Congenital glaucoma, Birth trauma
  - Ulcer: Herpes simplex virus, Bacterial, Neurotropic
  - Metabolic (rarely present at birth): Mucopolysaccharidoses, Mucolipidoses, Tyrosinosis
  - Posterior corneal defect: Peters' anomaly, Posterior keratoconus, Staphyloma
  - Endothelial dystrophy: Congenital hereditary, Posterior polymorphous corneal dystrophy, Stromal: congenital stromal corneal dystrophy
  - Dermoid

- **Sclerocornea**
  - Scleralization of the peripheral or the entire part of the cornea
  - Sporadically, familial or autosomal dominant
  - Bilateral but commonly asymmetric
  - Opacification of the cornea is smooth, white, and vascular; it appears to be an extension of the sclera without limbal landmarks
  - **Four groups (Waring et al)**
    1. Isolated peripheral sclerocornea
    2. Sclerocornea plana: <38D, High Hyperopia, Shallow AC, Pseudoptosis
    3. Sclerocornea associated with anterior chamber cleavage anomalies: Peter's
    4. Total sclerocornea: the **most common** form causing congenital corneal opacity,
  - **Histopathology in sclerocornea**
    - Corneal stroma resembles sclera morphologically
    - Precise arrangement of stromal lamellae absent
    - Irregular arrangement of collagen fibers; variable in diameter
    - Collagen fibrils thickened (up to 1500 Å in diameter); resemble scleral fibrils
    - Diameter of collagen fibrils decreases in posterior stroma
    - Changes in posterior cornea may resemble those seen in Peters' anomaly
  - Somatic abnormalities such as mental retardation, anomalies of the skin, facies, ears, cerebellum, and testes.
  - Differential Diagnosis: arcus juvenilis, interstitial keratitis, Peters' anomaly, and microcornea

- **Congenital glaucoma**
  - Epiphora, photophobia, and blepharospasm
  - First signs are elevated intraocular pressure, corneal enlargement and clouding, and optic nerve cupping
  - Increased corneal diameter
  - Tears in Descemet's membrane can be single or multiple, and appear as elliptical, glassy, parallel ridges on the posterior cornea, either peripherally or across the visual axis. In congenital glaucoma these breaks have a random distribution, most commonly ***horizontal or concentric to the limbus***, in contrast to the ***oblique and vertical orientation of the breaks in Descemet's membrane seen in birth trauma***

- **Birth trauma**
  - **Left eyes** seem to be affected more commonly than right eyes because neonates usually present in the **left-occiput-anterior position**
  - The Descemet's tears in birth trauma are usually **unilateral, central** and, in contrast to congenital glaucoma, line up in a **vertical or oblique** pattern, presumably because the tip of the forceps has slipped over the rim of the orbit and compressed the globe vertically, stretching it horizontally to create the tears.
  - Corneal edema usually clears within weeks to months.
  - High residual corneal astigmatism, which may range from 4 to 9 diopters, requires urgent correction and amblyopia treatment.

- **HSV Infection**
  - **80% HSV type 2** and 20% by type 1.
  - Primary ocular infection that can later become recurrent
  - CNS involvement are common and are associated with significant mortality
  - Usually apparent within 2 days to 2 weeks
  - **Macrodendrites, geographic epithelial defects, and punctate keratopathy**.
  - An **oral ACV–cesarean combination** provides maximal protection for the neonate.
  - The treatment for neonatal HSV keratitis or conjunctivitis is **intravenous aciclovir**.

- **Congenital rubella**
  - Congenital rubella infection, however, causes microphthalmia, cataract, retinitis, iridocyclitis, corneal clouding, strabismus, nystagmus, nasolacrimal duct obstruction, and viral dacryoadenitis.

- **Bacterial corneal ulcers**
  - Exceedingly rare in the neonate

- Gonorrheal ophthalmia neonatorum usually presents as a unilateral conjunctivitis with an incubation period of a few hours to 2–3 days.
- Ophthalmia neonatorum caused by Chlamydia: systemic erythromycin
- Congenital syphilis is not a cause of congenital corneal opacification.

Neurotrophic keratitis

- Familial dysautonomia (Riley–Day syndrome)

Metabolic diseases: They are all autosomally recessive, with the exception of mucopolysaccharidosis type II (**Hunter's** syndrome), which is X-linked recessive.

- ***Mucopolysaccharidosis***
  - **Hurler's syndrome** (MPS I-H) or gargoylism is caused by a deficiency of alfa-l-iduronidase and the gene involved with this error is mapped to 4p16.3. **Corneal clouding is significant** and helps differentiate this disease from Hunter's syndrome.
  - Hurler's, Scheie's, Morquio's, and Maroteaux-Lamy syndromes all demonstrate progressive corneal clouding. Hunter's and Sanfilippo's syndromes do not demonstrate clouding grossly, but may have slit lamp evidence of clouding at a later age.
- ***Mucolipidosis***
  - Episodic ocular pain is an important symptom in mucolipidosis type IV. It is caused by corneal epithelial cytoplasmic accumulation of abnormal material with subsequent corneal surface irregularities.
- Cystinosis: AR, needle-like cystine crystals in the cornea and conjunctiva is usually seen by 1 year of age.
- Fabry's disease: sphingolipidosis caused by a lack of alfa-galactosidase A
- Tyrosinemia: type II (**Richner–Hanhart syndrome**) is a rare congenital error of metabolism characterized by a triad of dendriform keratitis, hyperkeratotic lesions of the palms and soles, and mental retardation.

Peters' anomaly:

- Sporadic, AR, AD
- Central corneal opacity with corresponding defects in the posterior stroma, Descemet's membrane, and the endothelium.
- **Synechiae** frequently extend from the ***iris collarette to the edge of the posterior corneal*** defect
- **Glaucoma 50–80%** → incomplete development of angle
- Bilaterally 80%, asymmetric
- **Type I:** Corneal opacity + iridocorneal adhesions
  - systemic abnormalities are uncommon

- **Type II:** Corneal opacity + iridocorneal adhesions + lens abnormality (position or transparency)
  - **Peters'-plus syndrome**: Peters' anomaly + short stature, brachymorphy, mental retardation, abnormal ears, and, in some patients, cleft lip and palate
  - **Krause-Kivlin syndrome**: Peters' anomaly + facial abnormalities, disproportionate short stature, retarded skeletal maturation and developmental delay (probably inherited in an autosomal recessive manner)
- **Histopathology of Peters' anomaly**
  - Central concave defect in the posterior corneal stroma (posterior ulcer)
  - Disorderly stromal lamellae in ulcer bed
  - Absence of corneal endothelium and Descemet's membrane in the posterior ulcer
  - Corresponding area of central corneal edema and opacification
  - Keratolenticular adhesions to posterior cornea in some cases
  - Iridocorneal adhesions to margin of ulcer in some cases
  - Bowman's layer thickened or absent
- **Differential diagnosis:** Von Hippel's internal corneal ulcer, sclerocornea, dermoid, CHED, and PPCD
- **Proposed causes**: incomplete central migration of corneogenic mesenchyme (i.e., neural crest cells), accounting for posterior endothelial and stromal defects

Posterior keratoconus

- Very uncommon, mildest variant of Peters' anomaly
- Nonprogressive and usually sporadic
- Unilateral/ bilateral
- Descemet's excrescences can also be present in or just outside of the area of involvement. The corneal endothelium and Descemet's membrane are present.

Congenital anterior staphyloma

- Protuberant congenital corneal opacity.
- Secondary to an intrauterine infection or related to a developmental abnormality such as a severe type of Peters' anomaly

CHED

- 1960 by **Maumenee**
- **CHED 1**: **AD**, 20p11.2-q11, clouding is slowly progressive over 1–10 years. presents with photophobia and epiphora and the subsequent development of corneal clouding.

- **CHED 2**: **AR**, 20p13 (Solute Carrier Family), previously referred to as Maumenee cornea dystrophy. ***bilateral corneal clouding at birth*** or shortly thereafter. The corneal changes are stable and do not progress or regress. There are no associated symptoms, such as epiphora or photophobia, but patients often develop nystagmus.
- **Differential Diagnosis**: CSCD, congenital glaucoma, PPCD, Peters' anomaly, and inborn errors of metabolism, especially the mucopolysaccharidoses

PPCD

- Bilateral, nonprogressive, asymptomatic disease that rarely requires penetrating keratoplasty.
- One form may present with congenital corneal edema, It is important to differentiate PPCD from CHED, because the treatment is different

CSCD

- **Decorin** gene on chromosome 12
- Anterior stroma demonstrates a diffuse, flaky-feathery opacification caused by corneal lamellar irregularities

Congenital Dermoids

- Solid benign congenital tumors → **choristomas**
- Yellowish-white, solid, vascularized, elevated nodules straddling the corneal limbus.
- Sporadic, genetically mapped to chromosome Xq24-qter
- **Grade 1:** small, usually measuring 5 mm in diameter or less, single, limbal or epibulbar, 1/3 Goldenhar's syndrome → epibulbar dermoids, preauricular appendages, and pretragal fistulas.
- **Grade 2**: larger, covering part of or the entire corneal surface, with variable depth, generally does not involve Descemet's membrane or the corneal endothelium. It is the most important type in the differential of congenital corneal opacities.
- **Grade 3**: entire anterior segment, Microphthalmos is common, and posterior segment abnormalities
- **Management**: limbal dermoids are more of cosmetic problem → cut flush with the corneal surface, but it may recur. Penetrating keratoplasty for central dermoids if they are 7 mm or less. Larger central dermoids require a two-stage procedure: first the tumor is excised and a large lamellar graft is placed in the bed; once that is healed, a smaller central penetrating keratoplasty is performed

Corneal Keloids

- ***Fibrous tissue proliferations*** that represent the exuberant response of embryonic connective tissue to injury.
- White, sometimes protuberant, glistening, masses

- Presence of myofibroblasts in these lesions, differentiating them from Salzmann's nodules.
- Can be associated with Lowe's syndrome

Peripheral Corneal Disease

- Portion located between the central 50% of the cornea and the limbus.
- Thickest region of the cornea, which is directly adjacent to the corneal limbus and internal angle structures

- **Congenital/Developmental/Inherited Disorders:**
  - **Lattice dystrophy type II** is associated with systemic amyloidosis and primarily involves the peripheral cornea.
  - **Wilson's disease**: orangey-brown ring in the periphery of the cornea, Kayser–Fleischer ring consists of copper which is deposited in Descemet's membrane.
  - **Sclerocornea and cornea plana**:
  - **Posterior embryotoxon**: a thickened, prominent Schwalbe's line, which is more anteriorly located than normal. 15% of the normal eyes. When it is associated with other peripheral corneal abnormalities, including multiple peripheral iris strands, it is termed Axenfeld–Rieger anomaly

- **Inflammatory/Autoimmune Disorders**
  - **Rheumatoid arthritis**: KCS, sclerosing keratitis, peripheral corneal furrow
  - **Polyarteritis nodosa**: eye in 20% of cases, bilateral peripheral keratitis
  - **Wegener's granulomatosis**: Two forms of the ocular disease have been described: a severe progressive disease, which has a 1-year mortality of 82% if untreated; and a limited, less severe form.
  - **Marginal keratitis:** ocular hypersensitivity reactions to toxins produced by bacteria that commonly colonize the eyelids
  - **Phlyctenulosis** is an inflammatory disorder which is similar to marginal keratitis but involves a more severe reaction
  - **Mooren's ulcer** produces a painful progressive peripheral ulceration of the cornea.
  - **Vascular pannus**: blood vessels and fibrous connective tissue from the limbus grow onto the peripheral cornea
  - **Superior limbal keratoconjunctivitis (SLK):** inflammatory disorder of unknown etiology which is associated with a peripheral corneal pannus, a punctuate keratopathy, a thickened superior conjunctiva which is chemotic and hyperemic, and a filamentary keratitis.

- **Neoplastic Disorders**
  - Pterygium:
  - Pyogenic granuloma
  - Dermoid tumors
  - Squamous metaplasia
  - Carcinoma in situ or intraepithelial neoplasia (CIN)

- **Degenerative Disorders**
  - Corneal arcus
  - Lipid keratopathy: primary & secondary
  - White limbal girdle of Vogt: type 1 & 2
  - **Calcific band keratopathy**: intraocular inflammation, trauma, multiple eye surgeries, elevated serum calcium, or other systemic disorders. The deposition initially begins in the peripheral cornea, with a clear margin separating the deposit from the limbus. The clear interval is thought to represent the anatomic limit of Bowman's layer. Throughout the band are clear, small holes that give a 'Swiss cheese' appearance. The holes occur at sites where corneal nerves penetrate Bowman's layer.
  - **Calcific degeneration**: the calcium may be associated with a fibrovascular pannus or may occur deep in the corneal stroma, as opposed to calcific band keratopathy in which the calcium deposition is confined to the region of Bowman's membrane.
  - Corneal epithelial stem cell deficiencies
  - Terrien's marginal degeneration
  - Pellucid marginal degeneration
  - **Furrow degeneration**: elderly, not a true thinning but rather an optical illusion
  - Dellen: areas of thinning or excavation. The overlying epithelium is usually intact,

- **Infectious Disorders**
  - Microbial keratitis
  - Herpes

Corneal Ulcer

- Always search for →
  1. Infectious agent
  2. Local host factors

3. Exogenous risk factors
4. Endogenous factors: autoimmune disease, inflammatory, immunocompromised

Corneal Edema

1. **Primary endothelial failure**: FECD, CHED, PPCD, ICE
2. **Secondary endothelial failure**: Trauma, chemical, hypoxia
3. **Normal endothelium**: increased IOP
4. **Epithelial failure**: Epithelial Defect

- **Ancillary tests**
  - Pachymetry
  - Specular microscopy
  - In vivo confocal microscopy
  - Anterior segment optical coherence tomography
- **Treatment**
  - Treatment of inflammation and the underlying cause of inflammation
  - Decreasing the pressure can improve or resolve corneal edema and prevent further damage to endothelial cells. Inhibition of corneal carbonic anhydrase pumps by topical CAIs may lead to decreased fluid flow from stroma to aqueous and progression to corneal edema.
  - Hypertonic agents
  - Bandage contact lens
  - **Anterior stromal cautery**: Application of light burns to Bowman's layer using a thermal cautery (**Salleras procedure**)
  - Conjunctival flap
  - Amniotic membrane
  - Excimer laser
  - Penetrating keratoplasty
  - Endothelial keratoplasty

Corneal Deposits

- **Three depths**: superficial, stromal, and deep stromal.
- **Three categories**: pigmented, nonpigmented, and refractile/crystalline.

- **Epithelial iron lines**: Iron lines can be seen in the palpebral fissure **(Hudson-Stahli),** at the head of a pterygium (**Stocker**), surrounding the cone in keratoconus (**Fleischer**), at the head of a filtering bleb (**Ferry**), adjacent to areas of corneal elevation such as Salzmann's nodular degeneration, anterior to the sutures in keratoplasty (**Mannis**), and after keratorefractive surgery.
- **Coat's white ring** is a superficial ring of iron deposition that remains after a metallic foreign body is removed. Small white opacities may be seen inside the ring. These rings develop when a rust ring from an iron foreign body is not entirely removed.

Red Eye

- Redness is not a symptom, but a nonspecific sign. The three major processes responsible for the majority of cases are subconjunctival hemorrhages, inflammation, and vascular abnormalities.

Eye Banking

- First formally organized eye bank established in New York in 1944
- **The FDA required testing includes**:
    1. HIV 1–2 antibody
    2. Hepatitis B & C antibody
    3. Syphilis testing
    4. HIV & HCV NAT testing (nucleactic acid DNA/MNA)
- The Uniform Anatomical Gift Act (UAGA) of 1968 stated that a signed and witnessed donor card was sufficient legal permission for organ or tissue removal after death.
- ***CMV, HSV is not contraindications***
- Eye malignancy like RB, Anterior segment Carcinoma like Adenocarcinoma etc. are contraindication. *Systemic malignancies are* ***not*** *contraindications* ***except lymphoma/ leukemia***.
- **Primary Graft Failure**: currently believed to be about **1%**. Causes include pre-existing corneal endothelial abnormalities, damage during recovery or storage, and surgical trauma.

Corneal Storage Media

- First corneal preservation was done by **Magitot** in 1911. He stored cornea in **Hemolyzed blood serum** at 5-7deg.centigrade and Cornea was viable for 2 days. (JAMA)
- BASE MEDIA
    - **Tissue-culture199-**aminoacids, salts, buffer & energy to support life.
    - **Minimum Essential Media(MEM) with Earles salt**matches natural salts & buffers of human tissue, electrolytes similar to aqueous
- BUFFER: **HEPES**(N-2-hydroxyethyl-piperazine-N-2ethane-sulfonic acid)
    - used for cultivation of sensitive mammalian cells
    - provides optimal physiological PH in the range7-7.2
- ANTIBIOTIC: Gentamicin only /& Streptomycin
- DEXTRAN
    - Polysaccharide, negatively charged.
    - Prevents tissue swelling.
    - Used alone does not provide sufficient tissue stability & viability for extended storage.
- CHONDROTIN SULFATE
    - Polysaccharide, negatively charged
    - Endothelial integrity & acts as osmotic agent. Superior to dextran. Longer storage time

- ENRICHED
  - Various salts, amino acids essential &non-essential, vitamins, phosphates & antioxidants to enhance cell & tissue viability & health during storage.
- ATP precursors → Provide energy for pumping function.
- Anti-Oxidants → Neutralize metabolic waste, maintain DNS synthesis
- Vitamins → Provides additional nutritional cell supplements.
- Sodium Pyruvate & Glucose → Energy supply
- Color Phenol Red-->Visual aid for pH indication.
- *CHECK MEDIA*
  - The cornea which is stored in MKmedia, Dexol, optisolGS.
  - The following parameters to be checked before using
  - Intact seal, Expiry date, Turbity, Colour (rose red),precipitates & FB.
  - COLOUR CHANGE INDICATES
    - Yellow- Bacterial contamination.
    - Red- Unacceptable Ph.
    - Cloudy- Contamination
- STORAGE TYPES
  - **SHORT4 degree Celsius (days)**
    - Moist chamber(1day)
      - Filatov & Castroviejo.
      - Whole globe is stored in a sterile jar having saline Humidification at Temp of 4 degrees C.
      - Popular until 1970.
    - M.K. Media (4days)
      - Tc199
      - Dextran 40 1%
      - PH 7.0-7.5
      - Osmolality 295-355
      - gentamycin sulphate 75-150 micro gm/ml
      - HEPES as buffer.
      - Phenol red as indicator.
  - **INTERMEDIATE-14 days4 degree Celsius (wks)**
    - K-Sol
      - Tc 199, MEM & Earles media, HEPES, Gentamicin, Chondroin sulphate 2.5%
      - 1988 proprionibacteria contamination
    - Dexol

        - MEM
        - 1.35%Chondrotin Sulphate
        - 1mM Sodium pyruvate,
        - 1mM nonessential amino acids
        - Antioxidants
        - 1% dextran40.
    - Optisol GS
        - Introduced in 1991
        - MEM
        - 1.35% Chondrotin Sulphate
        - 1mM Sodium pyruvate
        - 1 mM non-essential aminoacids
        - Antioxidants
        - 1%dextran40, ATP, Iron, cholestrol,
        - L-hydroxyproline, Vitamins
        - 2 antibioticsGentamycin, Streptomycin
    - Procell
        - MEM,1.35%chondrotin sulphate,1mM sodium pyruvate1mM,Non-essential aminoacids,Antioxidants,Dextran40,
        - Humen insulin10mic.g/ml & Human epidermal growth factor(hEGF10ng/ml) to improve long term endothelial survival after PKP.
    - Eusol-C
        - Store at 4deg.C
        - Storage time 14 days
        - SIMILAR TO DEXOL
        - Dextran, Sodium Piruvate, Glucose, Essential & non-essential aminoacids, mineral salts, Vitamins, Gentamin, hepes buffer, Bicarbonate, Phenol Red.
- **LONG(months)**
    - Organ culture
        - 1936, by Archer & Trevor-Roper.
        - Being used since1974.
        - Refrigeration not required.
        - Complicated, expensive & well trained microbiologist.
        - Contents: Eagles media, Earles salt without L-glutamine, L-glutamine 1% final conc, Decomplemented calf serum 10% final conc.

Penicilllin 100 units/ml,, Gentamicin 100 microgram/ml.
Amphoterician B 0.25% microgram/ml.

- European Organ culture-120days (37deg.C)
  - 31-37deg.C, EMEM, MEM, IMDM ,
  - HEPES, NaHCO3, Peni, Strep, Ampo-B,
  - BOVINE SERUM 2-10ML, Dextran4-10%
- Eurosol 31 deg.C -28days(New)
  - Duration of storage 28days.
  - Temp 31deg.C.
  - Better than the European culture media.
  - Maintains intact endothelium, epithelium & Keratocyte
- Cryopreservation-Unlimited-(-80degC)
  - Kaufman & Capella.1954
  - Cornea is stored in Liquid Nitrogen with Dimethyl Sulfoxide (DMSO).
  - DMSO, Prevents intracellular damage by ice crystals.
  - Not a procedure used.Holds a lot of research interest.
- *GLYCERINE PRESERVATION*
  - Patch graft or Lamellar Keratoplasty.
  - Corneo-scleral button.
  - 100%glycerine.
  - Enothelium is nonviable
  - Use with in 1 year.
  - Stored at room temp.

Diseases of the Lid & Ocular Surface

Anatomic Abnormalities

- **Entropion**
- **Ectropion**
- **Trichiasis and Distichiasis**
- **Floppy Eyelid Syndrome**
  - Primarily a disorder of sleeping position
  - Ocular irritation, mucous discharge, and papillary conjunctivitis.
  - Histopathologic features of the floppy eyelid syndrome point primarily to a **marked reduction in eyelid tarsal elastin**
  - Identification of sleep apnea and institution of CPAP to allow a supine sleep position is paramount
- **Lid Imbrication Syndrome**
  - **Abnormality of lid apposition in which the upper lid overrides the lower**, thereby allowing the lower lashes and keratinized epithelium to rub chronically against the upper eyelid marginal tarsal conjunctiva.
- **Lagophthalmos**
- **Eyelid Retraction**

Conjunctivochalasis

- Redundant conjunctiva
- **Hughes** in 1942
- Most often located between the eyeball and the lower eyelid.
- Grading of the degree of CCh was found to have a high predictive value for diagnosis of KCS
- **Epidemiology**
  - Changes related to the aging eye
  - Thought to be due to elastotic degeneration and collagenolysis that leads to laxity of the adherence of the conjunctiva to the underlying connective tissue
  - Suggested that enzyme accumulation in the tear film due to delayed tear clearance may lead to degradation of the conjunctiva
- **Histopathology**
  - Senile process related to conjunctival laxity
  - Abnormalities in the extracellular components: **MMP-1 and MMP-3** were found to be overexpressed in the conjunctivochalasis fibroblasts. tissue inhibitors of metalloproteinases (**TIMPs**) expression remains unchanged, particularly TIMP-1

and TIMP-2. This ***change in the ratio of MMPs to TIMPs*** may facilitate the breakdown of the extracellular matrix and result in the clinical changes observed in conjunctivochalasis.

- **Clinical Features**:
  - Irritation in mild stages, marked tearing due to obstruction of the lower punctum in the moderate stage, and ocular surface exposure in more severe stages.
- **Diagnosis**
  - Rule out lid pathology
  - **LIPCOF classification**
    1. No persistent fold
    2. Single, small fold
    3. More than two folds and not higher than the tear meniscus
    4. Multiple folds and higher than the tear meniscus
  - **Meller's new grading system** for conjunctivochalasis
- **Treatment**
  - No treatment is recommended if the patient is asymptomatic
  - Medical therapy: surface lubricants, antihistamines, and topical corticosteroids
  - Surgical management:
    - 1. Excision of the area of conjunctivochalasis
      - A crescentic excision of the inferior bulbar conjunctiva 5mm away from the limbus followed by closure with absorbable sutures may be performed. Fibrin glue can be used in lieu of sutures to reduce suture related granuloma formation and inflammation
      - Amniotic membrane can be placed over the defect created after the crescentic excision of conjunctiva. This can be sutured or glued into place
    - Conjunctival tightening in the area of conjunctivochalasis
      - Suture placement
      - Transconjunctival cautery

Trichiasis & Dystichiasis

- **Etiology**
  - Trichiasis: Acquired misdirection of eyelashes that curve toward the ocular surface
  - Distichiasis: Accessory eyelashes growing posterior to the normal row of eyelashes
    - Acquired distichiasis: Extra eyelashes emerge from meibomian glands or Aberrant eyelashes emerge from tarsus
    - Congenital distichiasis: Extra row of eyelashes emerges from meibomian glands
- **Risk factors**

- Mucous membrane pemphigoid
- Stevens-Johnson syndrome
- Graft vs. Host Disease
- Chemical burn
- Rosacea blepharoconjunctivitis
- Trachoma
- Staphylococcal blepharitis
- Herpes Zoster blepharitis
- Distichiasis can be familial or part of a hereditary syndrome

- **Medical Management**
  - Lubricants
  - Bandage soft contact lens to protect ocular surface
  - Treatment of associated ocular surface disorder
- **Surgical Management**
  - Mechanical epilation of misdirected eyelashes
  - Electrolysis or electrocautery (hyfrecation) or laser destruction of eyelash follicles
  - Cryotherapy
  - Incisional procedure
    - Eyelid splitting along the gray line with excision, electrocauterization, or cryotherapy of the hair follicles
    - Resection of abnormal eyelash follicles without or with mucous membrane grafting and without or with tarsal rotation and incision of the tarsal cartilage of an eyelid
    - Surgical correction of concomitant entropion or other abnormal eyelid position

Blepharitis

- **Numerous classifications**
  - Fuchs
    - blepharitis squamosa, which is characterized by small, dry scales
    - blepharitis ulcerosa, characterized by marginal crusting covering frank ulceration
  - Duke-Elder and MacFaul
    - squamous blepharitis, which they described as a superficial, nondestructive dermatitis with eczema-like inflammation
    - Follicular blepharitis characterized as a deeply seated, purulent process
  - McCulley

- staphylococcal disease
- seborrheic blepharitis
- both staphylococcal and seborrheic diseases
- meibomian seborrhea
- Seborrheic with secondary meibomitis
- Primary meibomitis (also known as meibomian keratoconjunctivitis)
- blepharitis associated with other conditions such as psoriasis and atopy.

- Practical standpoint of McCulley's
  - anterior blepharitis (comprising the first three, aka Seborrhic)
  - posterior blepharitis (comprising the remaining meibomian-related groups, aka MGD).

- **Etiology**
  - Seborrheic blepharitis is a chronic inflammation of the eyelid, eyelashes, forehead and scalp skin
  - Meibomian gland dysfunction is a result of progressive obstruction and inflammation of the gland orifices
  - Rosacea is a skin disease characterized by dysfunction of meibomian glands and/or other cutaneous sebaceous glands of the skin of the face and chest
- **Clinical features**
  - Seborrheic blepharitis
    - Affects primarily anterior eyelid margin
    - Oily or greasy eyelid crusting
    - Increased and turbid meibomian gland secretions
    - Mild conjunctival injection
    - Corneal punctate epithelial erosions
    - Aqueous tear deficiency
    - May have evidence of seborrhea elsewhere on the body
    - May be associated with staphylococcal blepharitis or meibomitis
  - Meibomian gland dysfunction
    - Affects posterior eyelid margin
    - Increased opaque secretion in meibomian glands
    - Foamy secretions
    - Pouting, metaplastic meibomian gland orifices
    - Telangiectasias of the eyelid margin
    - Meibomian gland drop out (meibography)
    - Abnormal meibum after expression of glands (with slight pressure on lid margin with Q tip or finger)

- Bulbar and tarsal conjunctival injection
- Papillary conjunctival reaction
- Atrophy of meibomian gland acini
- Episcleritis
- Corneal punctate epithelial erosions
- Corneal marginal infiltrates
- Corneal vascularization
- Evidence of systemic rosacea in some individuals
- Lipid tear deficiency

✣ Rosacea
- Malar rash and telangiectasias of facial skin and eyelid margin
- Papules, pustules, hypertrophic sebaceous glands
- Rhinophyma
- Meibomian gland dysfunction, distortion
- Excessive sebum secretion
- Bulbar and tarsal conjunctival injection
- Marginal corneal infiltrates and sterile ulceration of cornea
- Episcleritis
- Iridocyclitis
- Corneal neovascularization (superficial) and scarring
- Atrophy of meibomian glands late in disease
- Lipid tear deficiency and aqueous tear deficiency

✦ **Four principal arms of therapy for all of the categories of blepharitis**
1. Lid hygiene
2. Topical antibiotics
3. Systemic antibiotics (specifically tetracycline)
4. Corticosteroids

Meibomian Gland Dysfunction (MGD)

✦ Term first suggested by **Korb and Henriquez.**

✦ The meibomian gland secretion, which is distinct from sebum has been termed meibum by Nicolaides et al.

✦ **Meibography** is a technique that uses transillumination biomicroscopy of the everted eyelid with infrared photography

✦ Meibomian gland dysfunction → increases tear electrolytes uniformly

- lacrimal gland disease → sodium ions rise disproportionately in secretion at low flow rates
- The lipid layer is about 40–100 nm thick.
- Blinking is important for the excretion of meibomian lipid.
- **Meibometry** is used to measure the amount of lipid on the lid margin by determining the degree of translucency induced on plastic tape applied to the lid margin.
- **Tear film break-up time** is reduced in meibomian gland dysfunction.
- **Classification**
  - **McCulley et al. (1982)**
  - **Mathers et al. (1991)**
    - Seborrheic:
    - Obstructive:
    - Obstructive with sicca:
    - Sicca:
  - **Bron et al. (1991)**
    - Reduced number (congenital deficiency)
    - Replacement (trichiasis, metaplasia)
    - Hyposecretion
    - Obstructive meibomitis subdivided into focal, primary, secondary to local disease or systemic disease, and chalazia
    - Hypersecretory (seborrhea)
    - Neoplastic
    - Suppurative
- **Diagnosis**
  - Burning, irritation, itching, red eyes, and decreased or fluctuating vision
  - The lid margin is often rounded with thickening, erythema, hyperkeratinization, vascularization, telangiectasia, or notching.
  - An increase or reduction in the number of orifices may be seen.
  - Orifices are frequently less well defined or may show pouting
  - Secretion instead of being clear, it is turbid, granular, or toothpaste-like
  - Meibography → narrowing or occlusion of the glandular orifices and glandular distortion or dilation
  - Meibometer: lipid imprint is then analyzed using a density measuring device
- **Differential Diagnosis**
  - Staphylococcal blepharitis
  - Lice infestation
  - Masquerade syndrome (eyelid neoplasm rare, but should be considered in chronic unilateral blepharitis)

- Discoid lupus
- Demodex blepharitis

- **Associated Conditions**
  - Lacrimal insufficiency
  - Rosacea
  - Giant papillary conjunctivitis (GPC)
  - Contact lens intolerance
  - Chalazia
- **Histopathology**
  - Obstruction, hyperkeratinization
- **Lipid Composition**
  - Neutral sterol and wax esters with lesser amounts of polar lipids, diesters, triesters, triglycerides, free fatty acids, and free sterols.
  - Cholesterol esters are always present in patients with meibomian gland dysfunction
  - Unlike meibomian gland secretion, ***sebum*** *contains more triglycerides and free fatty acids and considerably less sterol esters. Squalene is present in sebum and absent in meibomian gland secretion.* The wax ester proportion is similar in both secretions. Overall, sebum is much more polar and will contaminate the tear film when mixed with it.
- Three of the bacteria commonly isolated from eyelids, S. aureus, Corynebacterium species (CN-S), and P. acnes, produce lipases that can alter the composition of meibomian lipids.
- Tetracycline ***reduces lipase*** production in S. epidermidis, S. aureus, and P. acnes. It also decreases serum cholesterol in mice, has ***antichemotactic*** effects on neutrophils, and has activity against ***collagenase and other metalloproteinases***. Any of these properties may produce a marked therapeutic effect in many patients with meibomian gland dysfunction and rosacea.
- **Treatment**
  - Daily eyelid hygiene (warm compresses, eyelid massage, and eyelid scrubbing) with commercially available pads, washcloth or cotton-tipped applicators soaked in warm water +/dilute baby shampoo
  - Topical
    - Tear Substitutes: Artificial tears If aqueous tear deficiency or lipid-induced tear film instability present
    - Topical Azithromycin 1%: 1 drop twice daily for 2 days then once daily (at bedtime after lid hygiene) for 2 or 4 weeks.
    - Topical Cyclosporine: 0.05% Ophthalmic Emulsion
    - Topical steroids: for control of flare ups
    - Topical metronidazole or clindamycin for skin involvement
    - Topical Interleukin 1 Receptor Antagonist: IL-1Ra
    - Topical Androgen:

- Topical Diquafosol: 3 %, P2Y2 receptor agonist that promotes tear fluid and mucin secretion.
- Topical N-Acetylcysteine: 5% QID, effective in the treatment of MGD not only for its mucolytic properties but also for its anti-collagenolytic and antioxidant properties.
- Demodex treatment
  - Tea Tree Oil – suffocates the mites
  - Active ingredient: Terpinen-4-ol (T4O)
  - Lid Scrub 2x per day x several months

✣ Systemic

- Systemic antibiotic therapy consists of oral tetracycline, 250 mg four times a day; **doxycycline, 50–100 mg twice a day**, or minocycline, 50 mg twice a day.
- Essential Fatty Acids (EFAs)
  - Omega 6-FA (meat, seed oils, dairy, eggs)
  - Omega 3-FA (cold water fatty fish, seed oils)
  - Good ratio: 4:1
  - These EFAs produce prostaglandins that are either anti-inflammatory or pro-inflammatory

✦ **Recent Updates on Newer Modalities of Management**

✣ Automated thermal pulsation (LipiFlow)

- First described by Lane in *Cornea* in 2012 and funded by TearScience (bought by Johnson & Johnson; New Brunswick, NJ in 2017
- The 2017 TFOS DEWS II report recommended LipiFlow and IPL as level 2 therapies after level 1 treatments such as hot compresses/hygiene, environmental, dietary changes, and artificial tears have been used.
- LipiFlow is well tolerated and appears to be more efficacious in younger patients with less severe hyposecretory MGD.

✣ Intense pulsed light (IPL); sometimes paired with meibomian gland expression (MGX)

- First link of IPL to meibomian gland disease treatment by Toyos in 2007 with IPL-MGX protocol on Quadra Q4
- IPL can be painful for some patients and cannot be performed on darkly pigmented skin. Repeated monthly applications are usually required. Proper eye protection is needed for patient and user to avoid ocular injury.

✣ Intraductal probing (Maskin probing)

- Described by Maskin in 2010: Maskin probes (Rhein Medical; Tampa, FL)
- The long-term safety of the more invasive intraductal meibomian gland probing is not known based on the current Level I evidence.

✣ Lid Debridement-Scaling

- Remove surface debris and unroof meibomian gland orifices
- Lissamine green staining of line of Marx
- Debridement along line of Marx and keratinized lid margin anterior to line of Marx
- Manual debridement with golf club spud or automated brush with Blephex

Demodex Blepharitis

- Demodex is an ectoparasite commonly found in the humanskin. The rate of Demodex infestation increases with age, being observed in the great majority of those older than 70 years. Several publications described chronic blepharokeratoconjunctivitis due to demodicosis in children. Demodex infestation has been associated with various skin conditions such as rosacea, pityriasis folliculorum, and perioral dermatitis.
- **Pathogenesis**
  - Two species have been identified in humans: Demodex folliculorum and Demodex brevis. Demodex folliculorum can be found in the lash follicle, whereas brevis burrows into sebaceous and meibomian glands. Demodex's life span is limited outside the living body; thus direct contact is required for transmission.
  - The main nutrition source of the mites is meibum. Especially Demodex folliculorum consumes epithelial cells at the hair follicle, resulting in follicular distention, which may contribute to formation of loose, broken, or misdirected lashes.
  - Microabrasions caused by the mite's claws can induce epithelial hyperplasia and reactive hyperkeratinization around the base of the lashes, forming cylindrical dandruff. Demodex brevis can mechanically block the orifices of meibomian glands and lead to posterior blepharitis. Its chitinous exoskeleton may act as a foreign body, causing granulomatous reaction. Chronic infestation with Demodex can be the cause of recurrent and refractory chalazia. Demodex mite can also cause blepharitis by carrying bacteria on its surface, including Streptococci and Staphylococci. Superantigens produced by these bacteria are implicate in the induction of chronic blepharitis or blepharoconjunctivitis. In addition, Bacillus oleronius inside Demodex mites has been found an important trigger the host immune reaction
- **Clinical Manifestations**
  - The main symptoms of demodicosis are itching, burning, foreign body sensation, crusting and redness of the lid margin, and blurry vision. Presence of cylindrical dandruff is a classical sign of Demodex blepharitis. Persistent infestation of the lash follicles may lead to misalignment, trichiasis, or madarosis. Trichiasis may induce trauma to the corneal epithelium, causing punctate epithelial erosions followed by corneal ulceration and pannus formation in severe, long-standing cases. Blockage of the meibomian gland orifice may lead to distention, edema, and much enlarged glands. Chronic granulomatous hypersensitivity responses in meibomian glands may lead to hordeolum or chalazion. The mechanical blockage and the delayed host immune hypersensitive reaction can result in lid margin inflammation. Demodicosis can cause various sight-threatening corneal lesions, including

superficial corneal vascularization, marginal infiltrates, phlyctenule-like lesions, and eventual scarring.

- **Diagnosis**
  - Slitlamp examination demonstrating the typical cylindrical dandruffs at the root of eyelashes is suggestive of demodicosis. Microscopic confirmation of the presence of Demodex eggs, larvae, and adult mites in epilated lashes is necessary for appropriate diagnosis.
- **Treatment**
  - Lid hygiene with warm compresses and scrubs is the first step. Mercury oxide 1% ointment, pilocarpine gel, sulfur ointment, and camphorated oil have been used in the treatment of demodicosis. Most of these treatments involve spreading an ointment at the base of the eyelashes at night to trap mites and prevent mating. Tea tree oil has recently been suggested to eradicate the mites as well as larvae and eggs. Tea tree oil also leads to alleviation of symptoms and resolution of the ocular surface inflammation. Since the Demodex also serves as the vector of the skin organisms, the comorbidity based on a symbiotic relationship of Bacillus oleronius in mites also justifies the consideration of a therapeutic strategy directed at killing the symbiotic bacteria via oral antibiotics such as tetracyclines or macrolides.

Filamentary Keratopathy

- **Etiology**:
  - Filaments are composed of degenerated epithelial cells and mucus in variable proportions
  - Seen in various corneal conditions which have in common an abnormality of the ocular surface and altered tear composition
  - Predisposing condition: Ptosis, Lid lag, Incomplete lid closure, Punctate epithelial erosions associated with dry eye syndrome, Epithelial irregularity or epithelial defect
- **Clinical Features**
  - Foreign body sensation, ocular pain (may be severe), photophobia, blepharospasm, increased blink frequency, and epiphora
  - Filaments stain with fluorescein and rose bengal dyes, facilitating identification
  - Filaments range in length from 0.5 to several millimeters, and are relatively strongly attached to the cornea
  - Often a small, gray, subepithelial opacity will be present beneath the site of corneal attachment
  - Any underlying epithelial defect will stain with fluorescein
  - The location of the filaments may provide a clue as to the cause
  - Superior cornea: Associated with superior limbic keratoconjunctivitis, ptosis, or other causes of prolonged lid closure, After cataract extraction, filaments may be found superiorly

- Interpalpebral distribution: Associated with keratoconjunctivitis sicca, pharmacologic dry eye, or exposure keratopathy
- Graft-host junction: Filaments after penetrating keratoplasty typically reside on the graft, at the graft-host interface or at the base of the suture on donor side

- **Differential Diagnosis**
  - Dendritic lesions, such as HSV dendritic epithelial keratitis
  - Loose sutures
  - Corneal abrasion
  - Non-adherent mucus or foam
- **Medical Management**
  - Mechanical removal of filaments (temporary measure; care should be taken not to disrupt underlying epithelium)
  - Bandage contact lens or scleral lenses (for relief of discomfort))
  - Management of dry eye syndrome: Preservative free artificial tears, Punctal occlusion, Topical cyclosporine, Autologous serum drops
  - Mucolytics: N-Acetylcysteine
  - Topical sodium chloride (e.g. Muro 128 drops and ointment)
  - Pulsed topical steroid and nonsteroidal agents
- **Surgical Management**
  - Repair of contributory lid malposition
  - Tarsorrhaphy if secondary to severe dry eye syndrome
  - Superior conjunctival resection or cauterization if secondary to superior limbic keratoconjunctivitis

Recurrent Erosion Syndrome

- **Etiology**
  - Poor adhesion of the corneal epithelium because of underlying abnormalities in the corneal epithelial cell attachment (hemidesmosomes) to the epithelial basement membrane
  - Predisposing condition
    - Previous corneal trauma, such as a fingernail scratch
    - Epithelial basement membrane corneal dystrophy
    - Bowman layer or stromal dystrophy, such as the TGFBI dystrophies
    - Irregular corneal surface, such as Salzmann nodular degeneration
    - Previous corneal surgery, such as photorefractive keratectomy
    - Limbal stem cell deficiency
- **Clinical features**

- Epithelial findings vary with timing of presentation: frank epithelial defect, negative staining with recent episode, intact epithelium with microcysts with remote episode
- Loosely attached corneal epithelium to the underlying basement membrane in either eye
- Heaped up or edematous epithelium in area of erosion
- Signs of corneal epithelial basement membrane dystrophy (map-dot-fingerprint dystrophy)

- **Management**
- ***Minor Erosions***
  - Infrequent occurrence: topical lubrication
    - Tears
    - Nightly ointment
      - 5% hypertonic saline ointment
      - Preservative free lubricating ointment
  - Frequent occurrence
    - Mild topical steroid, t.i.d. x 2-3 weeks
      - Fluorometholone 1%
      - Loteprednol 0.5%
    - Systemic doxycycline, daily or twice daily for 60 days, 50-100 mg
  - If failure with above management
    - Silicone hydrogel therapeutic contact lens for 14-30 days continuous wear. Cover with broad spectrum topical antibiotic q.i.d.
    - If recurrence in the presence of contact lens:
      - Outside the visual axis
        - ✓ Manual debridement with a blade or
        - ✓ Corneal stromal puncture or
        - ✓ Light application of diamond burr
      - Within the visual axis
        - ✓ Manual debridement with a blade
        - ✓ Excimer phototherapeutic keratectomy
      - Topical broad spectrum antibiotic
      - Low potency steroid
      - Therapeutic silicone hydrogel contact lens
      - Nightly ointment after BCTL removed for 3-6 months
- ***Major Erosions***
  - Outside the visual axis
    - Manual debridement with a blade or

        - Corneal stromal puncture or
        - Light application of diamond burr
    - Within the visual axis
        - Manual debridement with a blade
        - Excimer PTK
    - Topical broad spectrum antibiotic
    - Low potency steroid
    - Therapeutic silicone hydrogel contact lens for 14 days
    - Nightly ointment after BCTL removed

Hordeolum

- **Etiology**
    - Inspissation and infection of sebaceous glands
    - Anterior lid (glands of Zeis, lash follicles): external hordeolum or stye
    - Posterior lid (Meibomian glands): internal hordeolum
    - Staphylococcus aureus is most common pathogen
- **History**
    - Rapid onset, painful, tender
    - Typically resolve in 1-2 weeks
    - May produce purulent discharge with rupture
- **Clinical Features**
    - Tender, red nodules near lid margin
    - Surrounding edema, erythema may indicate preseptal cellulitis
- **Risk factors**
    - Rosacea
    - Chronic blepharitis
- **Management**
    - Warm compresses and massage of lesions
    - Systemic antibiotics active against *Staphylococcus aureus* for accompanying preseptal cellulitis
    - Systemic tetracyclines for treatment of chronic accompanying meibomitis, rosacea

Chalazion

- **Etiology**

- Inspissation of Meibomian or Zeis gland
- Extrusion of sebum into adjacent tissues produces sterile granulomatous inflammation

- **History**
  - Slow onset or previous hordeolum
  - Either painless or mild soreness
  - Resolution in weeks to months or no resolution
  - May drain externally
  - Occasional blurred vision due to astigmatism from pressure on globe
- **Clinical Features**
  - Nontender nodules at lid margin or in region of tarsus
  - Redness of overlying skin
- **Risk factors**
  - Rosacea
  - Chronic blepharitis
- **Management**
  - Incision/excision and drainage: Curettage for larger lesions
  - Intralesional corticosteroid injection (0.1-0.2 mL Triamcinolone 10 mg/mL)

Exposure Keratopathy

- **Etiology**
  - Inadequate eyelid closure (lagophthalmos)
    - Cranial Nerve (CN) VII palsy, including Bell palsy)
    - Decreased blinking (e.g., Parkinson disease)
    - Ectropion
    - Eyelid deformity: Congenital, Acquired (Mucous membrane pemphigoid, Stevens-Johnson syndrome, Post trauma or surgery (blepharoplasty)
    - Trachoma
    - Altered mental status
    - Drug abuse
    - Unconsciousness
  - Proptosis
    - Thyroid eye disease (thyroid orbitopathy)
    - Orbital pseudotumor
    - Retrobulbar tumor
- **History**

- Ocular surface disease symptoms (dryness, irritation, foreign body sensation, burning, tearing, blurred vision, photophobia, redness)
- Symptoms worse on awakening (nocturnal lagophthalmos)
- History of eyelid surgery

- **Clinical Features**
  - Incomplete eyelid closure and/or proptosis
  - Dilated conjunctival vasculature
  - Punctate epithelial erosions
  - Epithelial defects of varying size
  - Lesions preferentially involving inferior third of cornea and conjunctiva, in exposure area and usually conjunctiva below the limbus
  - Absence of Bell phenomenon
- **Differential Diagnosis**
  - Neurotrophic keratopathy
  - Keratoconjunctivitis sicca
  - Toxicity of topical medications/preservatives
  - Factitious keratoconjunctivitis
- **Medical Management**
  - Treatment of underlying disease
  - Tear supplementation with frequent preservative-free lubricants
  - Ointment at bedtime
  - Reduce evaporative tear loss
    - Goggles, moisture shields
    - Taping lid shut at bedtime
    - Humidifier
  - Treatment of any concomitant dry eye (See Dry eye)
- **Surgical Management**
  - Punctal occlusion
  - Surgical correction of eyelid position, such as tarsorrhaphy, lateral canthal sling, medial canthoplasty or gold weight insertion
  - Orbital decompression for proptosis

Neurotrophic Keratopathy

- Neurotrophic keratopathy (NK) is a degenerative disease of the cornea caused by impaired or damaged corneal sensory nerves. A reduction in corneal sensitivity or complete corneal anesthesia is the main sign of this disease and is responsible for producing epithelial defects, ulceration, and sometimes even perforation.

- **Symptoms**
  - Dryness, discomfort, pain, photophobia, and reduced visual acuity.
  - Symptoms are worse in the morning and aggravated by external factors such as air conditioning, reading, and VDU use.
  - Visual impairment is often worse in cases with central cornea involvement.
- **Signs**
  - Reduced tear breakup time (TBUT), inferior corneal and conjunctival superficial punctate keratitis (SPK).
  - reduced blinking rate
  - persistent epithelial defect (PED) with smooth and rolled edges
- **Categories**
  - Congenital
  - Acquired ocular
  - Acquired systemic
  - Neurological
    - Escalate treatment if accompanying motor deficit.
    - Do not assume transient cases will improve before cornea is damaged.
- **Mackie's classification**
  - **Stage 1:** lissamine green staining of the lower palpebral conjunctiva, decreased TBUT, punctate corneal epithelial staining with fluorescein
  - **Stage 2:** punched out, round/oval epithelial defect with smooth edges and loose surrounding epithelium; stromal swelling with folds but without defect
  - **Stage 3:** stromal ulceration/melting that may lead to perforation
- **Investigations**
  - **Corneal esthesiometry:**
    - Reduced or absent corneal sensation should be measured in the center and the peripheral 4 quadrants and is essential for the diagnosis of NK.
    - This can be measured qualitatively using a "wisp" of twisted cotton or quantitatively with a direct contact Cochet-Bonnet or the Belmont noncontact gas esthesiometer (BNGA).
    - The CochetBonnet is a device that contains a thin, retractable, nylon monofilament that extends from 0.5 cm up to 6 cm in length. Variable pressure can be applied by adjusting its length. Corneal sensitivity is assessed observing the patient's subjective reaction to different lengths of the protruding nylon filament applied to the cornea. The shorter the length at which the patient feels the touch of the filament, the lower the corneal sensitivity.
    - The BNGA is not commercially available.
  - **In vivo confocal microscopy (IVCM):** IVCM allows qualitative and quantitative assessment of corneal nerves in NK. Corneal nerve findings can vary from normal

sub-basal plexus with mild preganglionic (trigeminal ganglion) NK to attenuated or lost sub-basal plexus nerves in postganglionic or complete ganglionic lesions.

- **Management**: The main goal is to arrest progression, promote epithelial healing, and prevent secondary bacterial infection
  - **Stage 1:**
    - Unpreserved lubricants (ie, artificial tears and ointments) ± punctal occlusion.
    - All other topical medication should be reviewed and possibly discontinued.
  - **Stage 2:**
    - Main treatment aims are to promote epithelial healing and to prevent stromal tissue loss.
    - In addition to stage 1 treatment, prophylactic unpreserved topical antibiotic is also recommended (eg, levofloxacin QDS).
    - Eyelid closure can be achieved with lateral tarsorrhaphy, taping, pad, or botulinum toxin injection to induce ptosis, which may be effective in closing the epithelial defect.
    - Additional treatment options include bandage contact lens, punctal occlusion, and amniotic membrane transplantation over the epithelial defect.
    - Gunderson Flap
      - First described for neurotrophic ulcers
      - Fallen into disfavor but useful where vascularised tissue can heal diseased storm
      - Also provides serum growth factors
  - Despite best management at stage 2, NK may still progress to stage 3 disease.
  - **Stage 3:**
    - Main treatment aims are to stop further stromal lysis and prevent perforation.
    - In addition to stage 1 and 2 treatments, matrix metalloproteinase inhibitors (ie, oral tetracyclines and topical acetylcysteine) are also recommended.
    - Tissue adhesives should be considered in very thin corneas and in case of small perforation (<3.0 mm) combined with a bandage contact lens. In cases of larger perforations, a lamellar or penetrating keratoplasty may be the only treatment option.
- There is no role of Topical NSAIDs or no likely role of Cyclosporine.
- **Newer Therapies**
  - **Regenerating agent (RGTA)**-based matrix therapy such as Cacicol20 (applied once on alternate days) appears to be an effective therapeutic agent for PED resistant to conventional therapy.
  - **Recombinant human NGF** (rhNGF, cenegermin, betaNGF): In July 2017, the European Medicines Agency (EMA) granted cenegermin 20 µg/ml (**Oxervate**) full marketing authorization for the treatment of moderate (PED) or severe (corneal ulcer) NK in adults

- **Corneal neurotization:** Direct corneal neurotization aims to restore corneal sensitivity in patients with NK using the contralateral supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve. In 2009, Terzis et al[3] described a novel surgical procedure in which the contralateral nerve branches are transposed to the contralateral anesthetic corneal limbus for sensory neurotization. Use of the sural nerve is also done for this purpose.

Corneal Neovascularization

- Corneal neovascularization (NV) is the "common denominator" of a vast number of corneal and ocular surface pathologies. As such, it is associated with the second most frequent cause of blindness worldwide, cornea scarring. Not only is the invasion of the normally avascular and transparent cornea by blood vessels a consequence of many pathologies, but it can also cause or amplify corneal pathologies by promoting leaky vessels that lead to lipid deposition and amplified immune responses (eg, as seen in the setting of corneal transplantation).
- **Pathogenesis**
  - Molecular and cellular bases of corneal avascularity
    - Soluble vascular endothelial growth factor (VEGF) receptors
    - Ectopic expression of epithelial VEGF receptor ("VEGF sink")
    - Pigment epithelium-derived factor (PEDF)
    - Other antiangiogenic factors
  - Molecular and cellular bases of corneal NV
    - Vascular endothelial cell proliferation and migration
    - Stromal matrix degradation and role of matrix metalloproteinases (MMPs)
    - Proangiogenic factors
      - Inflammatory cytokines
      - VEGFs
      - Platelet-derived growth factor
      - Fibroblast growth factor
- **Etiology**
  - Infections
    - Herpetic
    - Bacterial
    - Chlamydial
  - Chemical burns: Alkali > acid
  - Penetrating trauma
  - Degenerations: Terrien's, Pterygium
  - Limbal stem cell insufficiency states

- Autoimmune disorders: PUK
- Meibomian gland dysfunction
- Neurotrophic disorders
- Corneal transplant
- Contact lens–related (hypoxia)

- **Management**
  - Optimize treatment of underlying etiology or offending agent
    - Infection
    - Contact lens
  - Surgical
    - Excision of lesion (pterygium)
    - Superficial keratectomy ± amniotic membrane grafting
    - Limbal stem cell grafting
  - Laser
  - Photodynamic therapy
  - Diathermy/cautery
  - Pharmacologic
    - "Conventional" drugs Efficacy: Corticosteroids > NSAIDs > cyclosporin A
    - Biologic or small molecule approaches
      - Directed at one or more pathogenic factors
      - Anti-VEGFs
        - ✓ bevacizumab (Avastin)
        - ✓ ranibizumab (Lucentis)

Aniridic Keratopathy

- Congenital aniridia is a disorder that affects 1/64,000 to 1/96,000 live births.
- It is inherited in an autosomal dominant pattern but can also have an autosomal recessive or sporadic pattern.
- Aniridia affects all parts of the eye and results in iris deformities, foveal hypoplasia, optic nerve hypoplasia, nystagmus, glaucoma, cataracts, and aniridic keratopathy.
- Over 90% of patients with aniridia develop aniridic keratopathy.
- **Aniridic Keratopathy Grading Scale Based on Severity**
  - Stage 1 includes a thickened, irregular peripheral epithelium and late staining with fluorescein.
  - Stage 2 occurs when the peripheral epitheliopathy moves centrally but still spares the absolute central cornea.

- At Stage 3, the epitheliopathy involves the central cornea.
- At Stage 4, the cornea displays complete epitheliopathy and subepithelial fibrosis.
- At Stage 5, the cornea exhibits total epitheliopathy and deep scarring involving the stroma.
- Corneal neovascularization can occur during any stage and is not specific to any stage of keratopathy.

- **Management of Aniridic Keratopathy**
  - Supportive therapy (ie, lubrication, bandage contact lens, tarsorrhaphy)
  - Primary keratoplasty: Inevitable failure
  - Ocular surface stem cell transplantation (OSST)
  - Keratoprosthesis
- **Surgical Options**
  - Living-related conjunctival limbal allograft (LRCLAL)
  - Keratolimbal allograft (KLAL)
- **Preoperative Management**
  - Addressing glaucoma, iris, and cataract comorbidities
  - Laboratory testing
  - Medical evaluation for systemic immunosuppression candidacy
  - Identification of living related donors
  - Trial of systemic immunosuppression
- **Postoperative Management**
  - Follow-up
  - Laboratory monitoring
  - Systemic immunosuppression regimen
  - Subsequent keratoplasty
- **Complications**
  - OSST failure
  - Keratoplasty failure
  - Glaucoma
  - Infectious keratitis
  - Keratoprosthesis for aniridic keratopathy

Limbal Stem Cell Deficiency (LSCD)

Eyes do not have natural protective layer skin. But have multifactorial system which his system includes the eyelids and eyelashes, the tear film, and the ocular surface, which is made up of the conjunctiva and the corneal epithelium

Limbal stem cells

- Stem cells:
  - Undifferentiated
  - Long lived
  - Slow cycling
  - Clonogenic
  - Asymmetric division
  - Potency: usually pluripotent or multipotent
  - Plasticity: transdifferentiation
  - Niche: SC microenvironment
- SC progeny:
  - 'Transient cells'
  - Transient amplifying cells – basal epithelium
  - Postmitotic cells – wing cells
  - Terminally differentiated cells –superficial squamous cells

- Epithelial cells of the limbus and central cornea
  - **Limbus: CK 5/14+ve, CK 3/12–ve, CK 19+ve, P63+ve, CX 43–ve, Vimentin+ve**
  - **Central Cornea: CK 5/14 -ve, CK 3/12+ve, CK 19-ve, P63-ve, CX 43+ve, Vimentin-ve**
- The current evidence of the limbal location of corneal stem cells (Corneal Surgery BrightBill)
- lacks the corneal epithelial differentiation associated keratin pair keratin 3 (K3) and keratin 12 (K12)
- higher proliferative potential. limbal basal epithelium contains slowcycling cells identified as the 'label-retaining cells'.
- Abnormal corneal wound healing with conjunctivalization, vascularization, and chronic inflammation occurs when the limbal epithelium is partially or completely removed.
- relative preponderance of limbal neoplasms and the scarcity of corneal epithelial tumors, assuming that neoplasms arise mainly from relatively 'undifferentiated cells'
- corneal epithelium can be maintained by cellular proliferation originating from limbal stem cells without contribution of the adjacent conjunctiva.
- These are undifferentiated electron dense basal cells present at the limbus
  - Contains minimal cytoplasm and organelles
  - Surface markers are K19, Integrin ß1, Enolase α (lacks K3)
- The hallmark of limbal stem cell deficiency is 'conjunctivalisation' of the cornea and the most significant clinical manifestation is a persistent corneal epithelial defect

- **Symptoms:** decreased vision, photophobia, tearing, blepharospasm, and recurrent episodes of pain (epithelial breakdown), as well as a history of chronic inflammation with redness
- **Signs:** Mild → severe
  - Loss of limbal anatomy
  - Conjunctival epithelial ingress onto cornea – stippled fluorescein staining
  - Columnar keratopathy
  - Unstable tear film over affected area
  - Frank conjunctivalisation
  - Corneal vascularisation – superficial and deep
  - Fibrovascular pannus covering corneal surface
  - Persistent epithelial defect
  - Stromal melting
  - Perforation, scarring, calcification
  - Keratinisation

LSCD Classification

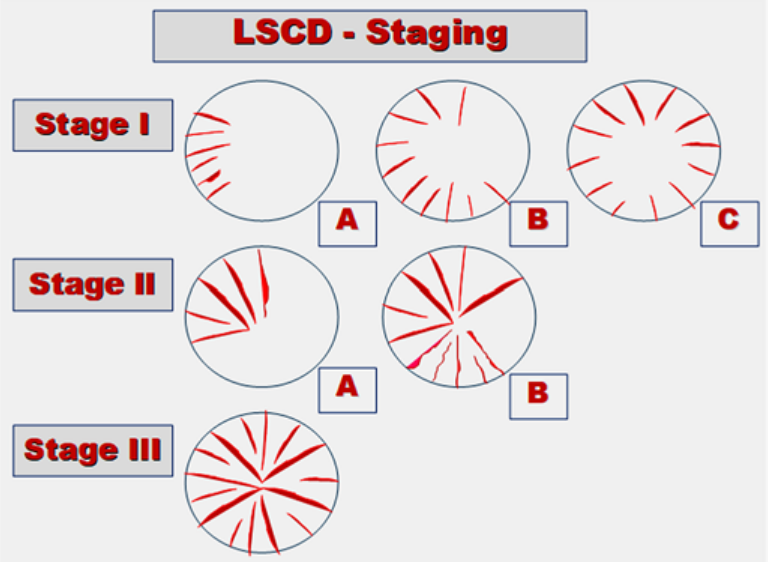
- **Hereditary LSCD**
  - Aniridia: most common cause of congenital limbal stem cell deficiency
    - 1 in 64K-96K
    - iris deformities foveal hypoplasia, optic nerve hypoplasia, nystagmus, glaucoma, and cataract.
    - Aniridic keratopathy occurs in 90% of patients with aniridia
  - Dominantly inherited keratitis
  - dyshidrotic ectodermal dysplasia
  - keratitis–ichthyosis–deafness (KID) syndrome → keratodermatous ectodermal dysplasia (KED)
  - Autoimmune polyendocrinopathy-candidiasis– ectodermal dystrophy/dysplasia
  - Xeroderma pigmentosum
  - Ectrodactyly-ectodermal dysplasia-clefting syndrome
  - Lacrimo-auriculo-dental-digital syndrome
- **Acquired LSCD**
  - Chemical injury
  - Thermal burns
  - Ultraviolet /ionising radiation
  - Autoimmune Disorders:
    - Steven-Johnson syndrome

- OCP
- Contact lens induced keratopathy
- Iatrogenic limbal stem cell deficiency
  - prior surgery involving the corneoscleral limbus
  - Chronic use of topical medications, including pilocarpine, beta-blockers, antibiotics, and corticosteroids

- **Staging of LSCD:**
- **Holland staging system**: system based on the status of the limbal stem cells and conjunctiva

Limbal stem cells lost (%)	Normal conjunctiva (stage a)	Previously inflamed conjunctiva (stage b)	Inflamed conjunctiva (stage c)
<50 (stage I)	Iatrogenic, CIN, contact lens (stage Ia)	History of chemical or thermal injury (stage Ib)	Mild SJS, OCP, recent chemical injury (stage Ic)
>50 (stage II)	Aniridia, severe contact lens, and iatrogenic (stage IIa)	History of severe chemical or thermal injury (stage IIb)	Severe SJS, OCP, recent chemical or thermal injury (stage IIc)

- **Other staging**: stages based on the extent of corneal and limbal involvement detected by clinical examination as shown in figure below.



- **Diagnosis**
- **Based on**
  - Clinical examination
    - Delayed fluorescence staining at slit lamp

        - In contrast to the epithelial defects that are immediately stained by fluorescein, the dye diffuses into the paracellular space of the conjunctivalized surface, and abnormal delayed staining is observed 10 or more minutes after fluorescein instillation. This abnormal staining pattern can be visualized even after rinsing with BSS or eye wash.
    - Presence of conjunctivalization
        - Total LSCD is characterized by conjunctivalization of the entire corneal surface because of complete loss of corneal epithelial stem/progenitor cells. The absence of the corneal epithelium phenotype or the presence of conjunctival epithelial cells (conjunctivalization) of the cornea produces clinical signs of LSCD.
    - Disappearance of palisades of Vogt
- **Confirmed by**
    - Impression cytology: Make a definite diagnosis by showing conjunctivalization by the **presence of conjunctival goblet cells (low sensitivity)**
    - Biopsy – multilayered epithelium, intraepithelial lymphocytes, vessels
    - Vimentin and CK 19 positive cells in central cornea (normally present in peripheral cornea and limbus)
    - *In vivo confocal microscopy (IVCM)* has emerged as a diagnostic tool for LSCD, in part, because this method does not require the removal of corneal epithelial cells for the analyses
    - ASOCT: useful in measuring epithelial thickness and pannus depth and assessing POV, limbal crypts, and the clear transition between the hyporeflective corneal epithelium and hyperreflective conjunctival epithelium in the limbal region.
- **Treatment algorithm**
    - General principles:
    - Manage underlying factors, e.g., chronic inflammation, contact lens wear, topical medications
    - Topical lubrication
    - All associated problems, e.g., raised pressure, conjunctival adhesions, lid malpositions, should be addressed before undertaking ocular surface reconstruction
    - Limbal transplants do not perform well in dry eyes
- ***In acute limbus injury:***
    - If partial, i.e. some limbus is surviving – allow corneal epithelialisation to occur from limbus derived cells – SSCE
    - If total:
        - Allow conjunctival epithelium to grow onto cornea
        - Transplant sheet of ex vivo expanded limbal epithelial cells
        - Avoid use of autologous or living related donor tissue until acute inflammation is well under control

- ***In established cases:***
  - Treat eye lid problems, glaucoma and conjunctival adhesions first
  - Partial or total
  - ***Partial:***
    - Visual axis not involved: symptomatic, lubricants of SSCE
    - Visual axis involved: SSCE
    - Dense fibrovascular pannus: sector limbal transplant
  - ***Total:***
    - Unilateral: auto-limbal transplant
    - Ex vivo expansion of autologous limbal cells
    - Bilateral: allo-limbal transplant
    - Ex vivo expansion of cells (living related, living non-related, cadaver)
    - Amniotic membrane and autologous serum drops as adjuncts
    - Allo-transplants require systemic immunosuppression
- **Surgical Management: (OSD & LSCD)**
- **Sequential Sector Conjunctival Epitheliectomy (SSCE)**
  - Removal of the conjunctivalised epithelium In cases with partial, mild to moderate conjunctivalisation of the cornea,without significant fibrovascular pannus
  - Advantage of not overstressing the small remaining sector of limbal ‘stem’ cells.
- **Conjunctival Limbal Autograft (CLAU)**
  - Unilateral limbal deficiency , partial stem cell loss,
  - Concurrent conjunctival inflammation
  - No risk of rejection
- **SLET: Simple Limbal Epithelial Transplantation**
  - Requires very minimal donor tissue, is relatively easy to replicate, and is much less expensive.
  - Indication
    - LSCD with a wet ocular surface and normal eye lid anatomy and function.
    - Patients with unilateral chronic ocular surface burns are the most suitable candidates for this procedure.
  - Technique
    - Typically, a one clock hour–sized limbal fragment is obtained from the healthy fellow eye and divided into 6 to 10 small pieces, which are then transplanted onto the affected eye over an amniotic membrane overlay graft after removal of the pathological fibrovascular pannus.
    - Complete epithelization of the cornea usually occurs by 7-14 days, and corneal clarity and visual acuity keep improving over time.

- SLET combines advantages of both traditional conjunctival-limbal auto transplantation and CLET, which means using a very tiny limbal biopsy for regenerating the entire damaged corneal epithelium and keeping epithelial-mesenchymal interactions intact, thereby enhancing clearing of scarring by stromal keratocyte stem cells. This advantage translates into reduced rates of penetrating keratoplasty after SLET as compared to CLET.
- SLET reduces the cost significantly, both to patients and to health care systems, as there is no need for expensive clinical grade laboratories and it is a single-stage procedure.
- SLET reduces the regulatory burden and oversight; because it is a surgical procedure, the surgeon is the key stakeholder in its application and further innovation.
- There is a real possibility of further simplification of procedures by introducing synthetic membrane instead of human amniotic membrane (AMG). We are working on a first-in-human clinical trial of PLGA membrane instead of AMG.

- **Living Related Conjunctival Limbal Allograft (lr-CLAL)**
  - Bilateral limbal stem cell loss: cicatricial pemphigoid (OCP), Stevens–Johnson syndrome (SJS), and atopic keratoconjunctivitis
  - Large risk of transplant rejection
- **Keratolimbal Allograft (KLAL)**
  - Disease entities that primarily affect the limbus with no or minimal involvement of the conjunctiva: Aniridia
- **Combined Conjunctival Limbal and Keratolimbal Allograft (C-KLAL)**
- **Cadaveric Stem Cell Allograft**
  - Fresh Tissue
  - Age: < 40 years
  - Good Quality Donor Material
  - Risk of transplant rejection
- **Annular Corneo-scleral Allograft**
  - Prompt re-epithelization
  - Minimal vascularization (mechanical barrier)
  - Less risk of graft rejection
- **Large diameter LK**
  - Advantages
    - Removes superficial stromal opacities
    - Tectonic function
    - Smooth surface
    - Less astigmatism
  - Disadvantage: More risk of allograft rejection

- **Ex Vivo Tissue Engineered Procedures**
  - Ex Vivo Cultivated Limbal Transplantation
  - Ex Vivo Stem Cell Allografts
  - Ex Vivo Cultivated Conjunctival Transplantation
  - Ex Vivo Cultivated Mucosal Transplantation
- **Limbal Stem Cell Culture**
  - This technique expands limbal epithelial progenitor cells from a small biopsy using a 3T3 fibroblast feeder layer or amniotic membrane.
  - Immunostaining techniques : resultant phenotype of HLEC grown on amniotic membrane retains a limbal origin, is predominantly basal epithelial cells, and remains undifferentiated
  - **Taking the Biopsy**
    - Avoid or eliminate the conjunctiva
    - as small as 1–2mm2 and 100 *m*m in depth.
    - Superior limbus if possible so as to include immature cells
    - The obtained tissue is placed with **Ham's F12 medium** containing 50 *m*g/ml gentamicin and 1.25 *m*g/ml amphotericin B until it is processed
    - exposed for 5min to **Dispase II** (1.2 U/ml in Mg2+ and Ca2+ free **Hank's balanced salt solution, HBSS**)
    - cultured in DMEM medium, which is a 1:1 mixture of DMEM and Ham's F12 medium
    - plated onto the basement-membrane side of the amniotic membrane, placed in the center
    - maintained for 2–3 weeks, by which time the epithelial cells have grown and spread to form a cell layer that covers an area 2–3 cm in diameter
  - **Failure of LSCT**
    - **Early Failure**
      - Rejection: acute rejection occurs in about 10–20% of cases and is most common in the first 1 to 12 months
      - Adnexal abnormalities
      - Inflammation
      - Dry eye
    - **Late Failure**
      - Sectoral conjunctivalization
      - Stem cell exhaustion
      - Late rejection
- **Amniotic Membrane Transplantation (AMT)**

Algorithm for an approach to treat patients with severe OSD

- Management of glaucoma
- Correction of eyelid and eyelash abnormalities
- Suppression of inflammation
- Ocular surface transplantation
    - Unilateral disease
        - Conjunctivo limbal autograft (CLAU)
        - Cultivated limbal epithelial transplantation (CLET)
        - Simple limbal epithelial transplantation (SLET)
    - Bilateral cases
        - Keratolimbal allograft (KLAL) for bilateral limbal deficiency with minimal to moderate conjunctival disease
        - Living related conjunctival limbal allograft (lr-CLAL) for bilateral limbal deficiency with moderate to severe conjunctival disease
        - Allogenic SLET/ CLET
        - Cultivated oral mucosal epithelial transplantation (COMET)
        - Combined conjunctival–keratolimbal allograft (C-KLAL) for bilateral limbal deficiency with severe conjunctival disease
- Keratoplasty
    - Lamellar (LK) for patients with stromal opacification with normal endothelium
    - Penetrating (PK) for patients with stromal opacification with loss of endothelial function
    - Keratoprosthesis (K-Pro) for patients with good fornices but are not good keratoplasty candidates.

Disorders of Tear Production

- **1995** National Eye Institute (NEI)/Industry Dry Eye Workshop: Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.
- **International Dry Eye WorkShop (DEWS)** in **2007**: dry eye is defined as multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface
- **Lacrimal Functional Unit (LFU):** ocular surface (cornea, conjunctiva, accessory lacrimal and meibomian glands), the main lacrimal glands, the blink mechanism that spreads tears, and the sensory and motor nerves.
- **Pathophysiology**
  - **Tear hyperosmolarity** is regarded as the central mechanism causing ocular surface inflammation, damage, and symptoms, and the initiation of compensatory events in dry eye.
  - **Tear film instability** can arise secondary to hyperosmolarity, or can be the initiating event
- The core mechanisms responsible for dry eye disease are tear hyperosmolarity and tear film instability. The major causes of tear hyperosmolarity are reduced aqueous tear flow and/or increased tear evaporation. Tear hyperosmolarity induces cascades of inflammatory events that result in damage to the surface epithelium, nerve endings, and ultimately tear film instability. This instability exacerbates ocular surface hyperosmolarity and completes the vicious circle. Tear film instability can also be initiated by other etiologies, including xerophthalmia, ocular allergy, topical preservative use, and contact lens wear.
- **Dry Eye Diseases DED** → aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE)
  - **Aqueous tear-deficient dry eye (ADDE)**
    - Sjögren's syndrome dry eye (SSDE)
    - Non-Sjögren's syndrome dry eye (NSSDE)
      - Primary lacrimal gland deficiencies
        - ✓ Age-related dry eye (ARDE)
        - ✓ Congenital alacrima:
      - Secondary lacrimal gland deficiencies
        - ✓ Lacrimal gland infiltration:
        - ✓ Obstruction of the lacrimal gland ducts
      - Reflex hyposecretion
        - ✓ Reflex sensory block: DM, Neurotrophic Keratitis
        - ✓ Reflex motor block
  - **Evaporative dry eye (EDE)**
    - Intrinsic causes
      - Meibomian gland dysfunction

        - Disorders of lid aperture and lid/globe congruity or dynamic
        - Low blink rate
    - Extrinsic causes
        - Ocular surface disease
        - Contact lens wear

- **Diagnosis**:
    - ***History***: foreign body sensation, burning, stinging, itching, dryness, soreness, heaviness of the lids, photophobia, and ocular fatigue. An important clue is exacerbation of symptoms by certain activities or environmental conditions.
    - Physical examination
        - **Dynamics of blinking**: a) frequency of blinking; b) variation of blink intervals; c) size of the palpebral aperature, and d) adequacy of lid closure.
        - **Malposition of the lids**: a) entropion; b) ectropion; c) eversion of the lacrimal puncta; d) cicatrical malposition; e) dermatochalasis; and f) swelling of the lacrimal gland.
    - Diagnostic tests
        - Tear film stability:
            - tear breakup time (TBUT) test:
            - noninvasive breakup time, or NIBUT: It involves projecting a target onto the convex mirror surface of the tear film and recording the time following a blink for the image to break up. The test has been performed using custom-built devices such as **Tearscope** or keratometry devices.
            - arbitrary cutoff time of 10 s for both fluorescein-added and noninvasive techniques appears quite specific
            - Ocular Ferning Test
            - Impression cytology
        - Diagnostic dye staining:
            - **Fluorescein sodium**: dye diffuses rapidly in the intercellular spaces and staining indicates increased epithelial permeability
            - **Rose Bengal**: more sensitive for staining the conjunctiva; however, it is not tolerated as well and frequently causes irritation, stains devitalized epithelial cells as well as epithelial cells that lack a healthy layer of protective mucin coating.
            - **Lissamine green B** is similar to rose Bengal in its staining characteristics, and produces much less irritation after topical administration than rose Bengal
            - **Van Bijsterveld** reported a grading scale that evaluates the intensity of staining based on a scale of 0–3 in three areas: nasal conjunctiva, temporal conjunctiva, and cornea.
        - Corneal sensation

- cotton swab
- Cochet–Bonnet esthesiometer

- Tear film composition
  - Osmolarity: well-validated cutoff value of 316 mmol/L for dry eye disease.
  - Tear protein analysis:
    - ✓ tear lysozyme: sensitivity and specificity >95%
    - ✓ Lactoferrin: Lactocard→ relative indicator of lacrimal gland function
- Aqueous tear flow and turnover
  - **Schirmer test:** Van Bijsterveld selected 5.5 mm strip wetting in 5 minutes for the Schirmer test without anesthesia to diagnose aqueous tear deficiency.
  - **phenol red-impregnated thread test (PRT):** cutoff value of 10 mm at 15 seconds, the sensitivity and specificity of the PRT have been shown to be 56% and 69%.
- **Delayed tear clearance:** increased tear cytokine concentration, which may contribute to chronic inflammation
  - fluorescein clearance test (FCT): detect the amount of residual fluorescein by Schirmer strip or use a fluorophotometer
- **Other noninvasive methods**
  - **Tear meniscus height (meniscometry):** meniscus radius of curvature <0.25 mm suggests a dry eye condition.
  - **Interferometry** of the tear film lipid layer is useful in screening and evaluating dry eye.
- **InflammaDry** (Rapid Pathogen Screening, Inc.) is a rapid in-office test that detects MMP-9. MMP-9 is an inflammatory marker that is elevated in the tears of patients with dry eye disease. In this disposable, low-cost test, a small tear fluid sample is obtained from the inside of the lower eyelid. The test works in a way similar to an at-home pregnancy test, and the results are displayed in the office in 10 minutes.
- **LipiView and LipiView II** (TearScience Corp.) are ocular surface interferometers that provide precise measurements of tear film thickness. LipiView II is also able to perform dynamic meibomian imaging so that one can see the true anatomy of the meibomian glands to determine whether or not the gland structure has been altered by meibomian gland disease. (**LipiFlow** is the treatment arm of the TearScience package. It applies heat to the inner eyelids to liquefy the meibomian gland contents and evacuate the glands.)
- The **TearLab Osmolarity System** (TearLab Corp.) is an objective and quantitative test for diagnosing and managing dry eye. The results are displayed in seconds and require only a 50-nL sample of tear fluid. Having a "number" to discuss with patients can be very helpful in improving

adherence to a treatment regimen and also may allow one to detect early disease. The TearLab system utilizes a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity.

- **Sjö (Nicox Corp.)** is an advanced diagnostic panel for the early detection of Sjögren syndrome. It is thought that one in ten patients with dry eye may have Sjögren syndrome. By testing patients early, the goal is to identify patients with Sjögren syndrome and treat them before the late stages of the disease occur. Sjö tests for traditional biomarkers, in addition to lacrimal gland-specific biomarkers such as salivary protein 1 (SP-1), carbonic anhydrase (CA-6), and parotid secretory protein (PSP). A small sample of blood is sent to the laboratory, and the results are delivered within 1-2 weeks.

- **Systemic Work-Up**: anti-SS-A, anti-SS-B, rheumatoid factor, ANA, ESR, CRP
- **Management**
  - Tear supplementation: lubricants
    - electrolytes, surfactants, and various types of viscosity agent
    - Osmolarity: 181 to 354 mmol/L
    - Compatible solutes are small nonionic molecules (e.g., glycerin) Optive and Refresh Endura (with 0.9% and 1% glycerin)
    - Colloid osmolality (which relates to macromolecule concentration)
    - **Viscosity** agents: Macromolecular complexes → carboxymethylcellulose, polyvinyl alcohol, polyethylene glycol, propylene glycol, hydroxypropyl-guar (HP-guar), and lipids such as those that make up castor oil or mineral oil.
    - **Lipid-containing** artificial tear products such as Refresh Endura (with castor oil) and Soothe XP (with mineral oil) are intended to reduce tear evaporation by restoring the lipid layer of the tear film; this may be particularly useful in patients with MGD.
    - **HP-guar** (in products such as Systane) is believed to form a bioadhesive gel when exposed to ocular pH, increasing aqueous retention and protecting the ocular surface by mimicking the mucous layer of the tear film.
    - two main types of preservative:
    - ***Detergent*** preservatives act by altering bacterial cell membrane permeability.
      - BAK
    - ***Oxidative*** preservatives penetrate the bacterial cell membrane and act by interfering with intracellular processes. They are sometimes referred to as ‘vanishing’ preservatives because they dissipate on contact with the eye and are therefore less likely than detergents to cause ocular damage.
      - Stabilized oxychloro complex
  - **Tear retention**
    - **Punctal occlusion**: Punctal and intracanalicular plugs, argon laser,

- 2 types: absorbable are made of collagen or polymers and last for variable periods (3 days to 6 months). The nonabsorbable 'permanent' plugs include the Freeman style, which consists of a surface collar resting on the punctal opening, a neck, and a wider base, and are made of silicone or hydrophilic acrylic.

- Moisture chamber spectacles:
- **Contact lenses**: Boston scleral lens, Mini-scleral lens (**Jupiter Lens**)
- Tarsorrhaphy
- **Tear stimulation**: secretagogues
  - diquafosol (P2Y2 receptor agonists)
  - Orally administered cholinergic agonists, in particular pilocarpine and cevilemine
- Biological tear substitutes
  - **Serum**: Concentrations between 20% and 100% o
  - Salivary gland autotransplantation
- Anti-inflammatory therapy
  - Ciclosporin
    - Decreases proinflammatory cytokines (e.g., conjunctival IL-6 levels)
    - Decreases activated lymphocytes in the conjunctiva
    - Decreases conjunctival inflammatory and apoptotic markers
    - increases conjunctival goblet cell numbers.
    - 0.05% and 1%, 2%
  - ***Corticosteroids***: inhibition of the activity of transcription factors such as activator protein-1 (AP-1) and nuclear factor κB (NFκB), that are involved in the activation of proinflammatory genes
    - loteprednol etabonate 0.5%
    - androgenic steroids
  - ***Tetracyclines***: antibacterial, anti-inflammatory, inhibits MMPs and IL1 production and protease inhibitory properties.
  - ***Essential fatty acids***: a higher omega-6:omega-3 ratio was associated with a significantly greater DED risk. omega-3 fatty acids (e.g., EPA found in fish oil) inhibit the synthesis of these lipid mediators and block the production of IL-1 and TNF-alfa.
- **Topical vitamin A** (retinol)
  - Reversal of squamous metaplasia
  - Increased production of type I collagen
  - Promotes regeneration of conjunctival goblet cells and can re-establish intracellular conjunction of conjunctival epithelium

- **Mucolytics**: Inhalational acetylcysteine is diluted to concentrations of 5–20% (most commonly 10%) for off-label use as a topical ophthalmic agent.

- **Treatment Guidelines**
  - In 2007 the Management and Therapy Subcommittee of the International Dry Eye WorkShop (DEWS) adopted a modified form of the ITF (International Task Force) severity grading. **(DELPHI Panel)**
  - ITFciclosporin at level 2 & Plugs at level 3
  - DEWSciclosporin & Plugs at level 2

Conjunctivitis

- The conjunctival epithelium is contiguous with the corneal epithelium and also lines the lacrimal passages and glands, a fact that has significant clinical implications.
- The substantia propria is composed of a superficial adenoid layer and a deeper fibrous layer.
  - The **adenoid** layer: **lymphoid** tissue from which follicles are formed. Within the lymphoid tissue are germinal centers with lymphoblasts in the center.
  - The **fibrous** layer: connective tissue, which attaches to the tarsal plate and contributes to the characteristic appearance of **papillae**.
- **Conjunctival injection**: superficial bright red blood vessels, most conspicuous in the fornices and fade toward the corneoscleral limbus
- **Conjunctival hyperemia**: secondary to dilation of the conjunctival blood vessels without accompanying exudation or cellular infiltration. Due to environmental factors including smoke, smog or chemical fumes, wind, ultraviolet radiation, and prolonged topical instillation of vasoconstrictors.
- **Conjunctivitis:** inflammation of the conjunctiva and is characterized by cellular infiltration and exudation in addition to vascular dilation.
- **Chemosis**: accumulation of fluid within or beneath the conjunctiva, is frequently present.
- **Morphologic responses**
  - **Papillae**: where the conjunctiva is attached to the underlying tissue by anchoring septae, folds or projections of hypertrophic epithelium that contain a central fibrovascular core whose blood vessels arborize on reaching the surface. Micropappile < 1 mm
    - giant papillae > 1 mm: vernal conjunctivitis, atopic keratoconjunctivitis, and as a foreign body reaction to suture material, contact lenses, or prostheses.
  - **Follicles**: yellowish-white, discrete, round elevations of conjunctiva produced by a lymphocytic response. Unlike a papilla, the central portion of the follicle is avascular. 0.5–2.0 mm in diameter.
    - Acute follicular conjunctivitis: Adenovirus, Inclusion conjunctivitis, Herpesviruses
    - Chronic follicular conjunctivitis: Chlamydial infections, Molluscum contagiosum, Moraxella
  - **Membranes**: primarily of fibrin that has attached to the epithelial conjunctival surface. True membranes leave a raw surface and cause bleeding when peeled off, which differentiates them from pseudomembranes.
    - C. diphtheria, β-hemolytic streptococci, adenoviral, HSV, vernal conjunctivitis, inclusion conjunctivitis, and Candida. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
  - **Cicatrizing changes**: Scar formation ensues only when there is destruction of stromal tissue.
  - **Conjunctival granulomas**: affect the stroma.

- **Conjunctival exudates** may be classified as: (1) purulent or hyperacute; (2) mucopurulent or catarrhal; and (3) watery.
- **Anatomic localization**:
  - **Upper tarsal**: trachoma, contact lens wearers, patients wearing prostheses, or from exposed suture material.
  - **upper palpebral**: SLK, FES
  - **upper pretarsal**: VKC, AKC (can be in lower lid)
  - **lower tarsal**: toxic papillary conjunctivitis and the 'mucus-fishing syndrome.' The follicular response in inclusion conjunctivitis is more pronounced inferiorly than superiorly.

Bacterial Conjunctivitis

- Disruption of the host's defense mechanisms are predisposing factors for the development of bacterial conjunctivitis:
- **Risk factors**
  - Dry eye
  - Exposure
  - Nutritional deficiency/malabsorption
  - Local or systemic immune deficiency often after topical and systemic immunosuppressive therapy
- An organism may be isolated in as many as 90% of normal subjects, with more than one organism found in up to 35%. In most subjects, ***the flora is composed of aerobic staphylococci (>60%) (mostly Staphylococcus epidermidis), diphtheroids (>35%), and the anaerobe Propionibacterium acnes***, but the spectrum of bacteria and sensitivity to antibiotics varies among major age groups.
- **Manifestations**
  - Discharge
  - Membranes and pseudomembranes
  - Papillae and follicles
- **Classification**
  - **Hyperacute**: lid edema, marked conjunctival hyperemia, chemosis, and copious amounts of purulent discharge. **N. gonorrhoeae and N. meningitidis**.
    - Treatment
      - ***Systemic treatment is mandatory for patients with Neisseria conjunctivitis***; concomitant topical antibiotic therapy is optional.
      - Single-dose intramuscular (IM) regimen of 1 g of ceftriaxone
      - To treat N. gonorrhoeae conjunctivitis in the newborn, 25–50 mg/kg intravenous (IV) or IM ceftriaxone administered in a single dose not exceeding 125 mg is currently recommended

- **Acute conjunctivitis**: velvety papillary reaction, 10-14 days
  - **S. aureus**, the most frequent cause
  - **H. influenzae** (nonencapsulated) is the most common cause of bacterial conjunctivitis in young children
  - Treatment
    - Topical antibiotic therapy hastens resolution, improves microbiologic cure, and may reduce morbidity, especially in culture-proven cases
- **Chronic conjunctivitis:**
  - Foreign body sensation, mild stickiness and matting of the lashes, and minimal discharge.
  - **S. aureus and M. lacunata**
  - Short-term topical therapy is often ineffective.
  - Long-term therapy is required and, if there is concomitant blepharitis, the therapeutic regimen should include lid hygiene, lid margin cleansing with a mild baby shampoo diluted 50% with water, and the nightly application of an antibiotic ointment with good Gram-positive coverage, such as bacitracin, to the lid margins.
  - Adjunctive oral therapy with 100 mg doxycycline one to two times a day.

Viral Conjunctivitis

- **Hallmark**: **follicular reaction** of the conjunctiva
- **RNA**: benign forms of conjunctivitis
  - Picornaviruses: most common causes of acute hemorrhagic conjunctivitis (AHC).
  - Paramyxoviruses: measles, Newcastle disease, and mumps
    - Measles: Catarrhal conjunctivitis, superficial keratitis, and photophobia are the most common clinical features in healthy individuals. Keratitis is usually severe in patients with vitamin A deficiency.
    - Newcastle disease is limited to poultry workers and laboratory personnel.
    - Mumps is an acute viral infection characterized by swelling (more commonly bilateral) of the parotid salivary glands.
  - Togaviruses: Rubella (German measles)
  - Flaviviruses: Yellow fever
- **DNA**: Associated with **vision-threatening forms** of inflammation
  - ***Adenoviruses***: MCC of viral conjunctivitis.
    - Six subgenera (A–F). **D is most common.**
    - Pharyngoconjunctival fever (PCF) is characterized by pharyngitis, follicular conjunctivitis, fever, and adenopathy (preauricular and cervical).

- Epidemic keratoconjunctivitis (EKC) is the severest ocular disease caused by adenoviruses. 8,19,37
- Acute nonspecific follicular conjunctivitis may be caused by many serotypes of adenovirus, including those classically associated with PCF and EKC.
- Chronic conjunctivitis is the least common form of adenovirus conjunctivitis.
  - Stages: 0 to 5
  - Treatment: preventing the transmission and complications. Cold compresses, Pseudomembranes and membranes should be removed, topical antiinflammatory agentSteroids/ NSAIDs.

- ***Herpes simplex virus (HSV)***
  - Usually a benign condition except in neonates when the herpetic infection can be associated with fatal disease and should be promptly treated.
  - Commonly diagnosed in dendritic/geographic ulcers, disciform keratitis, and keratouveitis
  - Treatment of HSV conjunctivitis in the neonate is mandatory and should include both topical antiviral and intravenous acyclovir. A pediatric consultation should be obtained.
- Varicella-zoster virus (VZV)
- Molluscum contagiosum is a human host-specific poxvirus.

Chlamydial Infections

- In humans the largest burden of ocular disease is caused by C. trachomatis.
  - Serovars **A, B,Ba and C** are associated with **trachoma**.
  - Serovars **D–K** are causative of adult or neonatal **inclusion conjunctivitis** as well as urogenital diseases.
  - serovars **L1–3** are associated with **lymphogranuloma venereum**.
- It uses the cellular machinery of the host to provide it with energy for metabolic activity.
- The RB is the classic metabolically active intracellular form. In contrast, the EB exists only in an extracellular form. This form is metabolically inactive, possessing a rigid cell wall which is relatively impermeable to stimuli in its extracellular environment.
- **EB → IB → RB → binary fission of RB and increase in number → release**

Trachoma

- Third most common cause of blindness worldwide after cataract and glaucoma.
- Transmission: directly from eye to eye, fomites, flies, eye make-up, low socioeconomic status, lack of water, and poor hygiene
- WHO classification: **FISTO**

- Trachomatous inflammation – follicular (TF): the presence of five or more follicles in the upper tarsal conjunctiva. Follicles must be at least 0.5 mm in diameter to be considered.
- Trachomatous inflammation – intense (TI): pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels.
- Trachomatous scarring (TS): the presence of scarring in the tarsal conjunctiva.
- Trachomatous trichiasis (TT): at least one eyelash rubs on the eyeball. Evidence of recent removal of inturned eyelashes should also be graded as trichiasis.
- Corneal opacity (CO): easily visible corneal opacity over the pupil.

- The follicles around the limbus may eventually break down, and necrosis of the tissue can occur with subsequent scarring. These scars are referred to as **Herbert's pits**.
- Linear or stellate scarring on the upper tarsus can coalesce and form an '**Arlt's line'**, which is suggestive of prior trachoma infection
- **Pathophysiology**
  - Following the initial infection with ocular C. trachomatis, a hypersensitive state occurs such that subsequent infections results in more intense inflammation
  - Candidate antigens for inducing this hypersensitive state include the **60 kDa chlamydial heat shock protein**, the major outer membrane protein surface antigen, and lipopolysaccharide from the bacterial cell membrane,
  - Reduced interferon (IFN), interleukin (IL)-2, and increased IL-4 secretion have been found to exist in subjects who progress to develop significant scarring
- **Treatment**:
  - TF/ TI → e/o azithromycin BD for 6 weeks = single dose 1000 mg oral azithromycin = 2-week course of oral tetracycline 250 mg four times daily or doxycycline 100 mg twice daily
  - TS/ TT → conservative, with ocular lubricants as well as close observation, managing trichiasis in order to avoid subsequent bacterial ulcers and corneal scarring
  - TO → manage the disability and to restore vision.
- **WHO's GET 2020 program** (Global Elimination of Trachoma by the year 2020) has adopted the so called **'SAFE'** strategy (Surgery for entropion/trichiasis, Antibiotics for infectious trachoma, Facial cleanliness to reduce transmission, and Environmental improvements such as access to clean water and control of disease-spreading flies)
- The currently accepted WHO guidelines include community-wide antibiotic treatment if there is ***>10% active trachoma in children aged 1–9 years***. This treatment should be reinstituted annually for 3 years, with reassessment at that time.

Neonatial inclusion conjunctivitis (NIC)

- Also known as ophthalmia neonatorum
- **0.4% and 5%**
- C. trachomatis is the single most common etiologic agent, accounting for up to 40% of cases. Other causes include Neisseria gonorrhoeae, other bacterial infections, herpes simplex virus (HSV), and chemical toxins
- NIC is associated with serovars **D–K**
- First manifestation is often bilateral conjunctival hyperemia, occurring **5–14 days** after birth. Other typical yet nonspecific signs include mucoid or mucopurulent discharge, lid edema, pseudomembranes, ***papillary reaction and not a follicular reaction,*** all occurring within the same timeframe
- Because of the systemic risk, the treatment for NIC should include **systemic antibiotics**. The current recommended therapy is oral erythromycin 50 mg/kg/day in four divided doses for 10–14 days.

Adult Inclusion Conjunctivitis

- D–K, 5-14 days

Lymphogranuloma Venereum

- L1–3
- Parinaud's oculoglandular syndrome, a condition in which patients present with a severe papillary conjunctivitis as well as massive tender posterior cervical and preauricular lymphadenopathy.

Ophthalmia Neonatorum

- Chemical: 1–36 hours
- Neisseria gonorrhoeae: 1–2 days
- Bacterial (Staphylococcus, Streptococcus, Haemophilus): 2–5 days
- Viral: 3–15 days
- Chlamydia: 5–14 days

Parinaud's Oculoglandular Syndrome

- The most common bacterial cause, **Bartonella henselae**, is particularly difficult to culture.

Allergic Conjunctivitis

- Ocular allergy may be classified into five categories –

1. Seasonal and perennial allergic conjunctivitis (Non-Vision Threatening Ocular Allergy (>90% of cases))
2. Vernal keratoconjunctivitis (Vision-Threatening Ocular Allergy)
3. Atopic keratoconjunctivitis (Vision-Threatening Ocular Allergy)
4. Giant papillary conjunctivitis
5. Contact allergic conjunctivitis

- Immunopathophysiology
  - **Mast cells**, the primary inflammatory cells involved in ocular allergy, normally reside within the vascular stroma (**substantia propria**), but can be present within the conjunctival epithelium in pathologic situations.
  - Early-phase response (EPR) and a dose related late-phase response (LPR)
  - Two components of mast cell activation. The first is the release of preformed mediators, including histamine. The second is the synthesis of arachidonic acid and the subsequent metabolic cascade, resulting in the production of prostaglandins and leukotrienes

Seasonal allergic conjunctivitis (SAC)

- The most common form of ocular allergy
- Tree and flower pollen in the spring, grass pollen in the late spring and early summer, and ragweed during the late summer and early fall
- **Hallmark** symptom, **ocular itching**.
- **Clear, ropy discharge** is characteristic
- Nasal and pulmonary symptoms, as the same allergens could trigger rhinitis and asthma
- Skin testing, both prick and intradermal methods, is the most widely accepted method for allergy testing.

Perennial allergic conjunctivitis (PAC)

- A year-round variant of seasonal allergic conjunctivitis
- 79% of these patients have seasonal exacerbations
- Most common aeroallergens implicated in PAC are found indoors, and include animal dander, dust mites, and feathers.
- Treatment
  - Avoiding known allergen triggers is critical.
  - Itch–rub cycle: Encouraging patients to stop rubbing their eyes
  - Over-the-counter topical decongestants containing vasoconstrictors with or without antihistamines
  - The more potent **topical antihistamines**, levocabastine hydrochloride 0.05% and emedastine difumarate 0.05%, selectively block H1 receptors.
  - The **dual-acting medications**, including olopatadine hydrochloride 0.1% and 0.2%, azelastine hydrochloride 0.05%, ketotifen fumarate 0.025% (available over the

counter), and epinastine hydrochloride 0.05%, have **antihistamine and mast cell stabilizing** properties

- Traditional **mast cell stabilizers** include sodium cromoglycate 4% and lodoxamide tromethamine 0.1%.
- Ketorolac tromethamine 0.5% and diclofenac are **NSAIDs**, which decrease the activity of cyclooxygenase, an enzyme responsible for arachidonic acid metabolism. This, in turn, reduces prostaglandin production, most notably the highly pruritic PGE2 and PGI2.
- Topical corticosteroids are highly effective therapy for ocular allergy, blocking most allergic inflammatory cascades
- Oral antihistamines are seldom used to treat isolated seasonal or perennial allergic conjunctivitis

Vernal (Spring) Keratoconjunctivitis

- Chronic, bilateral, conjunctival inflammatory condition found in individuals predisposed by their atopic background
- Onset: 2-10 year → lasts till puberty
- Young males in dry, hot climates
- Family history of atopy is found in 40–60%
- Pathogenesis of VKC: Th2 cells, mast cells, and eosinophils are involved. Increased tear VEGF may contribute to corneal neovascularization and giant papillae formation.
- Symptoms: Severe itching and photophobia, foreign body sensation, ptosis, thick mucus discharge, and blepharospasm
- Signs:
  - Papillary response, principally of the limbus or upper tarsus, classic ‘cobblestone’ papillae.
  - Limbal papillae tend to be gelatinous and confluent → **Horner-Trantas dots**, which are collections of epithelial cells and eosinophils
  - Punctate epithelial keratitis → frank epithelial erosion → shield ulcer (due to its shape) → subepithelial ring-like scar
- Pathophysiology:
  - Epithelium contains large numbers of mast cells (mast cells predominantly of the type containing the neutral proteases tryptase and chymase) and eosinophils
  - Basophils are found in the epithelium, and may indicate that one form of a delayed-type hypersensitivity reaction is occurring
  - Substantia propria contains elevated numbers of mast cells
- Diagnosis: intense photophobia, ptosis, and the characteristic finding of giant papillae.
- Differential Diagnosis: AKC
- Treatment

- Avoidance of allergens
- Hyposensitization in VKC has limitations (due to multiple allergens)
- Short-term, high-dose pulse regimen of topical steroids
- Cromolyn sodium, a mast cell stabilizer, has repeatedly been shown to be effective in VKC
- Topical calcineurin inhibitors of ciclosporin A 0.05-0.1% (CsA) and tacrolimus 0.03-0.1% have been demonstrated effective in the treatment of VKC
- Climatotherapy
- Cryoablation of upper tarsal cobblestones is reported to render short-term improvement
- Hydrogel or scleral contact lenses for severe epitheliopathy and nonhealing corneal epithelial defects
- Corneal neovascularization: steroids, laser photocoagulation, and subconjunctival bevacizumab injection

Atopic Keratoconjunctivitis

- Bilateral, chronic inflammation of the conjunctiva and lids associated with atopic dermatitis
- 15% to 67.5% of patients with atopic dermatitis have ocular involvement
- Male: female = 2.4: 1
- Pathogenesis of AKC: Increased expression of Th1 (IFN-γ) and Th2 (IL-4) cytokines and infiltration with eosinophils and neutrophils have been detected in the conjunctiva. IFN-γ concentration in tears is correlated with severity of corneal epithelial disease. Increased TGF-β expression promotes fibroblast activation, collagen deposition, and fibrosis.
- Symptoms: Itching >> watering, mucus discharge, redness, blurring of vision, photophobia, and pain
- Signs
  - Periocular skin often shows a scaling, flaking dermatitis with a reddened base
  - Lateral canthal ulceration, cracking, and madarosis
  - Lid margins may show loss of cilia, meibomianitis, keratinization, and punctal ectropion
  - In contrast to VKC, the papillary hypertrophy of AKC is more prominent in the inferior conjunctival fornix.
  - Perilimbal, gelatinous hyperplasia
  - Punctate epithelial keratopathy → Persistent epithelial defects → scarring → microbial ulceration → neovascularization
- Pathophysiology
  - Both type I and type IV hypersensitivity
  - Conjunctival epithelium containing Mast cells (tryptase) and eosinophils
  - Increase in the CD4:CD8 ratio →

- Substantia propria: increased number of mast cells, Eosinophils (never found normally), Increased fibroblasts

- Treatment
  - Topical application of a vasoconstrictor–antihistamine combination
  - Topical administration of steroids
  - Mast cell stabilizers two to four times daily is recommended year-round
  - Ciclosporin A 0.05-0.1% and tacrolimus 0.03-0.1%, both orally and topically, have been shown effective in treating AKC
  - Management of ***Dupilumab Conjunctivitis***
    - Conjunctivitis has been reported to develop in 2%-23% of patients treated with dupilumab for moderate to severe atopic dermatitis (anti-IL-4 receptor alpha that blocks IL-4 and IL-13 signaling). Loss of goblet cells may contribute to disease.

Giant Papillary Conjunctivitis

- Noninfectious inflammatory disorder involving the superior tarsal conjunctiva.
- Currently defined **as papillae greater than 0.3 mm** in diameter
- **Average length of time**: ***soft*** contact lenses → **8 months**, ***hard*** contact lenses → **8 years**
- Mild irritation, scant mucous discharge, and occasionally mild itching
- Slow, progressive character → ropy, whitish, mucoid discharge
- **Allansmith** has divided the superior tarsal surface into three zones.
  - Zone 1 is located proximally along the uppermost edge of the tarsal plate;
  - Zone 2 is upper tarsal plate
  - zone 3 is located distally adjacent to the lid margin.
- Papillae with **soft** contact lens → **zone 1 to 3**
- Papillae with **RGP** contact lens → **zone 3**
- **Pathophysiology**:
  - Combined effect of ***mechanical trauma and the subsequent immune response*** to antigens in the form of contact lens surface deposits
- **Treatment:**
  - Discontinuation of offending irritant if appropriate
  - Modifying the patient's contact lens care routine and wearing schedule
  - Appropriate surfactant cleaner and a 'rub' routine becomes mandatory
  - Reducing contact lens wearing time
  - Treat if any meibomian gland disease
  - Histamine antagonists and receptor blocking agent

- Topical corticosteroids have not proved particularly effective
- **Suprofen**, an NSAID, has been studied topically in contact lens-associated GPC.
- **Cromolyn sodium** has been studied extensively and has been shown to promote resolution of early giant papillary conjunctivitis when combined with meticulous lens hygiene.

Common Old and Upcoming Treatments for Allergic Conjunctivitis

- Older and Available Options
  - First-generation antihistamine with vasoconstrictor
    - Problem: Short duration of action (q.i.d. dosing necessary), tachyphylaxis, rebound effect
    - Examples: pheniramine maleate + naphazoline (Naphcon-A, Visine-A, Opcon-A)
  - Mast cell stabilizer
    - Problem: Ineffective in relieving existing signs and symptoms of ocular allergy, need to start prior to allergy symptoms
    - Examples: cromolyn sodium, lodoxomide tromethamine, pemirolast potassiurelem, nedocromil sodium
  - Antihistamine plus mast cell stabilizer
    - Excellent first-line therapy due to rapid onset of action and prolonged effect
    - Examples: olopatadine HCl (Patanol), ketotifen fumarate (Zaditor, Alaway), azelastine HCl (Optivar), epinastine HCl (Elestat), bepotastine (Bepreve)
  - Topical steroids: loteprednol etabonate (Alrex and Lotemax)
  - Nonsedating oral antihistamines
  - Immunotherapy: Allergy shots (subcutaneous immunotherapy [SCIT])
  - Nonpharmacologic
    - Education is very important.
    - Allergy testing to figure out the cause of allergy
    - Allergen avoidance, avoid being outdoors during high pollen days. Sunglasses can provide a barrier.
    - No eye rubbing because eye rubbing degranulates mast cells → makes itching worse, creates vicious cycle.
    - Ice cold compresses (stops itch), art tears (dilutes allergen). Avoid punctal plugs.
    - Wash hair, change clothes as soon as enter house. No animals sleeping in bed (if allergic).
    - If dustmite allergy: Hypoallergenic bedding, wash sheets in hot water. Put pillows in dryer on high heat.
- Newer and Upcoming options

- Sublingual immunotherapy (SLIT), in which a tablet is placed under the tongue daily
- 4 FDA approved products: Oralair (5 kinds of northern grass pollen), Grastek (timothy grass pollen), Ragwitek (short ragweed), and Odactra (house dust mites)
- Topical cetirizine
- Newer targets to block inflammatory cascade: spleen tyrosine kinase (Syk), aldehyde-trap, toll-like receptor 2
- New application of existing drug: tacrolimus
- Oral administration of staple foods engineered to express allergens for oral immunotherapy (transgenic rice seeds that express cedar pollen)

OCP: Ocular Cicatricial Pemphigoid

- Chronic cicatrizing autoimmune disease of the mucous membranes and skin.
- OCP affects primarily the **conjunctiva and the mucosae**, including oral, nasal, and esophageal, in lesser frequency
- Average age at onset of OCP is **65 years**
- ***Scarring*** (**Brusting-Perry dermatitis**) occurs in approximately 25% of cases, and ***cicatrizing conjunctivitis*** develops in 70–75%
- **Histology**: the conjunctival lesions show submucosal scarring, chronic inflammation, perivasculitis, and squamous metaplasia of the epithelium, with loss of goblet cells; mast cell participation in the inflammation is surprisingly great.
- **Pathogenesis**
  - Autoimmune disease with a genetic predisposition and probably a '**second-hit**' environmental requirement to trigger the onset
  - Increase in frequency in the HLA-DR4 and HLA-DQw3
  - Second-hit → microbial or chemical
  - **β4 subunit of α6β4 integrin**, 205 kilodalton (kDa) protein molecule in the BMZ of the conjunctiva → ***the target of attack***
- **Diagnosis**
  - **Conjunctival biopsy:**
    - Direct immunofluorescence (staining of the basement membrane)
    - Immunoperoxidase staining: complement 3, IgG, IgM, and/or IgA localized in the BMZ of the conjunctiva
    - End-stage disease may produce negative results because of destruction of the basement membrane
    - Additional confirmation can be sought from immunoblot analysis of patient serum, an identifying autoantibody that binds to the 205-kDa protein band from conjunctival or epidermal lysates: anti-β4 antibody.
- **Ocular Manifestations**

- chronic, recurrent unilateral conjunctivitis may be bilateral but not necessarily symmetric
- Conjunctival subepithelial fibrosis, that may lead to progressive conjunctival shrinkage and symblepharon
- Tear deficiency
- Keratinization of the ocular surface
- Abnormal position of the eyelids and eyelashes, including entropion, trichiasis, and distichiasis
- Lagophthalmos with exposure of the ocular surface
- Extraocular manifestations may also occur, but not necessarily with the same severity or timing of presentation: Mucosal lesions (uncommon): bullae of the mouth, nose, pharynx, or larynx; desquamative gingivitis; and esophageal strictures

- **Stages**:
  1. Subepithelial fibrosis
  2. fornix foreshortening
  3. Symblepharon
  4. end-stage disease, is characterized by ankyloblepharon and surface keratinization
- **Therapy**
  - **Sicca syndrome:** lubricants without preservatives, Punctal occlusion, Topical retinoid (0.01% tretinoin) ointment
  - **Chronic blepharitis and meibomitis**: vigorous warm compresses and lid hygiene, oral doxycycline, 100 mg BD
  - **Immunomodulatory therapy** (minimum 2 years)
    - Prednisone 1 mg/kg/day, and cyclophosphamide 2 mg/kg/day.
    - Methotrexate (15–25 mg once weekly) and mycophenolate mofetil (1–3 g/day) are used for cases that are less active and are not rapidly progressing.
    - Dapsone and prednisone can also be used for such cases; the initial daily dose of dapsone employed is 1 mg/kg/day
    - Intravenous immunoglobulin (IVIG) alone and especially in combination with rituximab therapy
  - **Surgical treatment:**
    - Tarsectomy for correction of entropion,
    - Strip peritomy to provide an avascular barrier against corneal neovascularization
    - Superficial keratectomy for removal of corneal vascular and scar tissue
    - Fornix incision for release of symblepharon
    - Ocular surface reconstruction including: Amniotic membrane transplantation, Limbal allografting, Mucous membrane grafting, Keratoplasty, Keratoprosthesis

- Optical corneal transplant (DALK/PKP)
- Keratoprosthesis if failed cornea transplant

- **Pearls**
  - Avoid ocular surface surgery if functional vision is achieved with scleral contact lenses.
  - Refer to internal medicine specialist to rule out malignancy as underlying cause of paraneoplastic pseudo-OCP
  - If keratinization is present, contraindication to ocular surface stem cell transplantation and KPro
  - Mucus membrane pemphigoid requires adequate systemic immunosuppression prior to any lid/fornix reconstruction, ocular surface stem cell transplantation.
  - Stevens-Johnson syndrome patients are at risk for fungal keratitis after ocular surface stem cell transplantation.
  - Amniotic membrane is useful to prevent recurrence of mild symblepharon after EKC (adenoviral epidemic keratoconjunctivitis).
  - Keratolimbal allograft segment(s) may be used to prevent recurrent symblepharon formation.
  - Biopsy unilateral symblepharon to rule out ocular surface squamous neoplasia (OSSN).

EM, SJS & TEN

- Erythema multiforme described in 1866 by van Hebra. Further elaborated upon by Stevens and Johnson in 1922. Lyell introduced the term “toxic epidermal necrolysis” in 1956.
- **Categories from Chan et al, 1990:**
  - EM minor: skin with classic target lesions, but with each lesion < 3 cm; no or minimal mucous membrane involvement
  - SJS: classic target lesions; involvement of at least 2 mucous membranes (typically oral and ocular)
  - TEN: bullae and/or erosions > 20% body surface area with skin peeling off in > 3 cm sheets; mucous membrane involvement frequent
- Across-the-spectrum manifestations of the same clinical entity, affecting the skin and mucous membranes.
- ***International classification*** was adopted in 1993
- **Ferdinand von Hebra**, in 1866, first described erythema multiforme
- Incidence: 4.2 per million person-years
- M:F = 1:1.5/2
- Drugs and infections are the most frequent identifiable precipitating factors
- **Clinical Features:**

- ***Eye findings***
  - Acute eye findings
    - nonspecific conjunctivitis: may precede the skin eruption
    - may be catarrhal or pseudomembranous
    - severe anterior uveitis
    - corneal ulceration (uncommon)
  - Chronic eye findings
    - Scarring, symblepharon formation, and cicatrization of the conjunctiva
    - entropion formation, trichiasis, and instability of the tear film
    - corneal scarring, neovascularization, and, in severe cases, keratinization
    - Keratin not only on the corneal surface but also along the posterior lid margin.
    - Subepithelial fibrosis of the conjunctiva
    - Cicatrization of the lacrimal ducts
    - destruction of the conjunctival goblet cells
- ***Diagnostic criteria for bullous skin diseases***
  - Erythema multiforme minor (EM)
    - Target (iris) lesions (typical or atypical)
    - Individual lesions less than 3 cm in diameter
    - No or minimal mucous membrane involvement
    - Less than 20% of body area involved in reaction
    - Biopsy specimen compatible with erythema multiforme minor
  - Stevens-Johnson syndrome (erythema multiforme major) (SJS)
    - Less than 20% of body area involved in first 48 hours
    - Greater than 10% body area involvement
    - Target (iris) lesions (typical or atypical)
    - Individual lesions <3 cm in diameter (lesions may coalesce)
    - Mucous membrane involvement (at least two areas)
    - Fever
    - Biopsy specimen compatible with erythema multiforme major
  - Toxic epidermal necrolysis (TEN)
    - Bullae and/or erosions over 20% of body area
    - Bullae develop on erythematous base
    - Occurs on non-sun-exposed skin
    - Skin peels off in >3 cm sheets
    - Mucous membrane involvement frequent

- Tender skin within 48 hours of onset of rash
- Fever
- Biopsy specimen compatible with toxic epidermal necrolysis

- ***Incidence of ocular complications***: average of 24% had ocular manifestations during their hospitalization
- **Differential Diagnosis**
  - ***Ocular disorders***: Cicatricial pemphigoid, chronic keratoconjunctivitis caused by bacteria or viruses, medications, allergies, chemical burns, avitaminosis A, and trachoma, drug reaction.
  - ***Dermatologic***: SSSS, urticarial viral exanthema, drug reaction, toxic shock syndrome, Kawasaki disease, Leiner disease, erythroderma secondary to other causes, contact dermatitis, thermal burns, or poisonings
- **Etiology**
  - Drug-related cases
  - certain infections
  - malignancy
- **Pathogenesis**
  - immune-mediated responses to certain drugs and infectious organisms
  - keratinocyte death occurs from extensive apoptosis
  - suicidal interaction between Fas and Fas ligand
  - soluble FasL is secreted by peripheral blood mononuclear cells
  - Cytokines released by T lymphocytes, macrophages, or keratinocytes may enhance the expression of Fas and FasL on keratinocytes or enhance skin recruitment of lymphocytes by up-regulating adhesion molecules
  - SJS: significantly increased incidence of HLA-B12, HLA-Aw33, and DRw53
  - HSV EM: HLA-DQw3
  - TEN: HLA-B12
  - ocular lesions of SJS: HLA-B44
- **Histopathology**
  - Skin: lymphocytic infiltrate at the dermal–epidermal junction with a characteristic vacuolization of epidermal cells and necrotic keratinocytes within the epidermis
  - Eye: nonspecific inflammatory response is seen in the acute phases. In chronic phase, absence of the mucus-producing goblet cells as sequel of cicatrization.
- **Management**
  - ***Systemic***:
    - Specialized nursing and medical care, fluid balance, respiratory function, nutritional requirements, and wound care
    - Systemic steroids: Controversial, Increased rate of complications (sepsis, UTI, GI tract bleeding) reported.

- IVIG (human intravenous immune globulin): Increased survival rates of 88%-100% in pediatric and adult patients. Main complication is acute renal failure.
- Plasmapheresis: Used with TEN. Overall, the results in TEN have been favorable, with reported survivals of 77% to 100% after 1 to 8 exchanges.
- TNF-alpha inhibitor: Prospective trial in TEN of thalidomide vs. placebo stopped due to higher than predicted mortality.

✣ ***Ophthalmic***:

✣ Acute:

- Ocular surface hygiene, preservative-free artificial tear, Cycloplegics, topical steroids (controversial)
- Amniotic membrane or Prokera: First described by Darren Gregory (Univ. of Colo). Should be placed in the first 5 days.
- Lamellar or penetrating keratoplasty

✣ Chronic stage

- Restore eyelid and forniceal anatomy and function: Epilation, cryotherapy, argon laser treatment, electrolysis, or blepharotomy for trichiasis
- Supply tear function: artificial tear supplementation, 10% N-acetylcysteine, tarsorrhaphy
- Restore ocular surface: Keratolimbal allograft (keratoepithelioplasty), Topical transretinoic acid can be used to reverse conjunctival transdifferentiation seen after ocular surface injury.

✦ **Prognosis**: AIDS patients who develop erythema multiforme do not have a worse prognosis. Elderly patients have a worse prognosis, and children have the best.

Toxic Conjunctivitis

✦ Keratoconjunctivitis caused by topical atropine was described by **Von Graefe** in 1864

✦ **Toxicity versus Allergy**

✣ Toxicity implies damage to the structure of the ocular tissues, or disturbance of function, with or without an accompanying inflammatory response. Allergic reactions may be of the anaphylactoid (type 1) or of the delayed (type IV) hypersensitivity type.

✣ Follicles are generally not seen in allergy alone, and may be a key sign suggesting toxicity.

✣ Allergic conjunctivitis is often associated with a mucous discharge that is typically thin and clear. A more purulent or mucopurulent discharge may be associated with toxicity.

✣ TOXIC: oval epithelial defects located primarily in the inferonasal quadrants, with coarse surrounding keratitis, resembling a **'comet's impact' crater**

✦ **Diagnostic testing**

- **Type 1** hypersensitivity → intradermal skin test
- **Type IV** hypersensitivity → the patch test

- **Hurricane keratitis**
  - Postoperative corneal transplant patients as a result of the toxicity of topical medications.
  - Whorl-shaped punctate keratopathy develops as early as 1 week
  - Related to the intrinsic pattern of corneal epithelial repair, which appears to be a spiral or whorl-shaped epithelial slide

Superior Limbic Keratoconjunctivitis SLK

- January 1963, **Frederick Theodore**
- Clinical features
  - Marked inflammation of the tarsal conjunctiva of the upper lid
  - Inflammation of the upper bulbar conjunctiva
  - Fine punctate staining of the cornea at the upper limbus and the adjacent conjunctiva above the limbus
  - Superior limbic proliferation
  - Filaments on the superior limbus or upper fourth of the cornea in about half of the patients.
- **Histopathology**: The superior palpebral conjunctiva shows goblet cell hypertrophy, while the bulbar conjunctiva, which is thickened and keratinized, shows very few goblet cells.
- **Origin and Pathogenesis**
  - The origin of SLK has not been determined: ***viral, immunologic***
  - interesting associations: thyroid disease (**hyperthyroidism, is present in patients with SLK in at least 30%**), KCS
- **Treatment**
  - Preservative-free artificial tear drops every 2 hours. Consider temporary or permanent punctal occlusion.
  - Cyclosporine 0.05% to 2% b.i.d. to q.i.d. may be helpful. Lifitegrast 5% b.i.d. may also be beneficial. Occasionally serum tears can be helpful.
  - Acetylcysteine (eg, Mucomyst) 10% drops q.i.d. for treatment of corneal filaments
  - Topical antihistamine / mast cell stabilizers (eg, azelastine, epinastine, ketotifen, nedocromil, olopatadine, bepotastine, alcaftadine) q.d. to b.i.d. may be helpful.
  - Application of silver nitrate 0.5% solution to superior bulbar and palpebral conjunctiva for 15 to 30 seconds
  - Localized cautery to superior conjunctiva
  - Double freeze-thaw cryotherapy

- Surgical resection with or without amniotic membrane graft of superior bulbar conjunctiva
- Therapeutic soft contact lenses
- Botulinum toxin injection of the orbicularis
- Topical vitamin A
- Supratarsal triamcinolone injection
- Liquid nitrogen cryotherapy: **Brymill E tip spray** (0.013-inch aperture) with a double freeze–thaw technique is another approach described by Frederick Fraunfelder
- N-acetylcysteine

- **Differential Diagnosis**
  - **Theodore's SLK and CL-SLK**: **CL-SLK** is not always bilateral and has no relationship with thyroid disease. SLK is more commonly seen in females, while CL-SLK is not. CL-SLK also occurs in younger patients than does SLK. While vision with SLK is usually not decreased, it can be severely decreased in patients with CL-SLK, since corneal involvement is greater. Corneal filaments are usually not seen with CL-SLK, but they are frequently seen with SLK. A final distinction between the two is that contact lens keratoconjunctivitis often improves quickly after cessation of lens wear, whereas SLK goes on with remissions and recurrences for many years.

Ligneous Conjunctivitis

- Protracted course of recurrent, membranous, conjunctival lesions, which has been associated with a ***systemic plasminogen deficiency***
- 1847, **Bouisson**
- **Borel** in 1933, assigned the name ligneous → meaning 'woody,' to this disorder because of the characteristic ***woodlike consistency of the membranes*** in severe cases
- Median age of first clinical manifestation was **9.75 months**
- **Clinical Features**
  - Chronic conjunctivitis
  - Ligneous lesion appears as a highly vascularized, raised, friable lesion.
  - Can be removed easily with forceps, although it tends to bleed
  - Pain and photophobia, almost constant discomfort
  - More severe lesions extend beyond the lid margin, giving rise to one of the worst complications of the disorder, the cosmetic deformity
- **Pathophysiology**
  - *Type I plasminogen deficiency*
- **Etiology**
  - Type I plasminogen deficiency has been reported to cause any form of pseudomembranous disease.

- **Treatment**
  - Plasminogen substitution: Topical plasminogen preparations,
  - Complete excisional biopsy of all ocular ligneous lesions
  - **Systemic and topical FFP** and started on a corticosteroid and broad-spectrum antibiotic four times daily with topical ciclosporin A 2% twice daily

Developmental Abnormalities of Cornea

Anomalies of Size and Shape

- Organogenesis (between the fourth and sixth gestational weeks)
- Period of anterior segment differentiation (between the sixth and sixteenth gestational weeks)

Absence of the Cornea

- Always accompanied by agenesis of various other anterior segment structures.
- **True cryptophthalmos**, otherwise known as complete cryptophthalmos or ablepharon, occurs when skin replaces the normal eyelid architecture and connects to the underlying globe, leaving the cornea and part of the conjunctiva unprotected and exposed.
- The term cryptophthalmos syndrome, also termed **Fraser syndrome**, has been used to describe patients who meet specific criteria as outlined by Thomas.
- **Pseudocryptophthalmos** (total ankyloblepharon) is a related condition in which the eyelids form but fail to separate, leaving a normal cornea and conjunctiva totally covered by skin. Unlike its true counterpart, both lashes and brows are present with an otherwise normal eye, and vision is restored by surgically creating a palpebral fissure.
- Cornea usually reaches adult size by 2 years of age.
- Newborn cornea measures approximately 10 mm in horizontal, adult 12 mm

Megalocornea

- Horizontal diameter greater than or equal to **13 mm**
- **XR** → Xq21, Xq12; nonprogressive, bilateral and symmetrical
- Steeper cornea usually results in **with-the-rule astigmatism** and **myopia**
- Pathognomonic biometric findings of X-linked megalocornea not present in congenital glaucoma or other forms of megalocornea: markedly increased anterior chamber depth, posterior lens and iris positioning, and a short vitreous length

Microcornea

- Horizontal diameter **less than or equal to 10 mm** in an otherwise normal-sized globe
- Nonprogressive, unilateral or bilateral
- Male = Female
- AD, AR, Sporadic
- Flatter than normal cornea → **hyperopia**
- Rarely an isolated condition and can have many ocular and systemic anomalies associated with it

- 20% of patients with microcornea develop **glaucoma**, with angle closure being most common

Oval cornea

- **Horizontal oval cornea**: exaggeration of scleral encroachment in the superior and inferior horizontal meridians. indicates the presence of some degree of sclerocornea and has no other associated findings.
- **Vertical oval cornea** exists when the vertical diameter of the cornea exceeds the horizontal diameter. a/w iris coloboma, microcornea, intrauterine keratitis, Rieger's anomaly, and Turner's syndrome.

Astigmatism

- **With-the-rule astigmatism in the first decade** of life progressing to against-the-rule astigmatism in later years.

Sclerocornea (cornea plana)

- Cornea is flat with a curvature of **less than 43 diopters** (D)
- Ranges from 30 to 35 D
- The embryologic explanation for sclerocornea: **absence of the limbal anlage**, the structure responsible for both limbal differentiation and corneal curvature.
- Bilateral & asymmetric, may be unilateral
- AD, AR (chromosome 12), Sporadic
- Male = Female
- Total or Peripheral
- Management: Refraction, PK, Glaucoma Management

Keratoglobus

- Typically develops during the **first 20 years** of life
- Bilateral, noninflammatory, ectatic disorder in which the entire cornea becomes thinned and takes on a globular shape, with keratometry readings as high as 60–70 D.
- Strong association with Ehlers-Danlos syndrome **type VI**

Congenital Anterior Staphyloma

- Bulging, opaque cornea lined posteriorly with uveal tissue protrudes through the palpebral fissure beyond the plane of the normal eyelids

- Result from the **abnormal migration of neural crest cells** into the developing cornea
- Cornea is vulnerable to perforation in utero and subsequently undergoes dermoid transformation to resemble the stratified squamous epithelium of skin
- Unlike cryptophthalmos, the **metaplastic change is limited to the cornea** and does not involve the conjunctiva or eyelids.

Keratectasia

- Congenital anterior staphyloma **minus** the posterior uveal lining.

Axenfeld Rieger Syndrome

- Axenfeld syndrome, which is Axenfeld anomaly with glaucoma.
- While the word 'syndrome' means systemic abnormalities in 'Rieger syndrome,' it means glaucoma when used in 'Axenfeld syndrome.'
- **Divisions of Axenfeld-Rieger syndrome**

  PARR → PAIS.

Disease	Posterior embryotoxon	Angle abnormalities	Iris stroma abnormalities	Systemic abnormalities	Glaucoma risk
Posterior embryotoxon	+	–	–	–	–
Axenfeld anomaly	+	+	–	–	+
Rieger anomaly	+	+	+	–	+
Rieger syndrome	+	+	+	+	+

Iridocorneal Endothelial Syndrome

- The diagnosis of the ICE syndrome is considered when two of the three main clinical features are present **unilaterally**: ***typical iris changes, abnormal corneal endothelium, and PAS.***
- Coincidentally, the acronym ICE also signifies commonly used names of these conditions – Iris nevus syndrome, Chandler's syndrome, and Essential (progressive) iris atrophy.
- **Etiology**
  - Unknown
  - Membrane theory of Campbell
    - Earliest stage of iris and anterior chamber angle involvement. Solitary peripheral anterior synechiae (PAS), but no pupil and iris abnormality.

- Growth and extension of abnormal membrane from posterior corneal surface over the anterior chamber angle
- contraction of membrane on iris surface, and early stretch-induced iris stromal atrophy in the quadrant opposite the membrane
- Diffuse anterior chamber angle and iris involvement with abnormal membrane growth

- **Essential iris atrophy**
  - **Most common**
  - First presents typically in young adults, unilaterally, and in women > men
  - Bare eccentricity of the pupil to severe corectopia
  - Iris atrophy and partial-thickness holes in the iris stroma appear on the side opposite the pupillary eccentricity
  - Glaucoma, iris atrophy, or nodules
  - Specular microscopy is an invaluable tool for early or confirmatory diagnosis. Although endothelial cell pleomorphism and a decrease in the percentage of hexagonal cells of the contralateral eye have been described, typical morphologic specular microscopic changes (ICE cells) are unilateral.
- **Chandler's syndrome**
  - Blurred vision or seeing colored halos around lights.
  - Corneal edema was first described as occurring at a normal or slightly elevated intraocular pressure and, because of the abnormal endothelium, is the dominating clinical characteristic of this subtype of ICE syndrome
  - The abnormal corneal endothelium, best seen with specular reflection, has a fine hammered silver appearance, which is finer in appearance than the guttata of Fuchs' endothelial dystrophy
- **Cogan-Reese syndrome**
  - The least common of the major variants of ICE syndrome
  - A hyaline membrane ('ectopic Descemet's membrane')
- **Iris nevus syndrome**
  - Unilateral diffuse nevus of the iris and several other signs including loss of surface architecture of the iris resulting in a matted appearance, ectropion uvea, heterochromia, PAS, corneal edema, and unilateral glaucoma.
- **Differential Diagnosis**
  - Posterior polymorphous dystrophy
  - Axenfeld-Rieger syndrome
- **Management**
  - Medical treatment is generally ineffective
  - Glaucoma develops it may be managed initially with aqueous suppressants. glaucoma filtering surgery is required

- Corneal edema may respond to lowering intraocular pressure. Hypertonic saline solutions and soft contact lenses may be helpful
- Cataracts may develop de novo or subsequent to glaucoma or corneal surgery.

Keratoconus & Noninflammatory Ectatic Disorders

Keratoconus

- Kerato= Horn, cornea
- Conus= cone
- Keratoconus is a noninflammatory , ectatic corneal condition characterized by central or paracentral stromal thinning , apical protrusion and irregular astigmatism
- British physician, **Jhon Nottingham** in 1854 did practical observations on conical cornea
- **50-230 / 100000** individuals
- M=F
- Starts at puberty, over a period of 10 to 20 years the process continues until the progression gradually stops
- **Familial incidence= 65%,** Autosomal dominant with variable penetrance
- **Pathophysiology**:
  - **Antioxidant deficiency**
  - **Proteinase and antiproteinase imbalance**: up-regulation of degradative enzymes and the down-regulation of proteinase inhibitors could result in a degradation of the extracellular matrix of the stroma
  - **Apoptosis**: Keratocytes from keratoconus corneas have been found to have four times the interleukin-1 binding sites, when compared to nonkeratoconus corneas. This may result in an increased sensitivity of the keratocytes in keratoconus to the effects of interleukin-1. Interleukin-1 has also been shown to induce apoptosis or controlled cell death of stromal keratocytes in vitro.
  - **Contact lens wear** is another form of corneal microtrauma: 17.5% to 26.5%
  - **ectodermal disease**, then associations with atopic disease and tapetoretinal degenerations
- **Pathology**:
  - **Breaks in the epithelial layer** can be associated with epithelium growing posteriorly into Bowman's layer and collagen growing anteriorly into the epithelium, forming Z-shaped interruptions at the level of Bowman's layer. These Z-shaped areas are typical of keratoconus.
  - **Fleischer ring** found at the base of the cone
  - **normal-sized collagen fibers**; however, the number of collagen lamellae was abnormally low. The number found within the cone was less than half (41%) the number outside of the cone.
  - **Endothelial cell pleomorphism** and polymegathism occur in keratoconus
- **Clinical Features**:
  - Late teens
  - Blurring of vision
  - Shadowing around images

- Glare, halos, ocular irritation
- Frequent changes in spectacle number
- Contrast sensitivity measurement may, however, uncover visual dysfunction before Snellen visual acuity loss can be measured
- Two types of cones have been described. The **round or nipple-shaped cone** is smaller in diameter, while the **larger oval or sagging cone** may extend to the limbus and is more prone to contact lens fitting problems.

- **Signs**:
  - Irregular astigmatism
  - Striae occur in the posterior stroma, just anterior to Descemet's membrane.
  - Red reflex Oil droplet sign
  - Scissoring reflex
  - Vogt ‘s straie
  - Fleischer’s ring
  - Prominent corneal nerves
  - Corneal topograph
  - Progressive corneal thinning
  - Munson’s sign
  - **Central corneal scarring**: Factors predictive of incident corneal scarring include corneal curvature greater than 52 diopters (D), contact lens wear, corneal staining, and age less than 20 years.
- **From Fruste Keratoconus (FFKC)** was originally described by Prof. Marc Amsler (1891-1961) based on reflection Placidodisk photography, prior to the development of computerized corneal imaging technologies. FFKC was used to describe an abortive form of the disease that may progress or may not.
- **Investigations**:
  - The **keratometer** is an invaluable, widely available tool for measuring corneal curvature. Inability to superimpose the central keratometric rings suggests irregular corneal astigmatism, a hallmark of keratoconus.
  - **Keratoscopy or videokeratography**, based on the Placido disk, can provide qualitative contour information. In early keratoconus, a focal area of increased corneal curvature appears as an isolated area of smaller ring spacing and distortion. As the condition progresses, the ring spacing decreases overall and becomes increasingly irregular
- **Rabinowitz has suggested four quantitative videokeratographic indices** as an aid for screening patients for keratoconus. These indices include
  1. Central corneal power value greater than 47.2 D
  2. Inferior–superior dioptric asymmetry (I-S value) over 1.2
  3. Sim-K astigmatism greater than 1.5 D
  4. Skewed radial axes (SRAX) greater than 21 degrees.

- **Indices**
  - Simulated keratometry (SimK)
  - Surface asymmetry index (SAI):
  - Asymmetric bow tie (AB) with skewed radial axes (SRAX): Skewing of more than 30° is described as significantly abnormal
  - **Rabinowitz/Mc Donnel diagnostic criteria** consists of two topography derived indices, which are as follows;
    - Central K-value > 47.20 D and
    - Inferior-Superior asymmetry (I-S value) > 1.4 D
  - Rabinowitz/Rasheed's described **KISA% index:**
    - Uses 4 parameters →
    - Keratometry; I-S value; the AST index, which quantifies the degree of regular corneal astigmatism (simulated flat and steep keratometry values, Sim K1 and Sim K2); and SRAX, which is an expression of irregular astigmatism.
    - KISA% > 100% is considered as highly suggestive of keratoconus.
  - **Keratoconus-prediction index(KPI) → Indices of Maeda and Klyce**
    - Derived from eight other quantitative videokeratographic indices.
    - Two simulated K values (steep and flat powers), differential sector index (DSI), center/surround index (CSI), opposite sector index (OSI), surface asymmetry index (SAI), analyzed area (AA), and the irregular astigmatism index (IAI).

- **Amsler-Krumeich classification**
  - Stage 1:
    - Eccentric steeping
    - Myopia and astigmatism < 5.00 D
    - Mean central K readings < 48.00 D
  - Stage 2:
    - Myopia and astigmatism from 5.00 to 8.00 D
    - Mean central K readings < 53.00 D
    - Absence of scarring
    - Minimum corneal thickness >400 μm
  - Stage 3:
    - Myopia and astigmatism from 8.00 to 10.00 D
    - Mean central K readings >53.00 D
    - Absence of scarring
    - Minimum corneal thickness 300 to 400 μm
  - Stage 4:

- Refraction not measurable
- Mean central K readings >55.00 D
- Central corneal scarring
- Minimum corneal thickness 200 µm

- **ABCD Classification**: The ABCD classification is measured at the cone.
  - A: Anterior radius of curvature from a 3.0-mm zone centered on thinnest point
  - B: Posterior (back) radius of curvature from a 3.0-mm zone centered on the thinnest point
  - C: Minimal corneal thickness (not apical)
  - D: Best spectacle-corrected visual acuity
- **Systemic Association:**
  - ATOPY
    - Asthma
    - Atopic keratoconjunctivitis
    - Hay fever
    - Eczema
  - CONNECTIVE TISSUE DISORDERS
    - Marfan's syndrome: An increased prevalence (38%[20] to 58%) of mitral valve prolapse has been found in keratoconus patients
    - EDS
    - Osteogenesis imperfecta
  - MISCELLANEOUS
    - Down's: 5.5% and 15%
      - structural or biochemical changes
      - habitual eye rubbing
    - Turner's syndrome
  - Diabetes offered a protective effect regarding keratoconus. (also smoking?? As they cause C3R like effect)
- **Ocular Associations:**
  - RP
  - Infantile tapetoretinal degeneration (Leber's congenital amaurosis) is frequently complicated by keratoconus and cataract.
  - retinopathy of prematurity, progressive cone dystrophy, aniridia, iridoschisis, and essential iris atrophy
  - VKC: 26.8%.
  - 17% in a group of patients with floppy eyelid syndrome.

- **Complications**:
  - **High Refractive errors**: Intolerance to glasses
  - **Acute Hydrops** : Rupture Descemet's membrane → Aqueous influx → Corneal edema → Sudden drop in vision / Opacity
- **Keratoconus Progression**
  - K-max (steepest keratometry) ≥ 1 D increase
  - K-max – K-min ≥ 1 D increase (K-min, flattest keratometry)
  - Kmean ≥ 0.75 D increase (Kmean = average of K-max K-min)
  - Pachymetry ≥ 2% decrease in central corneal thickness (CCT)
  - Corneal apex power ≥ 1 D increase (measured with cone location and magnitude index)
  - MRSE change ≥ 0.5 D
  - Several established decision trees exist based on combinations of the above, such as the Klyce indices of Surface Asymmetry Index (SAI) and Surface Regularity Index (SRI) and KISA% Index.

Management

- The management of keratoconus begins with **spectacle correction**.
- Once glasses fail to provide adequate visual function, **contact lens fitting** is required. Contact lens wear improves visual function by creating a new anterior refractive surface. Contact lenses **do not prevent progression** of corneal ectasia. While they seem to be associated with the development of keratoconus in some cases, this important mode of therapy should never be withheld for fear of causing progressive disease.
  - **RGP**: three-point touch technique, remain the mainstay of contact lens treatment for keratoconus. apical clearance fitting technique is also commonly used.
  - Other options include soft toric lenses, standard bicurved hard lenses, custom-back toric lenses, piggyback systems, hybrid lenses made of combined hard lens with a soft skirt, scleral lenses, and mini-scleral lenses.
  - Silicone-hydrogel (Si-Hy) lenses, keratoconus designs
  - **Hybrid lenses**, such as the SoftPerm lens (CIBA Vision Corp., Duluth, GA) and the newer SynergEyes KC lens (SynergEyes, Inc., Carlsbad, CA) may be more comfortable for patients who cannot tolerate an RGP alone.
  - **Mini-scleral lenses** have a diameter of 14–17 mm compared to scleral lenses with a diameter of 20–24 mm.
  - **PROSE** (prosthetic replacement of the ocular surface ecosystem): A medical model
  - Outcomes
    - Bigger is better. Size matters.
    - There is no cone that cannot be fit.
    - Scleral lens is an option after hydrops.
  - New Paradigm for Contact Lens in Keratoconus

- Not a “contact lens failure” without trial of “true” scleral lens > 18 mm
- Penetrating or lamellar keratoplasty only for axial opacity limiting vision (in specialty lens)
- No regraft for cylinder or recurrence of ectasia without trial of specialty lens
- New Si-Hy lenses with keratoconus designs have extended the use of soft lenses in keratoconus.
- New hybrid materials and designs address past failures from lens fragility and hypoxia.
- Scleral lenses are in the repertoire of an increasing number of specialty lens fitters.
- Scleral lenses are a useful option in cases of RGP corneal lens failure due to instability or tight lens syndrome.
- The definition of scleral lenses is evolving. “Miniscleral,” corneoscleral, and intralimbal lenses may not perform as well as scleral lenses.
- PROSE treatment is a good option for contact lens and even scleral lens failures and can accommodate any cone.
- PROSE treatment has favorable 1-year outcome in comparison to keratoplasty for moderate to severe keratoconus.

- **Contact lens-intolerant** keratoconus patients without central scarring, who have mild or moderate disease, may be candidates for intrastromal ring segment insertion. The ideal candidates also have low spherical equivalents and average keratometry readings of less than 53 D.
  - **Ferrara rings** (Ferrara Ophthalmics, Belo Horizonte, Brazil) and **Intacs** (Addition Technology Inc, Des Plaines, IL, USA), commonly used ring segments, are made of rigid polymethyl methacrylate. Ferrara rings have a fixed inner diameter of 5.0 mm and a triangular anterior contour. Intacs have an inner diameter of 6.8 mm, a flat anterior surface, and are available in thicknesses of 0.25–0.45 mm, in 0.05 mm increments.
- **C3R** (read from refractive chapter notes)
- While **penetrating keratoplasty** has traditionally been the surgery of choice, lamellar surgery is becoming more popular for patients with mild to moderate disease.
  - The iron ring, found at the base of the cone, should be used as a reference when planning graft size.
  - Postkeratoplasty myopia can be reduced by using the same-sized donor and host corneal buttons.
- **Lamellar Keratoplasty**
  - Deep anterior lamellar keratoplasty (DALK): host endothelium is preserved, thus reducing the risk of rejection. The risk of endophthalmitis is theoretically less because this is largely an extraocular procedure.
- **Corneal Allogenic Intrastromal Ring Segments (CAIRS)** Combined With Corneal Crosslinking for Keratoconus
  - Under study

- CAIRS trephined from donor cornea using a double-bladed trephine were implanted into mid-depth femtosecond laser– dissected channels in the cornea of patients with keratoconus in the 6.5-mm optic zone, followed by accelerated corneal crosslinking (A-CXL)—either conventional or contact lens–assisted CXL (A-CACXL), depending on minimum corneal thickness.

Acute Hydrops

- Acute hydrops is a relatively rare condition, occurring in 2.6%2.8% of patients diagnosed with keratoconus. There is a male preponderance,and mean age of onset is2 5. The pathogenesis of acute hydrops is the following: a break in Descemet membrane and endothelium is followed by aqueous humour entering the cornea, causing marked stromal and epithelial edema. Typically, the edema resolves progressively within 2-4 months, often leaving a visually significant scar in the central or paracentral cornea.
- **Conservative Management**
  - Observation is a possible option since corneal edema is typically self-limiting. To help with patient comfort, use of lubrication is recommended. This approach should mostly be considered if the break in Descemet membrane is small and corneal edema is mild. Some physicians recommend using a therapeutic contact lens; however, fitting can be difficult in cases of steeper corneas.
- **Medical Management**
  - Most ophthalmologists tend to use a combination of hypertonic saline drops, topical corticosteroids, cycloplegics, and hypotensives. The hypertonic saline drops cause an osmotic effect on the ocular surface to decrease epithelial and stromal edema. Topical corticosteroids, such as prednisolone acetate 1%, are often prescribed to reduce the inflammatory component of acute hydrops and to help decrease progression of stromal neovascularization. Moreover, topical cycloplegics are used to decrease pain. Topical hypotensives that decrease aqueous fluid production, such as timolol maleate 0.5%, reduce aqueous egress in the stroma.
- **Surgical Management**
  - In recent years, surgical treatment of acute hydrops has been advocated to hasten resolution of corneal edema and to decrease risk and/or progression of stromal neovascularization. Injection of intracameral gas, pre-Descemetic compression sutures, and keratoplasty have all been reported. Intracameral injection of 0.2 mL of isoexpansile perfluorocarbon, such as 14% C_3F_8 or 20% SF_6, is used to improve reapposition of the torn Descemet to the posterior stroma. This helps close the cleft and promote resolution of the corneal edema. Clinical resolution of edema in these patients is significantly faster than in patients treated solely with a medical approach.
  - Complication from surgical management are: pupillary block, cataract formation, and persistent mydriasis. With anterior segment imaging, either anterior segment OCT or ultrasound biomicroscopy, one can measure the size of the Descemet tear. If the tear is of appropriate size, injection of intracameral gas may be indicated. In cases where the tear is too large or too deep, the gas may infact impede recovery.

- Pre-Descemet compression sutures placed perpendicular to the tear may also speed up resolution of stromal edema. Finally, there are reported cases of progressive Descemet tears that have been managed with endothelial keratoplasty to close the gap from the hydrops. These novel therapies, from intracameral gas injection to compression sutures to endothelial keratoplasty, may become the mainstays in treatment for patients with acute hydrops in the future.

Keratoconus in Children

- Can present as early as age **4**
- Associated with trisomy 21, Turner syndrome, vernal keratoconjunctivitis, eye rubbing, Leber congenital amaurosis
- More severe disease at presentation (Amsler-Krumeich grade 3-4), with faster progression than in adults
- **Diagnosis**: Diagnostic criteria same as in adults
- **Corneal Crosslinking (CXL) in Children**: FDA approved for treatment in patients above age **14**.
- **Criteria for treatment**
  - Criteria for progression and diagnosis vary between studies.
  - Many authors advocate treatment after diagnosis, without waiting for progression.
  - Minimum corneal thickness: Usually 400 microns in most studies, but down to 350 microns described with use of hypo-osmolar riboflavin
- **Multiple techniques described in children**
  - Epithelium-on vs. epi-off: Mixed results, with comparative studies showing either equivalence or inferiority of epi-off technique. Perez-Straziota et al[1] recommend epi-off only in select patients (eg, trisomy 21 or with mild KC).
  - Accelerated vs. standard ("Dresden") protocols: Studies generally show equivalent results.
  - Iontophoresis: Early results, less effective in 1 study
  - CXL + intracorneal ring segments: Rate of extrusion (6%-7%) is higher compared to adults.
  - Single small case series describes success with use of topo-PRK and CXL in children.
  - Most reports describe treatment with use of topical anesthesia and mild sedation.
- **Outcomes**
  - Published case series are largely small with short-term follow-up (2 years or less)
  - Mazotta et al found 24% risk of progression 10 years post-CXL and recommended long-term topographic monitoring in young patients.
  - Most studies report stable or improved BCVA, up to 0.15 logMAR, and improvement in Kmax by 1-2 D.

- Decrease in thinnest pachymetry by up 40 microns, which can reverse over time
- Little published evidence on retreatments and on outcomes in patients with trisomy 21

- **Complications**: Microbial keratitis, uncommon (1%-2%) Sterile infiltrates described Haze (6% or less)
- Effect of atopy/vernal keratoconjunctivitis appear to be risk factors for progression after CXL and for microbial keratitis so it need to be treated aggressively in KC patients
- May cause inaccurate topography when active; topography should be repeated when disease is well-controlled.

Other Noninflammatory Ectasias

Pellucid marginal degeneration (PMD)

- **Schlaeppi** appropriately chose the name pellucid, meaning **clear**, to describe this thinning disorder. These corneas are generally clear and avascular, with no iron ring, infiltrate, or lipid deposition.
- Bilateral, peripheral corneal ectatic disorder characterized by a band of thinning **1–2 mm** in width, typically in the **inferior** cornea, extending from the **4 to the 8 o'clock** position.
- In contrast to keratoconus, ***maximal corneal protrusion typically occurs just superior*** to, rather than within, the area of thinning
- **Shift in the axis of astigmatism** from against-the-rule, superiorly, to with-the-rule, near the point of maximal protrusion.
- PMD and keratoconus can occur in the same eye
- Typical **crab-claw** illustrates the shift in astigmatism from the superior to the inferior cornea
- Poor candidates for refractive surgery because of the potential for an **undesirable outcome** and the risk that the surgical procedure might stimulate progressive ectasia.
- Present for treatment between the second and fifth decades of life with complaints of blurred vision resulting from irregular astigmatism.
- **Differential Diagnosis**:
  - The findings typical of **keratoconus**, specifically, protrusion within the area of corneal thinning, striae, and Fleischer's ring, are not seen in PMD.
  - **Terrien's marginal degeneration** can cause high astigmatism in a similar age group. However, in contrast to pellucid degeneration, this disorder has a male predilection. It commonly affects the cornea, superiorly as well as inferiorly, with vascularization and lipid deposition. When corneal protrusion occurs in Terrien's degeneration, it is usually within the area of thinning.
  - **Mooren's ulcer** is usually unilateral and is associated with marked inflammation and pain, an epithelial defect in the area of ulceration, undermining of the central edge of the ulcer, and vascularization up to the peripheral edge. Corneal changes in Mooren's ulcer are not confined to the inferior or superior cornea.

- **Idiopathic furrow degeneration**, while bilateral and noninflammatory, occurs in the elderly within a corneal arcus.

- **Management**
  - Spectacles usually fail to adequately correct the high irregular astigmatism associated with typical cases of PMD. Large-diameter, rigid gas-permeable contact lenses can be tried. However, because of the contour abnormality, a stable long-term fit can be difficult to achieve. The hybrid lenses, such as the **SoftPerm** lens, have been used successfully in PMD. The newer generation of scleral lenses made from gas-permeable plastic may also be of benefit.
  - **Large-diameter or eccentric penetrating keratoplasty** may be necessary to encompass the area of peripheral thinning.
  - **thermokeratoplasty, crescentic lamellar keratoplasty, and crescentic or wedge excision**

Keratoglobus

- Bilateral ectatic disorder that is usually nonprogressive or minimally progressive.
- Generalized thinning, most marked in the periphery
- ***Acute hydrops occurs less frequently*** than in keratoconus; however, the opposite is true about corneal perforation and rupture. Keratoglobus patients are prone to ***corneal rupture*** after minimal trauma, even when there is no history of trauma.
- **Associations**:
  - Unlike keratoconus, **keratoglobus is not associated with atopy, tapetoretinal degeneration, or hard contact lens wear**. Keratoglobus has been reported in association with ***inflammatory orbital pseudotumor, chronic marginal blepharitis, chronic eye rubbing, and in glaucoma*** following penetrating keratoplasty. Acquired keratoglobus has also been described in association with vernal keratoconjunctivitis and hyperthyroidism.
  - **No association with Down's syndrome**, keratoglobus has been reported in association with ***Rubinstein-Taybi syndrome***, in which intellectual impairment occurs
- **Management:**
  - Spectacle correction is the first step
  - There may be a role for a rigid gas-permeable scleral lens
  - Lamellar graft or epikeratoplasty

Posterior Keratoconus

- Thinning results from an increase in the curvature of the posterior cornea
- **Keratoconus posticus generalis** the entire posterior corneal surface has an increased curvature and the cornea typically remains clear.

- In the localized form, **keratoconus posticus circumscriptus**, there may be one, or occasionally more, central or paracentral areas of posterior excavation associated with variable amounts of stromal scarring
- Relative lack of involvement of the anterior refractive surface explains why posterior keratoconus results in only mild to moderate reduction in visual function.
- Developmental, usually **nonprogressive, noninflammatory, and unilateral**
- Does not develop into keratoconus, despite the fact that anterior steepening can occur in a central or paracentral affected area.
- Similarities between posterior keratoconus and Peters' anomaly. However, a difference is observed histopathologically. ***In Peters' anomaly the corneal endothelium and Descemet's membrane are either absent or markedly thinned,*** which is not the case in posterior keratoconus.

Corneal and Conjunctival Degenerations

- Degeneration of a tissue is defined as a deterioration and decrease in function.

Arcus senilis

- Gerontoxon in geriatrics
- Arcus juvenilis or anterior embryotoxon in the young
- Lipid deposition in the peripheral cornea
- Gray to yellow arc, first in the inferior cornea then the superior cornea
- Sharp peripheral border ending at the edge of Bowman's layer with a lucent zone (***lucid interval of Vogt***) to the limbus
- Histopathologically, the arcus has an **hourglass appearance** as the opacity extends into the corneal stroma from these two layers.
- Lipid particles are similar to a type found in human atherosclerotic lesions but accumulate in the absence of foam cells, unlike atherosclerotic lesions.
- Limbal vasculature is part of a low-pressure perfusion system. The endothelium of these blood vessels act as tight junctions but in the presence of elevated circulating LDL may become dysfunctional. Lipid in the peripheral cornea likely originates from LDL, it is modified LDL and apo B sparse.
- ***Affects men more than women.***
- Hyperlipoproteinemia types IIa and IIb are associated with premature corneal arcus formation
- Rare genetic disorders of high-density lipoprotein (HDL) metabolism causing corneal deposits include lecithin cholesterol acyltransferase ***(LCAT) deficiency, fish eye disease and Tangier disease.***

Lipid degeneration

- ***Primary lipid degeneration***
  - No prior history of the following: trauma, family history of similar conditions, corneal vascularization, and no known disorders of lipid metabolism.
  - Due to increased vascular permeability of the limbal vessels. Alternatively, the etiology may be an altered metabolic activity of the keratocytes
  - More common in women than men, with a ratio of 70 : 30
- ***Secondary lipid degeneration***
  - Associated with corneal neovascularization
- **Spheroidal degeneration (climatic droplet keratopathy)**
  - Bietti's nodular corneal degeneration, Labrador keratopathy, climatic droplet keratopathy, degeneratio corneae sphaerularis elaioides, corneal elastosis, fisherman's keratitis, keratinoid corneal degeneration, and chronic actinic keratopathy.

- **Type 1** occurs bilaterally in the cornea without evidence of other ocular pathology
- **Type 2,** or secondary spheroidal degeneration, occurs in the cornea in association with other ocular pathology.
- **Type 3** is the conjunctival form of the degeneration and may occur with types 1 or 2
- Clear to yellow-gold spherules are seen in the subepithelium, within Bowman's, or in the superficial corneal stroma. They measure from 0.1 to 0.4 m
- Etiology: ultraviolet radiation and microtrauma including sand, dust, wind, and drying.
- Histopathology: hyaline-like material are found in the corneal stroma, Bowman's layer, and subepithelium. Bowman's layer is disrupted, and in advanced cases the epithelium is elevated and thinned. They have a histochemical staining characteristic similar to degenerative connective tissue, such as in pingueculae, but ***fail to stain for other components found in elastotic material from pingueculae***.

Pterygium

- An Elastotic Degenerative condition of conjunctiva with a wing like encroachment of conjunctiva on to the Cornea.
- **Pathogenesis**
  - Environmental causesUV exposure, dust heat , wind exposure
  - Peri-equatorial '**pterygium belt' latitudes 37°** north and south of the equator.
  - Heredity:
    - Loss of heterozygosity (17q,9p) and microsatellite instability- *Spandidoras (1997), Detorakis et al(1998)*
    - p53 mutation--*Tan et al (1997)*-pterygium is not a degeneration but a growth abnormality.
  - **Coroneo Effect** -Nasal segment of cornea gets highest UV exposure effect
  - Limbal Stem cell defect with Fibroblast Activation: conjuctivalisation, inflammation and vascularisation
  - HSV & HPV --*Spandidoras et al (1994)*--HSV in 45% of pterygia, *Dushku et al(1999)* ruled out HPV. *Gallagher et al(2001)* –HPV may play a role in recurrence
- **Classification**
  - Primary Pterygium
  - Recurrent Pterygium
  - Atrophic Pterygium: Older pts, thin translucent body with thin vessels
  - Pogressive Pterygium: Thick fleshy growth seen in Younger pts
- **Grading**
  - Size

        - 1: just touching cornea
        - 2: midway between 1 & 3
        - 3: upto pupil margin
    - Tan Grading:
        - T1 (atrophic) denotes a pterygium in which episcleral vessels underlying the body of the pterygium are unobscured and clearly distinguished
        - Pterygia in which the episcleral vessel details are indistinctly seen or partially obscured are categorized as grade T2 (intermediate)
        - Grade T3 (fleshy) denotes a thick pterygium in which episcleral vessels underlying the body of the pterygium are totally obscured by fibrovascular tissue

- **Clinical features**
    - Males:female-2:1,
    - Young -20-40yrs and elderly,
    - Incidence proportional to proximity to equator.
    - Diminution of vision-astigmatism, usually with the rule, can be against / oblique/ irregular, late stages dv due to encroachment into pupillary area
    - Intermittent episodes of inflammation
    - Cosmesis
    - Diplopia-symblepheron formation (more common in recurrent cases)
    - Corneal topography is very helpful in determining how visually significant a pterygium is. When the topography rings are irregular within the central 6 mm or there is significant irregular astigmatism on the color-coded maps, then the pterygium should be treated prior to cataract surgery.
- **Medical Management**
    - Symptomatic Grade 1 and 2 pterygium
    - Protection from sunlight
    - Eye drops – Tear substitutes, Decongestants
    - Local injections – anti VEGFs, Steroid
- **Surgical Management Indications-**
    - Symptomatic patients: recurrent irritation, redness and watering
    - Visual need: covering visual axis or threatening visual axis, causing irregular astigmatism, Grade 2 and 3 Pterygium
    - Cosmetic
    - Therapeutic: suspected associated neoplastic degeneration, motility restriction
- **Four main groups**
    - Bare sclera excision
        - 1948, D'Ombrain

        - High recurrence rates ranging from 24% to 89%
    - Excision with conjunctival closure/transposition
        - High recurrence rates of 37% /29%
    - Excision with antimitotic adjunctive therapies
        - Beta irradiation: Strontium-90, recurrence rate – 10%
        - Mitomycin C: the postoperative use of topical mitomycin C as eyedrops, and the intraoperative application of surgical sponges soaked in MMC, recurrence rate – 0 to 38%
    - Ocular surface transplantation techniques.
        - Conjunctival autograft transplantation
        - Variations of conventional conjunctival autografting
        - Conjunctival rotational autograft
        - Annular conjunctival autograft
        - Cultivated conjunctival transplantation
        - Conjunctival limbal autograft transplantation
        - Amniotic membrane transplantation.
    - **PERFECT** for Pterygium (pterygium extended removal followed by extended conjunctival transplantation) was assessed in 2011. It has very low recurrence and low complication rate.

- **Adjuvants – to reduce recurrence**
    - Mitomycin CFor recurrent pterygia
        - Intra op or post op
        - Uncommonly used
        - Late Scleral necrosis & melt
    - Thiotepa – used post op
    - Beta radiation with Strontium 90
    - Excimer Laser in PTK mode – for corneal smoothening
- **Complications**
    - Graft contraction
    - Graft edema
    - Graft necrosis
    - Granuloma formation
    - Excessive cauteryscleral necrosis
    - Infection
    - Recurrence

- Corneal scaring
- Ocular motility restriction
- Surgical induced Necrotising Scleritis (SINS)

- **Pterygium Recurrence Rate**---*Alp et al 2002*
  - MMC: Intra OP: 3.33-42.7 /Post OP:0-54.5
  - Beta radiation: 0.5-33
  - Excimer PTK: 4.5-91
  - AMG: 3.8-37.5
  - CAG: 2.6-39
  - LCAT: 0-14.6
  - Simple Excision: 29.2 -89
- **Recurrent pterygium**
  - Surgical trauma-excess cautery, excess tenonectomy, post op inflammation and infection, incomplete removal .
  - Mean recurrence time – Hirst et al (1994): **1st recurrence – 123 days, 2nd – 97 days, 3rd – 67 days**.
  - *Avisar et al (2001)* – 91% recurrence in 1 year
- A true pterygium must be differentiated from a pseudopterygium, which may occur after trauma. Pseudopterygium has been reported secondary to inflammatory corneal disease. ***A probe may be passed at the limbus under a pseudopterygium.*** Further distinction can be made, since pseudopterygia may be found anywhere on the cornea and are usually found obliquely, whereas true pterygia are horizontal in the 3 or 9 o'clock positions.

Pinguecula

- **Etology**
  - Damage from ultraviolet radiation,
  - Other possible causes of pingueculae include trauma, wind, sand, or drying
- **Clinical features**
  - Yellow white conjunctival lesion
  - Most commonly located nasally, may be temporal, in the interpalpebral space
  - Adjacent to limbus
  - Does not involve the cornea
  - May be associated with an adjacent dellen
  - Gaucher's disease can be associated with a pinguecula that is brownish in color.
- **Histopathology**:
  - Normal, atrophic, or hyperkeratotic conjunctival epithelium.

- The substantia propria shows basophilic degeneration on hematoxylin and eosin staining.
- This material stains for elastin but is not broken down by elastase. Thus it is termed elastotic degeneration.

- **Differential Diagnosis**
  - Dermoid
  - Pterygium
  - Nonpigmented nevus
  - Conjunctival intraepithelial neoplasm
- **Management**
  - Observation or symptomatic management
  - Excision of pinguecula in rare cases when chronically inflamed, interferes with contact lens wear, or for cosmetic reasons.

Salzmann Nodular Degeneration (SND)

- **Etiology**
  - Postinflammatory fibrosis of subepithelial cornea
  - Idiopathic, reason for nodule formation is often unclear
  - Salzmann nodules may develop due to enzymatic disruption of the Bowman layer, anterior migration and proliferation of keratocytes, and secondary deposition of extracellular matrix
- **Clinical features**
  - Gray-white/blue-white subepithelial nodules
  - Adjacent to corneal scarring or corneal pannus, pterygia, or vascularization
  - Often localized to the midperiphery
  - Often overlying incisions, subepithelial scarring (e.g., following recurrent corneal erosions)
  - Surrounded by iron line or ring in some cases
  - Can be unilateral or bilateral
- **Risk factors**
  - More commonly seen in women
  - Fibrotic response following keratitis: Phlyctenulosis, Trachoma, Interstitial keratitis
  - Fibrotic response following epithelial disruption: Recurrent corneal erosions, Persistent epithelial defect, Keratoconjunctivitis sicca
  - Fibrotic response at incision site following corneal surgery: Penetrating and lamellar keratoplasty, Cataract extraction, Radial and astigmatic keratotomy, Laser in situ keratomileusis (LASIK)
- **Differential Diagnosis**

- Calcific band keratopathy
- Spheroidal degeneration
- Gelatinous, droplike corneal dystrophy
- Corneal keloid

- **Medical Management**
  - Artificial tear replacement
  - Punctal occlusion
  - Bandage soft contact lens
- **Surgical Management**
  - Lamellar keratectomy with a blade ± diamond burr polishing procedure
  - PTK ± MMC (mainly to decrease the chance of recurrence of the SND)
    - The nodules are removed manually with a sharp or semisharp blade, ideally down to a reasonably smooth Bowman membrane. If Bowman is fairly smooth, then large PTK ablation spots can be used to smooth it a little bit further. If Bowman is not smooth after the manual SND removal, then multiple small, medium, and large excimer laser spots need to be used to remove the irregularities and achieve as smooth a base as possible. After that, MMC on an 8-mm sponge is placed on the cornea for ~60 seconds and irrigated with 30 mL cold saline.
    - Success rate of PTK with MMC is ~90% successful in obtaining a smoother corneal surface.
    - Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent SND

Band keratopathy

- Two forms
- **Calcific band keratopathy**
- Deposition across the cornea at the level of Bowman's layer
- Causes
  1. Hypercalcemic states
  2. Chronic ocular disease
  3. Chemicals (eye drops and irritants)
  4. Inherited diseases
  5. Systemic diseases
  6. Idiopathic
- Sharply demarcated peripheral edge separated from the limbus by a lucent zone. This zone is due either to the lack of Bowman's layer at the periphery or from the buffering capacity of the limbal vessels, which prevent precipitation of calcium.

- Histopathology: Fine basophilic granules are first seen at the level of Bowman's layer. Calcium is deposited in the form of hydroxyapatite, a phosphate salt.
- Management:
    - When the patient becomes symptomatic, the mainstay of treatment is the application of ethylenediaminetetraacetic acid (**EDTA**). Epithelial debridement & 0.05 molar concentration on saturated cellulose sponges.
        - Remove all epithelium over the calcium deposition. Apply disodium EDTA 3% to affected area until all calcium is removed (usually takes 10-60 minutes, depending on the thickness of the calcium).
        - Success rate: EDTA chelation is ~98% successful in removing all the calcium.
        - Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent band keratopathy.
    - Excimer laser phototherapeutic keratectomy.

- **Calcareous degeneration**
    - Second type of calcific degeneration. Like band keratopathy, this degeneration occurs in diseased eyes. Unlike band keratopathy, calcareous degeneration involves the posterior stroma.

Benign Pigmentation of Cornea & Conjunctiva

Conjunctival nevus

- Usually small
- Intralesional cysts
- Very frequently stable in color and size
- Congenital melanocytic nevus: Pigmentation may increase with puberty or pregnancy
- Acquired melanocytic nevus
- Key clinical feature: presence of **pseudocysts**
- Associated syndromes: Carney complex and dysplastic nevus syndrome
- Management: Observation or surgical resection
- Prognosis: Rare (1/300) risk for transformation to melanoma

Conjunctival Melanosis

- Localized or diffuse pigmentation of the conjunctiva.
- New nomenclature (WHO)
    - Primary acquired melanosis (PAM)

- Conjunctival melanocytic intraepithelial neoplasia (C-MIN)
- Intraepithelial melanocytic proliferation (IMP)

Complexion-Associated Melanosis (CAM)

- Also termed “racial melanosis” Clinical features
- Clinical Features
  - Flat with microfolds and cobblestones
  - Bilateral, limbus
  - Dark complexion
  - Symmetric, somewhat
- Management
  - Observation
  - Resection
  - Cryotherapy
  - Laser photocoagulation
- Prognosis: No transformation into melanoma, but note that primary acquired melanosis (PAM) can occur in dark complexion patients and can simulate CAM. If asymmetric CAM, suspect PAM

Primary acquired melanosis(PAM)

- Also termed “conjunctival melanoma in situ” and “intraepithelial melanocytic proliferation with / without atypia”
- **Clinical features**
  - Flat, patchy pigmentation without cysts
  - Usually white / European descent
  - Looks like a flat freckle
  - Multiple or diffuse
  - Flat brown patches
  - unilateral/asymmetric, more common with light complexion, risk for melanoma
  - If severe atypia, 21% progress to melanoma
- **Management**
  - Surgical excision using no-touch technique
  - Cryotherapy
  - Reconstruction
  - Topical chemotherapy

- Mitomycin C 0.04% q.i.d. for 1 week on, 1 week off, 1 week on, 1 week off
- Interferon 1 million units/cc q.i.d. for 3-6 months

- **Prognosis**
  - Transformation to melanoma at 10 years is 12%, particularly if severe atypia.
  - Each additional clock hour of PAM contributes 1.7 times risk for transformation to melanoma compared to 1 clock hour of PAM.

Secondary acquired melanosis

- Postinflammatory melanosis, following chronic conjunctivitis
- Systemic conditions with flat pigmentary patches of conjunctiva:
  - Addison disease
  - Peutz-Jeghers syndrome
  - Von Recklinghausen disease
- **Management**: Observation
- **Prognosis**: No risk for melanoma

Brown, black, or gray deposits

- Carbon or metal deposits
- Adrenochrome (oxidized epinephrine) deposits
- Argyrosis (silver deposition)
- Oral medications: tetracyclines or phenothiazines

Episcleral or scleral pigmentation

- Nerve loops of Axenfeld
- Ocular melanocytosis (melanosis oculi) and oculodermal melanocytosis (nevus of Ota)
- Extraocular extension of uveal melanoma
- Alkaptonuric ochronosis
- Senile scleral plaques
- Foreign body

Corneal epithelial pigmentation

- Striate melanokeratosis: melanin pigmentation extending from limbus
- Iron line associated with uneven corneal topography or with aging
- Pigmented band keratopathy
- Spheroidal degeneration
- Cornea verticillata

- Fabry disease (X-linked lysosomal storage disease)
- Amiodarone

Corneal stromal pigmentation

- Intrastromal melanin following perforating corneal trauma or surgery
- Deposits associated with systemic medications, such as phenothiazines or gold
- Foreign bodies, including ocular siderosis
- Corneal blood staining associated with hyphema
- Kayser-Fleischer ring associated with copper deposition in Wilson disease

Misc Degenerations

- **Climatic proteoglycan stromal keratopathy**
- **Amyloid degeneration**
  - Primary localized
  - Primary systemic
  - Secondary localized
  - Secondary systemic

- **Corneal keloids**
  - After trauma or in association with chronic ocular surface inflammation
  - In association with Lowe's syndrome & Rubinstein-Taybi syndrome.
  - Clinically similar to SND but usually seen in a younger age group than Salzmann's degeneration and occur more frequently in men.
  - Superficial keratectomy or penetrating or lamellar keratoplasty may be performed for visually significant lesions.

- **Terrien's marginal corneal degeneration**
  - Peripheral inflammatory condition
  - 20 and 40 years of age.
  - **M:F = 3:1**
  - Bilateral and symmetric
  - Usually begins superonasally with fine punctate opacities in the anterior stroma with a lucent area to the limbus.
  - Vascularization from the limbal arcades leading to the lesion differentiates it from arcus.
  - Gutter similar to marginal furrow degeneration then forms between the opacity and limbus. The stroma progressively thins, usually over many years

- Two types of Terrien's degeneration have been classified.
  - The more common quiescent type is seen in older patients. These patients may be asymptomatic for a long time because the lesion produces no pain.
  - Inflammatory Terrien's degeneration usually occurs in the younger age groups. These patients may have recurrent episodes of inflammation, episcleritis, or scleritis. This is treated with steroids.
- **Against-the-rule astigmatism**, which may be the presenting symptom
- Histopathology: fibrillar degeneration of collagen, Epithelium may be normal, thick, or thinned; Bowman's layer is fragmented or absent. Breaks in Descemet's membrane may be seen in thinned areas

Limbal girdle (of Vogt)

- Two types
- Crescentic yellow-to-white band found in the interpalpebral limbus
  - Type 1 appears as a white band that may contain holes. The central border is relatively sharp with no extensions. It is separated from the limbus by a ***narrow lucent area***. Type 1 is generally thought to represent ***early calcific band keratopathy***.
  - Type 2, however, is thought to be a **true** limbal girdle. This **chalky band** has no holes or clear interval to the limbus. Centrally, there are irregular linear extensions.
- Histopathologically, the lesion is subepithelial and may have overlying epithelial atrophy. Destruction and calcification of Bowman's layer have been observed in type 1.

Reticular degeneration of Koby: Fine white reticulum at the level of Bowman's layer. Overlying epithelium may have a brownish discoloration. This degeneration is most commonly reported in patients with chronic inflammation.

Iron lines

- Most common iron line is the **Hudson-Stähli line**, which is located in the lower third of the cornea
- Iron deposition in filtering bleb after glaucoma surgery was described by **Ferry** in 1968. It appears on the cornea just anterior to the filtering bleb. He related its incidence to the size of the filtering bleb. Iron may be seen at the advancing edge of a pterygium (**Stocker's line**) and at the base of the cone in keratoconus (**Fleischer ring**).
- Histologically, iron, predominantly ferritin, is found intracellularly and extracellularly in the basal epithelial layer of the cornea, regardless of the type of iron line.
- The most common theory attributes the deposition to localized trauma at the site of contour change or to a pooling of tears at this site

- **Coats' white ring**
  - 1 mm or less in diameter
  - Inferior portion of the cornea.

- **Hassall-Henle bodies:** Descemet's warts are excrescences of Descemet's membrane found in the peripheral cornea.

- **Crocodile shagreen**
  - Corneal mosaic pattern resembling cobblestone or crocodile skin is seen in the anterior or posterior cornea.
  - Histopathologically, the stroma is thrown into folds, either at Bowman's layer in the anterior form or around Descemet's membrane in the posterior form.

- **Senile furrow:** Peripheral thinning is seen in the avascular zone between arcus senilis and the limbal vascular arcades

- **Cornea farinata:**
  - Tiny opacities, found bilaterally in the posterior stroma near Descemet's membrane.
  - 'Flour dust' appearance on retro-illumination

- **Dellen:**
  - Fuchs' dimples
  - Dellen may last only 24 to 48 hours and are found most commonly in the temporal peripheral cornea, usually adjacent to a paralimbal elevation.
  - Saucer-like depressions in the corneal surface
  - Histopathologically, thinning of the corneal epithelium, Bowman's layer, and anterior stroma is seen. Treatment with ocular lubricants or pressure patching will accelerate the healing process.

- **Concretions:**
  - White to yellow spots found on the palpebral conjunctiva occasionally encased in clear cysts.
  - Later stages of trachoma
  - Chronic inflammation causes hyperplasia and invagination of the conjunctival epithelium.
  - They may be easily removed for patient comfort.

Corneal Dystrophy

- dys = wrong, difficult; trophe = nourishment
- Dystrophy word was introduced in **1890** by **Arthur Groenouw** when he published his classic paper describing two patients with '***Noduli Corneae***.'
- Group of inherited corneal diseases that are usually bilateral, symmetric, slowly progressive and not related to environmental or systemic factors.
  - Exceptions:
    - Hereditary pattern is not present in most patients with→ EBMD
    - Unilateral corneal changes may be found→ PPCD
    - Systemic changes are found→ macular dystrophy, in which the level of antigenic serum keratan sulfate correlates with the immunophenotypes of the disease.
- The first classification by Bücklers of corneal dystrophies described the differences between granular, macular, and lattice dystrophy.
- The most commonly used classification system is anatomically based.
- International Committee for Classification of Corneal Dystrophies (**IC3D**) was created in **2005** in order to revise the corneal dystrophy nomenclature and create a current and accurate corneal dystrophy classification system.
- Four descriptive, evidential categories were created in the IC3D classification
  - Category 1. A well-defined corneal dystrophy in which the **gene has been mapped** and identified and specific mutations are known.
  - Category 2. A well-defined corneal dystrophy that has been mapped to one or more specific **chromosomal loci,** but the gene(s) remains to be identified.
  - Category 3: A clinically well-defined corneal dystrophy in which the disorder has **not yet been mapped to a chromosomal locus.**
  - Category 4. This category is reserved for a **suspected new**, or previously documented, corneal dystrophy, where the evidence for it being a distinct entity is not yet convincing.
- IC3D in **2015** updated its classification as **IC3D$_2$**: Changes made are as follow
  - Epithelial and subepithelial dystrophies
    - Meesman (C1) Stocker Holt variant
    - Epithelial basement membrane dystrophy (rarely C1)
    - Gelatinous drop-like corneal dystrophy (C1)
    - Subepithelial mucinous corneal dystrophy (C4)
  - Epithelial-stromal TGFBI (keratoepithelin) dystrophies:
    - Reis-Bucklers/ Thiel-Benke (C1)
    - Lattice I, III, IV (C1)
    - Lattice II familial amyloidosis removed
    - Granular type 1 & 2 (C1)

        - Grayson-Wilbrandt (C4) Removed
    - Stromal dystrophies
        - Macular (C1)
        - CHSD (C1)
        - Schnyder (C1)
        - Fleck (C1)
        - PASD (C1)
        - PreDescemet dystrophy (C1 or C4)
    - Endothelial dystrophies
        - Fuchs dystrophy (C1,2, or 3)
        - PPMD (C1 or 2)
        - CHED (C1)

Anterior Corneal Dystrophies

Meesmann's Juvenile Epithelial Dystrophy

- Least common
- Mutation in corneal **keratin (K3 or K12)**
- Seen in the first few years of life as intraepithelial microcysts or vesicles visible only at the slit lamp.
- Vision is usually good in the first few years of life but may diminish gradually if the cysts increase in number and cause slight irregularity of the corneal surface.
- *Recurrent erosion is not common*

Epithelial Basement Membrane Dystrophy

- Map-dot-fingerprint, Cogan's microcystic dystrophy
- **Most common** anterior corneal dystrophy and is classified as a corneal dystrophy because these changes occur more in some families
- **Pathogenesis**: Epithelial cells produce abnormal multilaminar basement membrane, both in normal location and intraepithelially. As the intraepithelial basement membrane thickens, it blocks normal migration of epithelial cells toward the surface. Trapped epithelial cells degenerate to form intraepithelial microcysts that slowly migrate to the surface. Abnormal basement membrane produces map and fingerprint changes, and microcysts produce the dot pattern seen clinically.
- **Clinical features**
    - Spontaneous recurrent corneal erosions and blurred vision. The erosions may be mild and transient, lasting minutes, or occasionally characterized by more severe pain.

- Often an incidental finding and does not cause significant central negative staining or disruption of the corneal topography rings.
- If the EBMD changes are causing central negative staining or irregularities in the corneal topography rings, then they may well be visually significant and it should probably be treated, especially prior to cataract surgery.

- **Treatment**: The treatment has been similar for recurrent corneal erosion, whether traumatic or dystrophic.
  - Anterior stromal reinforcement (puncture) seems to be the best way to treat recalcitrant recurrent erosions below the visual axis. It is effective in 80% of cases the first time it is done
  - Epithelial debridement with diamond burr polishing works best for anterior basement membrane dystrophy in the visual axis causing either blurred vision or recurrent erosion.
    - A sharp blade (eg, #15 blade) or semisharp blade (eg, Tooke knife) is used to remove a large area, ~6-8 mm diameter, of central epithelium. It is critical to remove all the irregular reduplicated basement membrane overlying the Bowman layer, which is usually very smooth. When a diamond burr polishing procedure is being performed, then a large 5-mm diameter diamond-dusted drill is used to smooth out the cornea in a uniform fashion for about 5 seconds. The idea behind using the diamond burr is that it removes all the irregular basement membrane and perhaps allows for better adhesion of the new epithelium.
    - Over 90% successful in obtaining a smoother corneal surface
    - Complications include delayed epithelial healing, infection, corneal scarring, decreased vision, and of course, recurrent EBMD.
  - Excimer laser phototherapeutic keratectomy (PTK) ± mitomycin C (MMC): Not usually necessary for EBMD alone

Corneal Dystrophies of Bowman's Layer

- **Küchle** et al divided the anterior membrane dystrophies into two classifications: corneal dystrophy of Bowman's layer types I (CDB-I) and II.
- Type I is synonymous with Reis–Bücklers' original dystrophy and equivalent to what has been called the superficial variant of granular dystrophy. It has an autosomal dominant inheritance, recurrent corneal erosions beginning in childhood, and is marked by early and fairly marked visual loss.
- Corneal dystrophy of Bowman's layer type II (CDB-II), which many people have confused with the Reis–Bücklers' dystrophy, is honeycomb-shaped and should be known as Thiel–Behnke corneal dystrophy. Similar to CDB-I, CDB-II's inheritance is dominant, with recurrent erosions starting early in childhood, but visual acuity is reduced later in life than with CDB-I. The clinical appearance of these dystrophies is similar, and differentiation can be made only with light and, particularly, electron microscopy. Interestingly, *CDB-I stains positively with Masson's stain, whereas CDB-II is only equivocally positive to Masson's stain (honeycomb-shaped, Thiel–Behnke dystrophy).*

- Transmission electron microscopy differentiates these two dystrophies. In CDB-I, ultrastructural deposits of **rodlike bodies** are present, similar to those seen in granular dystrophy. These changes are not seen in CDB-II. Instead, '**curly' fibers** appear in the region of Bowman's membrane.
- They can be managed similarly to the therapy of recurrent erosion due to epithelial basement membrane dystrophy.
- Phototherapeutic keratectomy (PTK) with the excimer laser is now the treatment of choice when vision is disturbed sufficiently or painful erosions occur, despite recurrences after PTK.

Stromal Dystrophies

Granular corneal dystrophy type 1 (classic)

- 1890 by Groenouw
- Small, discrete, sharply demarcated, grayish-white opacities in the anterior central stroma
- Drop-shaped, crumb-shaped, and ring-shaped.
- The stroma between the opacities remains clear.
- As the condition advances, individual lesions increase in size and number and may coalesce. They frequently extend into the deeper and more peripheral stroma. However, 2–3 mm of the peripheral cornea usually remain free of deposits.
- **Autosomal dominant** trait and appears in the first or second decade of life
- TGFBI gene-related dystrophy, 5q31 gene locus
- **Histopathology**
  - Light microscopy demonstrates eosinophilic, rod, or trapezoidal-shaped **hyaline** deposits in the stroma and beneath the epithelium.
  - Stain bright red with **Masson's trichrome** and stain weakly with **periodic acid-Schiff** (PAS)
- **Management**
  - Recurrent epithelial erosions should be managed routinely with therapeutic contact lenses and artificial tears.
  - The traditional surgical approach has been penetrating keratoplasty, which is uncommonly performed before the fifth decade. If the opacities are extremely superficial, epithelial scraping, superficial keratectomy, or lamellar keratoplasty can be performed.
- Granular dystrophy can recur in the grafts as early as 1 year after surgery,

Granular corneal dystrophy, type 2 (granular-lattice)

- **Avellino** corneal dystrophy

- (1) anterior, stromal, discrete gray-white granular deposits; (2) mid to posterior stromal lattice lesions; and (3) anterior stromal haze.
- foreign body sensation, pain, and photophobia, most likely secondary to recurring erosion.

Granular corneal dystrophy, type 3 (RBCD – Reis-Bücklers)

Macular Dystrophy (MCD)

- Fehr spotted dystrophy
- Corneal opacities resulting from intracellular and extracellular deposits within the corneal stroma
- Least common and the most severe
- Progressive loss of vision as well as attacks of irritation and photophobia. Vision is usually severely affected by the time the patient reaches the twenties or thirties.
- This opacification extends to the periphery and usually involves the entire thickness of the cornea by the second decade of life.
- Reduced central corneal thickness.
- Slit lamp examination demonstrates a ground-glasslike haze in the central and superficial stroma, which is best observed with oblique illumination. With progression of the dystrophy, small, multiple, gray-white, pleomorphic opacities with irregular borders are seen
- Autosomal recessive
- Chromosome 16, Type I has no detectable antigenic keratan sulfate; type II has normal amounts of antigenic keratan sulfate; in type IA the serum lacks detectable antigenic keratan sulfate, but the keratocytes react with antibodies to keratan sulfate.
- **Histopathology**
  - Accumulation of glycosaminoglycans between the stromal lamellae
  - Stain with Alcian blue, colloidal iron, metachromatic dyes, and PAS
  - Light microscopy demonstrates degeneration of the basal epithelial cells, and focal epithelial thinning is seen over the accumulated material. Bowman's membrane may be irregular, thinned, or absent in some areas. Electron microscopy shows accumulation of mucopolysaccharide within stromal keratocytes, which are distended by numerous intracytoplasmic vacuoles with pyknotic nuclei.
- **Management**
  - Tinted cosmetic lenses can be used to reduce photophobia
  - Recurrent erosions are treated with therapeutic contact lenses or lubricant drops.
  - Phototherapeutic keratectomy
  - Lamellar Keratoplasty
  - Penetrating keratoplasty is the surgical modality of choice

Lattice Dystrophy

- ***Biber-Haab-Dimmer dystrophy***
- Bilateral, inherited, primary, localized corneal amyloidosis.
- Ovoid or round subepithelial opacities, anterior stromal white dots, and small refractile filamentary lines that may appear in the first decade of life
- **Histopathology**
  - Sources of the amyloid include leakage from serum, extracellular breakdown of corneal collagen, and, most probably, localized intracellular production
  - Eosinophilic layer separating the epithelial basement membrane from Bowman's layer is present and is composed of **amyloid and collagen**
  - Stain orange-red with **Congo red**, and also stain with **PAS, Masson's trichrome, and fluorochrome thioflavin T**.
  - When viewed with a polarizing filter, amyloid deposits demonstrate green birefringence
- **Autosomal dominant** mode of inheritance, and the disease results from mutations at 5q31 gene locus
- **Management**
  - Lamellar or penetrating Keratoplasty
  - Recurs more frequently than does granular or macular dystrophy, and the recurrence can appear in the graft in as few as 3 years after Keratoplasty

Schnyder's Crystalline Dystrophy (SCD)

- Bilateral gray, disclike opacities are seen, primarily in the anterior stroma. These opacities are often central and also may include fine polychromatic cholesterol crystals in the anterior stroma

Other Stromal Dystrophies

- Fleck Corneal Dystrophy (FCD)
- Central Cloudy Dystrophy of François (CCDF)
- Posterior Amorphous Corneal Dystrophy (PACD)
- Congenital Hereditary Stromal Dystrophy (CSCD)
- Pre-Descemet Corneal Dystrophy (PDCD)

Descemet's Membrane and Endothelial Dystrophies

PPCD: Posterior Polymorphous Corneal Dystrophy

- Bilateral asymmetrical

- Asymptomatic to progressive
- Second or third decade of life
- Abnormalities in PPCD occur at the level of Descemet's membrane and endothelium and can be divided into three patterns:
  - **Vesicle-like lesions**: 0.10 to 1.00 mm, sharply demarcated large round areas that contain lighter thick ridges or cell aggregates
  - **Band lesions**: typically horizontal, have parallel scalloped edges, and do not taper toward the ends
  - **Diffuse opacities**: either small, macular, gray-white lesions or larger sinuous geographic lesions at the level of Descemet's membrane
- **Hallmark of PPCD is the vesicular lesion**
- Corneal edema occurs infrequently and ranges from minimal stromal thickening to bullous keratopathy
- PAS are also a characteristic feature of PPCD and an important prognostic indicator
- Angle closure is thought to result from endothelial cell migration across the trabecular meshwork onto the iris, forming synechiae. The mechanism of open angle glaucoma has been suggested to be compression of the trabecular meshwork secondary to a high iris insertion.
- **Differential Diagnosis**: ICE syndrome
  - Share many clinical features, including iridocorneal adhesions, glassy membranes over the angle and anterior surface of the iris, iris atrophy, corectopia, increased intraocular pressure, and corneal edema.
- **Management**:
  - Risk factors for severe disease included the presence of iridocorneal adhesions and increased intraocular pressure. Only 27% of patients had iridocorneal adhesions, yet 57% of patients with iridocorneal adhesions required corneal transplantation. Similarly, only 14% of patients in this series had increased intraocular pressure, yet 62% of patients with increased intraocular pressure required corneal transplantation.
- **Histopathology**:
  - Epithelium and stroma: chronic edema, subepithelial fibrosis, and band keratopathy
  - Descemet's membrane and the endothelium: thickening of Descemet membrane with rare foci of bilayered large endothelial cells, to 3–4 layered broad patches of flattened endothelial cells and irregular thickness of Descemet's membrane with focal absences
  - ABZ: Normal, thinner in early onset
  - PNBZ: Absent or minimal, Changes to a thick PCL-like layer with scant BM*

FECD: Fuchs' Endothelial Corneal Dystrophy

- Slowly progressive disease with initial onset in the **fifth** through seventh decades in life.
- **50% autosomal dominant, variable penetrance**
- **Females** are predisposed to Fuchs' dystrophy and develop corneal guttae **2.5 times** more frequently than males, progressing to corneal edema 5.7 times more often than males.
- **Pathogenesis**
  - Oxidative Stress suggested
    - Regional variability of cell death
    - Lifelong endothelial DNA damage
    - Decrease in antioxidant defense
- **Histopathology**:
  - LM: increase in cellular size and irregularity of shape, **DM thickens 2-3 times**
  - EM: normal ABZ of type 7 collagen, PNBZ is of type 4 collagen. Besides a thin or **absent PNBZ, the most typical finding in FECD is an abnormal posterior collagenous layer (PCL) which is responsible for most of the thickness.**
  - Thinning of the endothelium over the enlarging guttate bodies may result in complete baring of these bodies as the disease progresses: like those in peripheral Hassal-Henle warts
- **Genetics**:
  - Many patients have no known inheritance pattern
  - One family traced for → single locus at 13p
  - Mutations in COL8A2 in 2 additional families with early-onset FECD.
  - TCF4 has emerged as a major locus for FECD
  - Besides TCF4, 5 novel loci on chromosomes 1q and 11p also reached genomewide significance.

✦ **Clinical Features:**

- The **first stage** is **asymptomatic**. Slit-lamp examination discloses central corneal guttae, but vision and corneal thickness are normal. **Guttae**, irregularly scattered excrescences in the posterior cornea, are often associated with fine pigment dusting
- In this **second stage**, patients have **painless decreased vision**, especially upon awakening. Vision may improve as the day progresses as evaporation promotes corneal deturgescence. Glare and haloes may be noted. **Stromal edema** occurs in the setting of corneal guttae, most typically in the fifth decade of life
- **Epithelial edema** characterizes the **third stage**. Initially, fine epithelial **microcysts** are noted. The epithelial surface is roughened, with an irregular surface texture. **Vision invariably deteriorates** during this stage and marked fluctuations in vision are common. Occasionally, erosive symptoms are the presenting complaint. Large intraepithelial and subepithelial bullae may rupture, resulting in **severe eye pain** and rendering the patient susceptible to infection.

- In the **fourth stage**, growth of **avascular subepithelial connective tissue** occurs, causing reduced vision from scarring. The cornea is opaque and compact. Pain is decreased, but vision is severely reduced to the hand motions level. Corneal sensation is decreased or absent. With time, peripheral corneal vascularization may occur.

- **Differential diagnosis**
  - Gutta formation without corneal edema has been observed in **interstitial keratitis**
  - Gutta: **macular dystrophy and posterior polymorphous dystrophy**.
  - **Corneal pseudoguttae**: transient, representing edema of the endothelial cells, and disappear with resolution of the underlying condition → can be seen after trauma, intraocular inflammation, infection, toxins, and thermokeratoplasty
  - **Central herpetic disciform keratitis**: keratic precipitates (KP)
  - **Chandler's syndrome**: unilateral
- **Medical management:**
  - Topical hypertonic saline solutions
  - Dehydration of the cornea by a blow dryer in the morning or throughout the day
  - Lowering the intraocular pressure may reduce the hydrostatic pressure, which acts to push fluid into the cornea and thereby decrease corneal edema.
  - Bandage lenses may be helpful in the treatment of recurrent erosion caused by epithelial bullae. a loosely fit, high-water-content soft contact lens, e.g., Kontur lens, may be used to reduce the irritation and pain
  - Mitochondrial protection: **elamipretide** (ClinicalTrials.gov Identifier: NCT02653391)
    - Mechanism of action: Mitochondria-targeting peptide that protects against toxic reactive oxygen species and enhances ATP synthesis
    - Patient selection: Mild to moderate corneal edema
  - Genetic Modulation
    - Silencing of **TCF4** expression
      - Targeted gene editing (CRISPR-Cas9)
      - Enhanced degradation (RNase-H-activating antisense oligonucleotide)
    - Modification of TCF4 pre-mRNA splicing: Oligonucleotide steric blockage (antisense oligonucleotide)
  - Rho / Rho-kinase pathway inhibition
    - Promotes corneal endothelial cell migration and adhesion
    - Maintains endothelial cell phenotype (prevents cell state transition)
    - Patient selection
      - Combined with injection of ex vivo expanded allogenic human corneal endothelial cells (HCEnC)

- Combined with primary descemetorrhexis with or without Descemet membrane transplantation

- **Surgical Management:**
  - **Cell count of less than 1000** should raise concern about the possibility of corneal decompensation with intraocular surgery.
  - Corneal **thickness of over 640 microns** (μm) increases the risk of corneal decompensation with cataract surgery
  - **Central corneal thickness exceeds the mid-peripheral thickness**, this may be a indication of clinically significant corneal thickening.
  - **CCT < 600 microns, ECD > 1000 → cataract surgery f/by DSAEK-OPK**
  - Optical PK/ Triple Sx
  - **Descemet membrane endothelial keratoplasty (DMEK): Patient selection**
    - Hemiand quarter-DMEK: mild to moderate central corneal edema
    - Pull-through insertion techniques: Individuals who are not ideal candidates for DMEK using traditional insertion and unfolding techniques
      - Aphakia
      - Aniridia
      - Presence of an anterior chamber IOL
      - Prior tube shunt implantation
    - DSO: Descemet Stripping Only (avoiding keratoplasty): Primary descemetorrhexis with or without Descemet membrane transplantation: Patient selection
      - Younger age
      - Mild central stromal edema (< 625 microns)
      - Clear peripheral cornea with good endothelial cell density
  - **Cell based therapies**
    - Ex vivo expanded allogenic human corneal endothelial cells
      - Cell injection
      - Cell sheets
      - Allogenic human mesenchymal stem cells

CHED: Congenital Hereditary Endothelial Dystrophy

- Rare corneal dystrophy except in Saudi Arabia and south India
- Bilateral, symmetric, noninflammatory corneal clouding without other anterior segment abnormalities that is usually evident at birth or within the early postnatal period
- Differential diagnosis
  - **Mucopolysaccharidoses**: clouding is not present at birth, typically developing within the first few years, urinalysis or corneal biopsy will usually identify the abnormal metabolic

- **congenital glaucoma**: ncreased IOP, often an increase in corneal diameter, Haab's striae, and, in severe disease, buphthalmos.
- **Transient corneal edema** can occur in congenital rubella, but, in contrast to CHED, there is episcleral injection, typically a nuclear cataract, increased intraocular pressure, posterior synechiae, miosis, and chorioretinopathy.
- **Syphilitic interstitial keratitis** also produces an inflamed eye with corneal clouding, deep stromal vascularization, and iris atrophy, but it rarely occurs within the first year of life
- **Dystrophies at birth-natal age groups**: CHED, PPCD and CHSD.

- CHED 1 (AD)
  - Photophobia and tearing
  - Corneal clouding is not present at birth, developing late in the first year
  - Chromosome 20p11
  - ***As per IC3D updated classification of 2015,***
    - ***Autosomal dominant variant may not exist***
    - ***CHED1 eliminated***
    - ***CHED2 changed to CHED***
- CHED 2 (AR)
  - Gray-blue, ground-glass haziness of the corneal stroma noted within the first week to 6 months
  - Fine nystagmus
  - Chromosome 20p13-12
  - **Harboyan syndrome** (CHED 2 and perceptive deafness (CDPD)) is an autosomal recessive disease mapped at overlapping loci 20p13. Novel **SLC4A11 mutations** have been found in seven families.
  - Prognosis for graft clarity and visual rehabilitation is dependent upon the age of onset
  - Histopathology:
    - Corneal showed alterations secondary to chronic corneal edema, appearing thin or atrophic with hydropic changes of the basal epithelium
    - Stroma was generally thickened to two to three times
    - Descemet's membrane was usually observed to be thickened.
    - The endothelial cells were absent, markedly reduced in number, or showed evidence of significant degeneration
  - EM: Normal 110 nm ABZ of approximately 3 µm thickness, but an abnormal, poorly demarcated PNBZ merging into, or mixed with, a PCL.

XECD: X-Linked Endothelial Corneal Dystrophy

Immune Mediated Disorders

Thygeson's Superficial Punctate Keratits

- **Etiology**: Although a viral immune response is suspected, an etiological agent has not been confirmed.
- **Features**:
  - Common in second-third decade with no gender predilection
  - Intermittent photophobia with Tearing, Mild blurring of vision, Burning, foreign body sensation Usually without ocular redness
  - Spontaneously resolves to be followed by later exacerbations
  - Usually bilateral
  - Untreated episodes may last for weeks to 1-2 months
  - Scattered clumps of fine epithelial lesions which are round, oval, or stellate
  - Lesions are slightly elevated and may have mild punctate staining over them and subepithelial infiltrates beneath them
  - Lesions have positive staining centrally and surrounding negative stain
  - The lesions may be few or number up to 50 or more in each cornea with Minimal or no conjunctival reaction and may change in location over time
- **Differential Diagnosis**
  - Staphylococcal toxic keratitis
  - Rosacea
  - Herpes simplex virus (HSV) keratitis
  - Dry eye
  - Molluscum contagiosum
  - Epidemic keratoconjunctivitis
- **Management**
  - Usually exquisitely sensitive to low dose steroids tapered over several days
  - Topical cyclosporine tapered over many months may be of benefit
  - Topical trifluridine has been suggested by some authors but others have been disappointed with this treatment
  - Bandage soft contact lenses provide temporary relief of symptoms and may lead to temporary resolution of the lesions
  - Role of PTK is controversial

Staphylococcal Marginal Keratitis

- **Etiology**
  - Delayed-type hypersensitivity to staphylococcal antigens from lid margin organisms
  - Enhanced cell-mediated immunity to pathogenic immune-modifying antigens

- **Features**
  - Acute onset with photophobia, May have history of preexisting blepharitis, lid crusting, chalazia, but not essential
  - Usually round infiltrate in peripheral anterior stroma
    - May at times be elongated concentric with the limbus
    - Occur typically where lid margins cross the limbus at 2, 4, 8, and 10 o'clock
  - Relative clear zone between lesion and the limbus
  - Punctate overlying staining may develop and may become a frank epithelial defect that is usually smaller than the infiltrate
  - Conjunctival injection, diffuse or localized
  - Often lid margins shows changes of staphylococcal blepharitis
- **Differential Diagnosis**
  - Microbial keratitis: Bacterial or Herpes simplex virus (HSV)
  - Contact lens associated peripheral corneal infiltrates
  - Peripheral ulcerative keratitis
  - Phlyctenulosis
  - Rosacea keratitis
  - Atopic keratoconjunctivitis
  - Toxic/ allergic reaction (e.g., marginal infiltrates due to Neosporin)
  - Sterile limbal infiltrates during bacterial conjunctivitis
- **Management**
  - Therapy of blepharitis with warm compresses, lid scrubs, antibiotic ointment to lid margins or topical antibiotic
  - Topical corticosteroids or corticosteroid/antibiotic combination
  - Oral tetracyclines or macrolide may be considered

Mooren Ulcer

- **Etiology**
  - Diagnosis of exclusion
  - Immunologic disorder with autoimmunity to corneal antigens
    - Idiopathic
    - Secondary to previous corneal insults such as trauma, chemical injury, surgery, or infection
    - Hepatitis C, intestinal parasites, and other infections have been found in some patients, but causal association remains uncertain
- **Features**
  - Typically affects otherwise healthy, adult men with no evidence of systemic disease

- Older people with a more benign, often unilateral disease
- More aggressive bilateral painful disease, often in younger patients

- Pain, often severe, chronic, progressive and out of proportion to inflammation
- Conjunctival injection, Photophobia, Decreased visual acuity
- Ulcerative keratitis with peripheral stromal thinning that first spreads circumferentially and then centrally to involve the entire cornea.
  - A steep, overhanging anterior edge due to undermined stromal loss at leading edge.
  - Overlying epithelial defect
- Lack of scleritis
- Injection and chemosis of adjacent conjunctiva
- Peripheral corneal reepithelialization as the ulcer moves centrally, Healed ulcer results in corneal scarring and neovascularization

Tests

- Serologic testing to rule out collagen-vascular diseases (antinuclear antibody (ANA) panel, perinuclearstaining anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic-staining anti-neutrophil cytoplasmic antibody (c-ANCA), rheumatoid factor)
- Hepatitis C antibodies and LFTs
- RPR and VDRL or FTA-ABS

Differential Diagnosis

- Peripheral ulcerative keratitis secondary to autoimmune disease (rheumatoid arthritis, granulomatosis with polyangiitis, systemic lupus erythematosus, polyarteritis nodosa)
- Marginal keratitis (staphylococcal)
- Peripheral keratitis (bacterial, herpes simplex virus)
- Terrien marginal corneal degeneration peripheral, more slowly progressive, usually intact epithelium
- Senile furrow degeneration

Management

- Topical corticosteroids, especially in milder cases
- Systemic immunosuppression
  - Oral corticosteroids i. Prednisone
  - Antimetabolites: Methotrexate, Azathioprine
  - Immunomodulatory agents: Cyclosporine, Mycophenolate mofetil
  - Alkylating agents: Cyclophosphamide
- Systemic interferon (if associated with hepatitis c)
- Conjunctival resection adjacent to ulcer

- Superficial keratectomy for isolated de-epithelialized central corneal islands
- Corneal/scleral patch grafting for perforations
- Corneal gluing may be helpful occasionally for very small perforations

- **Complications**: Corneal opacification, Cataract, Glaucoma, Exacerbation of disease with surgical interventions, Corneal Perforation, Vision loss

Peripheral Ulcerative Keratitis

- Peripheral corneal ulcerative pathology opens up a Pandora's box
- PUK is classically described as peripheral crescent-shaped inflammation of corneal stroma adjacent to the limbus, with or without associated scleral inflammation, with or without underlying systemic or ocular diseases, characterized by thinning of the affected area. What makes PUK an important issue is that it is often the first sign or the presenting sign of a number of systemic collagen vascular disorders. The progressive nature of the disease demands aggressive therapy to curtail the devastating corneal destruction. Additionally, it is often important to identify the underlying ocular or systemic disease and also sometimes to differentiate this condition from a number of masquerades that may mimic as PUK.
- **Etiology**
  - Vasculitis and immune complex deposition: The exact pathogenesis of PUK is unknown, but studies indicate that both humoral and cell-mediated immunity are involved in the disease and matrix metalloproteinases lead to corneal melt.
  - High levels of proteolytic enzymes in the affected conjunctiva: inflammatory mediators gain access to peripheral cornea via vascular arcades
  - Collagenases and proteases secreted by neutrophils and macrophages lead to keratolysis
  - PUK often occurs in patients who have longstanding rheumatoid arthritis and ***positive serology*** for both rheumatoid factor and anti-cyclic citrullinated peptide antibody.
  - 50% have systemic diseases like RA, SLE, PAN, RP, UC, Polyangitis
- **Clinical features**
  - Peripheral epithelial defect, infiltration of the corneal stroma, and thinning
  - foreign body sensation, photophobia, decreased vision
  - Episcleritis or scleritis present in approximately half of PUK cases
- **Approach to PUK Patients:**
  - **Step 1: Assessment of corneal lesion**
    - Look for signs of disease activity: Ulcer location, size (in terms of clock hours of involvement), depth of stromal loss, infiltration, ulcer edges.
    - Presence of infiltration mark disease to be active. It is important to rule out an infectious process in these cases. Appropriate microbiological investigations including smears, cultures, and immunological tests (PCR) help to identify causative infectious organisms in case of infectious etiology.

- Look for vascularization of bed (suggests chronic disease), presence of lipid deposits with vascularization (Terrien's diseasepainless, non ulcerative process)
- Epithelial status: Absence of epithelial defect rules out an active PUK. Pellucid marginal corneal degeneration and Senile furrow degeneration are common etiologies that may seldom be confused with PUK and are differentiated by presence of an intact epithelium.
- Lucid interval between the epithelial defect and the limbus points toward etiologies such as phlycten and catarrhal ulcers.

Step 2: Examination of conjunctiva, sclera, and lids

- Associated scleritis rules out etiology such as Mooren ulcer. Presence of scleritis points toward underlying systemic collagen vascular disorders. Presence of meibomian gland dysfunction and blepharitis may be associated with marginal keratitis that may sometimes be confused with PUK.

Step 3: Systemic evaluation

- Thorough history of systemic manifestations may point toward possible underlying diagnosis:
  - Skin rash, easy sunburns, depigmentation: SLE
  - Respiratory symptoms: Wegener granulomatosis, Churg-Strauss syndrome
  - Joint pains: RA, SLE
  - Swollen ear lobes: Relapsing polychondritis
- Investigations:ESR,rheumatoidfactor,ANA,ANCA, CRP, x-ray chest, VDRL

Medical Management

- Treat systemic disorder to suppress systemically mediated inflammation and vaso-occlusive disease
  - Systemic corticosteroids
  - Cytotoxic agents
  - Immunosuppressive/immunomodulatory agents
  - Biologics/immunomodulatory agents
- Maintain adequate lubrication of the ocular surface
- Promote corneal re-epithelialization

Surgical Management

- Conjunctival resection:
  - Removes source of neutrophils and plasma cells, collagenolytic enzymes
  - Excise conjunctiva to bare sclera 2 clock hours on either side of ulcer and 3-4mm posteriorly
- Cyanoacrylate glue into gutter of thinning
  - Glue forms a physical barrier between host cornea and conjunctiva

- Decreases neutrophil migration and thus collagenolytic enzymes

- Perforation or impending perforation of the cornea may require treatment with tissue adhesive, amniotic membrane graft, perilimbal conjunctival resection, and/or lamellar or penetrating keratoplasty, often performed as a crescentic or circular peripheral graft.
- When possible, intraocular surgery should be avoided until systemic immunosuppression has commenced

PUK Features	PUK Management Regimen
Unilateral cases, less than 2 quadrants of peripheral corneal involvement, less than 50% stromal loss	Topical steroids
Bilateral cases, more than 2 quadrants of peripheral corneal involvement, more than 50% stromal loss	Oral steroids
Steroid intolerance, young patients (< 50 years), bilateral disease, single eyed	Oral methotrexate
Bilateral, single eyed, more than 3 quadrants of peripheral corneal involvement, > 50% stromal loss, impending perforation	IV methylprednisolone
Bilateral, single eyed, more than 3 quadrants of peripheral corneal involvement, perforation, early postoperative period after keratoplasty	IV methylprednisolone + IV cyclophosphamide

Interstitial Keratitis

- **Etiology**:
  - Humoral and cellular immune reaction to antigens (including viral glycoproteins and other microbial substances) in the corneal stroma resulting in cellular infiltration and inflammation
  - Previous ocular herpes, particularly previous herpes simplex virus (HSV) stromal keratitis
  - Previous chickenpox or shingles (herpes zoster virus)
  - Previous congenital syphilis with dental deformities, bone and cartilage deformities, or hearing loss
  - Systemic illness including infectious mononucleosis, measles, and Lyme disease
  - Recent upper respiratory infection with ear-related symptoms such as dizziness and reduced hearing (Cogan syndrome)
- **Features**
  - Stromal inflammation with stromal edema; may be focal or disciform, multifocal, or diffuse; endothelial pseudoguttata
  - Corneal epithelium intact
  - Keratitis often accompanied by iritis and keratic precipitates: stromal keratouveitis/ endotheliitis

- Presence and extent of stromal neovascularization
- Presence and extent of corneal scarring
- Interstitial keratitis associated with infectious diseases
- Subepithelial infiltrates and multifocal posterior corneal nodular infiltrates associated with Cogan syndrome

- **Tests**
  - Fluorescent treponemal antibody absorption or similar treponemal test
  - HSV antibody
  - Varicella zoster virus (VZV) antibody
  - Epstein-Barr virus (EBV) antibodies
- **Differential Diagnosis**
  - Microbial keratitis
  - Corneal transplant rejection
  - Contact lens-related corneal infiltrate
  - Diffuse lamellar keratitis following keratorefractive surgery
  - Rosacea keratitis
  - Atopic keratoconjunctivitis
  - Corneal edema
  - Sterile keratitis following trauma

Episcleritis

- **Etiology**
  - Idiopathic (most common)
  - Post-traumatic, post-surgical
  - Associated with underlying systemic condition
    - Connective tissue disorders: Rheumatoid arthritis, Systemic lupus erythematosus, Polyarteritis nodosa, Sjögren syndrome
    - Infectious diseases: Tuberculosis, Syphilis, Herpes simplex virus (HSV), Varicella zoster virus (VZV)
    - Miscellaneous: Gout, Atopy, Rosacea, Inflammatory bowel diseases, Sarcoidosis
- **Features**
  - Acute onset or recurrence of mild ocular discomfort
  - Localized or diffuse conjunctival injection
  - Blanching with topical (2.5% or 10%) phenylephrine Small peripheral corneal opacities

- Mild anterior chamber cell and flare

- **Subtypes**
  - Focal: Localized injection of the bulbar conjunctival and episcleral vessels
  - Diffuse: Diffuse injection of the bulbar conjunctival and episcleral vessels
  - Nodular: Conjunctival nodule
- **Tests**
  - CBC with ESR
  - Antinuclear antibody (ANA)
  - Rheumatoid factor
  - Fluorescent treponemal antibody-absorption test, Venereal Disease Research Laboratory (VDRL) test
  - Chest X-ray
- **Differential Diagnosis**
  - Anterior scleritis
  - Conjunctivitisinfectious, allergic, medication-induced
  - Superior limbic keratoconjunctivitis, Conjunctival abrasion
  - Pingueculitis
- **Management**
  - Observation
  - Artificial tear supplements
  - Topical nonsteroidal anti-inflammatory drug (NSAID) or mild corticosteroid
  - Stronger topical corticosteroid +/oral NSAID
- **No visually significant sequelae** but Persistent dilation of conjunctival or episcleral vessels may be of cosmetic concern

Scleritis

- **Etiology**
  - 50-75% idiopathic
  - **Non-infectious:** 44-50% have underlying systemic disease
    - More common: rheumatoid arthritis, Wegener granulomatosis, relapsing polychondritis
    - Less common: ankylosing spondylitis, systemic lupus erythematosus, polyarteritis nodosa, inflammatory bowel disease, gout, sarcoidosis
  - **Infectious:** 7% of all cases
    - Herpetic (zoster, 4.5%; herpes simplex virus, 1.5% of all cases)
    - Post-surgical (bacterial, fungal)

        - Post-traumatic (bacterial, fungal)
        - Tuberculous
    - Deposition of immune complexes in vessel walls appears to be important along with Disordered immune response leads to tissue and blood vessel damage
    - Surgically induced necrotizing scleritis
- **Features**
    - Severe eye pain, boring quality, Pain on movement of eye
    - Red eye, Tearing
    - Slow onset
    - Anterior: pain on palpation, red-violet hue to sclera (seen best with natural lighting), non-blanching with 10% phenylephrine drops , inflammation of sclera and episclera, scleral nodules, uveitis, adjacent peripheral keratitis
    - Posterior: hyperopia, proptosis, lid edema, ophthalmoplegia, disc edema, exudative retinal detachment, macular edema, choroidal folds, choroidal detachment
- **Types**
    - Anterior
        - Diffuse: most common presentation, least severe
        - Nodular
        - Necrotizing with inflammation: most severe, greatest potential for visual loss
        - Necrotizing without inflammation: (scleromalacia perforans)association with rheumatoid arthritis
    - Posterior
- **Tests**
    - CBC with ESR
    - rapid plasma reagin test or Venereal Disease Research Laboratory (VDRL) test
    - Fluorescent treponemal antibody absorption test (FTA) or MHATP
    - Rheumatoid factor
    - Antinuclear antibody (ANA) panel
    - Angiotensin converting enzyme (ACE) test
    - Cytoplasmic-staining anti-neutrophil cytoplasmic antibody (cANCA)
    - Perinuclear-staining anti-neutrophil cytoplasmic antibody (pANCA)
    - Chest radiograph
    - Purified protein derivative (PPD) (tuberculosis skin test) or QuantiFERON-TB gold
    - Urinalysis
    - Ultrasound helpful to look for posterior scleritis (T sign) and CT Scan if posterior scleritis is suspected
- **Sen scleritis scale**: Photographs can be used to grade severity
- **Differential Diagnosis**

- Infectious scleritis
- Episcleritis
- Conjunctivitis

- **Treatment-Based Classification**
  - Steroid sensitive (controlled with prednisone ≤ 7.5 mg/day)
  - Steroid receptive (controlled only at prednisone dose ≥ 10 mg/day)
  - Steroid insensitive (does not respond even to IV steroids)
- **Management**
  - Oral nonsteroidal anti-inflammatory drugs
  - Systemic corticosteroids (start with 1 mg/kg/day and slowly taper)
  - Immunomodulatory therapy
    - Methotrexate commonly used
    - Mycophenolate mofetil may be effective in cases failing other therapies.
    - Other agents used: azathioprine, cyclosporine, cyclophosphamide, chlorambucil
    - TNF-alpha inhibitors in more severe or refractory cases
    - Rituximab: anti-CD20 monoclonal Ab
    - Necrotizing scleritis: *Must use immunosuppressive therapy*
  - Consider periocular steroid injection for non-necrotizing scleritis if no evidence of infection
  - Surgical management (i.e., scleral patch graft) may be required to maintain or re-establish the integrity of the globe
  - Follow-up in 2-7 days depending on severity of presentation
- **Disease related complications:** Scleral melting, Scleral perforation, Cataract, Glaucoma, Cystoid macular edema, Retinal detachment

Scleral Melt/ Necrotising Scleritis

- Clinical implications from a systemic point of view: Increased morbidity and mortality from primary disease and also Leads to ocular morbidity and severe damage = blindness
- **Mechanism of action**: Autoimmune vasculitis of deep episcleral vessels complex/plexus that leads to occlusion and ischemia. In infections, direct invasion of organism associated with severe inflammation.
- **Diagnosis**: mainly clinical exam
- **Management**
  - Medical Therapy Is Always First Line of Therapy With or Without Patch
    - Steroids
    - Anti-metabolites

- Biological therapies: anti-TNF therapies and anti-CD20 therapies
- Alkalating agents

- Surgical approach to Patching:
  - Control of inflammation first!
  - Scleral tissue: Patch graft or whole sclera (preferable)
  - Need for healthy tissue around patch
  - Need to cover patch graft: conjunctiva, amniotic grafts, other mucosal tissue

Graft Rejection & Failure

- Graft "rejection" refers to immune-meditated attack on the graft. Acute endothelial rejection typically presents with keratic precipitates (KP) and anterior chamber inflammation
- Graft "failure" refers to graft that develops chronic stromal edema/opacity due to immunemediated or other cause. Most common reason for graft failure is immune rejection.
- **Low-risk grafting refers to keratoplasty:**
  - Performed in noninflamed eye
  - First graft
  - No other comorbidities (glaucoma, uveitis, etc)
  - Rejection rates in low-risk grafts range from 10% to 25%. Failure rates are much lower.
- **High-risk grafts refer to those performed in hosts with:**
  - Inflamed recipient eyes
  - Neovascularization (NV) in host bed
  - History of 1 or more graft failures (from immune rejection)
  - Rejection rates in high-risk grafts are upward of > 30%-50% (and can be universal in some settings)
- **Prophylaxis vs. treatment of graft rejection**
  - If rejection is picked up *early* in a low-risk recipient, more than 75% are partially or fully reversible with restoration of graft clarity. Timing of detection of graft rejection and institution of therapy are most critical factors.
  - On the other hand, in high-risk transplants, rejections are much more difficult to reverse. Delays of several weeks in starting antirejection therapy in inflamed and neovascularized host eyes are usually *not* reversible.
  - Thus, prevention of graft rejection is especially critical in high-risk transplants.
- **Host factors that complicate graft survival: Comorbidities that can decrease graft survival need to be managed preoperatively.**
  - Ocular surface inflammation (eg, dry eye disease)
  - Suture-related problems: Remove early in children and eyes with inflammation/NV

- Corneal NV
  - Multiple studies have identified this as greatest risk to transplant survival.
  - Principal clinical etiologies of corneal NV
    - Infections: herpetic, bacterial, chlamydial Chemical burns
    - Penetrating trauma
    - Degenerations (eg, Terrien's, pterygium) Limbal stem cell insufficiency states
    - Meibomian gland dysfunction
    - Corneal transplant (in setting of regraft)
    - Contact lens-related
- Therapeutic approaches for managing corneal NV
  - Optimize treatment of underlying etiology or offending agent (examples: infection, contact lens overuse, etc.)
  - Surgical
    - Superficial keratectomy ± amniotic membrane grafting
    - Limbal stem cell grafting
  - Laser and photodynamic therapy
  - Diathermy/cautery
  - Pharmacologic
    - "Conventional" drugs. Efficacy: Corticosteroids > NSAIDs > Cyclosporine-A
    - Biologic or small molecule approaches
  - Anti-VEGFs
    - Bevacizumab (Avastin)
    - Ranibizumab (Lucentis)

Corneal Infections

Stages of Corneal Ulcer

- **Stage of infiltration**
  - Infiltration of PMNL/Lymphocytes into the epithelium and stroma
- **Stage of progression**
  - Necrosis and sloughing of the necrotic material
  - Surrounding area is packed with leucocytes. Wall of the ulcer projects due to edema and infiltration of cells
  - Zone of infiltration extends beyond and underneath the ulcer margin
  - Ciliary congestion
  - Involvement of iris and ciliary body (due to absorption of toxin)–causing iritis/cyclitis
  - Hypopyon formation
- **Stage of regression**
  - Induced by immunodefence mechanism and treatment
  - Line of demarcation develops around the ulcer area
  - Necrotic material is sloughed off and the ulcer bed enlarges.
  - As the surrounding infiltration and swelling disappears, the floor and edges become smooth and transparent.
  - Superficial vessels grow in from the limbus near ulcer, to restore the loss of substance and supply antibody.
- **Stage of cicatrization**
  - Vascularisation of ulcer
  - Regeneration of collagen and formation of fibrous tissue (causes corneal opacity)

Acanthamoeba Keratitis

- 1% of all infectious keratitis
- Free-living protozoan that is ubiquitous in nature
- Found commonly in water, soil, air, cooling towers, heating, ventilating, and air conditioning (HVAC) systems, and sewage systems.
- Unlike disseminated Acanthamoeba infection, corneal disease is not associated with immunosuppression.
- **Three morphologic groups**: group 1,2,3
  - Major human pathogens belong to **Group II**

- Species: 25 species have been identified based on morphological features. The most common causes of Acanthamoeba keratitis are Acanthamoeba castellanii and A. polyphaga. Most microbiology laboratories do not report the species.
- Stages: trophozoite & cyst
  - Trophozoite: motile, replicates by binary fission. Feeds on algae, bacteria, and other protozoans; also thought to feed on keratocytes in the cornea. Encysts when exposed to a harsh environment. Roughly 25-50 microns in size.
  - Cyst: dormant form; resistant to extremes in temperature and pH, desiccation, and chemicals. Does not require food. Excysts into the trophozoite form in the presence of food and other favorable conditions. Roughly 10-30 microns in size.
- Genotypes: 15 genotypes of Acanthamoeba (T1T15) have been identified based on 18S RNA. Acanthamoeba keratitis is predominantly caused by **T4**.

Risk Factors

- Contact lens wear: usually soft lenses (including daily disposable lenses), although can also occur in rigid lenses, especially in orthokeratology lens wearers2
- Poor contact lens hygiene: washing lenses in tap water
- Water exposure: swimming in pools, hot tubs, fresh water, especially when water exposure happens in contact lenses
- Agricultural exposure to water and mud: This is the most common risk factor in India.

Pathogenesis

- Exposure to contact lens 70-85%
- Corneal trauma.
- Natural immunity exists.
- Host response by acute inflammatory cells especially around cyst & necrotic organisms. Contaminated contact lens solution + Microtrauma to Epithelium by contact lens
- acanthamoeba infection by trophozoite

Clinical features

- Symptoms:
  - Unilateral
  - Blurred vision with acute pain disproportionate to signs due to keratoneuritis
  - Immunocompetent patients
  - Fails to respond to antibacterial, antiviral or antifungal treatment
  - Pain: Often severe pain, disproportionate to the clinical signs. However, pain is not universal and some patients have no pain at all.

- Duration: Acanthamoeba keratitis is often not diagnosed promptly. Most larger series report a mean duration of symptoms of 4-6 weeks before the diagnosis is made. Acanthamoeba should be suspected when keratitis does not respond to other treatments (eg, treatment for viral, bacterial, or fungal keratitis).

- Early Signs (≤ 1 month)
  - Epitheliopathy: Often a punctate keratopathy, with a diffusely rough appearing corneal surface but no frank epithelial defect. In series from countries with a high prevalence of contact lens wear (ie, North America and Europe), 37%46% of cases have only an epitheliopathy, without an associated stromal involvement. Lack of stromal involvement is less common in India and China (0%-25% of cases), perhaps due to delayed presentation.
  - Pseudodendrite: This is a form of epitheliopathy where the epithelium has linear staining reminiscent of a dendrite. This is different from a herpetic dendrite in that there is no epithelial defect and no terminal bulbs. Pseudodendrites are not commonly reported (3%-17% of cases), though this may be under-reported since the finding is often subtle.
  - Epithelial irregularity & infiltration pseudodendrite or raised epithelial ridges: 25-50%
  - Radial keratoneuritis (pathognomonic)/ Perineural infiltrate: Usually present in peripheral cornea, and often only 1-2 nerves will be affected. Look for a linear, radial structure, often only 1-2 mm in length, with indistinct borders indicative of a cellular infiltrate surrounding the nerve. This finding is not very sensitive, with studies finding the presence of perineural infiltrate in 3%-41% of cases. This finding is thought to be quite specific for *Acanthamoeba* keratitis.
  - Limbitis: Very common; may be less marked in eyes being treated with topical corticosteroids
  - Patchy anterior stromal infiltrates: Often these are multifocal, diffusely scattered throughout the cornea. The infiltrates are usually not dense or purulent and often have no overlying epithelial defect. The differential diagnosis could include subepithelial infiltrates of epidemic keratoconjunctivitis or anterior stromal infiltrates associated with contact lens overwear.
  - Reduced corneal sensation: This is not unusual in Acanthamoeba keratitis and should always be assessed. Patients with reduced corneal sensation often have less or no pain.
  - Conjunctival follicles.
  - Preauricular nodes.
  - Ring infiltrates 19-90%
  - Absence of corneal neovascularization
- Late Signs (> 1 month)
  - Ring infiltrate: Usually a large ring involving the central cornea; often initially without an epithelial defect, but an epithelial defect usually forms over and

within the ring. The infiltrate usually has deeper stromal involvement than the earlier patchy anterior stromal infiltrates. Ring infiltrates are present in 20%-60% of Acanthamoeba cases.

- Frank ulceration: Large nonhealing epithelial defects with nonpurulent stromal infiltration are common. This is often accompanied by cornea vascularization and edema.
- Uveitis and scleritis: Keratic precipitates, anterior chamber cellular reaction, scleritis usually worse near limbus. The scleritis can be very painful and is often relieved with oral nonsteroidal anti-inflammatory drugs. Occurs in 11-40% (immunological response)
- Stromal opacification
- Descematocele formation

Diagnosis

- Microbiology
  - Corneal scrapings, CL, case, solution
  - In Vivo Confocal microscopy confirmatory pear shaped cyst & irregular trophozoite
    - Cysts: Round, hyper-reflective bright spots and double-walled cysts measuring approximately 10-30 microns
    - Trophozoites may be visualized, though the features are less well described than cysts, and probably should not be the focus when interpreting confocal images.
  - Corneal biopsy: For cases where *Acanthamoeba* is suspected but corneal scrapings are negative and clinical course does not improve with antiamoebic therapy. Send half of tissue for pathology and half for culture, then scrape the bed of the biopsy and send for smear and culture.
- Stains
  - Gram & Giemsa stain
  - Calcofluor white stain Cysts: polygonal and double walled appearance on calcoflour white 0.1%.
  - Acridine orange.
  - Immunofluorescent antibody stain.
  - PAS & methenamine silver.
- **PCR and Corneal Biopsy**
  - *Transported in:* **Page saline** with sample of contact lens saline & case.-Ideal.
  - Alternative media is buffered **charcoal yeast extract agar**-Lower efficacy (72%)
- **Culture**: non nutrient agar with e.coli/aeromonas/klebsiella, blood agar, chocolate agar (Gold Standard)
  - **E-coli on non nutrient agar** (1.5%) at 25 and 37 degree C, May require up to 14 days to grow Create track by eating E Coli.

- Phase contrast Microscope

- **Differential diagnosis**
  - Diagnosis By Exclusion: *Acanthamoeba* keratitis is often initially misdiagnosed. Consider *Acanthamoeba* before diagnosing the following:
  - Herpetic keratitis: Both can cause decreased corneal sensation, dendriform epithelial lesions, and a ring ulcer. Dendritic keratitis due to HSV has true dendrites, with fluorescein staining the base of the dendrite and terminal bulbs. Pseudodendrites due to *Acanthamoeba* usually do not have a frank epithelial defect. Interstitial keratitis due to HSV tends not to be multifocal and often affects the mid and deep stroma, whereas *Acanthamoeba* infiltrates are usually numerous and smaller multifocal anterior stromal infiltrates.
  - Subepithelial infiltrates (SEIs) from epidemic keratoconjunctivitis (EKC): Often SEIs will have punctate staining overlying the infiltrate, whereas Acanthamoeba often has a diffuse epitheliopathy, even over areas of the cornea without an infiltrate. Patients with EKC usually have a history of sick contacts.
  - Contact lens–related infiltrates: These are often in the peripheral cornea and usually consist of a small number of discrete small anterior stromal infiltrates.
  - Fungal Infection
- **Treatment**
  - Biguanides-Cationic Antiseptics inhibits membrane function
    - Chlorhexidine, Solution, 0.02%
    - Polyhexamethylene, Solution, 0.02% (PHMB)-BAQUACIL
  - Aromatic Diamidines inhibits DNA synthesis
    - Propamidine isethionate, Solution, 0.1% (BROLENE)
    - Pentamidine isehionate, Solution 0.1% (PENTAM)
  - Aminoglycoside inhibits protein synthesis
    - Neomycin Solution, 1.75 mg/ml Ointment 3.5 mg/g
  - Azoles destroys cell wall
    - Clotrimazole, suspension, 1%
    - Fluconazole, solution, 0.2%
    - Ketoconazole, oil solution, 5%
    - Miconazole, solution, 1%
    - Initially hrly x 48 hrs.
  - Corticosteroid reduces inflammation. Very Cautious use (While continuining anti-amoebic agents): Prevents encystment of Trophozoite in vitro and may therefore enhance effectiveness of Topical treatment. Topical steroids have shown to prolong effective treatment and used in specific conditions like Limbitis,Scleritis and uveitis
- **Uncanned approach for Treatment**

- The simplest approach is to use increased concentrations of existing biguanides and/or combine their use (eg, PHMB + chlorhexidine).
- Adjunctive use of secondary agents such as voriconazole (oral or topical), systemic pentamidine, caspofungin, and others have been described.
- The greatest interest has been the introduction of the orphan drug **miltefosine**, an anti-leishmaniasis drug, to the United States with an FDA designation for acanthamoebal infections, including *Acanthamoeba* keratitis,
- A great deal of interest has been generated around the application of collagen crosslinking to patients with *Acanthamoeba* keratitis.

- **Course & outcome:** Majority eradicated by medical therapy.
- **Treatment of Complications**
  - Scleritis:-consider immunosuppressant with steroids/ cyclosporine.
  - Corneal Scaring:Two Types Therapeutic or Penetrating Keratoplasty
- **Prevention**
  - Prevention is essential because the disease has great potential to cause marked visual acuity loss and blindness.
  - Patients should be instructed to always wash and dry their hands thoroughly before handling the CL.
  - A multipurpose cleaning and disinfecting solution should not be “topped-off” or reused in the CL case. The CL case should be washed daily with the multipurpose solution, not tap water.
  - The CL should not be exposed to nonsterile solutions or water from the faucet, pool, pond, bathtub, shower, or sauna, among others. The CL should be rubbed for at least 15 seconds before and after use, because this increases the effectiveness of cleaning and disinfection.
  - The CL and CL solutions should not be used beyond the expiration date; expired solutions should be discarded. If symptoms or signs of eye irritation occur, the CLs should be removed immediately from both eyes and emergency medical attention sought.

Bacterial Keratitis

- **Etiology**
  - Disruption of epithelial integrity
  - Bacterial adherence, replication, and stromal invasion
  - Polymorphonuclear leukocytes (PMN) initiate inflammatory cascade, release inflammatory mediators, and recruit other inflammatory cells
  - Production of matrix metalloproteinases and collagenases

- Common etiological agents: *Pseudomonas* species, other Gram-negative rods (*Serratia marcesans*), *Staphylococcal* species, *Streptococcal* species, non-tuberculosis mycobacteria, and anaerobes

- **Epidemiology**
  - People of all ages and both sexes
  - Increased risk with contact lens (CL) wear
  - Gram negative organisms in refractive CL population
  - Gram positive organisms in therapeutic CL population
- **Clinical features**
  - Epithelial defect
  - Stromal infiltrate
  - Stromal ulceration
  - Iritis
  - Hypopyon
  - Infectious crystalline keratopathy: Persistent bacterial infection with minimal inflammation may produce intrastromal branching pattern
- **Tests**
  - Corneal smears
    - Chromogenic stains: gram, acid-fast (mycobacteria, *Nocardia* species), Gomori-methenamine-silver (fungi, Acanthamoeba)
    - Fluorescent stains: acridine orange (bacteria, fungi, *acanthamoeba)*, calcofluor white (*acanthamoeba*, fungi)
  - Corneal cultures
    - Standard culture media
      - Blood agar x 2 (one anaerobic and one aerobic) (most bacteria)
      - Chocolate agar (most bacteria, especially *Neisseria gonorrhoeae* and *Haemophilus* species)
      - Thioglycolate broth (aerobic and anaerobic bacteria)
      - Sabouraud's dextrose agar (fungi)
    - Special culture medium
      - Lowenstein-Jensen medium (mycobacteria*, Nocardia* species)
      - Middlebrook agar (non-tuberculous mycobacteria)
      - Buffered charcoal-yeast extract agar or non-nutrient agar with bacterial overlay (*Acanthamoeba*)
- **Risk factors**
  - Exogenous factors: CL wear, Ocular trauma, Previous ocular and eyelid surgery

- Ocular surface disease: Trichiasis, Exposure and related eyelid malposition, Dry eye, Adjacent infections (blepharitis, conjunctivitis, dacryocystitis, or canaliculitis), Atopic dermatitis/blepharoconjunctivitis, Rosacea
- Corneal epithelial abnormalities: Neurotrophic keratopathy, Recurrent erosion syndrome, Herpes simplex virus keratitis, Corneal edema (bullous keratopathy), Persistent corneal epithelial defect
- Systemic conditions: Diabetes mellitus, Malnourishment, including vitamin A deficiency, Obtunded, hospitalized patient, Substance abuse, Mucous membrane disorders

Management

- Commercially available antibiotics: Fluoroquinolones (including ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin, besifloxacin)
  - Excellent against many gram-negative organisms
  - Susceptibility gaps against some gram-positive organisms (streptococcal species (a-strep), methicillin resistant staphylococcal species (MRSA))
    - Moxifloxacin: best cure rate, better vs. Gram positives
    - Gatifloxacin: better vs. Gram negatives
    - Besifloxacin: newest with no systemic use, more active than other FQ vs. resistant organisms.
- Formulated or fortified antibiotics
  - Gram-positive activity
    - Cefazolin (50 mg/ml)
    - Vancomycin (25-50 mg/ml) for multiresistant strains
  - Gram-negative activity
    - Aminoglycosides (tobramycin, gentamicin) (9-14 mg/ml)
    - Extended spectrum cephalosporins (ceftazidime or cefepime) (50 mg/ml)
- Methicillin Resistant *Staphylococcus Aureus*
  - Topical or intracameral vancomycin is the preferred therapy depending on the site of infection
  - Alternative systemic drugs include linezolid, daptomycin, tigecycline
  - Alternative topical ophthalmic medications include polymyxin B/ trimethoprim, chloramphenicol, bacitracin
- Nontuberculous mycobacteria: Amikacin, Clarithromycin, Moxifloxacin, Gatifloxacin
- Fluoroquinolone resistant pseudomonas: Aminoglycosides, Anti-pseudomonal penicillins (ticarcillin)
- Adjuvant therapy
  - Cycloplegic agents (e.g. cyclopentolate 1% or scopolamine 0.25%)
  - Role of topical corticosteroids

        - Inflammation but no infection = use
        - No inflammation = do not use
        - Infection = use cautiously + antimicrobials
    - Lubrication
        - Remove toxic substances from eye
        - Reduce abrasive action of lids
    - Doxycycline: MMP inhibitors, all ulcers especially alkali burns and blepharitis
    - Ascorbate and Citrate
        - Adjuvant to collagenase inhibitors
        - Especially useful in alkali burns where low levels seen
        - May modulate neutrophil effects
        - 1 gm vitamin C qday
        - 10% topical drops
    - Autologus serum
    - Restasis may inhibit IL and lymphocytes – help with PUK
    - Netraceuticals: flax seeds, canola, soybean and fish oils omega 3 fatty acid reduces surface inflammation
    - Acetylcysteine 3% – MMP inhibitor – especially useful in alkali burns
    - Surgical
        - Punctal Occlusion
        - Bandage Contact lens
        - Amniotic Membrane
        - Corneal transplant
        - Glue in case of perforation
        - Tarsorrhaphy
        - Gunderson's flap

- **Newer Modalities**
    - Steroids for Corneal Ulcers Trial (SCUT)
        - SCUT investigated adjuvant topical steroids in addition to antibiotics to reduce the inflammatory response in bacterial ulcers.
        - The trial failed to find benefit or harm overall.
        - Prespecified subgroup analyses suggested that earlier steroid treatment of large, central, non-Nocardia ulcers
        - Severe ulcers tended to do better with steroids.
        - Pseudomonas aeruginosa tended to do better with steroids.
        - Nocardia species did worse with steroids.
        - Steroids earlier in the course proved beneficial.

        - Longer-term results (1-4 years) suggested improvement with steroids.
    - Corneal Crosslinking (CXL) for Infectious Keratitis
        - In vitro studies suggest that photochemically activated riboflavin is effective against common ocular pathogens
        - CXL may also have anti-inflammatory effects and promote resistance of corneal tissue to enzymatic degradation.
        - Crosslinking-Assisted Infection Reduction (CLAIR) is a randomized outcome-masked clinical trial evaluating the benefit of adjuvant corneal crosslinking in moderate to severe bacterial keratitis.
    - **Ilomastat** – very powerful MMP inhibitor – decreased ulceration in alkali burns as well as pseudomonas ulcers
    - Growth factors – EGF, FGF and NGF are being evaluated in clinical trials
    - Gene therapy – ribozymes, SiRNAs
    - Organ cultured corneas

Fungal Keratitis

- 6-20% worldwide
- 49% india
- 65% in 21-50 years
- M:F= 1.5:1
- Season: monsoon, early winter
- Fusarium spp and Aspergillus spp are the most common fungi isolated from patients of tropics, while Candida albicans is the most common pathogen of mycotic keratitis in temperate region.
- **Risk factors:**
    - Ocular
        - Trauma: vegetative matter
        - Chronic inflammation
        - CL wear
        - Topical antibiotics and steroids
        - Prior ocular surgery (LASIK, PK, Cataract)
    - Systemic
        - NIDDM, HIV, Leprosy
- **Classification of fungi**
    - Filamentous septate
        - Non-pigmented

        - Fusarium solani
        - Aspergillus fumigatous, flaus, niger
        - Acremonium
        - Paecilomyces
    - Pigmented
        - Curvelaria
        - Alternaria
        - Cladosporium
        - Helminthosporum (diechslera)
- Filamentous non-septate: rhizopus
- Yeasts: candida albicans, tropicalis

Symptoms

- Indolent, FB sensations
- Increasing pain
- Diminution of vision

Signs

- Dry rough texture
- Feathery margins
- Abscesses
- Satellite lesion
- Endothelial plaques
- Fixed hypopyon

Classic Clinical Features

- Fungal keratitis classically presents as a slowly progressive disease characterized by a localized infiltrate.
- The infiltrate is dry, white and cotton wool like, and is raised above the plane of the cornea.
- The infiltrate has fine branching linear extensions in the surrounding cornea.
- There may be satellite lesions and an immune ring associated with the main infiltrate.
- Some patients may show brown to black pigmentation on the surface of the infiltrate.
- Other characteristic features of fungal infection of cornea are: the presence of thick fluffy endothelial exudates, and a thick hypopyon

Specific signs

- Dematacеous fungi: brown pigmentation
- Fusarium: severe source, deep extension, perforation

- Aspergillus: indolent course
- Yeast: collar button configuration

- **Laboratory diagnosis**
  - ***Non-invasive techniques***
    - Confocal microscopy
      - Fungal keratitis sensitivity 94% and specificity 84%: In Aspergillus keratitis, fungal hyphae have been imaged as high contrast filaments (60-500 µm long x 6 µm broad)
      - Acanthamoeba keratitis sensitivity 100% and specificity 84%
  - ***Invasive techniques***
    - Conventional Microbiological Investigations: Demonstration of fungus in smears or culture of corneal scrapings remains the gold standard for diagnosis of fungal keratitis.
    - Sample collections
      - Corneal scrapings, Corneal biopsy/ buttons, Contact lenses, Contact lens solutions
    - Culture media
      - Sabouraud dextrose agar (**without cycloheximide**)
        - ✓ Positive culture 52-68%
        - ✓ Initial growth occurs within 72 hours
        - ✓ Wait at least 7 days before culture negative report
      - Sheep blood agar (aerobic, anaerobic)
      - Sheep blood chocolate agar
      - Brain heart infusion broth
      - Thioglycollate broth
      - Non-nutrient agar with E.coli
    - Direct Microscopic Examination
      - Potassium hydroxide (KOH) 10% wet mount: 85% sensitivity and specificity
      - Gram stain sensitivity 45-73%
      - Giemsa Staining Sensitivity of 66-85%
      - Lactophenol cotton blue (LPCB) sensitivity 45-73%
      - Grocott's methenamine silver (GMS) sensitivity 80-90%
      - Calcofluor White Sensitivity of 80-90%
    - Molecular method
      - Polymerase chain reaction (PCR)
        - ✓ 75% in 4 hours

- ✓ Fusarium cutinase gene) was 89% sensitive and 88% specific
- Target Gene: **ITS**, the nuclear ribosomal internal transcribed spacer region, lies within the ribosomal DNA and contains the ITS1, ITS2, and 5.8S rDNA sites. It can identify the organism, the source of the organism, and its sensitivity profile, pathogenicity, and mycotoxin production. Other methods to identify the cause and extent of the infection are using the confocal microscope and anterior segment OCT.
- Histopathology

- **Medical Management**
- **Antifungal drugs**
  - Polyenes: natamycin, nystatin, amphotericin B
  - Azoles: fluconazole, itraconazole, voriconazole, posaconazole, ravuconazole
  - Fluorinated pyrimidines: flucytosine
  - Echinocandins: caspofungin, micafungin, Anidulafungin
  - Allylamines: Terbinafine, Naftifine, Butenafine
  - Others: Chlorhexidine
- **Topical antifungals**
  - 5% ***natamycin*** hourly – daytime, 2 hourly bedtime → 2 hourly daytime, taper in 4-7 days
  - If worsening → add 0.15% amphotericin or 2% fluconazole for candida
  - Therapy for 3-4 weeks
  - Limitations
    - Commertially available preparations less
    - Poor ocular penetrations
    - Poor bioavailability
    - Toxicity
  - Topical voriconazole 1%: powder for parenteral use, alternaria and scedosporium keratitis, inhibits CYP450 dependent 14-sterol demethylase, FUNGISTATIC
  - Voriconazole, despite having several theoretical advantages, does not result in a superior cure rate when compared to natamycin.
  - Rather voriconazole has a disadvantage of being associated with a higher risk of corneal perforation.
- **Systemic antifungals**
  - Indications
    - Large ulcers
    - Severe deep keratitis
    - Scleritis

        - Post-PK
        - endophthalmitis
    - Drugs
        - ketoconazole 200 BD
        - fluconazole 200 BD
        - itraconazole 100 BD
        - voriconazole 200 BD
        - LFT should be done every 2 weekly
- **Targeted drug delivery**
    - **Injections**
        - Anterior chamber wash with Intracameral Injections
            - Non responsive to medical therapy
            - Thick hypopyon
            - Endothelial exudates
            - Deep anterior chamber exudates
            - Amphotericin 5-7.5 ug/0.1ml/5%D
            - Voriconazole 50-100 ug/0.1ml
        - Intracorneal/ intrastromal (Voriconazole)
            - Deep mycotic keratitis
            - Non perforated corneal ulcer
            - Non responsive to conventional topical+ systemic anti-fungal therapy for 4 weeks
- **Surgical Management**
    - Therapeutic debridement,
    - Cyanoacrylate glue + bandage contact lens
    - Therapeutic keratoplasty (penetrating and lamellar),
    - Intraocular injections (amphotericin B) ± pars plana vitrectomy,
    - Evisceration
    - Collagen crosslinking.
- **Mycotic Ulcer Treatment Trial (MUTT)**
    - Topical natamycin is superior to voriconazole against filamentous fungi, is better for Fusarium cases, and showed no difference between treatments for non-Fusarium cases.
    - Further observations from molecular analysis show not only that molecular classification is important in assisting clinical decision making but that natamycin is better against F. solani, and voriconazole, not as effective, but equal against others.

- F. solani infections are less likely to respond to medical treatment and more likely to require a keratoplasty than are non-solani Fusarium.
- Use of steroids is not recommended, dangerous if used too early, but may be used as a diagnostic challenge.
- Topical drops can be augmented with intrastromal injections of voriconazole (50 micrograms) around the infiltrate, with repeated injections as necessary.
- The MUTT II showed that oral adjunctive voriconazole is indicated in the treatment of Fusarium keratitis.

Viral Keratitis

- Herpetic Eye Disease: HSV, HZV
- Non herpetic eye disease: adenoviral

- Primary ocular herpes
  - Confined to epithelium
  - Blepharoconjunctivitis
  - Preauricular LAP
- Recurrent ocular herpes
  - Infections:
    - Epithelial: dendritic, geographical
    - Stromal: necrotizing, immune → most devastating, heavy infiltration, deep vascularization, corneal thinning, perforation
    - Endothelial: disciform, linear, diffuse
  - Neurotrophic keratopathy
  - Herpetic marginal ulceration: peripheral corneal ulceration, underlying anterior stromal infiltrate, adjacent limbal congestion

Herpes Simplex Keratitis

- History
  - Herpes = crawl (Greek 'herpein')
  - 100 AD Roman physician Herodotus – fever blisters
  - 1830 – MacKenzie "erisipelatous ophthalmia"
  - 1919 – Lowenstein infectious
  - 1970 – Baringer et al sites of latency
- HSV-1 usually involves the oropharynx and HSV-2 usually involves the genital area
- Ocular disease is caused by type 1 rather than type 2, with the exception of herpetic keratitis in neonates in which 75% is caused by HSV-2

- Icosahedral-shaped capsid surrounds the core, which contains the double-stranded deoxyribonucleic acid (DNA) and associated phosphoproteins of the viral chromatin.
- HSV binds to one or more cellular receptors, heparin sulfate probably being one of them
- **Epidemiology**
  - Humans are the only natural reservoir
  - Primary infection manifests clinically in only 1–6% of people infected with the virus
  - High male:female ratio (1.67:1) in patients more than 40 years of age. In younger patients, no difference was observed.
- **Pathogenesis**
  - After peripheral entry into the host and primary infection with viral replication within an end organ, HSV travels in a retrograde fashion to various ganglia including the trigeminal, cervical, and sympathetic gangliae, and possibly the brain stem.
  - Latently infected neurons have not been found to produce infectious virus. However, a region of the viral genome that is retained within the host cell nucleus during latency is responsible for RNA transcripts termed latency-associated transcripts (LATS).
  - The trigeminal ganglion is the most common source of recurrent HSV infection.
  - Systemic antibodies have no known role in the development of recurrent disease despite their role in the host response to active primary and recurrent infection
  - Activation of recurrent HSV ocular disease:
    - Sunlight, trauma (including surgery), heat, abnormal body temperature, menstruation, other infectious diseases, and emotional stress, Prostaglandin F2 alpha analog and prostamide glaucoma medications latanoprost and bimatoprost have also been implicated in ocular or even periocular HSV
    - CD8+ T-cell inhibition of HSV-1 reactivation show viral inactivation via the use of lytic granules degrading precursors to viral gene expression. These CD8+ T cells maintain latency without causing neuronal apoptosis
  - Immune defense mechanisms

Congenital and neonatal ocular herpes

- HSV-2 accounts for 80%
- periocular skin lesions, conjunctivitis, epithelial keratitis, stromal keratitis, and cataracts.
- maternal IgG to HSV may cross the placenta, it does not appear to be sufficient to prevent ocular disease completely.
- The use of antibody titers for diagnosis is not useful because of pre-existing maternal antibody and the delayed production of IgM.

Primary ocular herpes

- By the age of 5 years, nearly 60% of the population has been infected with HSV. Latent infection → viral carrier state.
- Only 6% of infected actually develop clinical manifestations, which typically affect the perioral region rather than the eye.
- Can present as acute follicular conjunctivitis, keratoconjunctivitis, preauricular adenopathy, and periocular and eyelid skin vesicles
- Incubation ~ 1 week – 'round trip theory'
- Usually subclinical
- May have malaise, fever etc.
- Keratitis rare
- Rarely bilateral or life-threatening

Recurrent ocular herpes

- Liesegang's review: 36% at 5 years and 63% at 20 years
- ***HEDS study: 18%***
- HSV can affect any tissue of the eye, with common manifestations including blepharitis, follicular conjunctivitis, keratitis (epithelial, stromal, endothelia), and keratouveitis.
- Ocular HSV is almost always unilateral. Recurrent and isolated lid or conjunctival HSV is an unappreciated common entity. Unilateral follicular conjunctivitis is almost always caused by HSV.

Blepharitis

- Vesicular lesion involving a focal area of the eyelid with surrounding erythema
- Ulceration and crusting and heals without a scar unless secondarily infected.

Conjunctivitis

- Follicular conjunctivitis, self-limiting
- May develop follicular conjunctivitis. In many patients, this conjunctivitis is self-limiting
- May constitute up to 23% of cases of acute conjunctivitis

Keratitis

- Recurrent HSV keratitis is typically a unilateral disease. Bilateral herpetic keratitis occurs in approximately 3% of patients with ocular HSV.
- Infectious epithelial keratitis (Cornea vesicles, Dendritic ulcer, Geographic ulcer, Marginal ulcer)
  - Photophobia, pain, and a thin, watery discharge; DOV if central
  - Branching, linear lesion with terminal bulbs and swollen epithelial borders that contain live virus
  - True ulcer in that it extends through the basement membrane.

- Fluorescein staining with negative stain of terminal bulbs, rose Bengal is toxic to HSV and will decrease the yield of the culture.
- HSV dendritic epitheliopathy:
  - The dendriform lesions (dichotomous branching with terminal bulbs) are the classic findings and represent direct viral infection.
  - The center of the lesion stains with fluorescein; the borders stain with lissamine green or rose bengal.
  - not ulcerated and simply represents healing epithelium after the infection.
- An enlarged dendritic ulcer that is no longer linear is referred to as a geographic ulcer. (22% of all epithelial)
- Marginal ulcer: proximity the limbus, quickly infiltrated with white blood cells, more symptomatic because of the intense inflammation
- Four recognized sequelae
  - complete resolution
  - infectious epithelial keratitis
  - stromal scarring: 'ghost scarring' or 'footprints' of HSV keratitis.
  - stromal disease (25%) → Necrotizing keratitis represents true viral infection of the stroma, whereas immune stromal keratitis is mediated by antibody–complement reactions to viral antigen.
- Average healing time of an untreated HSV epithelial dendrite is 9-10 days, treatment with debridement and patching reduces healing time to 2.5 days.
- The healing time of HSV epithelial keratitis treated with topical antivirals is about 7 days.

Differential Diagnosis of HSV Epithelial Keratitis: infections from varicella zoster virus (VZV), Epstein-Barr virus (EBV), adenovirus, and *Acanthamoeba.* Noninfectious causes of dendritiform and/ or geographic epithelial ulcerations include a healing abrasion or topical beta-blockers, neurotrophic keratopathy, limbal stem cell deficiencies, recurrent epithelial erosion, persistent epithelial defect, exposure keratopathy, Thygeson superficial punctate keratitis, and amiodarone deposition. Differential diagnosis of HSV stromal keratitis without ulceration includes any cause of interstitial keratitis, including syphilis, Cogan syndrome, VZV or EBV keratitis, measles or mumps keratitis, Lyme disease, and others.

Stromal disease

- 2% of initial episodes, 20–48% of recurrent ocular HSV
- few cases where stroma is involved primarily. Necrotizing stromal keratitis occurs from direct viral invasion of the stroma, whereas immune stromal keratitis is the result of an immune reaction within the stroma.

Necrotizing stromal keratitis

- Necrosis, ulceration, and dense infiltration of the stroma with an overlying epithelial defect.
- Risk factor: use of topical corticosteroids without antiviral coverage

- **Immune stromal (interstitial) keratitis**
  - 20% of patients with ocular HSV
  - Due to retained viral antigen within the stroma. This antigen triggers an antigen-antibody-complement (AAC) cascade that results in intrastromal inflammation.
  - Stromal inflammation with overlying epithelium almost always intact
  - Often accompanied by anterior chamber inflammation, ciliary flush, and significant discomfort.
  - Immune ring: AAC precipitate similar to a Wessely ring
  - Stromal neovascularization: sectoral, with a single frond of vessels, to complete, involving all quadrants of the cornea. Ghost vessels, in and of themselves, do not cause decreased vision or increased risk of penetrating keratoplasty rejection.
- **Endotheliitis**
  - Corneal stromal edema without stromal infiltrate
  - Keratic precipitates (KP), overlying stromal and epithelial edema, and iritis.
  - Three forms of HSV endotheliitis are disciform, diffuse, and linear
  - Disciform endotheliitis: MC, ocular discomfort, Limbal injection, disc-shaped area of stromal edema,
  - Diffuse endotheliitis: rare,
  - Linear endotheliitis:
- **Iridocyclitis**
  - Most commonly accompanies immune stromal keratitis or endotheliitis, but, as previously stated, it may occur as the only inflammatory finding.
- **Diagnosis**:
  - Ophthalmic examination
  - Viral culture:
    - HSV cell culture isolation is the gold standard in laboratory diagnosis of HSV epithelial keratitis, with excellent specificity but low sensitivity and long incubation period.
    - Within several days of the onset and may require up to 1 week of incubation
    - Speed in culture is improved with use of shell vial culture assays.
  - Tzanck smear from corneal scrapings with a sterile platinum spatula can be smeared on a slide, stained using the Papanicolaou or Giemsa method, and examined by light microscopy. It is characterized by high specificity, ease of use, low cost, rapidity, and wide availability, but low sensitivity.
  - Brush or impression cytology can suggest HSV epithelial keratitis but with low sensitivity and specificity.
  - Direct fluorescent antibody (DFA) detection of HSV antigen is rapid and relatively reliable but has limited availability as it requires ultraviolet microscope and a skilled technician.

- Enzyme linked immunosorbent assay (ELISA) uses monoclonal antibodies against HSV-specific antigens; it has low sensitivity and high specificity, and Herpchek may not be more sensitive than a clinical exam.
- Polymerase chain reaction (PCR) is very specific and sensitive for epithelial keratitis or from the tear film, but a skilled technician and special instrumentation are required.
- Serology is useful only in children and young adults where testing may indicate or rule out a primary HSV infection.
- Metagenomic deep sequencing (research tool) for atypical cases

- **Management**:
  - **4 valuable insights of HEDS**
    1. Oral antiviral prophylaxis reduces recurrences of epithelial and of stromal keratitis.
    2. Use of topical corticosteroids is of benefit in stromal keratitis.
    3. Use of oral acyclovir may be of help in iridocyclitis.
    4. Prophylactic oral acyclovir helps prevent recurrences of herpetic keratitis, particularly stromal with a history of recurrence.
  - HSV Epithelial Keratitis
    - Topical antiviral:
      - Trifluridine 1% solution 9 times a day
      - Eyedrop ganciclovir 0.15% 5 times a day
      - Acyclovir eye ointment 3%
    - Oral antiviral:
      - acyclovir 400 mg 5 times a day
      - valaciclovir 1 gram 3 times a day
      - famciclovir 500 mg 3 times a day
  - HSV Stromal Keratitis
    - Oral antiviral: acyclovir, valacyclovir, famciclovir
    - Topical steroids are integral to preventing complications such as neovascularization and lipid keratopathy: prednisolone 1%.
  - HSV Endotheliitis
    - Oral antiviral: acyclovir, valacyclovir, famciclovir
    - Topical steroids: prednisolone 1%

- **Complications**
  - Neurotrophic cornea and ulcer
    - Arises from impaired corneal innervation in combination with decreased tear secretion.
    - Irregularity of the corneal surface and lack of the normal corneal luster.

- Oval in shape with smooth borders, in direct contrast to the geographic ulcer, which is irregular in shape with scalloped borders
- Management
  - Oral antiviral needed for therapeutic and prophylactic purposes
  - Rule out secondary infection with corneal cultures and treat with topical antibiotic.
  - Topical steroids may be needed if inflammation is preventing healing.
  - Bandage contact lens, tarsorrhaphy, serum tears, amniotic membrane for nonhealing ulcers
  - Cenegermin (nerve growth factor) shows promise.
  - Corneal neurotization procedure is under investigation.

- Corneal thinning
  - Cornea glue if risk for perforation
  - Temporary tarsorrhaphy
  - Anterior lamellar keratoplasty

Herpes Zoster Eye Disease

- Acute phase:
  - Punctate epithelial keratitis
  - Micrdendritic ulcers
  - Nummular keratitis
  - Disciform keratitis
- Chronic phase
  - Mucus plaque keratitis
  - Neurotrophic keratitis
  - Nummular keratitis
  - Disciform keratitis
- Laboratory Diagnosis
  - Giemsa staining sensitivity 57% and specificity 85%
  - PCR specificity 70%
  - Viral culture 70%
  - Immunological tests
- Topical antivirals
  - Acyclovir 3% ointment
  - Vidarabine 3% ointment
  - Trifluothymidine 1% solution

- Idoxuridine 1%
- Topical steroids: for stromal component
- Systemic acyclovir
  - Recurrent stromal-epithelial keratitis
  - Immunocompromised patients
  - HSV keratitis in a corneal graft
  - 400 mg 5 times a day for HSV, 800 mg 5 times a day for VZV

Varicella Zoster Virus (VZV)

- 10%-20% of cases involve first division of CN V, resulting in herpes zoster ophthalmicus (HZO).
- **Presentations of VZV**
  - Varicella/chicken pox is primary infection.
  - Herpes zoster is caused by reactivation of VZV virus in people who have had chicken pox.
  - Typically results in unilateral, painful, vesicular rash in dermatomal distribution obeying the midline.
  - "Zoster sine herpete" is term used to describe dermatomal (radicular) pain without a rash due to VZV, described in 1958. Thirty-seven percent of people with strokes due to VZV vasculopathy do not have history of typical rash, can result in HZO.
  - Evidence that VZV is trigger causing temporal/giant cell arteritis.
- **Diagnosis**
  - Clinical diagnosis is straightforward in presence of typical rash.
  - In absence of rash, diagnosis is difficult and can be missed.
    - Imaging and cerebral spinal fluid antibody to VZV used for diagnosis of central nervous system complications.
    - Rise in serum VZV antibody may occur.
    - Temporal artery biopsy specimens can be stained for VZV, but numerous (over 50) sections are necessary.
- **Features to distinguish VZV from HZV**
  - **History**: In a patient with a prior history of HSV eye disease, the diagnosis is most likely HSV. In a patient with a history of a *zoster rash affecting the first division of the fifth cranial nerve, VZV is more likely.* However, keep in mind that zoster keratitis can occur in the absence of a history of a zoster rash (zoster sine herpete). The age of the patient can also be helpful since the incidence of zoster increases with age. Finally, a history of neuralgia accompanying ocular disease favors VZV.
  - **Corneal Sensations**: Both HSV and VZV keratitis can be associated with decreased corneal sensation, the *loss of sensation with VZV can be quite profound*, with total loss of sensation over the entire cornea and bulbar conjunctiva. A case of

HSV keratitis with associated loss of conjunctival sensation is rare and HSV keratitis with total loss of sensation over the entire cornea is also rare. As a result, neurotrophic keratopathy is much more common in cases of VZV keratitis.

- **Epithelial lesion:** The appearance of epithelial lesions can also help distinguish HSV from VZV keratitis. The classic dendrite of HSV keratitis is hard to miss, with its beautiful branching pattern, central ulceration, and end bulbs. The staining pattern of an HSV dendrite is similarly beautiful, with central fluorescein staining of the ulceration and surrounding rose bengal or lissamine green staining of the surrounding infected corneal epithelial cells. In contrast, the *pseudodendrite of zoster is elevated or heaped up and appears pasted on*, reflecting an epithelial to mesenchymal change of the cells on the ocular surface with extremely variable staining patterns. In contrast to the beautiful fractal quality of the HSV dendrite, the zoster pseudodendrite looks like it has been drawn by a five-year-old.
- **Stromal disease:** Both HSV and VZV can produce many different forms of stromal disease that can be hard to distinguish; however, in my experience there is one pattern of stromal keratitis that is highly suggestive of VZV but not HSV. This pattern occurs in the very anterior corneal stroma and extends from the limbus across at least a third of the diameter of the cornea in an ovoid pattern with very well-circumscribed edges.
- **Iris:** Both HSV and VZV keratitis can be associated with iris atrophy, and both viruses have been associated with patchy, sectoral or diffuse iris atrophy. However, it has been my experience that VZV is more likely to cause diffuse atrophy. The atrophy of herpetic iritis can be associated with pigment and pigmented cells in the anterior chamber and along the trabecular meshwork. The greater the degree of pigment, the more likely the infection is due to zoster, and the more likely that there is an active viral infection, not just an immune response, that needs aggressive antiviral therapy (and less corticosteroids).

- **Treatment**:
  - Herpes zoster ocular disease is treated in a manner very similar to treatment of HSV ocular disease (oral antivirals to control the virus and topical corticosteroids to control inflammation), except that there is almost never a role for topical antivirals in treating ocular zoster.
  - Fortunately, treatment of HSV and VZV keratitis is very similar. Treat actively replicating viral disease of the corneal epithelium or anterior chamber with an antiviral (I prefer oral antivirals for both locations), and treat inflammation with a topical corticosteroid under antiviral cover.
  - Doses of the oral antivirals are higher than that generally used for HSV (acyclovir 800 5x/day, famciclovir 500 mg t.i.d., valacyclovir 1000 mg t.i.d.). Note that these doses of antivirals barely reach the ID50 for controlling VZV, so these full doses should always be used (except in cases of renal failure).
- **The key management issues for VZV**
  - Need for chronic corticosteroids to control chronic VZV ocular inflammation (the patient may be on topical corticosteroids for years)
  - Recurrent and chronic infectious ocular zoster (requiring chronic oral antivirals)
  - Neurotrophic keratopathy (this is ***not*** managed with topical lubricants)

- Postherpetic neuralgia.

Metaherpetic keratitis

- Medical
  - Withdraw epitheliotoxic drugs
  - Intensive lubricants
  - Cycloplegics
  - Steroids
- Surgical
  - Conjunctical flap
  - AMG
  - Glue for small perforation
  - Patch graft
  - Tectonic graft

Adenoviral keratitis

- EKC
- 8,19,37
- 10% transmission ot household contacts
- Severe follicular kerato conjunctivitis
- Hemorrhagic conjunctivitis
- Acute stage
  - Cold compresses
  - Lubricants
  - Prophylactic antibiotics
- Nummular opacity
  - Topical steroids: 6 weeks
  - Topical cyclosporine
  - Lubricants

Epidemic Keratoconjunctivitis (EKC)

- Several recent studies on adenoviral DNA recombination have made it pretty clear that our current methods of serotyping virus to identify strains of adenovirus responsible for EKC are deeply flawed. So, it is probably not a bad idea to empty your brain of the adenoviral

serotypes responsible for EKC, thus making room for some new concepts in the diagnosis and management of EKC.

- The AdenoPlus system has been heralded as a sensitive and specific point-of-care assay for the diagnoses of adenoviral conjunctivitis. The company reports an 85% sensitivity and 98% specificity for this assay, as compared to polymerase chain reaction (PCR). However, an independent study out of Moorfields Eye Hospital (Kam et al, *Br J Ophthalmol.*, 2015) could not replicate this level of sensitivity, finding that the AdenoPlus system reached a sensitivity of only 39.5% as compared to PCR. Ongoing studies are investigating the treatment of EKC with topical povidone iodine and a topical povidone iodine dexamethasone combination.
- For years topical corticosteroids have been used to manage the corneal infiltrates associated with ocular adenoviral infection. Tacrolimus and cyclosporine have also been reported to be useful in the management of the superficial keratitis of EKC.

Herpes zoster ophthalmicus (HZO)

- Incidence is increasing, and the age at which it occurs is decreasing, which may be related to the widespread vaccination of children against chickenpox.
- **Etiology**:
  - Zoster is caused by the decline in cell-mediated immunity (CMI), which allows latent herpes zoster virus in the trigeminal ganglion to reactivate.
  - Ocular involvement by zoster can cause long-term effects due to the live virus, as well as immune reaction to the residual viral DNA in the cornea even after resolution of the active infection.
- **Clinical features**
  - Zoster can affect nearly all parts of the eye and visual system and cause significant morbidity.
  - Acute effects such as corneal pseudodendrites are caused by live virus and treated with high doses of antiviral medications.
  - Late effects, such as nummular keratitis, endotheliitis, and uveitis, are thought to be immunogenic and are treated primarily with steroids.
  - The most problematic long-term complication is post-herpetic neuralgia, which is very difficult to manage and treat.
- **Prevention**:
  - Two vaccines are commercially available for zoster and result in an increase in host CMI.
  - Zostavax
    - was licensed in 2006 and is a live attenuated vaccine. Its efficacy ranges from 70% in 50to 59-year-olds to 34% in ≥70-year-olds, rapidly declining over the next few years.

        - Reduces burden of disease by 61%, postherpetic neuralgia (PHN) by 66%, incidence of HZ by 51%
    - A newer recombinant zoster vaccine, Shingrix, was licensed in 2017 and offers a significantly higher rate of protection, ranging from 97% in 50to 70-year-olds and 91% in ≥70-year-olds. It is effective longer but has been in short supply.
    - Whether to vaccinate individuals who have previously had HZO remains controversial. Both vaccines are labelled for use in patients with a previous history of zoster. However, there are several reports of reactivation of quiescent HZO after vaccination. Also, it is conceivable that exposure to a high load of zoster virus, as occurs in HZO, would be protective, at least for several years, so vaccination could be deferred.
- To summarize: an ounce of prevention is better than a pound of cure.

Corneal Complications of Intraocular Surgery

- Epithelial: Abrasion, Edema, Filaments, Toxic keratopathy
- Thermal burns: Cautery, Phacoemulsification probe
- Infection: Bacterial, Fungal, Herpes simplex keratitis
- Descemet's membrane: Tear, Detachment
- Endothelial injury: Aphakic bullous keratopathy, Pseudophakic bullous keratopathy, Brown-McLean syndrome, Phakic bullous keratopathy, TASS

Descemet's membrane Detachment

- Risk factors for Descemet's membrane detachment include blunt knife entry, oblique insertion of instruments, entry of instruments or viscoelastics into a false plane above Descemet's membrane, or history of ocular conditions disrupting Descemet's membrane such as congenital glaucoma, birth forceps injury, keratoconus, and Terrien's marginal degeneration.
- Can spontaneously reattach with medical treatment alone, with a ***mean resolution time of 10 weeks.***
- With large detachments or slow resolution, ***descemetopexy*** with air, sulfur hexafluoride (SF6), perfluoropropane 14% (C3F8) gas injections, sodium hyaluronate or through-and-through corneal mattress sutures may help
- Bullous keratopathy or corneal scarring may occur, requiring endothelial or penetrating ***keratoplasty in 7–8% of cases***

Aphakic/Psudophakic bullous keratopathy

Imbibition pressure = IOP Swelling pressure

- Incidence:
  - ICCE with IOL: 0-0.8%
  - Complicated Cataract Surgery: 0-11.3%
  - Iris clip lens: 9%
  - ECCE with ACIOL: 15%
  - ECCE/Phaco with PCIOL: 0.1% to 0.47%
- PBK with different IOL
  - PCIOL: 0.06%
  - ACIOL: 1.2%
  - Iris-clip lens: 1.5%
- Histopathology:
  - Attenuation and loss of corneal endothelial cells

- Epithelial bullae and stromal edema
- Thickening of the posterior collagenous layer of Descemet's membrane
- Decrease in stromal keratocytes
- Subepithelial and retrocorneal fibrous proliferation
- *Epithelial basement membrane has decreased amounts of* **fibronectin, laminin, and collagen type IV**, *which function as adhesive proteins leading to epithelial bullae*
- *Accumulation of antiadhesive proteins, such as* **tenascin-C and thrombospondin-1**

- **Pathogenesis:**
  - 12% reduction of the central corneal endothelial cell density in eyes having intracapsular cataract extraction
  - **9% central endothelial cell loss at 1 year** after phacoemulsification and posterior chamber lens insertion, with **11.5% loss at 3** years, followed by only 0.3% per year greater loss than in control eyes.
  - **Bates model** predicts decompensation of the cornea at **542cells/mm2** and a time to decompensation of almost **40 years** for uncomplicated cases.
- **Causes of ABK and PBK**

- ***Pre-existing endothelial disease***
  - Fuchs' dystrophy, cornea guttata
  - Pseudoexfoliation
  - Trauma
  - Angle-closure glaucoma

- ***Intraoperative factors***
  - IOL-to-cornea touch
  - Irrigating solutions
  - Instrumentation
  - Sterilization technique: **AbTox Plazlyte**, a sterilization technique that can degrade brass to copper and zinc on cannulated surgical instruments, resulted in irreversible endothelial cell destruction
  - Ultrasound damage
  - Vitreous loss, nuclear loss
  - Drug toxicity
  - Intracameral anesthesia
  - Descemet's membrane detachment
- **Postoperative factors**

- Long-term cell loss
- Vitreous-to-endothelial touch
- IOL dislocation – touch
- Flat anterior chamber
- Peripheral anterior synechiae
- Pseudophakodonesis
- Inflammation
- Toxic materials

- **Treatment:**
  - Anterior stromal puncture may help reduce tearing and pain, and improve vision through regression of epithelial bullae and epithelial edema in patients with early corneal edema
  - Annular keratotomy has also been reported with good success for patients with pain
  - Endokeratoplasty has become the treatment of choice over conventional penetrating keratoplasty for patients with diseased endothelium.
  - Conjunctival flap: In 1958, Gundersen introduced the technique of using conjunctiva alone without use of tenon's capsule to cover the cornea.
  - AMG with basement membrane surface up in all cases. *The side of BM could be distinguished from stromal side by touch with sponge. The former was not sticky, while the later was & could be caught by the sponge.*
  - Cauterisation of Bowman's membrane
  - Diamond burr polishing of basement membrane
  - Phototherapeutic keratectomy for bullous keratopathy
    - ***Superficial PTK showed improvement in 62% cases***
    - ***Intermediate PTK showed improvement in 40% cases***
    - ***Deep PTK: Mean ablation performed was of 206 um, 66% showed improvement***
    - Preterminal neural plexus of cornea is located just deep to Bowman's membrane. Hence moderately deep ablation would have superior effect on decreasing the pain; by ablation of neural plexus.

Brown-McLean syndrome

- Unusual form of peripheral corneal edema occurring long after cataract surgery
- Edema extends 2–3 mm centrally from the limbus and up to 360 degrees, although the superior limbus may remain clear
- Central corneal endothelium may have decreased cell density but rarely becomes edematous

TASS

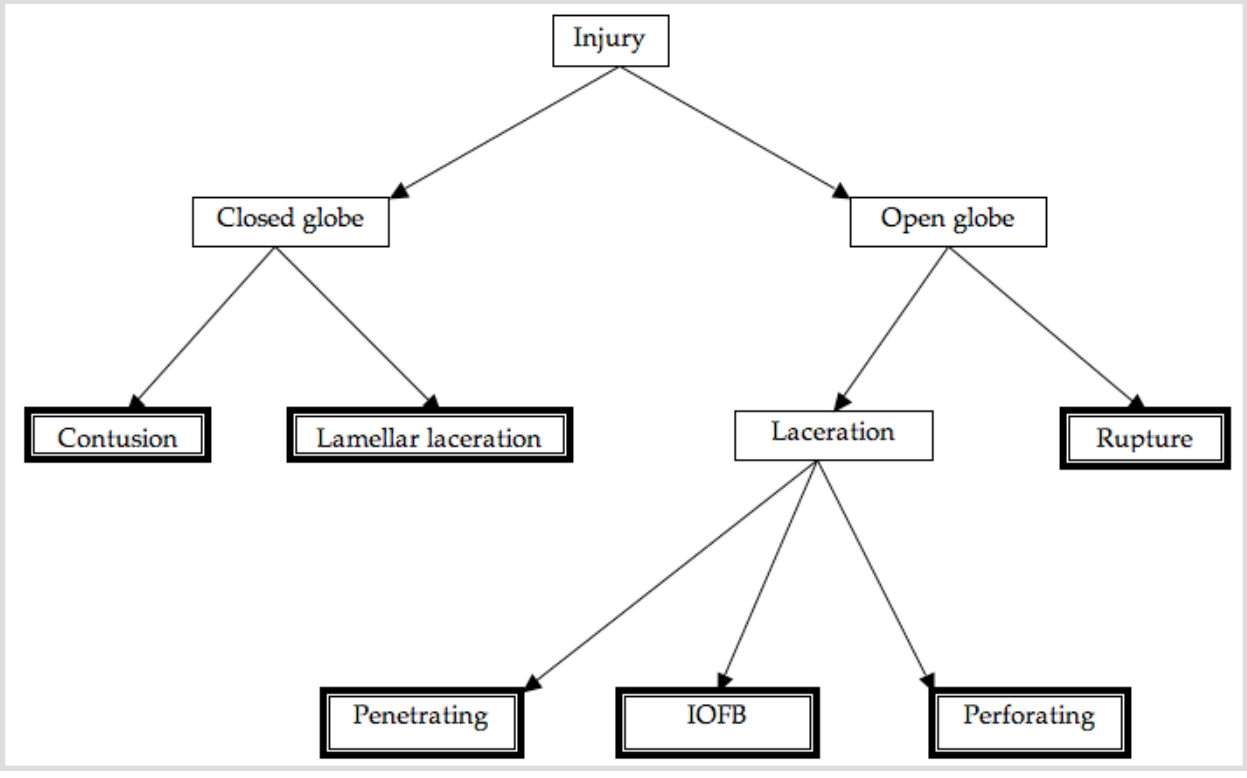
- Sterile postoperative inflammatory reaction most likely caused by a noninfectious agent that gains entry into the anterior segment at the time of surgery and results in toxic damage to intraocular lenses.
- 12 to 48 hours after anterior segment surgery
- Hallmark of this inflammation, which distinguishes it from infectious endophthalmitis is Gram stain and culture negativity
- Blurred vision (60%), anterior segment inflammation (49%), classically with limbus-to-limbus diffuse corneal edema and cell deposition.

Eye Injuries

BETTS: Birmingham eye trauma terminology system

- International society of ocular trauma
- Source – www.isotonline.org/betts

Term	**Definition** and *explanation*
Eyewall	**Sclera and cornea.** *Though technically the eyewall has three coats posterior to the limbus, for clinical and practical purposes violation of only the most external structure is taken into consideration*
Closed globe injury	**No fullthickness wound of eyewall.**
Open globe injury	**Fullthickness wound of the eyewall.**
Contusion	**There is no (fullthickness) wound.** *The injury is either due to direct energy delivery by the object (e. g., choroidal rupture) or to the changes in the shape of the globe (e. g., angle recession)*
Lamellar laceration	**Partialthickness wound of the eyewall.**
Rupture	**Fullthickness wound of the eyewall, caused by a blunt object.** *Since the eye is filled with incompressible liquid, the impact results in momentary increase of the IOP. The eyewall yields at its weakest point (at the impact site or elsewhere; example: an old cataract wound dehisces even though the impact occurred elsewhere); the actual wound is produced by an inside out mechanism*
Laceration	**Fullthickness wound of the eyewall, caused by a sharp object.** *The wound occurs at the impact site by an outside in mechanism*
Penetrating injury	**Entrance wound.** *If more than one wound is present, each must have been caused by a different agent* **Retained foreign object/ s.** *Technically a penetrating injury, but grouped separately because of different clinical implications*
Perforating injury	**Entrance *and* exit wounds.** *Both wounds caused by the same agent*



Mechanical Injury

- Perform a complete examination and not to become distracted by the injury itself
- Errors are rarely made by commission; rather, errors of omission are the rule.
- **Abrading Injuries:**
  - ***Epithelial abrasions:***
    - If Bowman's membrane has not been disturbed, the surface will heal without scarring. If Bowman's membrane is removed, or the corneal stroma is involved, corneal scarring of some degree will result.
    - Quite symptomatic, often out of proportion to the degree of visible injury. The exception to this rule is found in patients with ultraviolet keratitis (welder's 'burn') or contact lens overwear.
    - Pain, photophobia, foreign body sensation, and tearing
    - Cycloplegic agent, topical antibiotics, and application of a tight patch/ BCL.
    - NSAIDs for pain control, did not result in a delay in healing.
    - Most corneal abrasions heal spontaneously without difficulty in 24 to 48 hours
  - ***Stromal abrasions***
    - Occur in the setting of a tangential blow with an abrasive or sharp object.
    - Abrasion without a flap, the therapeutic options depend on the amount of tissue remaining.
    - If a corneal flap is present, the therapeutic goal becomes stabilization of the remaining tissue in its proper anatomic location.
    - Major complications seen in these patients is keratorefractive alteration, which can be difficult to correct.
- **Blunt Trauma**
  - ***Contusion injuries:*** result from direct impact and may involve tissue bruising and fractures.
  - ***Concussion injuries***, on the other hand, arise from the rapid acceleration, deceleration, or oscillation of tissues as a result of the impact and energy transfer to the surrounding tissues
  - ***Diffuse endotheliopathy:*** eyes with angle recession <180 degrees had a 12% decrease in endothelial cell density compared to the fellow uninjured eye. Eyes with greater than 180 degrees of recession had a 21.2% decrease compared to their fellow eyes.
  - ***Endothelial rings***
  - ***Stromal injuries and fractures***
  - ***Obstetric injuries***

- **Injuries Caused by Radiant Energy**
  - UV Radiation
  - Infrared Radiation
- **Thermal Burns**
- **Foreign Body Injuries:**
  - Second to corneal abrasions, corneal foreign bodies are the most common form of ophthalmic trauma.
  - Sclerotic scatter may highlight transparent intrastromal foreign material, whereas retroillumination from the iris or fundus will help delineate discontinuities in the stroma.
  - In most cases of superficial foreign bodies, a tuberculin syringe with an attached 27or 30-gauge needle is an effective instrument for removal.
  - Rusting begins almost immediately after the object is embedded, and a ring may begin to form as early as 3 hours after injury
- **Stings**
  - Bee and wasp stings
  - Jellyfish stings

Corneal & Corneoscleral Laceration

- **Etiology**:
  - blunt or penetrating globe trauma
  - Incidence is highest in industrial and farm workers, and in young males
- **Clinical Features**
  - Clinically evident corneal, corneoscleral, or scleral laceration
  - Uveal prolapse
  - Flat or shallow anterior chamber
  - Hypotony
  - Aqueous humor efflux as detected by Seidel test
  - Iris defect, irregular pupil, or unilateral cataract after trauma may indicate occult corneal or scleral laceration and possibly an intraocular foreign body
  - Blood in anterior chamber (hyphema; "8-ball hyphema" usually tell-tale sign)
  - Subconjunctival hemorrhage may hide underlying scleral laceration
- **Tests**
  - Assess extent of injury to formulate medical or surgical management: Partial thickness versus full thickness, Seidel testing for smaller lacerations, Length and depth of laceration, Iris prolapse, Lens injury

- Perform ophthalmic evaluation to rule out concomitant ocular injury (e.g., traumatic optic neuropathy, intraocular foreign body, vitreous detachment may indicate posterior injury)
- Evaluate other eye
- X-ray or CT scan; MRI if metallic foreign body not suspected

- **Management**
  - Protective shield until intervention is possible
  - Consider obtaining cultures of external eye
  - Bandage soft contact lens for small lacerations with no wound gape
  - Aqueous suppressant (e.g. carbonic anhydrase inhibitor)
  - Cyanoacrylate tissue adhesive for pinpoint perforations
  - Possible need for corneal tissue if portion of cornea is missing from wound
  - Topical and/or subconjunctival antimicrobial prophylaxis (partial thickness lacerations); systemic antimicrobial prophylaxis (full-thickness lacerations)
  - Pain medication, Antiemetics and Tetanus prophylaxis may be applicable depending on mechanism of laceration
- **Surgical Repair of Laceration**
  - General anesthesia (avoid agents that cause contraction of the extra-ocular muscle such as succinylcholine, use nondepolarizing muscle relaxants instead) and perioperative antibiotics
  - Inspect for iris prolapse and incarceration: May need to excise necrotic or epithelialized tissue
  - OVD: Can be used to deepen the chamber and relieve iris incarceration
  - Align wound at limbus first
  - Use 9-0 nylon for limbus and 10-0 nylon for clear cornea with spatulated needle
  - Use large, compressive sutures to close the peripheral aspects of the wound and smaller bites to close the central cornea
    - This flattens the peripheral cornea and steepens the central cornea, resulting in some reduction of astigmatism
    - Suture placement should avoid posterior wound gape
  - Orient suture bites 90 degrees to wound with 90% stromal thickness
  - Stellate lacerations may require a purse string suture for closure
  - Remove the lens if anterior capsule disrupted
  - Anterior vitrectomy if indicated
  - Conjunctival peritomy when scleral laceration suspected
  - Inspect carefully to insure watertight globe

Chemical Injuries of the Eye

- A strong acid or base can be thought of as being more or almost completely dissociated into cations (+) and anions (–) in solution. And they have ph towards extremes of limits.
- In biologic systems, **alkaline agents saponify the lipids of cell membranes**, causing both rapid and deep penetration. **Acids, on the other hand, precipitate and denature proteins** somewhat limiting further penetration. Alkalis penetrate lipid layers more readily and rapidly; however, acids bind proteins, limiting penetration but potentially increasing the local duration of exposure to the anion. Acid anions with higher binding potentials can cause damage at higher pH than anions with lower binding potentials.
- An **amphoteric substance** is loosely related to buffers in that it is capable of acting like either an acid or a base, and as such, it can neutralize both acids and bases. Two products have been introduced taking advantage of this phenomenon: ***Diphoterine, and Hexafluorine***, both developed by Prevor Laboratories in France. Diphoterine is an amphoteric, hypertonic, polyvalent compound for use in ocular and skin decontaminations of about 600 chemicals, including acids, alkalis, reducers, oxidizers, alkylating agents, and radionucleotides. Additionally, the binding reaction is not exothermic. Hexafluorine is its counterpart for ocular and dermal exposures to hydrofluoric acid as well as fluorides in acidic environments.

Acid Injury

- Acids are components in ***rust removal products, pool cleaners, and car batteries***
- **Most serious is hydrofluoric acid & MC is sulfuric acid. (Survey)**
- Traditionally, acid injuries have been considered ***less destructive*** to the eye than alkali injuries.
- **Collagen shrinkage** immediately raises the intraocular pressure, and the effect persists for at least 3 hours through the elaboration of prostaglandins, possibly from the presence of H+ ions in the aqueous. Additionally, the **stroma liberates ascorbic acid** (vitamin C). In severe acid injuries, ascorbate levels in the aqueous plummet after 24 hours, probably due to either breakdown of the blood–aqueous barrier or damage to the active transport mechanism of the ciliary body. Ascorbate is an essential element in the elaboration of collagen, and its loss can lead to stromal ulceration.
- **Mucopolysaccharides**, which are initially unharmed by acid, are either liberated from damaged tissue or destroyed, contributing to decreased tear breakup time, punctate staining (PEE), or slow-healing epithelial defects.
- **Epithelial breakdown** can result in stromal edema, especially in the first 24–36 hours; however, as long as the endothelium is undamaged, stromal hydration largely normalizes upon reepithelialization.

- ***Hughes Classification and prognosis in acid injuries of the eye (ESCLator) (for Chronic Injury)***

Grade	Epithelial opacity, defect	Stromal edema, opacity	Conjunctival involvement	Limbal ischemia	Recovery	1 Vision impairment, 2 scarring, 3 vessels
(I) Mild	Opacified white	None to minimal, none	Erythema, opacification, chemosis	None	Rapid	1, 2, 3 none to little
(II) Moderate	Opacified white,common at 24–36 hours	Mild to moderate, none	Opacification, chemosis, petechia or subconjunctival hemorrhage	None to minimal	Epithelial healing likely within 10 days	1 mild, 2 faint anterior scar possible, 3 little tendency
(III) Severe	Entire epithelium opacified white	Moderate to severe, mild opacity obscures iris details	Opacification, hemorrhages, necrosis	≤1/3	Epithelial healing possible in weeks to months, ulcers/ perforation possible	1 moderate to severe, 2 moderate anterior scar, 3 peripheral usual
(IV) Very severe	Opacified white (if present) and sloughs rapidly	Marked, severe	Necrosis may be extensive	>1/3	Protracted (months–years), sloughing of stroma possible with ulceration/perforation	1, 2, 3 extensive, like severe alkali injuries

- **Treatment**
  - **Copious and continuous irrigation** of clean water or other nontoxic irrigant: low osmotic washes such as tap water or high buffer capacity agents such as ***diphoterine or Cederroth Eye Wash Solution*** should be considered for use as initial rinsing agents.
  - Never use a base to neutralize an acid because it can magnify the injury.
  - Irrigating lens should be inserted into the fornices while the solution is flowing.
  - Checking the fornices for particulate matter by double inversion of the lids and sweeping them with moist, sterile cotton swabs
  - End point, a ***pH check of the tears 5 to 10 minutes following irrigation*** might be useful, and if the pH is less than 7, irrigation should continue.
  - Following irrigation, a more thorough ophthalmologic examination should ensue, including vision, external and slit lamp examinations, epithelial and limbal involvement, stromal edema, and intraocular pressure.
  - **Broad-spectrum topical antibiotic** to guard against infection in the face of an epithelial defect
  - Moderately long-acting **cycloplegic** agents
  - Topical or oral **anti-glaucoma** agents

- Topical ***NSAIDs drugs should be used cautiously*** due to the possibility of corneal melting in conjunction with epithelial defects
- Significant inflammation and/or secondary iritis may benefit from cautious use of ***topical steroids in the first 7 to 10 days***; however, the use of steroids beyond this time may increase corneal ulcerations or perforations.
- **Systemic ascorbic acid (vitamin C)** has been shown in an animal study to reduce the rate of corneal ulceration in acid injuries.
- **AMT** is being utilized in both acute and chronic chemical
- **LSCD** occurs most frequently in high-grade chemical injuries with extensive perilimbal ischemia.
- Limbal stem cell transplants range from conjunctival limbal autografts (CLAU), living related and cadaveric donors, to ex vivo culture expanded limbal epithelium.
- (DALK) with limbal stem cell transplantation with or without AMT
- Limbus-to-limbus penetrating grafts.

Alkali Injuries of the Eye

- Nonperforating ocular injuries of this type result in destruction of cellular components, denaturation and degradation of collagenous tissues, and release of inflammatory mediators by alkaline ***hydrolysis of a broad range of intracellular and extracellular proteins***, invading cells, and basal epithelial cells.
- The hydroxyl ion (OH) saponifies the fatty acid components of cell membranes, resulting in cell disruption and death, while the cation is responsible for the penetration of the specific alkali. Cations react with carboxyl COOH group of stromal collagen and GAGs.
- The type of alkali causing eye injury can be ammonia, lye, potassium hydroxide, magnesium hydroxide, or lime. Most serious is ammonia/ lye & MC is Lime. (Survey)
- The pain, lacrimation, and blepharospasm following an ocular alkali injury result from direct injury of free nerve endings located in the epithelium of the cornea, conjunctiva, and eyelids.
- A **wave of hydroxyl ions** rapidly penetrates the eye, causing saponification of cellular membranes with massive cell death and partial hydrolysis of corneal glycosaminoglycans and collagen.
- ***Spiking rise in the intraocular pressure***, lasting about 10 minutes, caused primarily by shrinkage of the collagenous envelope of the eye. A more prolonged rise in pressure quickly follows, secondary to prostaglandin release.
- ***Repair***:
  - loss of epithelial adhesion might result from accelerated degradation of fibrinogen by plasminogen activator, a substance probably secreted in excessive amounts by the basal epithelial cells in the alkali-injured eye.

- Healing of the corneal stroma: (1) degradation and removal of necrotic debris, and (2) replacement of portions of the fixed cells, collagenous matrix, and glycosaminoglycans.
- Moderate injuries probably cause some endothelial cell death but mostly interfere with the pump mechanism, leading to a variable degree of reversible corneal edema. Severe injuries will destroy endothelium, which leads to severe corneal thickening.

- ***Classification of Alkali Injuries***:
- **Roper Hall classification (for Chronic)**

Grade	Prognosis	Cornea	Conjunctiva/limbus
I	Good	Corneal epithelial damage	No limbal ischaemia
II	Good	Corneal haze, iris details visible	<1/3 limbal ischaemia
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	1/3–½ limbal ischaemia
IV	Poor	Cornea opaque, iris and pupil obscured	>½ limbal ischaemia

- **Dua's classification**
  - A new classification has been proposed by Dua et al that take into account the extent of limbal involvement in clock hours and the percentage of conjunctival involvement.
  - Dua et al stressed the inadequacy of the currently followed RoperHall classification that is reflected in the inconsistencies of success rates reported in literature. This is particularly true for grade IV burns (50-100% limbal ischemia) which are equated with poor prognosis.

Grade	Prognosis	Clinical findings	Conjunctival involvement	Analogue scale
I	Very good	0 clock hours of limbal involvement	0%	0/0%
II	Good	⩽3 clock hours of limbal involvement	⩽30%	0.1–3/1–29.9%
III	Good	>3–6 clock hours of limbal involvement	>30–50%	3.1–6/31–50%
IV	Good to guarded	>6–9 clock hours of limbal involvement	>50–75%	6.1–9/51–75%
V	Guarded to poor	>9–<12 clock hours of limbal involvement	>75–<100%	9.1–11.9/75.1–99.9%
VI	Very poor	Total limbus (12 clock hours) involved	Total conjunctiva (100%) involved	0.12%

- **Treatment:**
- **McCulley's 4 stages:**
  - **Immediate, Acute 0-7 days, early repair 7-21 days, late repair after 21 days.**
  - **Immediate**
    - Thorough washing of eye with saline or water for at least 30 min
    - Assessment of injury with history and examination

- **Acute**
  - Topical steroids 2 hourly inhibits PMN proliferation and function
  - Topical sodium citrate 10% 2 hourly inhibits PMN degranulation by Ca chelation
  - Tetracycline 1% ointment QID inhibits collagenase enzyme by chelating with Zn.
  - Oral sodium ascorbate 500mg QID promotes collagen synthesis
  - Topical sodium ascorbate 20% 2 hourly promotes collagen synthesis
  - Tear substitutes 2 hourly promotes epithelial healing
  - Cycloplegics TDS or BD relieves pain
  - Topical/oral antiglaucoma therapy, if needed
  - Conjunctival/tenons advancement for grade-IV. Improves vascularization
- **Intermediate stage**
  - Review of patient
  - Rapidly taper steroids after 10 days
  - Continue topical and oral medication
  - Look for stromal ulceration
  - Prevent symblepharon formation
  - Look for re-epithelialisation
- **Sequelae**
  - Symblepharon formation
  - Limbal stem cell deficiency

- ***Immediate irrigation*** at the scene of the accident with clear water and subsequently the emergency room for 1 to 2 hours with isotonic buffered saline.
- ***Reformation of the aqueous humor*** with buffered phosphate solution lowered the pH by an additional 1.5 pH units. It is premature to suggest that all severe alkali injuries should undergo paracentesis.
- **Diphoterine (Prevor)** is a proprietary amphoteric compound which has been much heralded as a universal emergency irrigant for eyes injured with acidic or alkaline compounds.
- Sticky paste of lime: ***EDTA 0.01 M***
- Intraocular pressure rise after alkali injury can usually be treated by topical alpha or beta-blockers and topical and/or systemically administered carbonic anhydrase inhibitors

- **Limbal stem cell ischemia is looked for and graded by the newer classification.**
  - Grade-I Involves little or no loss of limbal stem cells and presents with little or no evidence of ischemia

- Grad-II Involves subtotal loss of limbal stem cells and presents with ischemia of less than one half of the limbus.
- Grade-III Involves total loss of limbal stem cells with preservation of proximal conjunctival epithelium and presents with ischemia of one half the entire limbus.
- Grade-IV Involves total limbal stem cell loss as well as loss of proximal conjunctival epithelium and extensive damage to entire anterior segment.

- **The severity of injury will show the following healing patterns.**
  - Grade-I Healed cornea with normal epithelium
  - Grade-II Epithelial defect, smaller in size
  - Grade-III No epithelization, inflammation
  - Grade-IV Sterile corneal ulcer + conjunctival defect, inflammations

Neoplastic Disorders

OSSN: Ocular Surface Squamous Neoplasia

- Ocular surface squamous neoplasia (OSSN) is a blanket term currently used for precancerous and cancerous epithelial lesions of the conjunctiva and cornea that includes the spectrum of dysplasia, conjunctival intraepithelial neoplasia, and malignant squamous cell carcinoma.
- **Etiology**
  - Neoplasia of the epithelium of the limbal conjunctiva and/or cornea
  - Varies from partial thickness dysplasia to full thickness disease to invasive squamous cell carcinoma
  - Human papillomavirus found in some cases of conjunctival intraepithelial neoplasia
  - Higher prevalence with untreated acquired immune deficiency syndrome (AIDS)
- **Morphological Types of OSSN**
  - Placoid
    - Gelatinous
    - Papilliform
    - Velvety
    - Leukoplakic
  - Nodular
  - Diffuse
- **Clinical features**
  - Conjunctival intraepithelial neoplasia
    - Vascularized limbal lesion
    - Keratinization (e.g., leukoplakia) and inflammation may indicate increased risk of dysplasia
    - Conjunctiva may stain with Rose Bengal
  - Corneal intraepithelial neoplasia
    - Gray epithelium, often with fimbriated margin usually contiguous with limbus although free islands may occur
    - May slowly change size and shape
    - Adjacent limbus may appear clinically normal or corneal lesion may be associated with signs of conjunctival intraepithelial neoplasia
  - Squamous cell carcinoma of the conjunctiva
    - Limbal lesion may appear papilliform, gelatinous, or leukoplakic
    - Most often occurs in the interpalpebral fissure
    - Pigmentation of lesion may be present in dark-skinned individuals
    - May be affixed to the underlying tissue

- Types of Invasive Conjunctival SCC
  - Spindle cell variant
  - Mucoepidermoid carcinoma
  - Adenoid squamous carcinoma

- **Tests**
  - Histopathological examination of incisional or excisional biopsy
  - Impression cytology
  - Anterior segment OCT is used as a diagnostic aid
  - Optical biopsy: A novel technology of ultrahigh-resolution spectral domain OCT, has proven useful in detecting epithelial lesions
  - UBM
  - Orbit CT
- **Risk factors**
  - Light complexion
  - Advancing age
  - Environmental risk factors such as cigarette smoking, sunlight exposure, and exposure to certain chemicals such as pesticides and petroleum products
  - Immunosuppression and human immunodeficiency virus (HIV) infection may increase incidence of conjunctival squamous neoplasia and/or potential for growth
  - Possible role of human papilloma virus 16,18, 8, and 5
  - Papillon-Leferve syndrome, a rare syndrome with palmoplantar keratoderma, is also associated with OSSN in younger individuals
  - There is a strong systemic association with xeroderma pigmentosum that may present as multiple recurrent lesions requiring long-term follow-up
- **Differential Diagnosis**
  - Conjunctival intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva
    - Pterygium
    - Pinguecula
    - Nodular episcleritis or scleritis
    - Foreign body reaction
    - Pyogenic granuloma
    - Epibulbar dermoid tumor or other choristoma
    - Melanoma of the conjunctiva
    - Sebaceous carcinoma of the conjunctiva
    - Conjunctival primary localized amyloidosis
    - Benign hereditary intraepithelial dyskeratosis
  - Corneal intraepithelial neoplasia

- Limbal stem-cell failure or deficiency
- Superior limbic keratoconjunctivitis
- Vernal or atopic keratopathy
- Rosacea keratopathy
- Toxic epithelial keratopathy
- Corneal epithelial basement membrane dystrophy
- Spheroidal/Salzmann degeneration

- **Medical Management**
  - **Indications for Topical Chemotherapy in Noninvasive OSSN**
    - >2 quadrants of conjunctival involvement
    - >180 degree of limbal involvement
    - Clear corneal extension encroaching the pupillary axis
    - Positive margin after excision
    - Patient not fit for surgery
  - **Protocol for Interferonalpha 2b**
    - Topical eye drops 1 million IU 4 times a day for 3 to 12 months
    - Injection sublesional 3 to 10 million IU once monthly until resolution
    - Refrigeration required
  - **Protocol for Topical MMC: Rule of 4**
    - 0.04% (0.4 mg/mL)
    - Four times a day
    - Four days a week
    - Four weeks
    - Two weeks of treatmentfree interval
    - Refrigeration required
  - **Protocol for Topical 5-Fluororacil**
    - 1% eye drops 4 times a day for 4 weeks (1 cycle)
    - Two weeks of treatment-free interval
    - Refrigeration *not* required
- **Surgical Management**
  - Conjunctival intraepithelial neoplasia: excisional conjunctival biopsy with cryotherapy
  - Corneal intraepithelial neoplasia: chemical or mechanical debridement with limbal excision and cryotherapy
  - Squamous cell carcinoma: excisional biopsy with margin control, may involve lamellar sclerectomy and adjunctive cryotherapy

- **Surgical technique: NO-TOUCH technique:** Complete but gentle surgical excision using a technique without touching the tumor is called the “no-touch” technique

- **Complications**
  - Incomplete removal and destruction of lesion, recurrence
    - Reported recurrence rate is 15%-52%. Lee et al reported a 17% recurrence after excision of conjunctival dysplasia, 40% after excision of CIN, and 30% for squamous cell carcinoma
  - Conjunctival scarring
  - Ulceration, inflammation, punctal stenosis, or other adverse effect due to topical 5-FU or mitomycin C
  - Limbal stem cell deficiency (LSCD) /failure

Primary Acquired Melanosis (PAM) of Conjunctiva

- **Etiology**: Neoplasia of conjunctival melanocytes
- **History**
  - Unilateral pigmentation in typically light-skinned ethnicity, in contrast to bilateral involvement of racial melanosis
  - Size and shape of lesion: stable or progressive, may be associated with hormone changes such as puberty or pregnancy
  - Usually has little or no conjunctivitis
- **Clinical features**
  - Flat, brown lesion of the conjunctival epithelium
  - Unilateral or may be asymmetric between two eyes
  - May be single or multiple
  - Irregular margins
  - Signs of malignant transformation: Enlargement, Increased pigmentation, Nodularity, Increased vascularity of inflammation, Conjunctival feeder vessel
  - Rare pigmentary variations
    - No visible pigmentation (amelanotic)
    - Eyelid margin pigmentation
    - Corneal epithelium may have fine pigmentation
- **Tests**
  - Slit lamp photography
  - Biopsy with histopathological examination to determine malignant potential
    - Excisional biopsy if possible
    - Incisional or map biopsy if diffuse lesion, involving palpebral, fornix, caruncle region.

- Map biopsy obtain approx. 2mm x 2mm specimen from various quadrants of the ocular surface, from least involved area to most involved area, placing them in the corresponding area of the Telfa-type paper with eye drawing

- **Differential Diagnosis**
  - Congenital pigmented lesions of the conjunctiva or episclera
    - Benign racial melanosis of conjunctiva (complexion-associated conjunctival pigmentation)
    - Congenital conjunctival nevus
    - Ocular melanosis (melanosis oculi) and oculodermal melanosis (nevus of Ota)
  - Acquired pigmentation of the conjunctiva
    - Acquired conjunctival nevus
    - Secondary acquired melanosis of conjunctiva
    - Melanoma of conjunctiva (See Melanoma of the conjunctiva)
- **Management**
  - Observation: Serial examination with photography
  - Therapeutic intervention
    - Excisional biopsy
    - Cryotherapy
    - Topical mitomycin C: Adjuvant therapy for positive margins/large lesions and for primary treatment for nonsurgical patients
- Lower melanoma risk if no or mild atypia on histopathology
- Higher melanoma risk if severe atypia on histopathology

Conjunctival Melanoma

- **Etiology**: Often arises from primary acquired melanosis of the conjunctiva, may evolve from preexisting conjunctival nevus or may appear de novo
- **Clinical examination**
  - Location of lesion (bulbar versus palpebral conjunctiva vs forniceal)
  - Size, thickness, number, and nodularity of lesion(s)
  - Check whether lesion is attached to the underlying sclera or is freely movable
  - Palpation of ipsilateral preauricular, submandibular, and cervical lymph nodes
  - Rule out uveal melanoma with dilated fundus examination, transillumination, or ultrasonography
  - Examine skin or recommend dermatology consult to look for cutaneous melanoma
- **Tests**

- Excisional biopsy for suspicious lesion, such as large or nodular lesion or lesion having progressive increase in size or thickness
- Histopathological examination to determine presence and severity of cellular atypia and prominent cell type: epithelioid, spindle, or mixed.
- Consider ultrasonography for thick lesion or possible intraocular extension
- UBM or ASOCT
- Obtain imaging (e.g., computerized tomography (CT) or magnetic resonance imaging (MRI)) of orbit and paranasal sinuses
- Consider roles of orbital surgery and/or radiotherapy if extensive disease
- Consider sentinel node biopsy if clinically indicated (large thicker lesion)
- Consult with oncologist to detect metastasis, which tends to involve lung, liver, brain, or skin

Risk factors

- Middle-age or elderly
- White race or light-skinned ethnicity (e.g., European and Eurasian descent) more common, but can rarely occur in darker-skinned races/ethnicities (Asian or African descent)
- Previous primary acquired melanosis of the conjunctiva or conjunctival acquired nevus
- Severe atypia on histopathology of primary acquired melanosis
- Site of lesion on conjunctiva (lesions of limbal and bulbar conjunctiva may have less risk of post-excision recurrence than lesions of palpebral conjunctiva, fornix, or caruncle)
- Number of pigmented lesions
- Other histopathologic characteristics: tumor thickness, growth pattern, ulceration, mitotic figures, and scleral invasion

Differential Diagnosis

- Conjunctival nevus
- Primary acquired melanosis
- Pigmented epithelial tumor, including squamous cell carcinoma
- Ocular melanocytosis
- Staphyloma
- Implantation of foreign substances: calcium, medications, cosmetics

Management

- Surgical excision
  - Key techniques: no touch, alcohol keratectomy, partial lamellar scleroconjunctivectomy, 2-4 mm margins, double freeze-thaw cryotherapy
  - The first surgery is the most important.

        - Sentinel lymph node biopsy: Consider if malignant melanoma with tumor thickness >2 mm
    - Adjunctive therapy to destroy residual tumor cells
        - Intraoperative cryotherapy of margins and scleral bed
        - Alternatively, absolute alcohol to adjacent corneal epithelium (if limbal involvement) and scleral base
        - Mitomycin or Interferon Alpha 2b for topical chemotherapy
    - Orbital exenteration or radiotherapy may be considered for diffuse, multifocal, or extended melanoma
    - Role of Molecular Medicine in Conjunctival Melanoma
        - Biomarkers for prediction of metastatic risk and targeted therapy: BRAF, KIT, NF1, NRAS, PD-1, PD-L1, PTEN, TERT
        - Targeted systemic medications
            - BRAF inhibitors: vemurafenib (Zelboraf), dabrafenib (Tafinlar), encorafenib (Braftovi)
            - Checkpoint inhibitors: ipilimumab (Yervoy), pembrolizumab (Keytruda), nivolumab (Opdivo), atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi)
- **Atypical presentations of ocular surface malignancy**
    - Amelanotic melanoma can mimic squamous cell carcinoma.
    - Pigmented squamous cell carcinoma can mimic melanoma.

Conjunctival Lymphoma

- **Etiology**: Monoclonal proliferation of lymphocytes, most commonly B cells
- **Epidemiology**:
    - Usually young to middle aged adults
    - Ocular involvement represents only 2% of extranodal lymphoma
    - Lymphoid tumors of the conjunctiva associated with systemic lymphoma in up to 31% of patients
    - Systemic lymphoma found more often in patients with forniceal or mid bulbar conjunctival involvement and those with multiple conjunctival tumors, and bilateral disease
    - May have infectious etiology such as Chlamydia or H. pylori
- **Clinical features**
    - Painless with chronic redness, FB sensations
    - Diffuse; slightly elevated pink mass located in the stroma or deep to Tenon fascia
    - Color similar to salmon, hence the term "salmon patch"
    - Lesions are fleshy, often originate in fornix or adjacent to the limbus

- **Tests**
  - Incisional biopsy of lesion for histopathologic diagnosis, must send fresh tissue for flow cytometry and gene rearrangement
  - Evaluation for systemic lymphoma in conjunction with oncologist if biopsy is positive Tumor staging with complete blood count (CBC) and differential, imaging studies, including PET scan, bone marrow aspiration
- **Differential Diagnosis**
  - Benign lymphoid hyperplasia
  - Scleritis and episcleritis
  - Ectopic lacrimal gland
  - Amyloid deposition
  - Foreign body with pyogenic granuloma
  - Lymphangiectasia
  - Sarcoidosis
  - Cat Scratch Disease
  - Degenerative conjunctival changes (e.g., pinguecula, pterygium)
- **Management**
  - Treatment options depend on the presence of systemic disease
    - Radiation considered for symptomatic lesions, especially if they threaten vision
    - Chemotherapy for aggressive histological subtypes and for systemic diseased
    - Anti CD 20 immunotherapy (e.g., Rituximab)(intralesional or systemic)
    - Intralesional interferon alpha-2b
  - Surgical incisional biopsy for histopathologic diagnosis, rarely as a therapeutic modality

Conjunctival Papilloma

- Conjunctival papilloma is related to human papillomavirus (HPV) infection.
- HPV is a common virus that can cause cervical, vaginal, and vulvar cancers in females and penile cancer in males. HPV can also cause anal cancer, throat cancer, genital warts, and conjunctival papillomas.
- **HPV types**
  - There are > 100 types of HPV.
  - Types 6 and 11 cause the common wart of skin, genitals, and conjunctiva. At delivery through the vaginal canal, a child can pick up the mother's HPV and eventually develop conjunctival papilloma or respiratory papilloma.
  - Types 6a, 33, and 45 are less commonly found in conjunctival papilloma.

- Types 16 and 18 can cause carcinoma of the cervix and conjunctiva.

- **Features**
  - Can occur in children (10%) or adults (90%)
  - Related skin warts (18%), genital warts (3%), and HIV (1%) are noted.
  - Occurs in the fornix (19%), tarsus (14%), or plica / caruncle (40%)
  - Those in children are larger and more multifocal, with greater recurrence
- **Treatment**
  - Surgery: Excision and cryotherapy, “no-touch” technique
  - Immunotherapy: Good choice
    - Interferon, topical: 1 million IU/cc q.i.d. for 3 months
    - Interferon injection ≤ 10 million IU per cc under the mass every 1 month x 4
    - Cimetidine: 300 mg PO t.i.d.
  - Chemotherapy: We avoid mitomycin C and 5-fluorouracil for papillomas due to toxicity.
  - Antiviral therapy: Cidofovir
  - Photodynamic therapy: Can be effective
  - Laser therapy: Be careful, as this aerosolizes the HPV and can cause throat papillomas in healthcare workers.
  - What to do with failures: Check immune status and use immunotherapy.
- **Prevention by HPV Vaccine**
  - Cervarix: Bivalent against types 16 and 18
  - Gardasil: Quadrivalent against types 6, 11, 16, 18
  - Gardasil 9: Nonavalent against types 6, 11, 16, 18, 31, 33, 45, 52, 58
    - Released 2014 for girls and boys ages 9-15 years old
    - Three injections
    - Anticipate 90% of genital warts and cervical cancer prevented

Pigmented Iris Tumors

- **Two basic type**
  - Cystic (21%)
  - Solid (79%): melanocytic (68%) and nonmelanocytic (11%)
- Most common specific diagnosis: nevus (42%), iris pigment epithelial (IPE) cyst (19%), and melanoma (17%)
- Iris freckles: associated with older age, more sunburn history, more sun-damaged skin, more skin freckles, and great skin total nevus count.

- Relationship between cutaneous and iris nevi with uveal melanoma: atypical cutaneous nevi, common cutaneous nevi, cutaneous freckles, and iris nevi were all associated with risk for uveal melanoma
- **ABCDEF Guide for Risk factors**
  - A Age (≤40 yrs)
  - B Blood
  - C Clock-hour inferior
  - D Diffuse configuration
  - E Ectropion
  - F Feathery margin
- **Iris Melanoma:**
  - can manifest as a circumscribed nodule or as a flat diffuse mass with extensive seeding.
  - Treatment of iris melanoma includes resection for small tumors; plaque radiotherapy for small, medium, and large tumors or those with seeding; and enucleation for those with secondary glaucoma.
  - A comparison of adults versus children with iris melanoma revealed children with smaller tumor size, less tumor seeding, lower incidence of glaucoma, and better prognosis.
  - metastatic disease in 5% at 5 years, 9% at 10 years, and 11% at 20 years, much lower than the rates found with ciliary body and choroidal melanoma.

Keratoplasty and Other Surgical Procedures

Sir Benjamin Rycroft in his Doyne lecture divided keratoplasty evolution into four periods:

(Mnemonic: In The Future of Cornea, All R Innovating..!!)

1. Inspiration (1789–1824)
2. Trials and Frustration (1825–1872)
3. Conviction (1873–1905)
4. Achievement (1906–1965)
5. Refinement and Innovation (1966-present) (added by others later)

- **Von Hippel** favored lamellar transplantation, performing the first successful human corneal transplant in 1886, in which a full-thickness rabbit cornea was placed into a human recipient corneal lamellar bed.
- First documented successful corneal **penetrating** transplant performed by **Eduard Konrad Zirm** in 1906
- **Franz Reisinger**, who first described the term '***keratoplasty'***
- Work of Ramon Castroviejo that had the most profound influence on modern-day keratoplasty.
- First **eye bank** by R. **Townley Paton** in **1945**
- Max Fine led to the recognition that keratoplasty could be successfully performed for the treatment of aphakic bullous keratopathy
- Immunologic discoveries of A. **Edward Maumenee** and the simultaneous introduction of topical ***corticosteroids***
- **PLK**
  - 1998, **Melles** el al. described the technique of PLK→ just like DLEK
  - **Terry and Ousley** developed new instrumentation and performed a similar procedure in the United States, calling it DLEK.
  - 2004, **Melles**→ DSEK
  - **Gorovoy** advocated the use of a microkeratome→ DSAEK
  - **Melles** et al. described a technique, currently known as DMEK
- **ALK**
  - 1985, **Archila**→ deep lamellar dissection by injecting 1 cc of air
  - 1994, **Sugita and Kondo**→ removed the anterior stromal tissue by standard lamellar dissection, followed by hydrodelineation with saline through a 27-gauge cannula
  - 1998, **Morris** et al. modified the technique Sugita utilized by adding a viscoelastic after hydrodelineation
  - **Anwar and Teichmann's** description of the 'Big Bubble Technique for DALK' in 2002
  - **Vajpayee**→ Double Bubble Technique for DALK

Decision-Making in Keratoplasty

- EBAA statistics from 2009 revealed that **45%** of all keratoplasty procedures performed in the United States were **partial-thickness** corneal grafts.
- **Ocular surface reconstruction procedures**
  - Dry eye states
  - Neurotrophic states
  - Limbal stem cell deficiency states
    - They include, but are not limited to punctal occlusion, tarsorrhaphy, superficial keratectomy, amniotic membrane transplantation, and limbal stem cell transplantation.
- **ALK:**
  - Anterior 85–95% of the cornea, definitely sparing Descemet's membrane and endothelium
    - Corneal ectasias (keratoconus, keratoglobus, pellucid marginal degeneration)
    - Stromal dystrophies (granular, lattice, macular, and others)
    - Scars from previous infections (bacterial, fungal, viral, parasitic, atypical)
  - Lamellar keratectomy (LK)
    - Manual peeling technique
    - Microkeratome-assisted keratectomy
    - Excimer laser phototherapeutic keratectomy
    - Femtosecond laser-assisted keratectomy
  - Tectonic, reconstructive, and excisional anterior lamellar Keratoplasty
  - Automated lamellar therapeutic Keratoplasty (ALTK)
    - conditions affecting the anterior one-half to two-thirds of the cornea and usually sparing the surface.
  - Deep anterior lamellar Keratoplasty (DALK)
    - takes advantage of the potential space between Descemet's membrane and the stroma to cleave the entire host stroma off Descemet's membrane
  - Femtosecond laser-assisted lamellar Keratoplasty (FALK)
- **PLK**
  - Posterior corneal dystrophies (Fuchs', nonguttate endothelial dystrophy, posterior polymorphous)
  - Aphakic and pseudophakic corneal edema and bullous keratopathy
  - Iridocorneal endothelial syndrome (ICE)

- Other causes of endothelial dysfunction (trauma, foreign body, age, etc.)
- Advantages
  - Rapid visual rehabilitation
  - No suture-related complications
  - Decreased incidence of allograft rejection
  - Intact globe, resistant to traumatic wound dehiscence
  - Predictable corneal toricity, minimal topographic change
  - Predictable, small hyperopic refractive shift (1.0–1.5 diopters)
- Transplanted tissue usually measures **100–200 μm** in thickness and includes the donor endothelium, Descemet's membrane, and a lamella of posterior stroma. Thinner donor tissue is associated with a lower incidence of **graft dislocation (<1%)** and rapid clearing of vision.
- Most endothelial cell loss from the donor appears to take place during the insertion of the graft into the recipient's anterior chamber, various injectors, cartridges, and inserters have been developed to ameliorate this problem. One example is the Neusidl Corneal Inserter (NCI)

- **PK**
  - Combined endothelial and stromal disease (Fuchs' dystrophy with corneal ectasia or macular stromal dystrophy)
  - Severe corneal opacification and inability to ascertain the status of the endothelium by history or examination
  - Keratoconus after hydrops with tears in Descemet's membrane; successful deep anterior lamellar keratoplasty is unlikely
  - Other causes of corneal opacification and lack of familiarity with selective keratoplasty techniques
  - Conventional PK
  - Femtosecond Assisted PK

- **Permanent keratoprosthesis surgery**
  - Eyes with multiple graft failures
  - Stem cell deficiency states (aniridia, etc.)
  - Corneas with four-quadrant deep stromal vascularization

Role of Imaging before and after Keratoplasty

- Preoperative Ultrasound Biomicroscopy
  - Assess anterior segment status behind corneal opacities: Anterior chamber (AC) depth, Angle, Lens and anterior capsule, Membranes, Adhesions, Vitreous in AC

- Advantages: Can image ciliary body and through corneal opacities
- Disadvantages: supine position, water immersion, patient cooperation

- Preoperative Anterior Segment OCT (AS-OCT)
  - Assess depth of pathology
  - Advantages: noncontact, sitting position
  - Disadvantages: poor view of ciliary body, poor view through corneal opacities
- Intraoperative OCT
  - Microscope-integrated OCT devices with images observed through: Surgeon's microscope, External screen
  - Aims to improve surgical outcomes for lamellar keratoplasty
  - Deep anterior lamellar keratoplasty: Evaluate needle/dissection depth, Evaluate big bubble dissection plane, Evaluate residual stromal thickness, Detect microperforation
  - DSAEK-DMEK: Evaluate graft–host apposition Assess the extent of interface fluid, Verify graft orientation (DMEK; avoids marking tissue), Faster graft positioning with less graft manipulation
- Postoperative OCT
  - Assess DSAEK/DMEK graft: Thickness, Centration, Location and extent of detachment, Epithelial ingrowth
  - Influences management: Graft reshaping, Graft repositioning, Rebubbling
  - Assess graft–host junction and graft interface
- Postoperative in vivo confocal microscopy/specular microscopy:
  - PK late endothelial graft failure
    - Preop donor endothelial cell density (ECD) not predictive
    - Low ECD at 6 months post-PK
  - DSAEK late endothelial graft failure
    - Preop donor ECD not predictive
    - Low ECD at 6 months post-DSAEK
    - Intraoperative difficulties

Penetrating Keratoplasty

- **Patient Selection:**
  - Age: advantages of advancing age is that the immune system is less likely to mount a graft-destroying rejection
  - Mild to moderate mentally challenged individuals sometimes greatly benefit
  - Ocular surface disease is a leading cause of corneal transplant failure. Dry eye, neurotrophic, or exposure keratitis patients often benefit from topical ciclosporin, punctal occlusion, and tarsorrhaphy.

- **Preoperative glaucoma** is a risk factor for graft failure, with a ***relative risk factor of 2.5.***

Preoperative Preparations

- Infection control
- Intraocular pressure control
- Lens management
- Donor corneal tissue management
  - Allow approximately **60 minutes of warming time**
  - **Donor rim fungal** culture is associated with endophthalmitis in the recipient in **3%**
  - **Donor rim bacterial** culture is associated with recipient endophthalmitis in **1%**
- Anticipate **suprachoroidal hemorrhage**
  - **0.45% to 1.08%** of cases
  - 0.56% with general anesthetic and 4.3% with local anesthetic.
  - ***Risk factors*** include older age, glaucoma, previous vitrectomy, tachycardia, systemic hypertension, arteriosclerosis, anticoagulant therapy, and prior suprachoroidal hemorrhage

Phakic Penetrating Keratoplasty

- Goals
  - Obtain good wound alignment with minimal astigmatism
  - Avoid endothelial cell damage.
- Lid speculum
- Scleral fixation ring: potential scaffold to maintain scleral support, exerting its influence once the eye is opened if scleral rigidity is insufficient. Another option is to proceed without a fixation ring or sutures, to avoid associated globe distortion and astigmatism.
- Marking of host cornea: donor graft is usually centered on the host cornea or over the pupillary axis
- ***Donor tissue trephine is routinely sized 0.25 mm larger*** than the host trephine because, using current techniques, donor corneal tissue cut with a trephine from the endothelial surface measures approximately 0.25 mm less in diameter than host corneal tissue cut with the same diameter trephine from the epithelial surface. ***Keratoconus patients also may benefit from using same-diameter trephines*** for both donor and host tissue, which in effect undersizes the donor button and helps reduce postoperative myopia.
- Trephination of donor cornea: endothelial side facing up using a sharp disposable blade in a guillotine punch block apparatus
- Trephination of host cornea:
- Placement of viscoelastic material in the anterior chamber

- Placement of the donor corneal tissue in the host bed
- Placement of four interrupted radial 10/0 nylon **cardinal sutures**:
  - Suture depth is approximately 90% to prevent wound gape
  - The second suture, placed 180° away at 6 o'clock, is the **most critical** in terms of tissue alignment and subsequent astigmatism.
- Complete suturing
  - the ***most prevalent suturing error*** in corneal transplantation surgery is tying ***too tightly***.
- Readjustment of sutures to minimize astigmatism: An **inexpensive plastic ring (Karickhoff keratoscope, DORC keratoscope**, or the like) or even the **round end of a safety pin** can be used effectively for this purpose.
- Administering medications: **Subconjunctival** dexamethasone, 4 mg; subconjunctival gentamicin, 20 mg; and subconjunctival cefazolin, 25 mg, or another suitable antibiotic are injected.

Femtosecond Laser-assisted Penetrating Keratoplasty

- Creation of a more structurally stable and predictable wound configuration with the objectives of faster recovery of vision and higher optical quality compared to conventional blade trephination.
- The first femtosecond laser platform to accomplish the full-thickness corneal cuts for PKP was the **Intralase**™ (IntraLase Femtosecond Laser, AMO, Irvine, CA)
- A second femtosecond laser platform, **FEMTEC** (20/10 Perfect Vision, Heidelberg, Germany) has also subsequently created stable full-thickness PKP wounds and demonstrates short-term visual results analogous to other femtosecond laser-assisted PKP studies.
- Intralase enabled keratoplasty (**IEK**)
- The two most popular patterns remain the '***top-hat' and 'zig-zag' incisions***.
- 'Zig-zag' incision may prove to be the most biomechanically sound incision pattern.

Keratoplasty Suturing Techniques

- **Castroviejo's original suturing technique** utilized a continuous silk suture coursing back and forth in multiple passes across the external surface of a **square graft**, using the suture to support the graft in place against the intraocular pressure.
- After four cardinal sutures, a **diamond-shaped pattern of corneal striae** will appear in the donor cornea. At this point, the wound approximation should be symmetric in all four quadrants.

1. Interrupted sutures (IS)

- Standard means of keratoplasty wound closure.

- 10-0 nylon using a 160-degree single-curve 6-mm needle
- A **2-1-1 closure** facilitates burial of the knot, but adequate suture tension is more difficult to establish than with a **3-1-1 knot**. **Slipknots (1-1-1-1)** allow for intraoperative adjustment.
- **Eight** sutures, in general, is the minimal number required to keep the wound **watertight**, and **16** sutures is the average number for a **complete** interrupted suture wound closure
- A total of 24 or 32 interrupted sutures may be necessary in pediatric grafts, keratoconus patients, same-size donor–host grafts, or large-diameter grafts.
- **Knots can be buried in the host tissue** so that when the suture is removed there is less tension on the graft–host junction, ***reducing the chance of dehiscence*** should the sutures be removed during the early stages of wound healing. Alternatively, the knots **can be buried in the donor** tissue to help ***reduce inflammation and vascularization*** since the knot is farther from the limbal vessels.

2. Combined continuous and interrupted sutures (CCIS)

- With a continuous suture in place the interrupted suture may be removed for astigmatism control earlier than if interrupted sutures were used alone.
- 2 interrupted 10-0 nylon sutures and a continuous 12-bite 10-0 or 11-0 nylon running suture
- Should not be used if there is vascularization or infectious keratitis or any other need for total suture removal in some portions of the wound before others

3. Single continuous suture (SCS)

- Technically more unforgiving than interrupted sutures, because one irregular bite can impair the integrity of the closure and once passed cannot be removed without removing the entire suture
- **Ease of placement**, the ease with which the suture can be removed at a later date, and the potential for suture adjustment intra and postoperatively to reduce astigmatism.
- Antitorque suturing is not necessary for continuous sutures with 12 or more bites.
- **Antitorque suture**: radial overlying sutures and antitorque intrastromal suture bites. The overlying radial sutures produce minimal suture torque and induce astigmatism.
- **Torque suture:** radial intrastromal sutures and overlying torquing suture bites. These torquing suture bites rotate the graft and induce astigmatism.

4. Double continuous suture (DCS)

- **Benefits of a single continuous suture with the added safety** of a second suture should one suture break or need to be removed early.
- Requires **more expertise** than a single continuous suture, because both continuous sutures must have regular and symmetric bites to close the wound without disturbing the wound.

- **Suture Adjustment**
  - Topographical analysis using **keratometry, photokeratoscopy, or videokeratography**, individually or in combination, is helpful in planning suture adjustment
- **Suture removal**
  - If corneal astigmatism is satisfactory with sutures in place, ***sutures should remain until there is some indication for removal, such as graft rejection, scarring, vascularization, patient discomfort, suture breakage, infection, or decreased vision (residual astigmatism)***. Leaving sutures in place as long as possible maintains topography, if acceptable, and decreases the risk of dehiscence.
  - All the dehiscences occurred within 2 weeks of suture removal, which was performed between 14 and 42 months postoperatively.
  - **Single interrupted sutures**
    - A tight suture, or any suture felt to be distorting the corneal topography, can be removed as early as 6–8 weeks postoperatively in a well-constructed keratoplasty with 16 interrupted sutures. However, adjacent sutures should generally not be removed for 6 months postoperatively.
  - **Combined continuous and interrupted sutures**
    - One to three weeks later, the patient's corneal topography is remeasured to assess changes induced by suture removal and to determine whether removal of additional sutures is indicated.
    - ***The average astigmatism is 4 diopters after all sutures are removed, using most suturing techniques***.
  - **Single continuous suture**
    - ***Adjustment*** of the single continuous suture can change corneal topography and still support the wound suture
    - McNeill first described adjustment of a single continuous suture to reduce postkeratoplasty astigmatism in 1988
    - The ***suture is advanced from the flat meridian toward the tight meridian*** to equally distribute suture tension around the wound.
  - **Double continuous suture**
    - Adjusted the deeper, tighter 10-0 nylon suture to alter corneal topography and reduce astigmatism, and left the shallower suture in place as a safety net

Intraoperative Complications of Penetrating Keratoplasty

- **Scleral perforation** with fixation sutures: Flieringa rings, the McNeill-Goldman blepharostat
- Improper trephination

- power of the lens must be adjusted to account ***for 2 to 3 diopters of induced hypertropia***
- eccentric placement of the trephine can result in large amounts of postoperative astigmatism.

- Damaged donor button
- **Retained Descemet's membrane**: The iris architecture should be inspected carefully, and the iris should be gently picked up and identified with forceps
- Iris–lens damage
- Torn posterior capsule
- Vitreous loss with pseudophakic bullous keratopathy and posterior chamber intraocular lenses
- Anterior chamber hemorrhage
- **Expulsive choroidal hemorrhage: 0.47% to 3.3%**

Postoperative Management

- **Immediate postoperative care (first 24 hours)**
  - Antibiotics should be given preoperatively, intraoperatively, and postoperatively
  - ***Oral fluoroquinolone*** administration may also be considered in high-risk cases (ciprofloxacin has highest ocular penetration among all fluoroquinolones)
  - Prophylactic Antiglaucoma
  - A pressure patch and Fox shield
  - **Systemic steroids** are commonly administered in high-risk keratoplasty in the early postoperative period, usually at a dose of 1 mg/kg per day over the first 5 to 7 days. **Acyclovir** in a prophylactic dose of 400 mg twice daily or **valacyclovir** 500 mg daily is given perioperatively in cases with previous known herpetic involvement, especially previous stromal keratitis.
  - **Azathioprine at a dose of 1–2 mg/kg/day** and **ciclosporin A** orally have been used as an adjuncts to oral and topical steroids in high-risk cases but the side-effects profile has limited their widespread use. **Tacrolimus at a dose of 0.16 mg/kg per day** has been shown to be effective in prevention of rejection with less systemic impact.
- **Early postoperative care (1 to 7 days)**
  - Should be examined in the first 36 hours following surgery
  - Presence of concomitant **external eye and eyelid disease** including blepharitis, lagophthalmos, spastic entropion, and trichiasis.
  - Without topical fluorescein to assess the surgical wound, level of corneal edema, anterior chamber reaction, and overall status of the anterior segment
  - Fluorescein allows for a better evaluation of the status of the corneal epithelium, wetting of the ocular surface, and tension on the suture material

- The **intraocular pressure** may be measured in more regular corneas by applanation.
- Treatment of early intraocular pressure elevations involves the use of **topical beta-blockers** followed by carbonic anhydrase inhibitors and brimonidine.

Postoperative care (1 to 12 weeks)

- Period of **greatest change** and highest risk for the corneal graft.
- **Topical antibiotics should generally be discontinued once the epithelium is intact.** Continuing long-term topical antibiotic therapy selects out more resistant organisms, but does not act significantly to prevent infection in the absence of other problems such as persistent epithelial defects, suture removal, exposure, trauma, or wound leaks.
- **Persistent elevated anterior chamber flare may be associated with higher incidence of rejection.**
- **Epithelial rejection lines** begin at the graft periphery and migrate towards the center of the graft with time. They are seen as hazy elevations in the epithelium and may stain with either fluorescein or rose Bengal. These lines are usually seen in a relatively quiet or mildly inflamed eye. They are seen at a median of approximately 3 months following surgery and may occur in up to 14% of corneal transplants.
- **Signs of stromal rejection** are seen as a haze or infiltrate spreading from the graft periphery towards the center of the donor cornea. These are associated with findings of **endothelial rejection**, and are frequently accompanied by stromal vascularization. The classic finding of endothelial rejection is a rather sharply demarcated line (**Khodadoust line**) that is seen as contiguous keratic precipitates.
- **Epithelial downgrowth**, occurring 1 to 12 weeks after penetrating keratoplasty or suture manipulation, may also appear as an advancing line with signs of inflammation.
- In the absence of complications, topical **steroids should be tapered during the first 6 months** following penetrating keratoplasty.
- An assessment of **intraocular pressure should be done on each postoperative visit**.
- **Macular edema** is often suspected when the visual function does not match the surgeon's estimation of the anterior segment in the postoperative period.

Postoperative care (after 3 months)

- Average postoperative astigmatism was in the **4 to 6 diopter range**
- **Contact lens correction** is generally indicated for convenience when the other eye requires contact lenses, in cases of high toricity and anisometropia, and in aphakia.
- **Higher oxygen permeability** (Dk value) lenses with base curves flatter than the flattest K-reading are generally used.
- **Corneal sensitivity may take years** to return to normal in the corneal graft, and this may be a significant factor in the development and late recognition of microbial keratitis from contact lens wear or suture erosion.
- Significant iatrogenic complications may be induced by the chronic long-term administration of topical steroids in the postkeratoplasty patient.

- **Postoperative care in infants and children**
  - **Intense inflammatory reaction** in the anterior segment following Keratoplasty
  - Epithelial and stromal **healing is very rapid** in children, resulting in early suture loosening, exposure, secondary vascularization, and subsequent rejection. Infants and young children may need to be examined every 2 days until the sutures are removed, usually in a few weeks following surgery.

Early Postoperative Complications

- **Wound Leaks and Wound Displacement**: Pupillary block or choroidal detachment can also cause a shallow or flat anterior chamber, but a coexistent wound leak must be ruled out. **Seidel's test** is useful for detecting an area of leakage and may be positive even in the presence of a flat anterior chamber. If nonsurgical attempts fail to seal the leak after 24 to 48 hours, surgical repair is recommended.
- **Persistent Epithelial Defects**: reepithelialization and the maintenance of an intact epithelium is critical for postoperative wound healing, improved visual acuity, graft transparency, graft survival, and protection of the stroma against infection and melting.
  - The postoperative prevention and treatment of epithelial defects may include the use of a ***permanent or temporary tarsorrhaphy, pressure patching, a bandage soft contact lens, a collagen shield, or an amniotic membrane transplant***. Using nonpreserved artificial tears and limiting medication toxicity to the epithelium are essential. Once an epithelial defect is present, it must be treated aggressively. If the defect persists for more than 1 week, it will heal more slowly. The risks of stromal scarring and ulceration increase significantly with defects present longer than 3 weeks.
  - The possibility of ***active herpes virus infection*** must always be considered when an epithelial defect does not respond to treatment. Surgical incision of the trigeminal nerve has been shown to reactivate latent herpes simplex virus in humans.
- **Filamentary Keratitis**: abnormal collections of mucus and epithelial cells on the corneal surface. Patients with minimal symptoms should be treated with **hypotonic artificial tears** because more mucoid solutions may contribute to the formation of filaments. In patients with severe symptoms, the filaments should be carefully removed with a forceps followed by treatment with hypotonic tears and/or topical **acetylcysteine**, which has a mucolytic action. **Punctal occlusion** can also be beneficial, and in severe cases a soft bandage contact lens may be indicated.
- **Suture-related Complications**:
  - Suture exposure:
  - Suture-related infection:
  - Suture-related immune infiltrates:
    - Suture-related immune infiltrate: Multiple, Usually occurs on the host side of the graft–host interface, No overlying epithelial defect
    - Infectious suture abscess: Solitary, May occur on the graft or host side of the graft–host interface, Associated with an overlying epithelial defect

- **Kaye dots**: discrete white dots in the donor corneal epithelium in a 1–2-mm region central to the graft sutures. found primarily in the depressed zone central to the swollen donor cornea edge. Their formation may be a ***non-specific response of the epithelium*** to an area of tissue angulation. Disappears within 30 days.

- **Elevated Intraocular Pressure**:
  - Pneumotonometer or an electronic tonometer
  - Tight suturing, long suture bites, larger trephine sizes, a smaller recipient total corneal diameter, same-size donor–host trephination, and increased recipient peripheral corneal thickness were shown to result in greater iridocorneal angle compression and elevated intraocular pressure.
  - Retained viscoelastic, intraocular inflammation, anterior synechia causing angle closure, and pupillary block.
  - Topical beta-blocker, topical alpha-2 receptor agonists, and/or an oral carbonic anhydrase inhibitor may be considered at the conclusion of surgery. ***Prostaglandin analogs and miotic agents should be avoided since they may worsen anterior segment inflammation***.
- **Postoperative Inflammation**: uncontrolled inflammation may lead to the formation of intraocular fibrin due to ***breakdown of the blood–aqueous barrier***. Fibrin can serve as a scaffold for the formation of strands or membranes, leading to the development of pupillary block and glaucoma or direct damage to the endothelial cells.
  - Intense hourly topical corticosteroids & Mydriatics.
  - **Intraocular TPA -25 micrograms**.
- **Anterior Synechia** Formation:
- **Pupillary Block**:
- **Choroidal Detachment and Choroidal Hemorrhage**:
- **Hyphema**:
- **Fixed Dilated Pupil**: The development of a fixed, dilated pupil following penetrating keratoplasty for keratoconus has been observed as part of a syndrome associated with iris atrophy, scattered pigment on the lens capsule and corneal endothelium, and secondary glaucoma with posterior synechia: ***Urrets Zavalia Syndrome***
- **Postoperative Infection**: The incidence of **endophthalmitis after penetrating keratoplasty ranges from 0.2% to 0.77%.**
- **Primary Donor Failure**: irreversible edema of the corneal graft in the immediate postoperative period. It is due to inadequate endothelial cell function of an unhealthy donor endothelium, inadequate tissue preservation, or surgical trauma.

Postkeratoplasty Astigmatism

- **Host factors:** Peripheral corneal thinning or Ectasia, Scleral Ectasia, Scarring, Aphakia, Wound healing, Wound edge profile, Epithelial healing, Shape, Postoperative melting
- **Donor factors**: Diameter, Intrinsic astigmatism, Edge profile, Shape

- **Surgical factors:** Suture tension, Suture length, Suture depth, Suture radiality, Intraocular pressure, Suture technique, Intraocular lens implantation, Timing of suture removal, Surgeon experience, Trephine tilt, Scleral ring placement
  - Large-diameter penetrating keratoplasties (LDPKs), defined as grafts that are 8.75 mm or larger
- **Donor–host interaction**: Override/underride, Wound healing, Postoperative trauma
- **Management**
  - **Relaxing incisions**
    - can be placed in the graft–host junction or in the graft itself.
    - A relaxing incision placed in the graft is termed '**astigmatic keratotomy (AK)**'.
    - The term '**arcuate keratotomy**' describes the creation of one or more arc-shaped relaxing incisions in the corneal stroma or graft–host interface.
    - Relaxing incisions in the graft–host junction are of the arcuate variety and astigmatic keratotomy incisions can be of the arcuate or straight (transverse) variety. Relaxing incisions and astigmatic keratotomy incisions are associated with a coupling effect. **Coupling** is defined as the simultaneous flattening of the steep meridian in which the incision is placed and the steepening of the flat meridian 90 degrees away from the incision. When the ***coupling ratio*** (the amount of flattening in the meridian of the incision divided by the induced steepening in the opposite meridian) is 1.0, the spherical equivalent remains unchanged. When there is a positive coupling ratio (>1.0), a hyperopic shift occurs. When there is a negative coupling ratio (<1.0), a myopic shift occurs
  - If the relaxing incisions themselves cannot correct the astigmatism, **compression sutures** may be placed across the graft–host interface 90 degrees away from the relaxing incisions
  - **Wedge resections** involve the excision of a wedge of corneal tissue in order to reduce post-PKP astigmatism.
  - **LASIK** has been introduced as another attempt to surgically correct post-PKP astigmatism.
  - **Photorefractive keratectomy**

Corneal Allograft Rejection

- Allograft rejection is a form of delayed hypersensitivity.
- Studies Streilein and associates, have raised the possibility that **anterior chamber associated immune deviation (ACAID) phenomena** contribute to graft survival and that allograft rejection represents a breakdown in the protection afforded the graft by ACAID.
- **Risk Factors**
  - Young recipient age (less than 40 years) (CCTS)

- Large-diameter corneal grafts (nearby limbal vasculature, Langerhans cells in periphery)
- Prior graft failure, particularly due to rejection (8% in one, 40% in two)
- Pre-existing inflammation

- **Clinical Features**
  - Circumcorneal (ciliary) flush
  - Anterior chamber flare indicates elevated levels of protein in the aqueous humor
  - Cellular infiltration of the cornea as discrete subepithelial infiltrates: an early sign of rejection
  - Epithelial rejection 10%, earlier in the postoperative period (1 to 13 months)
  - Isolated stromal rejection: uncommon but can be seen as stromal infiltrates and neovascularization. In very aggressive episodes of graft rejection the stroma can become necrotic during severe or prolonged bouts of rejection.
  - Endothelial rejection is the most common of the three types, with reported rates of from 8% to 37% of cases undergoing rejection. Endothelial keratic precipitates occur as scattered lesions or as a linearly oriented wave of leukocytes migrating from the peripheral cornea toward the center. Referred to as the **Khodadoust line**: hallmark of corneal allograft rejection, but it is not a sine qua non for rejection. In patients who have received posterior lamellar donor tissue (DSAEK) cellular keratic precipitates occur only on the transplanted endothelial layer. Often, there is associated edema of the stroma overlying the area that has been traversed by the advancing keratic precipitates.
  - Edema of the graft
  - Corneal thickness usually stabilizes by the third postoperative month, and if the corneal ***thickness is greater than 0.59 mm at the sixth postoperative month there is a greater risk of ultimate graft failure***.
  - elevated intraocular pressure can be a sign of rejection
- **Differential Diagnosis**
  - **Recurrence of herpes simplex keratouveitis** is the most difficult condition to differentiate from corneal allograft rejection: typical dendriform epithelial lesion, endothelial keratic precipitates in herpetic inflammation are not confined to the graft but involve as well the peripheral host endothelium.
  - **Epithelial downgrowth**: inflammation is not a prominent part, not respond to steroid therapy.
  - **Low-grade corneal infection**: candida
- **Management**:
  - Corticosteroid therapy by topical, periocular, or systemic administration is the treatment of choice for acute corneal allograft rejection reaction.
    - CCTS: higher-frequency postoperative topical steroids, close follow-up of the patient, and the aggressive treatment of suspected or diagnosed rejection reaction (including the use of hourly topical prednisolone acetate for mild reactions plus intravenous methylprednisolone pulse therapy [3–5 mg/kg IV

push] followed by 5 days of oral prednisone [1 mg/kg/day] for severe reactions)

- Immunosuppressive agents such as ciclosporin, tacrolimus, and mycophenolate mofetil
- Biologic methods: intracameral administration of anti-T-lymphocyte monoclonal antibodies.

Infections after Penetrating Keratoplasty

Microbial Keratitis

- **1.76% to 12.1%,** most within first year
- Three general categories
  - contaminated donor button
  - intraoperative contamination
  - recurrence of host infection.
- ***Streptococcus pneumoniae (27%) and Staphylococcus aureus (20%)*** followed by Gram-negative organisms (20%) and fungal organisms (13%)
- Topical corticosteroids should be stopped in the presence of an acute graft infection. Only when the organism has been identified and the infection brought under control should the clinician consider restarting corticosteroid therapy.
- Preferably, the epithelium should be intact before corticosteroids are reintroduced.
- Graft decompensation was documented in 13–57% of eyes.

Suture Abscess

- Infiltrate in either the donor or recipient cornea which is in direct contact with, or adjacent to, suture material
- **2–3.3%** of penetrating keratoplasties after an average of 21.5–30.8 months
- S. epidermidis, S. pneumoniae, and S. aureus, although cases of Gram-negative infection
- Differential Diagnosis: A ***sterile suture infiltrate*** occurs with an exaggerated inflammatory response usually within the first few weeks after surgery. In this situation there are usually multiple lesions typically on the host cornea, and the overlying epithelium is intact.
- Careful removal of the offending suture followed by corneal scrapings for smears, cultures, and sensitivities

Infectious Crystalline Keratopathy

- 1983, as a noninflammatory, intrastromal bacterial colonization of a corneal graft
- ***Crystalline branching opacities in the anterior or midstroma*** due to intralamellar aggregates of Gram-positive cocci occurring several months following penetrating keratoplasty and after the long-term use of topical corticosteroids.

- Most commonly reported causative organism in ICK is **Streptococcus viridans**.
- Bacteria are thought to gain access to the corneal stroma via epithelial ingrowth into a suture track or by direct access through an epithelial defect.
- Scrapings or corneal biopsy
- **Fortified topical antibiotic** drops given in an intensive dosing regimen. Antibiotic coverage for S. viridans includes topical penicillin G 333 000 units/mL, cefazolin 33–50 mg/mL, or vancomycin 33–50 mg/mL.
- Use of **Nd:YAG laser** to disrupt the protective glycocalyx matrix surrounding the organisms causing ICK

Endophthalmitis

- Incidence: **0.08% to 0.77%.**
- **immediate postoperative period (within 72 hours)**
  - Contaminated donor tissue or corneal storage media
  - Prolonged storage of corneal tissue for more than 5 days
  - Preoperative warming of corneal tissue to room temperature for 1 hour prior to transplantation
  - ***50% had positive donor rim cultures out of which, in 97% cases organism maching cultures***
  - Additional risk factors for postoperative endophthalmitis include intraoperative communication with the vitreous, placement of an intraocular lens with polypropylene haptics, and a history of drug allergy.
- **Late postoperative period (months to years)**
  - Secondary to an acquired infection. Ulcerative keratitis within the graft or at the graft–host interface may progress to perforation and subsequent endophthalmitis. Concurrent endophthalmitis and ICK from the same organism has been reported 3 months after penetrating keratoplasty.
- Overall rate of **donor rim culture positivity was 14%,** with the predominant organism being **S. epidermidis (39%)**
- 75% bacterial in origin, whereas fungi are implicated in another 20%
- **Clinical Features:**
  - Pain
  - Marked inflammation with or without hypopyon
  - Diminished or poor red reflex.
  - Wound dehiscence may also be present
- Aspiration of aqueous humor as well as vitreous sampling
- Diagnostic vitrectomy or vitreous aspiration
- Management:
  - Intraocular injection of **vancomycin** 1 mg in 0.1 mL and **ceftazidime** 2.25 mg in 0.1 mL should be carried out after a diagnostic or therapeutic Vitrectomy

- For fungal endophthalmitis is very high, intravitreal injection of **amphotericin B** 0.005 mg in 0.1 mL should be performed.
- **Intravitreal dexamethasone** may help in the early reduction of inflammation in exogenous bacterial Endophthalmitis
- Broad-spectrum fortified topical antibiotics should be administered with an intensive dosing regimen of at least every hour around the clock.

- Only 3% of all eyes with endophthalmitis after penetrating keratoplasty had a visual acuity of 20/40 or better. Acuity of 20/50 to 20/200 was achieved in 17% of cases. An additional 17% of eyes had acuity ranging from 20/300 to hand motions.

Herpetic Keratitis after Keratoplasty

- HSV keratitis: relatively infrequent indication for penetrating Keratoplasty → **4.2%.**
- Recurrent herpetic dendritic keratitis in 10–25% of patients during the first year of follow-up and in 9–21.6% during 2 to 5 years of follow-up
- In case of recurrence or without prophylaxis: **15–28%** of patients having recurrences in the ***first*** year and **18–45%** during the ***second through fifth*** years.

Transmission of Unusual Infections

- Rabies: Total 8 cases till now- death within 7 weeks
- Creutzfeldt-Jakob disease: 1-2 cases
- Hepatitis virus: 2 cases
- Human immunodeficiency virus: No cases

Retrocorneal Membranes

- **Epithelial downgrowth***: epithelialization that extends into the anterior chamber*
- ***Epithelial ingrowth****: epithelialization under the LASIK flap.*

Epithelial Downgrowth

- **0.6%** of all traumatic and surgical perforations
- **0.27%** after PK
- Cataract extraction remains the most frequent cause
- Pathogenesis:
  - delayed closure or dehiscence of the surgical wound, often with a fistula or inadvertent bleb and incarceration of tissue in the surgical margin.
- Dull aching pain, photophobia, and blurred vision. Clinical examination reveals a hypotonous, normal, or elevated intraocular pressure, and the incision site may contain incarcerated tissue, a conjunctival bleb, or a fistula.
- Argon laser photocoagulation and specular microscopy are often sufficient for diagnosis when combined with the clinical picture
- The **argon** laser settings ***of 0.1–0.2 s, 100–500 µm spot size, and 100–500 mW*** are used to outline the extent of epithelial invasion over the iris. The involved areas turn white when the laser energy is applied as opposed to an inapparent burn to the normal iris. The specular microscope can also confirm the diagnosis if the leading

edge of the epithelium can be visualized by focusing just posterior to the endothelium.

- Confocal microscopy has been shown to aid in the diagnosis of epithelial downgrowth.
- **Glaucoma** is the most common presenting sign and a common pathway for eventual enucleation.
- **Management**:
  - Radiation was the treatment of choice from 1930 to the 1960
  - Maumenee's eradication technique:
  - Naumann and Rummelt ‘s block excision:
    - Endoscopic photocoagulation

Fibrous Ingrowth

- Fibrous proliferation and invasion of the tissues surrounding the surgical site
- ***Distinct from epithelial downgrowth, less likely to result in enucleation***
- **Penetrating keratoplasty** is the most recognized source
- **50-60%** of failed Keratoplasty
- **Pathogenesis**:
  - Subepithelial connective tissue and corneal stromal fibroblasts participate in normal traumatic and surgical wound healing, and an exuberant response leading to fibrous ingrowth can be easily imagined.
- Translucent membrane on the posterior surface of the cornea near the wound. The edges may be frayed or irregular, and, ***unlike epithelial downgrowth, the stroma of the membrane may be vascular***
- No ancillary diagnostic tests have been useful to confirm
- Medical management of inflammation, glaucoma, or corneal edema is sufficient, and the fibrous proliferation matures into a quiescent scar and can even fade considerably

Differential Diagnosis:

- Beveled corneal incisions
- Peripheral corneal edema
- Pigmented membrane can appear on the posterior surface of the cornea as a result of proliferation of iris stromal melanocytdes from trauma or surgery.

Glaucoma after Penetrating Keratoplasty

- Most devastating complication after penetrating Keratoplasty

- Practical definition of PKP glaucoma is an IOP > 21 mmHg after penetrating keratoplasty, with or without associated visual field loss or optic nerve changes, necessitating the addition of medications to reduce the intraocular pressure.
- PKP glaucoma treatment escalation definition: Treatment escalation was either surgical or medical; in the case of medical escalation, only sustained increases in medication burden compared to baseline were included; treatment to deal with brief IOP spikes in the early postoperative period was excluded from analysis.
- **Incidence**: IOP > 25 mmHg occurred in 37% of phakic eyes, 88% of aphakic eyes, and 100% of eyes undergoing combined cataract extraction with penetrating Keratoplasty
- **Risk factors:**
  - Preexisting glaucoma
  - Aphakia
  - Anterior segment inflammation
  - Corneal diagnosis
  - Intraocular lens removal
  - Vitrectomy
  - Postkeratoplasty/extracapsular cataract extraction/intraocular lens
- **The Pre-Keratoplasty Evaluation**
  - Tonometry and a careful pupillary examination
  - ASOCT
  - UBM
  - Afferent pupillary defect is an ominous clinical sign
  - Visual fields are frequently unreliable in the patient with cloudy media
  - Flash VEP was the single best predictor of postoperative vision
- **Clinical Presentation**
  - Most important is its detection
  - Astigmatism and alterations in corneal thickness can influence the accuracy of applanation measurement techniques, with thinner corneas under-reading ‘true’ IOP
  - Pneumotonometer, Tono-Pen and the dynamic contour tonometer all provide reasonable results in PKP eyes.
- Glaucoma is a risk factor for corneal graft failure, whether it is preexisting or develops after penetrating keratoplasty.
  - graft survival probabilities using Kaplan–Meier analysis were 82% at 1 year and 66% at 2 years, versus 93% at 1 year and 87% at 2 years
  - high IOP causes damage to endothelial cells.
  - BAK found in most glaucoma medications
- Causes of glaucoma after penetrating Keratoplasty
  - Preexisting glaucoma: Primary, Secondary
  - Secondary angle-closure glaucoma

- Trabecular meshwork collapse (aphakia): Six factors were found to be related to iridocorneal angle compression: (1) diameter of the host cornea, (2) size of the recipient bed, (3) length of the suture bites, (4) tightness of the sutures, (5) thickness of the recipient cornea, and (6) size of the donor button relative to the size of the recipient bed.
- Postoperative glaucoma: Pupillary block, Iritis, Hemorrhage, Lens induced, Steroid response, Malignant, Viscoelastic induced

- **Medical management**
  - use of aqueous suppressants preoperatively and close monitoring
  - Miotics are generally ineffective and contraindicated in the early postoperative period.
  - Topical CAIs: reports of corneal decompensation
  - prostaglandin analogue: CME
- **Surgical management when medical therapy fails**
  - Laser iridoplasty and trabeculoplasty
  - Filtering surgery
  - Glaucoma Drainage Devices: corneal graft failure in eyes with GDD: immune, mechanical
  - Cyclodestructive Procedures

Pediatric Penetrating Keratoplasty

- **Special problems:**
- ***Preoperative problems***
  - Complete preoperative evaluation of the corneal pathology is usually not possible.
  - Need for specialized investigations such as ultrabiomicroscopic examination.
  - IOP evaluation usually not accurate in opaque corneas.
  - Patient should be evaluated for systemic associations in cases of congenital corneal opacities.
- ***Intraoperative problems***
  - Small size of the palpebral fissure reduces the working space available for manipulations.
  - Excessive lowering of the intraocular pressure is to be avoided as severe hypotony prevents optimal trephination of the recipient cornea.
  - Caution is to be exercised while performing the scleral fixation due to the higher risk of perforation as the sclera is thinner in pediatric eyes.
  - Use of Flieringa rings with unequal placement of fixation sutures may also result in increased distortion resulting in difficulty while suturing.
  - Need for performing associated procedures such as lensectomy, anterior vitrectomy, glaucoma procedures, and so on, is high.

- Increased positive pressure of vitreous with forward shift of lens–iris diaphragm due to the low scleral rigidity and increased elasticity of pediatric eyes.
- Increased difficulty in suturing and cheese wiring due to the thin peripheral corneal tissue in certain cases.

- ***Postoperative Problems:***
  - Need for frequent examinations under anesthesia for postoperative follow-up evaluations
  - Frequent loosening of sutures necessitating replacement/early removal
  - Increased risk of rejection and infections
  - Difficulties with repeated refractive error assessments, and reversal of amblyopia.
  - Even with increased anatomic success of pediatric corneal grafts, visual rehabilitation remains a concern.

- Prevalence of congenital corneal opacities is approximately 3/100,000. With congenital glaucoma included this rises to 6/100,000
- Most common primary cause of congenital corneal abnormalities in the developed nations is Peter's anomaly (40.3%), followed by sclerocornea (18.1%), dermoid (15.3%), congenital glaucoma (6.9%), microphthalmia (4.2%), birth trauma, and metabolic disease (2.8%).
- **Indications**:
  - Congenital:
    - CHED
    - Non CHED with Glaucoma: Congenital glaucoma, peter's, anterior segment dysgenesis
    - Non CHED without Glaucoma: Sclerocornea, dermoid, birth trauma, metabolic dz, keloid, aniridia
  - Acquired, nontraumatic: Herpes simplex keratitis, Bacterial keratitis, Stevens–Johnson syndrome, Keratoconus, Neurotrophic keratitis, Interstitial keratitis, Fungal keratitis, Exposure keratopathy
  - Acquired, traumatic: Corneal or corneoscleral laceration, Blood stain, Nonpenetrating injury with scar
- Clear grafts in 80% of pediatric patients at 1 year and 67% at 2 years. excellent prognosis for graft survival in eyes with CHED and a fair prognosis for graft survival in eyes with non-CHED congenital opacities and acquired opacities.
- **Reasons for graft failure:**
  - Allograft rejection
  - Primary graft failure
  - Graft decompensation
  - Infection
  - Corneal ulcer
  - Glaucoma

- Trauma
- Phthisis bulbi

- **Complications of pediatric Keratoplasty:**
  - Allograft rejection: 22 to 44%, lower reversal rate, CsA 2% QID → OD in 3 months
  - Graft infection: 10 – 50%
  - Persistent epithelial defects (PED): poor graft host junction apposition and faulty suturing, early suture loosening, drug toxicity, tear, and surface abnormalities
  - Corneal ulcer
  - Cataract: 2%
  - Glaucoma: 5 – 9%
  - Retinal detachment: 3-5%
  - Endophthalmitis: 2%
  - Wound leak or dehiscence: 2 – 10%
  - Expulsive choroidal hemorrhage: 2-3%
  - Inadvertent lens loss
  - Phthisis bulbi: 4-13%
- **Outcomes**
  - Congenital:
    - CHED (25% to 90%)
    - Non CHED with Glaucoma: Congenital glaucoma (50% or less), peter's (62%), anterior segment dysgenesis
    - Non CHED without Glaucoma: Sclerocornea (70% in eyes with sclerocornea and 83% for partial sclerocornea), dermoid, birth trauma, metabolic dz, keloid, aniridia
  - Acquired, nontraumatic: Herpes simplex keratitis, Bacterial keratitis, Stevens–Johnson syndrome, Keratoconus, Neurotrophic keratitis, Interstitial keratitis, Fungal keratitis, Exposure keratopathy
  - Acquired, traumatic: (55-100%)Corneal or corneoscleral laceration, Blood stain, Nonpenetrating injury with scar

Large-Diameter Corneal Grafts

- 1951 Castroviejo: large-diameter penetrating keratoplasty, or sclerokeratoplasty,
- Two types
  - Total penetrating Keratoplasty: sclerokeratoplasty
  - Large-diameter lamellar grafts: Malbran procedure → advanced keratoconus
- **Indications**

- uncontrolled Pseudomonas corneal ulcers, keratomycoses, and other severe necrotizing corneal
- chronic progressive peripheral corneal ulceration, corneal melting (as in some cases of Mooren's ulcer), rheumatoid keratolysis, or descemetocele formation
- large-diameter lamellar graft: pellucid marginal degeneration, advanced or eccentric keratoconus, and keratoglobus

- Topical and systemic antirejection medications must be administered postoperatively.

PK in Herpes Simplex Disease

- Stromal keratitis is the leading cause of permanent corneal transparency loss
- penetrating corneal graft survival for herpetic eye disease/scar is ***86% at 1 year, dropping to 75% at 5 years, and to 59% at 10 years postoperatively***
- A recurrence-free or **inflammation-free interval** for transplantation of such cases has not been determined yet, but it is considered as a period of at least **6 months**.
- **Preoperative Measures**
  - Control of inflammation
  - Vascularization
  - Corneal sensation: Reduced corneal sensation may cause reduced epithelial growth and differentiation with consequent development of epithelial defects
  - Antiviral prophylaxis**: Oral antiviral agents** inhibit viral replication at the trigeminal ganglion, avoiding recurrence of ocular disease. Topical antivirals do not have the capability of arresting viral replication in the central nervous system but, if the recurrence appears, they may locally inhibit viral replication.
  - Uveitis, glaucoma, and recurrent graft rejection episodes – all of which damage the corneal endothelium – are common after PKP for herpetic keratitis.
- **Operative Technique**
  - Graft size
  - Perforated eyes
  - Suture: interrupted
  - 'Triple procedure'
  - Anterior lamellar Keratoplasty
  - Femtosecond laser
  - Boston keratoprosthesis
- **Postoperative Management**
  - Use of corticosteroids
  - Suture removal

- **Persistent epithelial defects**: **33% and 44%**, ***Herpetic keratitis must be in the differential*** diagnosis of early and late-onset postkeratoplasty epithelial defects with or without a history of previous infections.
- **Recurrence of HSV keratitis**: **6% and 44%**. 23% of corneal grafts performed for herpes simplex keratitis that develop a recurrence may undergo an episode of rejection.
- **The allograft rejection**: **29% and 46%**
- Herpes simplex virus in corneas for transplantation
- Secondary graft failure
- Glaucoma
- Wound dehiscence
- Secondary infections

High-Risk Penetrating Keratoplasty

- 'transplantation antigens,' fall into two categories: major and minor
  - The genes that encode the **major transplantation antigens** in humans are located within the major histocompatibility complex (**MHC**) and individually are called human leukocyte antigen (HLA).
    - **Class I** antigens are transmembrane glycoproteins designated **HLA-A, HLA-B, and HLA-C.** They are expressed on most nucleated cells.
    - **Class II** antigens are encoded by HLA-D genes and include **HLA-DP, DQ, and DR** antigens. Class II antigens are found on specific immunocompetent antigen-presenting cells (APCs) of the lymphoreticular system.
  - **Minor transplantation antigens** are encoded by genes outside the MHC at numerous loci spread throughout the genome. They are only available for detection if processed and presented on the surface by class I or II MHC molecules of the host. ABO blood group antigens, which differ from most classic minor antigens because they are highly glycosylated. In the cornea, ABO antigens are expressed by epithelial cells, and are upregulated during graft rejection.
- **CCTS Risk factors**
  1. Corneal stromal vascularization >= 2 quadrants, deep, 7% per quadrant
  2. Prior graft loss, especially from allograft rejection: Rejection rates in patients with comparably vascularized recipient beds are approximately 40% after the first graft, 68% after the second graft, and 80% after the third graft.
  3. Increased graft diameter and eccentric grafts: but in recent study → smaller ?? independent ??
  4. Anterior synechiae: three or four quadrants of iris synechiae
  5. Previous intraocular surgery
  6. Herpes simplex keratitis

7. History of anterior segment inflammatory disease
8. Ocular surface disease
9. Young age, especially infants and children

- **Management:**
  - Controlling ocular inflammation
  - Rehabilitating the ocular surface
  - Tissue matching: HLA is conflicting, ABO has some definitive role
  - Surgical technique
  - Postoperative considerations: Teaching each patient the symptoms of rejection facilitates its early recognition. A useful acronym is **RSVP**, which stands for ***redness, sensitivity to light, visual loss, and pain.***
  - Immunosuppression
    - **Corticosteroids**: large systemic doses prednisone (1 mg/kg) around the time of surgery, which can then tapered on an individualized schedule within 2 months. A typical regimen involves prednisolone acetate 1% every 2 hours for the first few weeks with a gradual decrease over the next several months.
    - **Calcineurin inhibitors**
      - Ciclosporin A: It inhibits the transcription of many factors necessary for T-cell activation, most prominently IL-2. Topical & Systemic
      - Tacrolimus
    - **Antimetabolites**
      - Azathioprine
      - Mycophenolate mofetil
      - Rapamycin
    - **Monoclonal antibodies**
      - **Daclizumab** (Zenapax) and basiliximab (Simulect)
      - **Campath-1H** is a 'humanized' monoclonal antibody

Anterior Lamellar Keratoplasty

- **Indications**
  - **Tectonic**: to restore normal corneal thickness by using tailor-made lamellar corneal patches to match the defect on the patient (lesion-fit keratoplasty)
    - Descemetocele
    - Pellucid marginal degeneration
    - Advanced Terrien's marginal degeneration
    - Sterile Mooren's ulcer and other forms of peripheral corneal melts related to autoimmune disorders (as in rheumatoid arthritis and Wegener's granulomatosis).

- **Optical**: to enhance vision:
  - Ectatic disorders: keratoconus, keratoglobus, keratotorus (Schlappi's pellucid marginal degeneration)
  - Scars:
  - Dystrophies: epithelial, Bowman's membrane, stromal dystrophies
  - Degenerations:
  - Post refractive surgery complications:
  - Advanced recurrent pterygium involving central cornea
  - Special circumstances:
- **Therapeutic**: Resistant corneal infections, Dermoids and some tumors, Inflammatory mass, Perforations
- **Cosmetic**: Corneal opacity

Contraindications

- Endothelium is unhealthy
- Big-bubble technique is contraindicated if there is a pre-existing break in the Descemet's membrane (post hydrops) or there are deep scars (however small) involving the Descemet's membrane

Benefits of anterior lamellar Keratoplasty

- Extra ocular surgery:
- No risk of endothelial graft rejection:
- No need for long term steroid prophylaxis:
- Rapid functional recovery of vision:
- No interface haze: in DALK
- Very good BSCVA.
- No significant endothelial cell loss:
- Lesser postoperative glaucoma:
- Less astigmatism then penetrating keratoplasty:
- Penetrating Keratoplasty can be done if recurrences.
- Better long-term graft survival
- No late failures
- Easier follow-up
- A lower-quality donor cornea can be used
- Allows larger grafts when needed without risking rejection

Techniques can be grouped into: (4)

- Stroma to Stroma (manual, microkeratome, and laser-assisted)
- DM to DM

- DM to Stroma (2 & 3 can develop subgraft clefts, pseudochambers, or folds in donor Descemet's membrane; hence this type of interface is not recommended)
- Stroma to DM (only manually)

- **Two main categories**
  1. pre-Descemet's membrane procedures
  2. Descemet's membrane procedures,
- **Techniques**
  - Layer-by-layer dissection
  - Stromal delamination
  - Automated therapeutic lamellar Keratoplasty
  - Intrastromal dissection
  - Cleavage separation
  - Donor preparation
- **Additional Equipment for DALK**
  - Pachymeter
  - Slit lamp microscope
  - Blunt-tipped scissors and spatula
- **Intraoperative Complications**
  - Perforations and ruptures of Descemet's membrane: Most common complication
- **Postoperative Complications**
  - Pseudoanterior chambers, or double anterior chambers
  - Pupillary block and fixed dilated pupil (Urrets-Zavalia syndrome)
  - Sclerocorneal inflammation: Postkeratoplasty atopic sclerokeratitis (**PKAS**) is a rare form of acute inflammation of the ocular surface associated with suture loosening and melting of the graft.
  - Suture-related complications
  - Interface infection
- **Outcomes of ALK:**
  - Visual Outcomes: no statistically significant difference in best corrected visual acuity (BCVA) from 6 months postoperatively through to 5 years postoperatively in DALK vs PK in KC.
  - Graft Survival: endothelial cell count 12 months to 2 years postoperatively was significantly greater following DALK than PK
  - Suture Management: in PK early removal of sutures can result in unpredictable refractive changes, graft movement, and instability.
  - Resistance to Trauma: DALK must theoretically be stronger than a cornea which has undergone PK.

- Surgical Planning: no risk of endothelial rejection and there may be a reduced risk of suture-related events and full-thickness wound dehiscence.

DALK: Deep Anterior Lamellar Keratoplasty

- **Indications for Deep Anterior Lamellar Keratoplasty (DALK)**
- Conditions resulting in stromal ectasia and opacification: DALK is indicated for all corneal stromal pathological conditions where endothelial and epithelial functions are preserved.
  - Corneal ectasias
  - Stromal dystrophies
  - Scarring from previous infection or trauma
- **Contraindications of DALK**
  - Endothelial dysfunction (absolute contraindication to DALK!)
    - Posterior dystrophies (Fuchs, posterior polymorphous corneal dystrophy)
    - Corneal edema (pseudophakic corneal edema, pseudophakic bullous keratopathy)
    - Procedure of choice: endothelial keratoplasty (EK)
  - Epithelial dysfunction (relative contraindication to DALK)
    - Limbal stem cell deficiency states (aniridia, etc.)
    - Chronic surface disease (keratoconjunctivitis sicca, etc.)
    - May combine DALK with other procedures that optimize the surface (punctal occlusion, tarsorrhaphy, limbal stem cell transplantation)
- **Advantages of DALK over penetrating keratoplasty (PKP):**
  - Preservation of host endothelium
  - No requirement for donor endothelium
    - Eliminates endothelial graft failure
    - Eliminates endothelial graft rejection
    - Decreases overall incidence of allograft rejection
  - Allows for the incorporation of more diseased stromal tissue (ie, larger graft, ideal in keratoconus)
    - Includes entire ectatic area
    - Minimizes suture / wound induced astigmatism
  - No open eye time: Less concern over posterior pressure and suprachoroidal hemorrhage
  - Allows for earlier suture removal, if necessary
- **Disadvantages of DALK**
  - Surgical difficulty
  - Optical effect of interface (minimal)
  - Persistent Descemet separation (double anterior chamber)

- **Advantages of BB DALK over other DALK procedures (without Descemet's exposure):**
  - Highest chance for Descemet's membrane (DM) exposure, less risk of perforation, no stromal interface complications, less stromal rejection, faster recovery and better visual outcome
- **Steps to successful BB-DALK (Anwar Big Bubble Technique):**
- Centration & sizing, partial Trephination, air Bubble Injection, paracentesis, keratectomy, bubble puncture, removal of remaining stroma, trimming, donor preparation and sutures.
- Partial Trephination:
  - Objectives: Deep partial trephination, proper centration and parallel to visual axis.
  - What can go wrong: Decentered trephination, shallow and deep trephination.
  - Tips: Know your trephine; number of turns. Deepen the wound if needed.
  - Videos to illustrate the above.
- Air Bubble Injection:
  - Objective: Create a DM detachment as large as the trephination diameter.
  - What can go wrong: Failed 1st injection, total corneal emphysema, secondary injections, small bubble, perforation and how to recognize type 1 and type 2 bubbles.
  - Tips: Deep central injection, enlarging of small bubble, guard against perforation.
  - Videos to illustrate the above.
- Paracentesis:
  - Objectives: Lowers the pressure, makes the bubble easier to identify (sure sign), used to drain aqueous or inject air / BSS if needed.
  - What can go wrong and what to do: Excessive drainage leading to endothelial loss, too oblique may puncture the bubble, too central and gaping with graft suturing.
  - Tips: Paracentesis is better performed after the anterior keratectomy to minimize trauma to the endothelium.
  - Videos to illustrate the above.
- Anterior Keratectomy (debulking)
  - Objectives: Debulking the stroma and Exposure of the Bubble.
  - What can go wrong: Premature bubble rupture.
  - Tips: In case of no bubble, stay in the mid cornea, in case of positive bubble the deeper the better and don't make the dissection too smooth.
  - Videos to illustrate the above.
- Bubble Puncture:
  - Objectives: Allows air to escape and expose Descemet's membrane.
  - What can go wrong & what to do: difficulty in finding the track, multilevel track.
  - Tips: Lower the pressure, keep the tack open, and create a clean and large puncture.

- Videos to illustrate the above.

- Removal of remaining stroma
  - Objectives: Expose predescematic layer and undermine the wound edge.
  - What can go wrong: Descemet's split and perforation.
  - Tips: Use blunt scissors, start centrally, deal with microperforations and keep it wet.
  - Microperforations can be sealed with air, stromal plug or tissue glue.
  - Videos to illustrate the above.
- Edge Trimming:
  - Objectives: To fashion a wound edge as perpendicular as possible for easier suturing and better anterior surface coaptation.
  - Tips: Undermining the edge during dissection leads to neater edges.
- Donor Preparation
  - Objective: Remove endothelium; with non-toothed forceps, sponge or blade.
  - What can go wrong: Stromal injury, leaving healthy endothelium.
  - Videos to illustrate the above.
- Wound Suturing:
  - Objectives: Secure the graft in place with minimal postoperative astigmatism.
  - Tips: Mark donor & recipient, tension distribution, torque antitorque…
- Postoperative complications and management:
  - Descemet's detachment, stromal rejection, delayed epithelial healing and suture-related complications.

Femto-DALK

- Creates precise cuts at specified depths
- Infinite custom trephination possibilities
  - Mushroom
  - Top-hat
  - Zigzag
  - Christmas tree

Endothelial Keratoplasty

- **Indications**
  - Endothelial dystrophy: Fuchs', posterior polymorphous,
  - Bullous keratopathy: pseudophakic, aphakic

- Endothelial failure: from trauma, previous surgery, angle closure, tubes
- Iridocorneal endothelial (ICE) syndrome
- Failed penetrating Keratoplasty (if acceptable refractive result was achieved)

- **Contraindications**
  - Stromal opacity or scarring that limits visual potential
  - Keratoconus, ectasia
  - Hypotony/pre-phthisical eye
- **Established Benefits of EK**
  - Better quality of vision than PK: Less aberrations, smoother surface
  - Astigmatically neutral when a scleral incision is used
  - Induced refractive hyperopic shift that averages 1.0 to 1.5 D—likely primarily from posterior curvature changes of the hourglass donor
  - Stronger eye with substantial resistance to postoperative trauma
  - More predictable “triple procedure” than PK
- **Most Common Complications of EK**
  - Dislocation: Rates from 1% to 82% reported in literature.
  - Iatrogenic primary graft failure: Rates from 0% to 29% reported in literature.
  - Pupillary block glaucoma: Rates from 0.1% to 9.5% reported in literature.
  - Eccentric donor trephination: Rates from 0% to 10% reported.

History

- Descemetorrhexis, 2004: Melles GR: A technique to excise the Descemet membrane from a recipient cornea.
- Descemet-stripping EK (DSEK), 2005: Price FW Jr, Price MO: Descemet’s stripping with endothelial keratoplasty
- Descemet-stripping automated EK (DSAEK), 2006: Gorovoy MS: Descemet-stripping automated endothelial keratoplasty

Classification

- **DSAEK: endothelium (endo), Descemet membrane (DM), stroma (>100 µm)**
- **Ultrathin DSAEK: endo, DM, stroma (60-100 µm)**
- **Pre-Descemet EK (PDEK): endo, DM, pre-DM (25-30 µm)**
  - Graft includes pre-DM, DM, and endo → 25-30 µm
  - Slight increase in graft strength to allow for ease of manipulation and unfolding; can use younger donor tissue
  - Graft preparation done by surgeon.

        - Increased endo loss, risk of tissue loss
        - Smaller diameter graft
- **DMEK: endo, DM (15 µm)**
    - Purest form of EK, replacing only DM and endothelium
    - Slower in adoption than DSAEK
        - Need older donor tissue
        - Surgical technique for insertion and unrolling is challenging.
        - Need good visibility of anterior chamber
        - Increased challenges in eyes with glaucoma device, poor iris anatomy, phakic
    - Differences between DSAEK and DMEK
        - Rejection
        - Surgical complexity
        - Anatomy
        - Visual outcomes
- **Descemet stripping only (DSO)/descemetorrhexis without EK (DWEK): no endo/no tissue**
    - Only for Fuchs dystrophy (central dense guttae)
    - Central 4-4.5 mm DM stripped (not scored)
    - Allows migration of endo cells and clearing over 1-6 months
    - However, rate of recovery is variable.
    - Surgical technique is important in visual recovery.
    - Centration and stripping are essential for a good outcome; avoid scoring

Common Procedures

- **Assessment of anterior chamber space and specialized techniques advised in eyes with:**
    - Anterior synechiae
    - Glaucoma tubes
    - Iris abnormalities
    - Anterior chamber intraocular lens
- **Benefits**
    - maintenance of the **structural integrity of the eye**
    - more **rapid visual** recovery
    - **minimal change in refractive spherical** equivalent.
- **Patient Selection**

- Age: There is certainly no upper age limit for the procedure. 2-90 years
- Duration of corneal edema:
  - some eyes can achieve 20/20 vision within a week of EK.
  - longstanding corneal edema: remodeling by keratocytes appears to progress from the periphery inward, with the central area over the pupil clearing last.
- Lens Considerations
  - generally preferable to **perform cataract surgery before the transplant**, either as a staged or combined procedure
  - Removal of the crystalline lens first also creates more room in the anterior chamber
  - opportunity to preserve accomodation by leaving an eye phakic after EK must be weighed against the additional risk and cost of subsequent cataract surgery.

Challenging Eyes

- Failed penetrating grafts: **EK graft that is 1 mm larger in diameter than the failed PK**, avoid stripping Descemet's membrane and endothelium from the failed PK
- Glaucoma tubes:
- Shallow anterior chambers: Performing a peripheral iridectomy, use of microforceps
- ACIOLs: to be replaced by SFIOLs
- Iris abnormalities, aniridia and aphakia: generally avoid stripping the recipient Descemet's membrane, pull-through technique helps ensure that the graft is secured at all times

Donor Preparation

- Issues to Consider
  - General: Preparation immediately before surgery or ‘pre-cut tissue.’
  - Uniform thickness: donor of approximately **180 μm** → much easier handling and unfolding of the tissue
  - Diameter: **3 mm less than the smallest diameter of the recipient cornea**, larger EK are more difficult to unfold
  - Shape: meniscus shape is produced by most microkeratomes and femtosecond laser → thinner in the center than at the edges → 1.5 diopter (D) hyperopic shift
  - Stromal bed consistency: smooth stromal bed surface is desired for improved Snellen vision.
  - Scleral rim size: 16–18 mm total diameter
  - Endothelial cell count: 2000–3000 cells/mm2
  - Donor age: 2-75 years

- Preservation to cutting to surgery time: death due to implantation time longer than 165 hours as well as a cut to implantation time of less than 94 hours is acceptable

- **Methods-4**
  - **Manual dissection**: PLK & DLEK
    - Securing donor rim onto the artificial anterior chamber. Trephination of the donor rim with a 9.0-mm Hessberg-Barron vacuum trephine. Manual dissection of the anterior stroma with 0.12 forceps and a crescent knife is started at the keratectomy edge. After removal of the anterior cap, the residual stromal bed is smooth and ready for final resection.
  - **Automated microkeratome dissection**: smoother but bed profile is often of a meniscus shape, which has been associated with postoperative hyperopic shift.
    - Donor disc secured into position with the anterior ring lock. Microkeratome track is placed on top of the anterior ring lock. The applanation lens is used to verify adequate vacuum. (<< refers to the circular gauge within the applanation cone; < refers to actual corneal applanation reflex; when within the circular gauge, the vacuum is considered to be adequate.) The cornea is moistened with BSS and the microkeratome pass is made. Microkeratome has produced a free anterior cap and a smooth residual bed. The donor is placed endothelial-side up onto a Barron vacuum trephine, while the trephine diameter is confirmed with calipers. After trephination with a 9.0-mm trephine blade, the donor is ready for insertion.
  - **Femtosecond laser dissection:**
    - The donor rim is placed onto an artificial anterior chamber and centered with the femtosecond laser applanation cone. A spiral ablation pattern is started centrally. The ablation extends to the 9.0-mm zone, while the side cut is visible. A 15-degree hinge is located at the 6 o'clock position. The anterior flap is lifted with a flap elevator. The residual bed is evaluated and has surface irregularity that corresponds to the spiral ablation pattern, an inherent weakness of the IntraLase.
    - many promising applications such as customized EK lenticules with a smooth central zone (i.e. to improve Snellen vision) and a roughened peripheral zone (i.e. to facilitate adhesion), it is very expensive compared to other methods.
  - **Submerged cornea using backgrounds away (SCUBA) technique:** addresses the challenges of handling and visualizing a thin EK donor which consists of just Descemet's membrane and the endothelium (i.e. 20 μm thickness) → DMEK
    - After securing the donor rim to a Barron vacuum trephine and stabilization with 0.12 forceps, a closed tying forceps are used to scroll the peripheral Descemet's membrane. The donor endothelium is stained with trypan blue. Under submersion with either BSS or Optisol GS, the Descemet's/endothelial layer is gently peeled with tying forceps to begin the process. At this point, the process is two-thirds complete, with an intact Descemet's endothelial layer. After removal, the tissue usually scrolls with the endothelium facing outward. It is placed into trypan blue to allow visualization after insertion.

- **Surgical Techniques**
  - **Barraquer** first proposed selective replacement of the corneal endothelium for treatment of corneal edema in 1950
  - **Donor Tissue Preparation:**
    - avoid an eccentric cut of the posterior corneal tissue
    - potential **priming effect on donor endothelium from glutathione and/or glucose in BSS Plus,** thereby maximizing the endothelial pump function of the donor endothelium, allowing for better adherence when presoaking prepared donor tissue.
  - **Intraoperative Techniques:**
    - The horizontal and vertical diameters of the eye
    - centration point is determined on the recipient cornea followed by marking the epithelium
    - **Wound creation**
      - one to three paracentesis incisions, Marking the noncutting edge blade prior to paracentesis, as peripheral as possible to minimize graft touch or graft dislocation with cannula
      - anterior chamber maintainer
      - incision into the anterior chamber is typically created using a diamond or metal keratome, 3 mm and later enlarged to 5 m, scleral, limbal, or clear cornea
    - **Recipient preparation**
      - **reverse Sinskey hook** or similar device is typically used to **underline or score** the endothelium/DM 1–2 mm inside the previously made epithelial trephine mark
      - Once the circular zone of recipient tissue has been removed, it can be unfolded on the corneal epithelium for careful inspection to detect any potential retained fragments left inside the eye.
- **Techniques to Improve Donor Adherence**
  - **'vent incisions'** as described by Price and Price
  - **Vent incisions + surface massage** with a specially designed roller or a long cannula
- **Donor Insertion Techniques**
  - **endothelium should be coated with viscoelastic** to minimize future endothelial trauma with avoidance of any gentian violet touch to the corneal tissue directly, as it is endothelial toxic.
  - compression forceps such as Kelman-McPherson forceps.
  - noncompression forceps (Irrigation must be in the 'off' position)

- A trifold technique or 'burrito' fold has also been described for tissue insertion with forceps through a 3-mm incision.
- A shovel may also be used as an insertion device
- suture pull-through insertion technique
- Injectors like The Busin glide

- **Donor Apposition Techniques**
  - Two to four sutures are typically required to close a 5-mm wound
  - Once sutures are placed, the tissue is unfolded unless a pull-through or inserter technique was used, in which case the tissue is already in proper orientation with endothelium down and stroma side up.
  - BSS or air may be irrigated through the paracentesis or wound between the fold of the tissue to complete the unfolding process
  - The pressure must be high after air insertion to ensure tissue apposition, as the inability to achieve a high pressure at this point of the surgery is the single most important risk factor for dislocation.
  - Pressure is maintained for at least 10 minutes, an air–fluid exchange can be performed to reduce the risk of pupillary block from an anterior chamber full of air.
  - Phenylephrine should be avoided as it may increase graft dislocation in a similar manner as it increases flap slippage with LASIK.
- **Early Postoperative Management**
  - Shield is typically placed after topical cycloplegic, antibiotic, and antiinflammatory drops
  - Supine position 6-24 hours

DSAEK: Descemet-stripping automated EK

- **Indications**
  - Endothelial dysfunction that has become visually disabling in the absence of severe stromal opacity or scarring
    - Fuchs endothelial dystrophy
    - Bullous keratopathies
      - Glaucoma drainage device
      - Aphakia
      - Anirdia
      - Anterior chamber IOL
  - Iridocorneal-endothelial (ICE) syndrome
  - Late failure of penetrating keratoplasty (PKP), if refractive outcome was acceptable prior to endothelial failure
  - Failed DSEK

- **Advantages of DSAEK**
  - Easier to unfold than DMEK initially
  - Works in deep chamber
  - Very good BCSA
  - 15% rejection rate
  - Less steroid dependence than PK
- **Disadvantages of DSAEK**
  - Needs larger incision
  - More need to consider glaucoma
- **Technique**
  - Methods of Insertion:
    - Forceps insertion with “taco” folding: Most established method, most surgeon dependent
    - Busin glide pull through: Popular but sparse literature data; appears similar to forceps insertion by experienced surgeons
    - Cartridge loaded pull through: Appears comparable to forceps
    - All others (sheets glide push in, Healon on sclera, or sheets glide push in, pull in, etc.): No literature on complication rates or endothelial survival
    - Tissue inserters
  - Methods of Avoiding Dislocation and Other Complications
    - Dislocation
      - Minimize endothelial trauma by minimizing donor manipulations
      - Evacuate interface fluid
        - ✓ Surface sweeping with IOP increased with air filling chamber: Fully effective but epithelial damage can occur.
        - ✓ “Venting” full-thickness corneal incisions: Effective but eye is put at risk for postoperative epithelial ingrowth and infections in interface, and late corneal melting.
      - Bubble size, bubble time, IOP pressure: Common practice prejudices, but there is nothing in literature to support one method over another.
    - Iatrogenic primary graft failure
      - Minimize endothelial trauma by minimizing donor manipulations.
      - Use larger diameter wounds for insertion or use tissue inserter.
    - Pupillary block glaucoma
      - Leave a small, freely mobile air bubble in eye at end of surgery: Lowest rate of pupillary block, highest rate of donor attachment.

        - Place an inferior peripheral iridectomy/iridotomy: Not always effective and can result in bleeding.
    - Eccentric donor trephination
        - Can result in primary graft failure (PGF) and epithelial ingrowth to interface
        - Completely avoided by using the microscope to trephinate donor tissue; never use the naked eye to assess edge clearance within a tolerance of only 0.25 mm.
- DSAEK Tissue Inserters
    - Platform inserters: NCI and Endoserter
    - Glide inserters: Tan endoglide
    - Cartridge inserter: InJEk technique

- **DSAEK Challanges**
    - Limited best corrected vision: lamellar interface abnormalities
    - Refractive error
        - Hyperopic shift
        - Astigmatism
    - Endothelial injury: graft failure
        - Primary
        - Long-term survival

Ultrathin Descemet-Stripping Automated Endothelial Keratoplasty

- **Indications**
    - UT-DSAEK is indicated for any form of endothelial failure, but it may be more appropriate than DMEK in the following situations:
        - Phakic eyes
        - Aphakic eyes
        - Aniridic eyes
        - After glaucoma filtering procedures
        - In long-standing or severe corneal edema
- **Relative Contraindications**
    - Eyes with very poor visibility, requiring a fixation suture
    - Post-PK eyes likely to require full-thickness relaxing incisions in the future
- **Complications**
    - Primary graft failure: Almost absent (0 of 86 cases)
    - Graft detachment: Rare (circa 5%) with UTDSAEK, more often (up to > 50%) with DMEK

- Pupillary block almost abolished by inferior peripheral iridotomy.
- Cataract formation: Rarely seen to date in phakic eyes
- No increased risk of complications in glaucomatous eyes

DMEK: Descemet membrane EK

- Idea of DMEK was first introduced by Melles in 1998, the first successful report of DMEK did not occur until 2006
- **Advantage**:
  - Avoidance of expensive mechanical microkeratomes, femtosecond lasers, and an artificial anterior chamber.
  - Avoidance of a recipient stroma–donor stroma interface as in DSEK, quicker visual acuity recovery and better final visual acuities
  - Smaller incision
  - Slightly better BCSA
  - 1%-2% rejection rate
  - Even less intense and less long steroid use
- **Disadvantages of DMEK**
  - Needs older (>70 y/o) donor—tough to unfold if donor is young (under 70)
  - Steeper learning curve
  - Hard (if not impossible) to use with prior vitrectomy; chamber flattening can be impossible if prior vitrectomy.
  - Chamber flattening can make vitreous come forward if prior YAG.
- **Indications**
  - Fuchs corneal dystrophy
  - Pseudophakic bullous keratopathy: visually disabling in the absence of stromal opacity or scarring
  - Descemet detachment after cataract surgery: graft failure
    - Following DSAEK
    - Late failure of PKP
- **DMEK Advantages Over DSEK**
  - No additional stroma transplanted
  - Faster and more complete visual recovery
  - Minimizes surgically induced astigmatism
  - No additional equipment to prepare tissue
  - Lower rejection rate

- A **SCUBA technique** (submerged cornea using backgrounds away) has been described for donor tissue preparation by Geibel
- **Graft unfolding technique**
  - Technique I: standardized 'no-touch' graft unfolding using a 'double-roll'
  - Technique II: carpet-unrolling while fixating one graft-edge ("Dirisamer technique")
  - Technique III: small air-bubble assisted unrolling ("Dapena maneuver")
  - Technique IV: the "single sliding cannula maneuver"
- It is important to not leave extra endothelium/DM within the 9-mm trephine mark, unlike with DSEK, as recipient–donor overlap is a risk factor for dislocation with DMEK.
- Graft detachment: a new complication emerged in EK
- Re-bubbling rates up to 82%
- **Evolution of EK**
  - 2006: DMEK
  - 2008: DMET
  - 2014: Hemi-DMEK
  - 2016: Quater-DMEK
- **DMEK Challenges**
  - Donor graft preparation: thin graft and removal of endothelium–Descemet membrane (EDM) without tears
  - Donor EDM insertion: proper orientation in anterior chamber
  - Lack of standardized unfolding technique
- **Critical Components of DMEK Surgery**
  - Control anterior chamber depth at all times.
  - Avoid direct manipulation of the tissue.
  - Learn variations in scroll configurations and associated tapping steps in unscrolling.
  - Use an "S" or "F" stamp to verify graft orientation.
- **Variations in Tissue Injection**
  - Endo-out tapping method: Mark Terry
  - Endo-in pull-through method: Donald Tan
  - Endo-in pull-through method: Massimo Busin
- **Tips for DMEK**
  - Totally different skill set than DSAEK
  - DMEK scroll always spontaneously rolls up with the endothelium on the outside of scroll, so touching the tissue directly kills the endothelium.
  - Always create "fluid waves" to manipulate and unscroll the tissue.
  - Keeping the chamber very shallow (but not flat) is critical to unscrolling.

- Every tissue has different scroll tightness, so the "dance" to unscroll it will be slightly different for every case; patience is a virtue.
- Donors older than 60 years old tend to be thicker and easier to unscroll.
- When you think the tissue is right-side up, it can be upside down, so double check every time before finally injecting air/gas to place tissue up into position.

PDEK: Pre-Descemet Endothelial Keratoplasty

- The evolution of endothelial keratoplasty (EK) has moved toward thinner tissue. That trend has yielded smaller incision size, less rejection, less steroid use, and small improvements in BCVA.
- There were obvious advantages of Descemet-stripping automated EK (DSAEK) over full-thickness penetrating keratoplasty (PK):
  - A smaller wound size
  - Predictable refractive result
  - Faster visual recovery
  - Less chance of rejection
- Descemet membrane EK (DMEK) sought to improve on that, but there is a learning curve for the transition from DSAEK to DMEK as the tissue unfolding is quite different and the ideal anterior chamber characteristics are different.
- ***Pre-Descemet EK (PDEK) is an evolution of DMEK.*** *It basically is DMEK tissue (endothelium+ Descemet membrane) with the addition of the Dua layer (20 microns).*
- Mainly comprised of the separation of pre-Descemet layer (PDL) along with DM-endothelium complex from the residual donor stroma by the formation of a type 1 bubble.
- Harvesting your own tissue is possible but made unnecessary with easy eye bank preparation of tissue (precut, preloaded, prestamped, and preverified that the endothelium has survived processing). It fits through a 2-mm incision so it is very astigmatically neutral and friendly to prior premium IOLs
- **Air Dissection and Type of Bubbles**
  - Air dissection is a well-established entity that relegates the use of microforceps or a microkeratome for dissection of the corneal stroma. An air-filled syringe is used to inject air into the stroma with the endothelial side up and is advanced under direct observation at a required depth beneath the endothelium. The advantage of air dissection is that it is cost-effective, as it is done manually by the surgeon; the major drawback is that it requires a certain amount of surgical skill, as the needle that is employed to inject air must be introduced at the correct depth below the DM-endothelium complex.
  - **Type 1 bubble:** This kind of bubble is essential for performing a PDEK procedure. This bubble typically spreads from center to periphery and is dome shaped. The diameter of the bubble usually varies from 7.5 to 8.5 mm, never extending to the extreme periphery due to adhesions between the PDL and the residual stroma. Injection of air leads to separation of the PDL-DM-endothelium complex in toto from

the residual stromal bed. This type 1 bubble is created using a 30-gauge needle connected to a 5-mL syringe with bevel up.

- **Type 2 bubble:** This type of bubble is typically formed when the air enters the plane between the PDL and the DM-endothelium complex. The Type 2 bubble typically spreads from periphery to center and is around 10-11 mm in diameter. It extends up to the extreme periphery as there are no adhesions between the PDL and the DM. With the formation of this bubble, it becomes essential to perform a Descemet membrane EK (DMEK) instead of a PDEK procedure. Immense care should be taken when a type 2 bubble is formed, as it has a thin wall and if it is subjected to excessive air-push then the bubble can rupture, leading to perforation of the graft and eventually transcending into donor tissue wastage.
- **Type 3 (mixed bubble):** When both type 1 and type 2 bubbles are formed and they coexist, a mixed bubble is said to have been achieved. This is a type 3 big bubble. These bubbles pose a surgical challenge to the surgeon, as they require delicate handling and manipulation to avoid the rupture of the bubble.

Advantages of PDEK

- PDEK shortens the learning curve toward thinner tissue.
- Stiffer tissue is easier to unscroll than with DMEK yet still fits though a 2-mm incision.
- The chamber doesn't have to be flattened as in DMEK.
- PDEK tissue can be used in vitrectomized eyes, open capsule—ie, chambers you don't want to and often can't shallow.
- PDEK expands pool of donors—younger donors are possible.
- Same fast visual recovery as both DMEK and DSAEK.

Disadvantages of PDEK

- Smaller graft diameter (7.0 to 7.5 diameter)
- Not all eye banks offer it.
- Takes more skill on part of the eye bank staff
- Not as many current users for data and long-term studies

EK & Glaucoma

- Risk factors for increased corneal endothelial damage,
  - Whether from carbonic anhydrase inhibitor toxicity to the endothelium
  - Intraocular pressure (IOP)-induced endothelial damage
  - Shallow angles with increased risk of peripheral iris synechiae and resulting iris–cornea touch
  - Endothelial trauma from trabeculectomy or a glaucoma drainage device (GDD)
- Main difficulty: ability to maintain an air bubble after air insertion, as both types of fistula immediately shunt air from the anterior chamber

EK & Phacoemulsification

- Cataract surgery is performed prior to the EK procedure to avoid exposing the donor to unnecessary ultrasound energy and other potentially traumatic insults related to the cataract removal
- Paracentesis in the triple procedure should be more vertical than the standard
- While EK has minimal effects on postoperative keratometry, it does affect the postoperative corneal power. hyperopic shifts between 0.75 and 1.5 diopters.
- **Intraoperative Issues**
  - Small vertical paracenteses
  - Mark all paracentesis blades with gentian violet
  - Use a cohesive viscoelastic for all aspects of the surgery
  - Adequate incision size is important to minimize endothelial trauma: 4-5 mm
  - To minimize the tendency for this anterior displacement, it is helpful to make sure that the capsulorhexis is smaller than the IOL optic.
- **Postoperative Results**
  - Refractive spherical equivalent was within 1 diopter of emmetropia in 73% of eyes
  - Postoperative refractive results had a mean shift of +1.46 diopters from the targeted outcome

Intraoperative Complications

- Damaged donor tissue: small scleral rim, during insertion
- Eccentric trephination: increase the risk of graft detachment,
- Thin donor tissue: tend to fold over on itself, prismatic optical effect that an uneven graft
- Retained Descemet's membrane: prevent proper attachment of the DSAEK graft, with subsequent graft detachment
- Air management: keep the patient in a strict supine position or the use of higher buoyancy gases
- Others complications: Expulsive choroidal hemorrhage, Anterior chamber hemorrhage, Lens damage

Postoperative Complications

- **Donor dislocation**: most common complication → reported upto 23-35% ,with newer techniques its <1%
- **Primary graft failure**: any graft that fails to clear within the first 2 weeks after the DSEK surgery. donor cornea should have at least 2000 cells/mm2. 2% to 45% in the literature.
- **Secondary graft failure** is the term used when the donor endothelial tissue is detached from the recipient stromal cornea, therefore preventing the cornea from clearing.

- **Graft rejection**: presence of anterior chamber cells with or without keratic precipitates and concomitant corneal edema. 2.2% to 14%.
- **Pupillary block glaucoma**: may lead to formation of PAS. high intraocular pressure, peripheral anterior synechiae, iridocorneal adhesions, and a shallow AC.
- **Endothelial cell loss**: 31% to 50% at the 6-month postoperative examination.
- **Refractive change**: hyperopic refractive shift
- **Interface deposits and epithelial ingrowth**:
- **Retinal complications**: Suprachoroidal hemorrhage, RD, CME

- The speed of visual recovery after DSAEK is generally superior to that of traditional PK, with many patients recovering excellent uncorrected and corrected vision in a matter of weeks rather than months or years.

DSO: Descemet Stripping Only

- For Fuchs endothelial corneal dystrophy (FECD)
- Despite having been described over 100 years ago, FECD remains an enigmatic disease. Multiple different mechanisms have been suggested to play a role in its underlying pathophysiology, including oxidative stress, mitochondrial dysfunction, unfolded protein response, and epithelial-mesenchymal transition. Numerous genetic mutations have been associated with FECD, although the vast majority of cases in white patients manifest a trinucleotide repeat expansion on chromosome 18. Exactly how this repeat expansion causes disease in FECD is unproven. Interference with cellular homeostasis via nuclear RNA foci (“RNA toxicity”) or by cytoplasmic translation products from the expanded repeats (“RAN peptides”) have been suggested as possible mechanisms.
- Modern-day endothelial keratoplasties, including Descemet membrane endothelial keratoplasty (DMEK) and Descemet-stripping endothelial keratoplasty (DSEK), are safe and effective surgeries, with generally rapid visual recovery and low risks of immunologic rejection.
- A number of years ago, however, several lines of evidence suggested that the endothelium in FECD might be capable of self-rejuvenation. These included isolated case reports of corneal clearance after inadvertent removal of Descemet membrane, after detachment of endothelial grafts, or after destruction of the corneal endothelium by cryotherapy.
- Several studies shows that corneal clearance in FECD can be achieved after deliberate central Descemet stripping only without graft-replacement.
- Recent work suggests that ripasudil, a topical Rho kinase inhibitor, can facilitate corneal clearance after DSO.

Management of Corneal Perforations

- **Etiology**
  - Infectious (bacterial, fungal, viral [herpes simplex, herpes zoster])
  - Inflammatory (collagen vascular disease, acne rosacea, atopic disease, Wegener's granulomatosis, Mooren's [idiopathic] ulcer)
  - Trauma (chemical, thermal, ultraviolet [UV], penetrating)
  - Xerosis (idiopathic, Sjögren's syndrome, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, vitamin A deficiency)
  - Exposure (seventh nerve palsy, thyroid-related ophthalmopathy, ectropion, floppy eyelid syndrome)
  - Neurotrophic (postviral, tumor, trauma, postsurgical [cataract extraction, penetrating keratoplasty])
  - Degeneration/ectasia (Terrien's marginal degeneration, keratoconus, keratoglobus, pellucid marginal degeneration)
  - Surgical (cataract extraction, LASIK, PRK, epithelial sparing PRK, pterygium excision with mitomycin-C, glaucoma filtering/shunt surgery)
  - Toxic/keratolytic (topical NSAIDs, topical antibiotics [gatifloxacin], topical corticosteroids, silicone oil)
- **Know difference between terms**
  - Corneal Ulcer
  - Descemetocele
  - Perforation
- **Symptoms**
  - Pain
  - Decreased visual acuity
  - Increased ‘tearing’
- **Signs**
  - Shallow or flat anterior chamber (perforation)
  - Positive Seidel test (perforation)
  - Uveal tissue to the posterior cornea or frank prolapse (perforation)
  - Hypotony (perforation)
  - Central clear zone (often bulging) within area of infiltrate or thinning (descemetocele)
  - Radiating folds in Descemet's membrane emanating from the base of the ulceration (descemetocele)
- **Treatment**
  - Tissue adhesives

        - Cyanoacrylate glue: 1960, Webster, small, relatively central perforations 1–2 mm or less,
        - 2-octyl-cyanoacrylate: DERMABOND
        - Iso-Dent: DENTAL GLUE
        - Human Fibrin Glue
        - Commercial superglue ??: methyl-2-cyanoacrylate
    - Penetrating keratoplasty
        - Larger perforations not amenable to repair using tissue adhesive or tissue adhesive failures
    - Patch graft
        - lesions that are too large to use tissue adhesive but small enough to obviate the need for a full-sized penetrating
    - Amniotic membrane transplantation
        - multilayed procedure
    - Medical management

- **Prevention of Corneal Perforation**
    - Bandage soft contact lens
    - Conjunctival flap
    - Tarsorrhaphy
    - Amniotic membrane transplantation
    - Miscellaneous: simple pressure patching, aggressive lubrication, punctal occlusion, and the use of topical ciclosporin

Therapeutic Lamellar Keratoplasty

- Optical Indications
    - Reis-Bücklers' dystrophy, spheroidal degeneration (Labrador keratopathy), and superficial leukomas
- Tectonic Indications
    - Peripheral noninflammatory corneal thinning disorders: PMD, TMD
    - Peripheral inflammatory corneal disease
    - Central thinning and Ectasia

Therapeutic Keratoplasty

- Primary purpose is either to restore the structural integrity of the eye (tectonic keratoplasty) or to resolve an infectious or inflammatory keratitis that is refractory to conventional medical therapy.
- Indications
  - Infections
  - Persistent epithelial defects and sterile melts
- Postoperative Management
  - Eradicate all remnants of infection, and prevent reinfection.
  - Promote reepithelialization of the cornea and wound healing.
  - Control inflammation with corticosteroids.
  - Patient's intraocular pressure should be followed carefully. Glaucoma is seen in approximately 50% of optical penetrating keratoplasties.
- Prognosis
  - Clear therapeutic grafts in 73% of bacterial corneal ulcers, 60% of fungal corneal ulcers, 50% of Acanthamoeba corneal ulcers, and 36% of herpes ulcerations with inflammation.

Surgical Management of Superficial Corneal and Conjunctival Disease

Molluscum Contagiosum

- Completely excised with a blade or cautery
- Can be treated with cryotherapy
- Simply curetting the central umbilication and making the lesion bleed

Superior Limbic Keratoconjunctivitis

- Patients should undergo thyroid testing
- Medical treatments: artificial tears, antihistamine and mast cell stabilizer drops, ciclosporin drops, nonsteroidal antiinflammatory drops, steroid drops, autologous serum, and steroid injection.
- Surgical treatments: punctal occlusion to silver nitrate solution cautery, cryotherapy, thermal cautery, suture stabilization, and conjunctival recession or resection, with or without amniotic membrane grafting.

Conjunctivochalasis

- An ellipse of excess conjunctiva is marked and removed with Westcott forceps.

Recurrent Corneal Erosions

- Two most common underlying conditions:
  - previous corneal trauma
  - corneal dystrophy (typically anterior basement membrane dystrophy [ABMD]).
- Ointment lubrication
- BSCL
- ASP
- Epithelial debridement alone, or combined with a diamond burr (DB) polishing procedure or with excimer laser phototherapeutic keratectomy (PTK)

Band Keratopathy

- Simple observation in asymptomatic cases to lubricating drops, gels, and ointments for irregular corneal surfaces to removal of the calcium in more advances cases.
- Chelation with disodium ethylenediamine tetraacetic acid (EDTA), **not calcium EDTA**.
- 2-3% solution.

Conjunctival Flaps

- 1958, Gundersen
- **Indications**
  - Persistent corneal epithelial defect
  - Unresponsive ulcerative microbial keratitis
  - Corneal thinning and perforation
  - Corneal limbal disease
  - Scleral necrosis
  - Glaucoma surgery complications
  - Surface preparation for a cosmetic scleral shell
- **Disadvantages**
  - vision may be significantly decreased in cases where the flap covers the visual axis
  - prevents monitoring of disease progression by making direct visualization
  - limited assessment of the intraocular pressure
  - compromises the donor site should the patient need a trabeculectomy in the future
- **Types**
  - Total conjunctival flap: thin, bipedicle, bridge flap described by Gundersen
  - Bipedicle bridge flap
  - Single pedicle flap

- Advancement flap

- **Complications**
  - Intraoperative complications
    - Buttonhole formation
    - Dissection of an inadequate flap
    - Excessive hemorrhage
  - Postoperative complications
    - Retraction of the flap
    - Ptosis
    - Cystic flap
    - Opacification and vascularization

Iris Reconstruction Surgery

- Iris Suture Techniques: **McCannel's** technique and its modification
  - The sliding knot intracameral suture: **Siepser**
  - Pupil cerclage procedure
  - Iridodialysis Repair
- Iris Relaxing Incisions
- Scissors Sculpting
- Vitrector Sculpting
- Iris Prostheses
  - Large-incision, rigid diaphragm devices: Morcher GMBH, PMMA
  - Rigid small-incision devices: multipiece 'IPS' prosthesis, Morcher 50 Series in the bag prosthesis
  - Flexible small-incision iris prostheses: Custom Flex,

Keratoprosthesis

- ***Guillaume Pellier de Quengsy*** in 1789, who first proposed that an artificial cornea could be implanted in place of a natural cornea opacified by disease or infection: ***Father of Keratoprosthesis***
- ***Nussbaum***– First human KPro (1855)
- Candidates for keratoprosthesis implantation can be classified into ***three main prognostic groups***. In increasing order of success, these groups are:
- **Bilateral** blindness in severe cases of

- **autoimmune-related** corneal opacity and ulceration (SJS & OCP)
- chemical injury
- corneal **allograft failure** (nonautoimmune).

- **Contraindications**
  - Children (less than 17 years)
  - No PL/ Phthisis/ Advanced glaucoma/ RD
  - Failure to grasp gravity of surgical program/ mentally unstable
  - Refusal to commit to long term follow up
  - The “happily blind”
  - Unreasonable expectations of outcome
  - Cosmesis
- **Types of keratoprosthesis**
  - **PERMANENT**
    - Intralamellar
    - Penetrating
      - Anterior
      - Posterior : Choyce
    - Perforating
      - Anterior fixation: Cordona, Ceramic, Dohlman
      - Posterior fixation: Nut and Bolt type
      - Intralamellar fixation: Osteo Odonto Keratoprosthesis, chondrokeratoprosthesis, onychokeratoprosthesis
  - **TEMPORARY**
    - Disposable: Eckardt, Aachen keratoprosthesis
    - Multiple use: Landers Foulk type2, Landers widefield, Venu
- **Designs and Materials:** The design of a KPro can be likened to some extent to that of an IOL, consisting of an optic (PMMA cylinder) and a haptic. It is the haptic of the KPro that determines the type of prosthesis.
  - Optical cylinder
    - Polymethyl methacrylate (PMMA) – most commonly used material
    - Glass, Ceramic, Quartz, Silicon
  - Supporting flange/haptic
    - ***Biological Skirts***
      - Tooth root & alveolar bone (OOKP– Strampelli)
      - Bone (Temprano)
      - Cartilage (Casey)
    - ***Synthetic Skirts***

- PMMA (Choyce, Boston KPro)
- Dacron (Pintucci KPro)
- Polycarbonate (Champagne cork KPro)
- Hydroxy-apatite (Leon-Barraquer KPro)
- Hydrogel (AlphaCor KPro)
- Polyurethane (Seoul KPro)
- Expanded PTFE (Legeais KPro)

- **THREE devices are most widely used.**
- **OOKP (Osteo-odonto-keratoprosthesis)**
  - first used in Italy by ***Strampelli*** in the 1960s and later modified by ***Falcinelli***.
  - integrates biologically an inert plasticPMMA optical cylinder in a lamina fashioned from the patient's own tooth and its surrounding alveolar bone. The device is covered by a tough buccal mucous membrane or rarely by other biological membranes including lid skin. This allows it to withstand the hostile environment of a keratinized, dry eye with lower rates of extrusion compared with KPros supported by nonbiological material.
  - **Stage 1a** surgery involves harvesting a full-thickness **buccal mucous membrane graft and suturing this in place on the recipient eye**.
  - In **stage 1b**, the preselected **donor tooth is harvested from the mouth with its root** and surrounding alveolar bone. This is used to prepare the **osteo-odonto-lamina**. The bone surrounding the tooth is shaped with a diamond-dusted flywheel and a hole is drilled through dentine to receive the anterior part of the PMMA optical cylinder, which is cemented into place. The osteo-odonto-lamina is ***implanted deep to the orbicularis oculi muscle of the lower lid in the fellow eye.*** This remains in place for 2–4 months during which time the bone is invested with soft tissues.
  - **Stage 2** surgery is carried out after an interval of 2–4 months. The lamina is retrieved from its submuscular location, inspected, and excess soft tissues trimmed ready for implantation onto the eye. The **dentine side** which faces the cornea requires ***thorough soft tissue removal*** to avoid ingrowth into the eye. A Flieringa ring suture is used to support the eye. The cornea is trephined. The iris is removed with forceps and lens extraction by ECCE or ICCE is carried out. Posterior capsulotomy and anterior vitrectomy are then performed. The lamina is sutured to the cornea with the posterior part of the optical cylinder traversing the corneal opening. **PMMA optical cylinder** into an excised **monoradicular tooth root**, and is implanted in two stages in conjunction with a mucous membrane graft.
  - **Retention rate of 66–85%** at 10–18 years from implantation.
  - **Most invasive** and technically difficult of the keratoprosthesis techniques and the one associated with the **worst cosmesis**, and would not be considered for any patient with functional vision in the other eye.
- **AlphaCor artificial cornea:**
  - Developed by **Chirila** and coworkers in **Australia**

- Totally different skill set as the device is placed **intrastromally** and often utilizes a full **conjunctival (Gunderson) flap**.
- Soft, flexible prosthesis with a peripheral opaque skirt and a clear central portion
- Have an advantage in not requiring a donor cornea.
- Half-thickness limbus-to-limbus stromal dissection
- Central 3.0-mm trephination is completed through the cornea stromal bed.
- Conjunctiva is used to cover the implanted AlphaCor.
- Nonporous transparent **optic** of poly-2-hydroxyethyl methacrylate (**pHEMA**) and peripheral porous **skirt** of the same material to allow infiltration with tissue stromal cells and blood vessels.
- Also requires **two surgeries**
- Device is **hydrophilic**, a **healthy tear film** is essential to prevent tissue melting.
- The most common indication for the AlphaCor is corneal **allograft rejection**.
- Reportedly contraindicated in herpes simplex keratitis and autoimmune disorders, and can become opaque with specific combinations of topical medications.

- **Boston keratoprosthesis:**
  - Formerly known as the **Dohlman-Doane** keratoprosthesis, was developed at the Massachusetts Eye & Ear Infirmary and the Schepens Eye Research Institute
  - Boston KPro comes packaged with the following components: **anterior front part** (optic), **posterior back plate** (small or large size by surgeon choice), **titanium locking ring**, 3.0-mm dermatologic punch, white plastic hollow pin, double-sided adhesive tape, and a contact lens.
  - The Keratoprosthesis Unit (KPro plus donor graft carrier) is typically assembled prior to addressing the patient's cornea.
  - The **type I device** consists of **two plates sandwiched around a donor corneal allograft** or the patient's own cornea. Implantation is performed in **one stage**, and is technically similar to standard corneal transplantation. A soft contact lens is used indefinitely to prevent corneal desiccation and thus minimize the risk of corneal melts.
  - When conjunctival cicatrix is significant or the patient has severe keratinizing dry eye, it is preferable to implant the **type II device**, which has an ***anterior extension of the lens to allow implantation through the surgically closed eyelid***.
  - Most commonly used in the world
  - Common indications include corneal allograft rejection, opacity when accompanied by extensive corneal neovascularization making allograft success unlikely, opacity with limbal stem cell deficiency syndromes including but not limited to aniridia, and chemical injury.
  - Common complications specific to the Boston keratoprosthesis design include retroprosthetic membrane formation, sterile vitritis, and worsening of glaucoma.
- **Cardona device** remains a paradigm in keratoprosthesis design

- **Pintucci** and coworkers developed a biointegrated keratoprosthesis with a PMMA optical cylinder and a porous Dacron mesh haptic, similar to that of Girard
- The **Worst 'champagne cork' keratoprosthesis** has been implanted in a large number of cases, particularly in India
- **Auro KPro (Indian-made Pro device)**
  - Auro K pro design is similar to Boston Keratoprosthesis
  - Made of clinical grade PMMA
  - 3 parts: the front plate, the back plate & Lock ring
  - For the eye that is pseudophakic and therefore, approximately emmetropic, and where the IOL is left in place at surgery, a single standard power (45 D) is manufactured
  - For aphakic eyes of different axial lengths, however, devices with varying degrees of power are made to allow a match to the patient's need as closely as possible.
- **Postoperative Management of Keratoprosthesis**
  - All Boston Type I keratoprosthesis surgery patients require postoperative antibiotics, steroids, and, if possible, a bandage contact lens.
    - Antibiotics
    - Corticosteroids
    - Glaucoma management
    - Soft contact lens: decreases the evaporative forces on the ocular surface, and creates a moist chamber around the neck of the keratoprosthesis, maintaining hydration and viability of the carrier donor tissue. **Kontur lens**, 16.0 mm in diameter and 9.8 mm base curve with no power.
  - AlphaCor™ artificial cornea is very similar to that of the Boston Type I keratoprosthesis with two notable differences:
    - There is no role for a bandage contact lens over the AlphaCor™ device.
    - AlphaCor™ researchers have documented the usefulness of topical medroxyprogesterone 1% suspension postoperatively. Its anticollagenase properties may decrease the incidence of melt/extrusion.
  - As for the osteo-odonto-keratoprosthesis, it is essentially an all-or-none proposition. If and when it is successfully performed, there is very little postoperative care required other than a short course of systemic antibiotics, systemic steroids for the management of chronic or recurrent inflammation, and oral carbonic anhydrase inhibitors, as needed, for intraocular pressure control.
- **Complications and Management**
  - Retroprosthetic membrane:
    - Most common complication
    - 25 to 65% of the cases
    - Increasing the topical steroids or placing a peribulbar injection of triamcinolone (20–40 mg).

- Early membranectomy with the YAG laser is indicated to avoid thickening of the membrane

- Loss of the soft contact lens:
- Sterile vitritis
- Elevated intraocular pressure
- Infectious and Sterile Endophthalmitis.
  - Infectious endophthalmitis is more frequent related to Streptococcus , Staphylococus , P Acnes , Candida and Cryptococcus and its incidence has been reduced with antibiotic prophylaxis (Vancomicin) ,and by wearing a contact lens. Pars plana vitrectomy is performed to obtain vitreous specimen and /or to remove debris, fibrin and the scaffold for the organisms to proliferate . Visualization of the periphery may be cumbersome and meticulous exam with scleral depression is advisable to detect any iatrogenic break that may result in postoperatory retinal detachment.
- Retinal detachment
  - In the preop, the examination of the peripheral retina with the indirect ophthalmolocope through the 3.3 mm central diameter stem of the k Pro may be not enough ,specially in the far periphery where the RD tends to begin. The use of **ultra-widefield imaging systems (Optos Optomap**) may be of great help to detect initial .During the surgery different wide field systems may be used but contact systems may be superior to non contact in obtaining a wider field of view.
  - Pars plana vitrectomy alone is preferred in the majority of cases because of the presence of chronic inflammation of the ocular surface in K Pro eyes.
  - Silicone oil is frequently used as tamponade specially in eyes with hipotony. Unfortunately in cases with hipotony and silicone oil , retroprosthetic membrane is more frequent and the effect of YAG laser is clearly less effective and recurrence is almost the rule
- Corneal melts and keratoprosthesis extrusion

Amniotic membrane Transplantation

- **Important History**
  - In **1910**, Davis first reported in English literature on use of amniotic membrane in human medicine. He used living amniotic membrane for skin transplantation. Since then, living rather than preserved amniotic membrane has been used in various areas of human medicine.
  - In **1940**, De Roth first reported on the use of amniotic membrane in the eye. He used living amniotic membrane for the reconstruction of conjunctival defects.
  - In **1995**, Kim et al showed experimentally that the use of preserved amniotic membrane graft is efficient in the corneal surface reconstruction in rabbits after epithelial removal and limbal lamellar keratectomy.
- **Five layers from within outward:**

1. A single layer of highly metabolically active, columnar to cuboidal epithelium
2. A thin basement membrane
3. A compact layer made of reticular fibres virtually devoid of cells
4. A loose network of reticulum containing fibroblasts, called the fibroblast layer
5. A spongy layer of wavy bundles of reticulum bathed in mucin,which forms the interface with the chorion

- **Mechanisms of action**
  - Promotes epithelialization
  - Inhibits scarring
  - Inhibits vascularization
  - Reduces inflammation
  - Provides a substrate for cell growth (**The most uncontroversial mechanism of action)**
  - Antimicrobial effects
  - As a biological bandage
- **Composition**
  - **Enzymes:**
    - Prostaglandin synthesis → phospholipases, prostaglandin synthase and cyclo-oxygenase
    - Prostaglandin-inactivating → Prostaglandin dehydrogenase
  - **Cytokines:**
    - Anti-inflammatory cytokines → IL-1Ra and IL-10
    - Pro-inflammatory → IL6 & 8
  - **Growth Factors:** EGF, TGF*a*, KGF, HGF, bFGF, TGF-*b*1, and -*b*2
  - MMP & TIMPs:
  - Collagen IV, a component of corneal epithelial basement membrane, is present in the stroma of amniotic membrane.
- **Processing and Preservation**
  - **Now not used** → lyophilisation, air drying, glutaraldehyde and polytetrafluoroethylene treatment and irradiation
  - Now used → freezing is the commonest mode
- **Solutions**
  - DMSO in phosphate buffered saline
  - Eagle's minimum essential medium (MEM) & glycerol
- **Methods**
  - Graft (epithelial-side up): When the membrane was used with the intention of it becoming incorporated into the recipients tissue

- Patch (epithelial-side down): when the intention was for it to come away or be removed at a certain point following surgery
- Combined approach:

- ***Primarily as a graft or a patch with four objectives:***
  - Establish epithelial cover in an area where none existed
  - To prevent corneal perforation in eyes at risk due to stromal melting
  - To limit scarring where the clinical likelihood was high or where scarring (symblepharon/adhesions) previously existed
  - To limit inflammation and neovascularisation.
- **Outcomes**
  - ***Success***: when the membrane served the purpose that was intended
  - ***Partial success***: when the membrane did not serve the purpose that was intended but the objective was achieved
  - ***Failure***: when the objective was not achieved even though the purpose may have been achieved
- ***Must remember following chart:***

AM layer	Constituents	Biological properties
Epithelium	Growth factors* Cytokines	Maintains undifferentiated epithelial phenotype when culturing limbal stem cells
Basal lamina	Collagen IV/VII Laminin 1/5 Fibronectin	Improves epithelial cell migration Strengthens adhesions on basal cells Induces epithelial differentiation (including goblet cells in conjunctiva) Prevents apoptosis
Stromal matrix	TGF-beta Anti-inflammatory and antiangiogenic proteins Protease-inhibition factors	Suppresses corneal myofibroblasts, limbal and normal and pathological conjunctival fibroblasts proliferation and differentiation – inhibits cicatrization Traps inflammatory cells from other tissues, inducing rapid apoptosis Inhibits inflammation and neovascularization

Prokera

- Prokera is a medical devise designed by Dr Tseng where AM has been clipped into a dual, concave, polycarbonate ring set, acting as a biologic bandage. It can be inserted much like a contact lens without needing any sutures or glue.
- ProKera® is developed via the support of an NIH grant and approved by the FDA as a type II medical device to deliver amniotic membrane's anti-inflammatory, anti-scarring and anti-angiogenic actions to promote corneal epithelial wound healing
- Prokera is a conformer type device made of amniotic membrane with a rigid frame so that it can be inserted into the conjunctival sac. It affords both cover to the surface and also keeps the bulbar and palpebral conjunctival surfaces apart. I have not used Prokera

directly (its cost is prohibitive) but was effectively using a home made similar device even before Prokera was introduced: I place a sheet of 2 x 2 inches amniotic membrane over the surface of the eye and tuck the membrane into the superior, inferior, medial and lateral fornices of the conjunctival sac, with a squint hook or similar blunt instrument. I then take a plastic conformer shell of the desired size and insert it in the conjunctival sac such that a layer of the membrane is beneath it and the folded surface, above it. In patients who are bed ridden for example patients in acute stage of Stevens Johnson syndrome in the intensive care unit, that is all that is required. The membrane can be changed every other day or so.

- In ambulatory patients, after inserting the membrane and conformer in the eye, I approximate the membrane covering the anterior surface of the plastic conformer shell and suture the edges together. I then trim off the excess membrane. It effectively becomes a conformer shell wrapped in membrane. It can stay in situ up to a week and even can be removed for examination of the eye and reinserted.
- **Indications**
  - Acute Stevens Johnson syndrome/Toxic Epidermal Necrolysis
  - Acute Chemical/Thermal Burns
  - Post-infectious Recalcitrant Corneal Inflammation (e.g. herpetic, vernal, and bacterial)
  - Neurotrophic Persistent Corneal Epithelial Defect
  - Recurrent Corneal Erosion
  - In conjunction with Superficial Keratectomy
  - In conjunction with High-Risk Corneal Transplantation
  - In conjunction with AmnioGraft® (single/multiple layers) for corneal ulcer, descemetocele or perforation
  - In conjunction with AmnioGuard® (pericardium/sclera/cornea) for scleral melt
  - In conjunction with Limbal Graft for partial or total limbal stem cell deficiency
  - In conjunction with Plastic Lid, Fornix, and Socket Reconstruction

Refractive Surgery

Decision Making

- ***Three major challenges***: to select the right patient, to select the right procedure, and to achieve the right outcome
- Preoperative subjective questionnaires, such as the ***Dell Vision Questionnaire***, have two values: (1) to assess the **patient's attitudes and expectations** – documenting them in the clinical record, and (2) to **assess postoperative outcomes** by using the same or a related questionnaire.
- Patient age: previously 18–21 years. Now **14** years
- Refractive error: 0.50 D to **10 D of myopia** and **4 D of hyperopia**, **Astigmatism up to 5** D
- Corneal thickness: adequate residual stromal bed thickness of **300 *µm***. A residual thickness of 250 µm is a customary target. Abnormally thick corneas (greater than 620 µm) raise suspicion of endothelial dysfunction and warrant endothelial specular microscopy.
- Corneal topography: characteristics of early ***keratoconus or PMD, FF-KC*** should not receive LASIK, because they may be predisposed to further steepening (ectasia) after surgery.
- Keratometry: postoperative minimum value of 38 D and a maximum value of 50 D set the limits after surgery.
- Pupil size: very large pupils under mesopic conditions – 7.5 to 8 mm – seem at greater risk of optical aberrations.

Patient Evaluation and Selection

- Complete ocular history: patients with a history of ocular herpes simplex virus (HSV), strabismus, diplopia, previous refractive surgery, dry eye, or contact lens intolerance, Previous radial keratotomy (progressive hyperopic shift)
- **Examination**
  - Visual acuity
  - Refraction
  - Contrast sensitivity
  - Keratometery
  - Computed topography
  - Pupil examination: patients with pupils >6.5 mm will often have increased scores for total higher-order aberrations both pre and postoperatively
  - Slit lamp examination
  - Fundus examination
  - Tonometry
  - Pachymetry
  - Endothelial cell evaluation

- Anterior chamber depth
- Dry eye testing
- Monovision testing
- Ocular dominance determination
- Wavefront testing: unit of measure in wavefront testing is the root mean square (**RMS**) in microns (μm)
  - Lower-order aberration → defocus (MC)
  - Higher-order aberrations → spherical aberration and coma
  - **Wavefront-optimized versus a wavefront-guided treatment:**
    - Wavefront-optimized treatment, the laser treatment is designed to **minimize the increase in spherical aberration** which commonly occurs in myopic conventional ablation
    - Wavefront-guided treatments virtually always provide **superior** visual results compared to conventional treatment on other platforms, such as the VISX laser.
- Informed Consent: geometrically greater need as it being elective procedure

Tomography

- TBI
- **Tomography Biomechanical Index (TBI),** which aims to combine tomography and biomechanics to improve ectasia detection.
- The TBI included indexes from Pentacam HR and Corvis ST exams and provided higher accuracy for detecting ectatic corneal diseases than all previous analyzed parameters, including CBI. The random forest method provided the most efficient strategy for developing TBI.
- TBI provided 98.8% specificity with 96.2% sensitivity. TBI had 100% sensitivity to detect frank ectasia cases

Topographic Analysis

- True topography implies knowledge of the exact contour or shape.
- The term 'videokeratoscope' more accurately describes the technology of these instruments.
  - Orbscan combines optical sectioning with Placido reflection
  - Pentacam and Galilei utilize Scheimpflug imaging to measure the corneal surface.
- 'form fruste' keratoconus
- Displaced apex syndrome

OCT Systems for Corneal Epithelial Mapping

- FDACleared
  - Optovue: Avanti (9-mm map), iVue (6-mm map)
  - Carl Zeiss Meditec: Cirrus (9-mm map)
- **Parameters**
  - Pachymetry map: minimum (Min), minimummaximum (Min-Max), superonasal-inferotemporal (SN-IT)
  - Epithelial thickness map: standard deviation (Std Dev)
- Corneal anterior topography is not sufficient for detection of early keratoconus among LASIK candidates.
  - Topography may be normal in forme fruste keratoconus (FFK) due to epithelial masking.
  - Contact lens–related corneal warpage and dry eye can mimic keratoconus on topography.
- OCT epithelial thickness map and pachymetry map provide additional information to aid in more accurate diagnosis of subclinical and FFK.
    - OCT is the only noncontact imaging technology with sufficient resolution to measure epithelial thickness.
    - Confocal microscopy and ultrahigh-resolution ultrasound both require contact.
    - Scheimpflug camera cannot resolve the epithelium.
    - Keratoconus causes coincident focal thinning of epithelium and pachymetry on OCT corneal maps.

TMR Topography Modified Refraction

- Introduced by “A John Kanellopoulos MD” by comparison of the up-till-now “gold standard” clinical refraction and TMR for Myopic Lasik patients.
- **Compare the corneal and refractive astigmatic data.**
  - The corneal and refractive astigmatic data may not be identical. In that situation, if you’re using topography-guided LASIK, you can decide whether to “blend” the corneal and clinical refraction data, modifying the treatment amount and axis of astigmatism based on the topographic data. This is what we’ve described in the past as a topography-modified refraction or TMR adjustment of the topography-guided treatment. On rare occasions you may find that you also need to account for posterior corneal astigmatism, but this is seldom an issue.
- **Remember that altering the topography changes the spherical refraction.**

- A common mistake that surgeons new to this technology make is thinking that topography-guided treatment will give them the perfect outcome when combined with the clinical refraction.
- If there's a significant amount of topographic correction, the refractive outcome will change. It won't be what you'd expect if you had treated using wavefront optimized. This is certainly true when correcting astigmatism; when we change the amount of astigmatism, an appropriate adjustment needs to be made to the spherical equivalent. If we decrease the astigmatism by a diopter, we'll need to adjust the spherical correction to take this into account.
- The clinician can see the amount of change that will be created by the topography-guided treatment by looking at the ablation plan with the amount of sphere and cylinder set to 0. This will clearly show what the laser is going to do for that specific cornea in order to normalize it. This will allow the clinician to adjust the spherical correction accordingly.
- If a clinician finds this daunting, it's probably best to treat using a more familiar technology such as a wavefrontoptimized procedure. If a problem arises in the future, you can refer the patient to an expert in topography-guided treatments to address it.

- More details can be found from website at: http// www.topo-guided.com.

Incisional Corneal Surgery

- Dutch ophthalmologist: Lans

Radial Keratotomy

- Obsolete procedure
- -1.00 to -4.00 D of myopia
- Does not involve removal of tissue
- **PERK study**: Prospective Evaluation of Radial Keratotomy
  - -2.00 to -8.75 D (mean: 3.875 D)
  - 8 radial incisions were used for all patients
  - 53% of the 435 study patients had 20/20 or better uncorrected visual acuity (UeVA) and 85% were 20/40 or better.
  - Most important finding in the 10-year PERK study was the continuing long-term instability of the procedure. A hyperopic shift of 1.00 D or greater was found in 43% of eyes between 6 months and 10 years postoperatively. There was an association between length of the incision and hyperopic shift, particularly if the incisions extended into the limbus.
- Not only the curvature of the central cornea but also its overall topography, creating a multifocal cornea → flatter in the center and steeper in the periphery.
- 2 phenomena of postoperative refractive instability-
  - Diurnal fluctuation of vision

- Progressive flattening effect of surgery

Incisional Correction of Astigmatism

- **Coupling**: When one meridian is flattened from an astigmatic incision, an amount of steepening occurs in the meridian 90' away. This phenomenon is known as coupling. When the coupling ratio (the amount of flattening in the meridian of the incision divided by the induced steepening in the opposite meridia n) is 1.0, the spherical equivalent remains unchanged. When there is a positive coupling ratio (greater than 1.0), a hyperopic shift occurs.
- **Arcuate Keratotomy**
  - Arcuate incisions of approximately **95% depth** are made in the steep meridians of the **midperipheral** cornea at the 7-mm optical zone
  - Oldest corneal refractive surgery procedure
  - Partial-thickness incisions are placed perpendicular to the steep corneal meridian to induce flattening and a coupled effect of steepening 90 degrees away. Also called astigmatic keratotomy, the most frequent indication for the technique is astigmatism correction at the time of cataract surgery with limbal relaxing incisions.
  - The closer the incision is to the center of the cornea, the greater the effect.
  - Generally effective technique to treat 1–4 D of astigmatism.
- **Limbal Relaxing Incisions**
  - LRIs are incisions set at approximately **600u depth**, or 50u less than the thinnest pachymetry at the **limbus**, and placed just anterior to the limbus
  - Louis D “Skip” Nichamin MD
  - Mid 1990
  - Patients who suffer with advanced autoimmune or rheumatoid disease that might predispose to healing problems following use of such peripheral corneal incisions.

Onlays and Inlays

Keratophakia

- plus-powered lens is placed intrastromally to increase the curvature of the anterior cornea for the correction of hyperopia and presbyopia.
- The lenticule can be prepared either from donor cornea (homoplastic) or synthetic material (alloplastic).
  - Homoplastic Corneal Inlays
    - Obsolete
    - Aphakia and hyperopia of up to 20 D
  - Alloplastic Corneal Inlays

- Ability to be mass-produced in a wide range of sizes and powers that can be measured and verified
- AcuFocus, ReVision Optics, and Presbia
- The Kamra Inlay (AcuFocus Corneal Inlay): for the treatment of presbyopia.
  - **Ultrathin (5 um**), biocompatible polymer that is microperforated to allow improved near vision and perhaps nutrient flow.
  - The **3.8-mm** diameter inlay has a central aperture of 1.6 mm.
  - In the nondominant eye, a corneal flap that is 200 flm thick is created, and the inlay is placed on the stromal bed, centered on the pupil. Although the inlay has no refractive power, the goal of the device is to have the central aperture function as a pinhole to increase depth of focus and improve near vision without changing distance vision.

Epikeratoplasty

- Also called epikeratophakia
- Obsolete
- Suturing a preformed lenticule of human donor corneal tissue directly onto the Bowman layer of the host cornea

ICRS: Intrastromal Corneal Ring Segments

- Intracorneal ring segments (ICRS) are synthetic elements employed as a surgical alternative in the management of corneal ectatic disorders.
- **1978:** Reynolds proposed the idea of introducing a peripheral ring into the corneal stroma in order to change the curvature of cornea
- ICRS are one of the so-called corneoplastic techniques that allow surgeons to reshape the cornea for therapeutic and refractive purposes.
- Treat low amounts of myopia by displacing the lamellar bundles and shortening the corneal arc length
- Placed in the midperipheral corneal stroma
- Thicker the segment, the greater the flattening
- Commercially available
  - **INTACS (intrastromal corneal ring segments (INTACS, Addition Technology Inc))**
    - 1999, FDA approval
    - The most widely used (and the only ring segment used in the United States) is the Intacs Ring Segment (Addition Technology, Inc.; Sunnyvale, California).
    - The Intacs segments consist of a pair of PMMA semicircular pieces, each having an arc length of 150° and a hexagonal cross-sectional shape.

- When implanted surgically, the Intacs rings have an external diameter of 8.10 mm and an internal diameter of 6.77 mm.
- The refractive effect is determined by the ring thickness.
- In the United States, the FDA-approved rings are available in sizes ranging from 0.21 mm to 4.5 mm. (0.210, 0.250, 0.275,0.300,0.325,0.350,0.400 and 0.450 mm thickness)
- approximately 68%-70% stromal depth
- Current designs have a predicted myopic range of correction from -1.00 D to -4.10 D.
- Recently a new Intacs design (Intacs SK) with an inner diameter of 6 mm and an oval cross-sectional shape has been introduced.

Keraring (Mediphacos, Ophthalmic Professionals) & Ferrara rings (AJL Ophthalmic)

- PMMA
- Triangular in shape, they are manufactured with different arc lengths and a variable optical zone, ranging between 5 and 7 mm
- smaller optical zone
- more of a flattening effect
- *not FDA approved*

MyoRing (Dioptex GmbH)

- 360° full ring
- has a greater capacity to flatten and reduce the spherical equivalent than segments
- does not usually significantly reduce astigmatism
- use is limited to cases in which patients have a high spherical error and low astigmatism.

Advantage: potentially REVERSIBLE

Patient Selection

- 21 years or older
- with documented stability of refract ion, as demonstrated by a change of <0.50 D for at least 12 months prior to the preoperative examination
- with 1.00 D of astigmatism or less

Indication

- low levels of myopia (1.00 to 3.00 D spherical equivalent)
- KC
- KC+PMD?
- Ectasia After LASIK

contraindication

- Patients with collagen vascular, autoimmune, or immunodeficiency diseases

- Pregnant or nursing women
- The presence of ocular conditions (such as recurrent corneal erosion syndrome, or corneal dystrophy) that may predispose the patient to future complications

- In cases of peripheral KC, single segment can be applied. When a Single segment is placed, it flattens the adjacent cornea but causes steepening of the cornea 180 away-the "**bean bag effect**" (when one sits on a bean bag, the bag flat tens in one area and pops up in another area).
- **Complications**
  - Anterior chamber perforation
  - Microbial keratitis
  - Implant extrusion
  - Shallow ring segment placement
  - Corneal thinning over Intacs
  - Reduced corneal sensitivity (5 .5%)
  - Induced astigmatism between 1 and 2 D (3.7%)
  - Deep neovascularization at the incision site (1.2%)
  - Persistent epithelial defect (0.2%)
  - Iritis/uveitis (0.2%)
  - Visual symptom
    - Difficulty with night vision (4.8%)
    - Blurred vision (2.9%)
    - Diplopia (1.6%)
    - Glare (1.3%)
    - Halos (1.3%)
    - Fluctuating distance vision (1.0%)
    - Fluctuating near vision (0.3%)
    - Photophobia (0.3%)

Orthokeratology

- **Corneal refractive therapy CRT**
- Overnight use of rigid gaspermeable contact lenses to temporarily reduce myopia.
- The contact lens is fitted at a base curve flatter than the corneal curvature
- **Paragon CRT**: FDA approved rigid contact lens

Photoablation

- **Two broad groups:**
  - **Surface Ablation:**
    - Photorefractive keratectomy (**PRK**), laser subepithelial keratomileusis (**LASEK**), and epipolis LASIK (**epiLASIK**)
    - Bowman layer is exposed either by debriding the epithelium through various methods or by loosening and moving, but ultimately preserving, the epithelium
  - **LASIK**
    - Laser in situ keratomileusis
    - Excimer laser ablation is performed under a lamellar flap that is created with either a mechanical microkeratome or femtosecond laser
- **Wavefront-Optimized and Wavefront-Guided Ablations**
  - W**G**A
    - The treatment is aimed to correct the pre-operative HOAs
    - Profiles that are customized for individual patients.
    - W**G**A are **G**ood.
  - WOA
    - The treatment attempts to reduce HOAs generated during surgery.
    - Profile corrects expected HOAs for an average eye, and those that are anticipated as a result of the surgery. This means that an eye with higher than normal HOAs, will end up with near equally high HOAs after treatment in WOA.
- **Potential Contraindictions**
  - Connective tissue disease
  - Dry-eye syndrome
  - Stromal/ endothelial dystrophies
  - Previous herpes infection
  - Pregnant or nursing mother
  - Ectatic corneas
- Patients with ***EBMD are better candidates for surface ablation than for LASIK*** because surface ablation may be therapeutic, reducing epithelial irregularity and improving postoperative quality of vision while enhancing epithelial adhesion
- **Steeper** than 48.00 D are more likely to have **thin flaps or frank buttonholes** (central perforation of the flap) with mechanical microkeratomes. Corneas **flatter** than 40.00 D are more likely to have smaller-diameter flaps and are at increased risk for creation of a **free cap** due to transection of the hinge with mechanical microkeratomes.
- Formula is used to calculate residual stromal bed thickness (RSBT): Central corneal thickness thickness of flap depth of ablation = RSBT

PRK: PhotoRefractive Keratectomy

- PRK was the first widely accepted surgical procedure to ablate corneal tissue
- 1980s, PRK using the 193 nm argon fluoride excimer laser
- up to −10 D of myopia and +4 D of hyperopia
- **PRK Epithelial Removal**
  - Mechanical:
    - scraping using a Paton spatula, scalpel blade, Desmarres blade, or blunt no. 67 blade,
    - motorized brush such as that described by Pallikaris or the Amoils Epithelial Scrubber
  - Chemical: 18–20% ethanol, 20 seconds
  - EBK
    - **Epi-Bowman keratectomy (EBK)** is a new method for removing corneal epithelium for surface ablation, phototherapeutic keratectomy, and epithelium-off ("epi-off") crosslinking.
    - It was first developed by **Yariv Bar-on** of Israel.
    - The technique involves the use of a disposable hand-held instrument with a soft polymer tip and no moving parts.
    - This instrument, the **Epi-Clear device**, lifts and removes the epithelium in strips and sheets, without removing or damaging the basement membrane; it disturbs fewer epithelial cells than standard techniques.
    - This gentler removal process also provides faster re-epithelialization, less pain, faster return of vision, and better final clinical outcomes (higher percentage of 20/20 uncorrected and fewer enhancements) than the standard techniques.
- **Laser**
  - Excimer laser: Broad-beam lasers & scanning laser
- **Postoperative Management**
  - Broad-spectrum antibiotic
  - Topical NSAID
  - Topical steroids
- **Complications**
  - Intraoperative
    - Eccentric ablations and decentrations
  - Postoperative Complications
    - Epithelial problems
    - Dry eyes

- Corneal infiltrates and infectious keratitis
- Central islands
- Irregular astigmatism
- Undercorrection
- Overcorrection
- Haze, scarring
- Regression

- **New Matrix Therapy Agent, Cacicol**: It may improve the re-epithelialization rate after PRK, in order to lower the epithelial defect–related complications.

LASEK

- In the LASEK variant of surface ablation, the goal is to preserve the patient's epithelium.
- Instead of debriding and discarding the epithelium or ablating the epithelium with the excimer laser, the surgeon loosens the epithelium with 20% alcohol for 20 seconds and folds back an intact sheet of epithelium

Epi-LASIK

- Largely supplanted LASEK because there is no alcohol damage to the epithelium.
- In epi-LASIK, an epithelial flap is fashioned with a microkeratome fitted with a modified dull blade and a thin applanation plate that mechanically separates the epithelium. In this manner, epiLASIK preserves more viable epithelial cells, may improve results compared with LASEK

LASIK

- **History**
  - Jose I. Barraquer, Bogota, Colombia → father of lamellar corneal refractive surgery
    - 1949: keratomileusis → keras ('horn,' here applied to the cornea) and mileusis (carving or chiseling).
    - myopic keratomileusis (MKM) → freeze myopic keratomileusis, or F-MKM.
    - Keratophakia
  - **Kaufman and Werblin**: Epikeratophakia
  - **Ruiz**: automated lamellar keratoplasty (ALK), and the keratome was named the automatic corneal shaper (ACS)
  - Barraquer–Krumeich–Swinger (BKS) refractive system and its refined microkeratome (the BKS 1000)
  - **Srinivasan**, an IBM researcher: ablative photodecomposition with argon fluoride 193

- **Trokel and L'Esperance**: photorefractive keratectomy (PRK)
- 1989, **Peyman**: erbium:YAG laser to ablate rabbit corneal stroma using infrared (thermal) rather than ultraviolet energy
- 1990, **Pallikaris**: laser in situ keratomileusis
- 1999, the **Summit Excimer Laser** (Summit Technologies, Waltham, MA) was the first laser to be approved by the FDA for use in LASIK.

Suction Ring

- The suction ring has 2 functions:
  - to adhere to the globe, providing a stable platform for the microkeratome cutting head
  - to raise the IOP to a high level, which stabilizes the cornea.

Microkeratomes

- Five major types of microkeratome exist:
  1. nondisposable horizontal motor
  2. nondisposable vertical moto
  3. disposable
  4. Waterjet
  5. picosecond or femtosecond laser microkeratomes

Femtosecond laser

- Creates flaps by performing a lamellar dissection within the stroma.
- Several extra steps
  - Suction ring is centered over pupil and suction is applied
  - Docking procedure
  - Applanation lens is then centered over the suction ring
  - Femtosecond laser treatment applied
- **Advantages of FEMTO**
  - Less increase in IOP required
  - More control over flap diameter
  - Size and thickness of flap less dependent on corneal contour
  - Centration easier to control
  - Epithelial defects on flap are rare
  - Less risk of free cap and buttonhole
  - More reliable flap thickness
  - Hemorrhage from limbal vessels less likely
  - Ability to re-treat immediately if incomplete femtosecond laser ablation
- **Disadvantages**

- Longer suction time
- More flap manipulation
- Opaque bubble layer may interfere with excimer ablation
- Bubbles in the anterior chamber may interfere with tracking and registration
- Increased overall treatment time
- Difficulty lifting flap >6 months
- Increased risk of diffuse lamellar keratitis
- Increased cost
- Need to acquire new skills
- Delayed photosensitivity or good acuity plus photosensitivity (GAPP), which may require prolonged topical corticosteroid therapy

- Application of laser Treatment
  - Tracking
  - Centration
  - Ablation
- **Refractive Outcomes**
  - For Myopia: mild to moderate
    - 90% achieved 20/20
    - ~100% achieved 20/40
  - For Hyperopia
    - 46%-59% of eyes had postoperative UCVA of20/20 or better, 92%-96% had UCVA of 20/40 or better, and 84%-91 % were within 1.00 D of emmetropia

Thin-flap LASIK

- 100–110 µm flaps, also referred to as sub-Bowman's keratomileusis
- more safely with regard to ectasia and corneal hypoesthesia

Customised LASIK

- **Wavefront Optimised**
  - Standard module
  - A pure refractive change
  - Designed to treat spherocylinder errors without affecting higher-order aberrations (especially spherical aberration)
  - Range:
    - Myopia: 0 to −14 D
    - Myopic astigmatism: 0 to −6 D

        - Hyperopia: 0 to +6 D
        - Hyperopic astigmatism: 0 to +6 D
        - Optical zone: 4.5 to 8.0 mm
- **Wavefront Guided**
    - A-CAT Module
    - Line of sight
    - Preop higher-order root mean square (RMS_H) distribution
- **Topography-Guided LASIK**
    - T-CAT is aligned on the vertex.
    - Developed to correct higher-order aberrations based on corneal topography
    - Provides an alternative to the correction of higher-order refractive errors based on aberrometry
    - Not dependent upon pupil size
    - Can be measured reproducibly
    - Unaffected by lenticular opacities and vitreous opacities
    - Accurately measures peripheral corneal irregularities, which are responsible for many visual complaints
    - Fitting Targets for Topography Guided
        - The fitting objective for topography-guided treatments is based on the individual topography.
        - The reference body and its asphericity are designed to balance ablation (cosine effect) within the optical zone.
        - The fitting asphericity (Q) can be selected by the physician, within the limits set by the software (0 o -1.0), but alteration is not advised.

LASIK enhancement Techniques

- Integral aspect of refractive surgery, 5%-30% rate Increased enhancement rates with:
    - Conservative primary surgery
    - Higher postop visual acuity goal (20/20 goal will need enhancement more often than 20/40 goal)
- Methods of Retreatment
    - Surface ablation (PRK)
    - Relift original flap
    - New side cut in the original LASIK flap (investigational)
    - Recutting with microkeratome/femto (Not recommended)
- Major Complication: Epithelial Ingrowth
    - Isolated nests/sheets of cells

- Decreased UCVA and/or BCVA
- Induced astigmatism on refraction
- Irregular astigmatism on topography

- Transepithelial PRK
  - 65 micron PTK
  - PTK diameter: 6.5 mm
  - Transition zone: 0.5 mm
  - Spherical adjustment: 0.65 D
  - Standard PRK: 6.0 mm
  - 125 MMC if indicated. Apply in all enhancements.
  - Frozen/cold BSS irrigation

Complications

- **Surface Ablation and LASIK**
  - Overcorrection
  - Undercorrection
  - Central Islands: steepening of at least 1.00 D with a diameter of 1 mm compared with the paracentral flattened area.
  - Optical Aberrations:
    - glare, ghost linages, and halos
    - Night-vision complaints are often caused by spherical aberration
  - Decentered Ablation: Centration is even more critical for hyperopic than myopic
  - Corticosteroid-Induced Complications
  - Endothelial Effects
  - Dry Eye and Corneal Sensation
  - Infectious Keratitis
- **Complications Unique to Surface Ablation**
  - Persistent Epithelial Defects
  - Sterile Infiltrates
  - Corneal Haze
    - Early: within 6 months
    - Late: after 6 months
    - Subepithelial corneal haze will typically appear in the first few months after PRK, with a peak of intensity at 2 months, and then typically improve over 6-12 months.

- Topical steroids are often used after surface ablation to reduce the incidence of haze.
- Mitomycin C (MMC) is often used at the time of the treatment to reduce the incidence of haze and has been used in varying concentrations for varying lengths of time with no clear evidence for specific dosing. Effective concentrations appear to be from 0.02 mg/cc (0.002%) to 0.2 mg/cc (0.02%) for 10-120 seconds. The safety profile of MMC appears to be excellent.
- If haze does occur, then mechanical removal followed by laser removal and MMC and steroids during healing can often improve the haze significantly. Keratoplasty for haze is rare.

- Decentration
  - Irregular astigmatism can occur because of decentration of the optical aspect of the ablation. This can occur due to misalignment, poor patient fixation, or malfunction of the laser.
  - Decentration may result in a patient complaining of glare or halo; in severe cases it may lead to loss of BCVA.
  - Prevention includes understanding the alignment process for your laser equipment as well as verifying proper patient fixation on the target of the laser. Pupil tracking technology has improved but has not eliminated decentration.
  - Detection of a decentration is done through topography once the epithelium has healed and stabilized after surface ablation. Wavefront analysis will typically show large amounts of coma when performed in an eye with a decentration.
  - Symptoms are greater in patients who have larger amounts of decentration, or deeper ablations.
  - Wavefront-guided ablation may reduce the amount of decentration of the optics because it takes into consideration changes in the center of the pupil in bright and dim light. Most wavefront optical systems work to center the optical aspect of the distance correction on the dim light pupil of the aberrometer instead of the bright light pupil center that the laser treats under. This may reduce small amounts of error in alignment for the patient.
- Irregular ablation
  - Uneven ablation may occur when fluid, sponge material, or residual epithelium is blocking the laser treatment. It is important to make sure that the epithelium is completely removed in the area of the ablation, and that no excess fluid blocks the ablation of the laser. Other debris such as sponge material or meibomian gland secretions should be removed from the surface of the eye prior to the ablation.
  - These other reasons for irregular astigmatism may also cause symptoms of glare or halo as well as potential for loss of BCVA. Detection of irregular astigmatism is also done through topography and wavefront analysis.
- Often irregular astigmatism can improve over time through epithelial remodeling, and so waiting 6-12 months for this to occur is often helpful in mitigating symptoms.

Glasses may help in some mild cases of irregular astigmatism. Rigid contact lens wear can also mitigate symptoms in patients with more severe irregular astigmatism. Miotics may be helpful in some patients. Wavefront-guided and topographic-guided laser correction are also helpful in patients who have significant irregular astigmatism where a surgical process for improvement is desired.

- In treating patients with irregular astigmatism, rule out ectasia by reviewing old topographies if possible. Ectasia is less common with surface ablation but may be present. Understand whether there are other issues related to the irregular astigmatism like corneal haze, dryness, basement membrane dystrophy, or pre-existing corneal scarring.
- Patients with fixation errors on the original treatment may exhibit variable fixation on testing, such as corneal topography or wavefront analysis, and may be more prone to variable fixation with retreatment.
- Dry eye
  - Many patients who seek refractive surgery do so because of contact lens intolerance.
  - Much of the contact lens intolerance is from aqueous deficiency and meibomian gland dysfunction– related evaporative dry eye.
  - Identification of this group of patients preoperatively allows management of the dry eye and education of the patient as to the chronicity of the dry eye.
  - Many patients will have an increase in dry eye symptoms and findings after corneal surgery.
  - Lid hygiene, tear supplementation, and oral omega-3 are often helpful.
  - In patients with more severe disease, topical cyclosporine, lubricant ointments, and oral doxycycline may be useful.
  - Typically, the tear function and epithelial health will return to baseline at 6-12 months.
  - In many patients, even though they return to baseline, there may still be dissatisfaction if they were unaware that they originally had the problem with their tear film.
- Infiltrative Keratitis
  - Sterile or infectious infiltrates can be found after surface ablation.
  - Careful monitoring of the cornea can help to detect the occurrence of these issues.
  - In suspected infectious keratitis, culturing and antibiotics tailored to the infection can help to resolve the infectious process and hopefully minimize scarring that might affect long-term vision.
  - Sterile infiltrates can occur due to overuse of topical nonsteroidal drugs or in patients with significant ocular rosacea and staph marginal keratitis.
- Steroid Response Pressure Problems
  - Elevated IOP can occur with use of topical steroids in some patients.
  - Monitoring the IOP at the postoperative visits can help to monitor the IOP.

- Fortunately, elevated IOP is uncommon.

✦ Complications Unique to LASIK

✣ Microkeratome Complications

- Buttonhole
  - Buttonholing of the flap is a dreaded complication, as it often occurs in the visual axis and heals with scarring and loss of BCVA.
  - Poor quality blades, inadequate IOP, keratome malfunction, and steep corneas are predisposing factors.
  - With the microkeratome, corneas steeper than 48 D may buckle centrally, leading to a buttonhole.
  - Buttonholing should be recognized immediately by the surgeon and the surgery aborted. Proceeding with ablation can cause severe irregularities and a loss of BCVA.
  - Though a smaller suction ring can help, femtosecond flap creation and surface ablation are better options. In case of buttonholing with a microkeratome, the procedure should be aborted and the flap realigned. The patient should be followed up for epithelial ingrowth or opacity. Fibrin glue may be used to prevent this. The patient can undergo a PRK/ PTK with application of mitomycin C at a later date or can have a deeper recut with customized ablation.
- Free cap
  - The cap is carefully placed epithelial side down in a drop of BSS to avoid stromal hydration.
  - Alignment marks help in identifying the side, as well as in realigning the flap in the appropriate position.
  - Time should be allowed for the flap to adhere well. Sutures or a bandage contact lens may also be used to secure the flap. Incomplete or partial flaps may also occur. The procedure generally has to be aborted, and a new flap with a deeper cut is made 3 to 6 months later. Alternatively, a surface ablation may be performed. Manual dissection of the flap should never be attempted, as this can lead to severe topographical abnormalities and loss of BCVA.

✣ Inadequate suction or Suction loss

- The result may be a thin or superficial flap, a buttonhole or interrupted flap, or an irregular flap.
- If chemosis is induced from repeated suction ring:
  - An incision in the conjunctiva may allow drainage of excess fluid.
  - The handle of a swab can be used in an attempt the fluid away from the limbus.
  - Alternative approach is to wait 30 to 45 minutes and then try again.

        - Postpone the procedure for 1 to 2 days and allow the subconjunctival edema to reabsorb.
    - Inadequate exposure: Microkeratome placement is difficult in sunken globes, in eyes with narrow palpebral fissures and small corneas.
        - The use of the newer generation microkeratomes with down-up flap
        - By turning the head of the patient slightly to the opposite side
        - By exerting a gentle pull and tilt on the eye through the suction ring handle
        - Manual dissection can be considered.
        - PRK or LASEK should be considered if appropriate.
        - Lateral canthotomy
- **Incomplete flap/irregular flap**
    - If the exposed stromal bed is not large enough to allow adequate laser ablation:
        - Flap should be repositioned.
        - The laser procedure should be postponed.
        - Irrigation of the flap interface is performed.
    - Irregular cuts
        - The surgeon should not proceed with the ablation.
        - The flap and fragments should be carefully replaced and realigned.
        - Additional waiting/drying time
        - Bandage contact lens overnight
        - 3-6 months waiting
        - Deeper and more peripheral cut during the retreatment
- **Thin/irregular flap**
    - Flap is repositioned.
    - Operation repeated 10-12 weeks later
    - Deeper flap (20-60 microns deeper) may be recut.
    - Alternatively, a no-touch transepithelial PRK within 2 weeks, especially in low myopes
- **Corneal perforation (full-thickness anterior chamber entry)**
    - Immediate closure of the cornea wound with 10-0 nylon sutures
    - Patient is asked to try to relax and minimize coughing.
    - Transfer to operating room
    - Repair may involve corneal repair, iris repair, lensectomy.
- **Epithelial defects (microkeratome and femto): Treatment**
    - Try to replace loose epithelium.

- If significant amount, consider bandage contact lens to be removed at 1 week.

- **Decentered flaps (microkeratome and femto): Treatment**
  - If large enough flap and small optical zone that can still be centered on the pupil, proceed.
  - If not, lay flap down and allow to heal for 1-3 months, awaiting refractive stability and corneal stability. Retreat with surface ablation technique.
- **Striae**
  - Macrostria: Hyperthermic ironing and suturing the flap
  - Microstria
  - Management
    - Relift, refloat flap
    - Reposition
    - Flap traction with forceps or sponge
    - Hyperthermic treatment
    - PRK
- Flap subluxation has been reported to occur in up to 1.4%
- Traumatic Flap Dislocation
- ***Diffuse Lamellar Keratitis (DLK)***
  - "sands of the Sahara" (SOS),
  - first described by Smith and Maloney
  - Pathogenesis
    - Endotoxins (tears, spears, blade, instruments, plaster dust, dead microbe spores in autoclaves)
    - Inflammation cells → enzymes → necrosis
    - Prevention and management
  - can range from asymptomatic interface haze near the edge of the flap to marked diffuse haze under the center of the flap with diminished BCVA.
  - ***Four Stages***
    - Peripheral faint white blood cells; granular appearance
    - Central scattered white blood cells; granular appearance
    - Central dense white blood cells in visual axis
    - Permanent scarring or stromal melting
  - ***DLK Management***
    - Grade 1:hourly Pred forte
    - Grade 2: lift flap + irrigate, hourly Pred forte
    - Grade 3:lift flap + irrigate, hourly Pred forte

        - Grade 4:lift flap + irrigate, hourly Pred forte DO NOT SCRAPE !
- **Pressure-Induced Stromal Keratitis (PISK)**
- **Central Toxic Keratopathy:**
    - noninflammatory condition that can mimic DLK
    - The difference is that DLK is more diffuse and CTK is more central CTK slowly resolves over several months after surgery and it is typically unresponsive to steroids.
- **Epithelial defect/corneal erosions**
    - Contact lens
    - Non-preserved artificial tear drops
    - Topical antibiotic
    - Nonsteroidal anti-inflammatory
- **Corneal limbus bleed**
    - Apply a dry sponge to the bleeding area.
    - Leave the flap in position and wait until coagulation begins.
    - Pressurized air can be used as a vasoconstrictor and to encourage coagulation.
    - In uncontrolled bleeding, the suction ring may be reapplied and pressure reactivated for the duration of the ablation.
- **Epithelial Ingrowth**
- **Interface Debris**
    - Try to minimize risk by decreasing meibomian gland fluid, lint, and fibers on the ocular surface using BSS to irrigate before the flap lift and after the excimer
      ablation.
    - If debris is noted under the flap after it has been replaced, you can use and irrigating cannula to flush the debris from the interface.
- Transient Dry Eye: Lubrication, plugs, topical cyclosporine
- **LASIK Interface Fluid Syndrome**
    - first described by Lyle and Jin in 1999. Corneal flap architecture, which is inherently weak, has been previously reported in 2007 by Dawson et al as a hypocellular primitive stromal scar.
    - 2 distinct etiologies:
        - increased IOP
        - endothelial cell dysfunction.
    - Usually, the condition manifests 1-3 weeks after the LASIK procedure secondary to steroid-induced IOP rise; however, there have been several reports of interface fluid syndrome years after LASIK secondary to a rise in IOP or endothelial decompensation.

- **Infection Microbial Keratitis in LASIK**
  - Incidence: 1/1000 to 1/5000 procedures (underreported?)
  - Intraoperative intrastromal contamination likely
  - Sterility measures greatly vary, but are imperative.
  - ABTs prophylaxis is essential (Gram + eyelid flora and mycobacterial coverage)
  - Differential diagnosis: DLK, debris, ABT/steroid deposits
  - Fungal keratitis must be suspected when epithelium is intact ± multiple lesions (satellites), quiet eye (no pain!!).
  - Difficult to diagnose and treat! Results can be challenging:
    - Flap necrosis
    - Stromal scarring
    - Visual loss
- Infection Fungal Keratitis (Acremonium)
- Decentered irregular ablations: Topography-guided therapeutic ablations may be the best solution.
- Irregular Flaps: PRK after flap has healed may be the best solution.
- Corneal ectasia

- **Disturbances Related to Femtosecond Laser LASIK Flaps**
  - Good acuity, postoperative photophobia **GAPP**
  - Rainbow glare
  - Buttonhole when attempts to make flaps less than 100 microns, previous scars, old surgery, and breaks in the epithelium involving the Bowman membrane. This is recognized intraoperatively as a clear area in the advancing raster pattern or as an escaping bubble and is also called vertical gas breakthrough (VGB).
    - Don't lift flap.
    - Postpone operation.
    - Wait 3-6 months.
  - Suction loss
    - Incomplete flap: second pass, recut
    - Same level flap
  - Anterior chamber gas bubbles
    - Attempt pupil tracking and proceed with excimer laser if able to obtain.
    - Otherwise wait for dissipation and then proceed when pupil tracking is obtained.
  - Opaque bubble layer
    - Allow the opaque bubble layer to clear.

- Proceed with excimer ablation but Recut deeper
- Can occasionally interfere with pupil tracking; can use Weck-Cel to sweep and lighten opaque bubble layer.

- Transient light sensitivity syndrome (TLSS)
  - Use lower energy and faster femtolaser.
  - Intensive corticosteroids
  - Oral corticosteroids

Corneal Ectasia following Keratorefractive Surgery

- Progressive keratectasia is an uncommon but also a very severe complication of laser vision correction (**LVC**) procedures.
- Progressive "iatrogenic" keratectasia occurs due to a biomechanical failure of the corneal stroma to support the unremitting stresses caused by IOP, extraocular muscle actions, eyelid blinking, and other forces such as eye rubbing, causing thinning and protrusion of the cornea.
- It was first reported in 1998 by **Seiler**.
- Ectasia can occur immediately or years after refractive surgery. The incidence of ectasia is unclear, but it is likely between 0.04% and 0.6% of cases.
- **Risk Factors**
  - Preoperative structural abnormalities such as keratoconus (clinical or subclinical), including cases with higher susceptibility of the cornea due to weak innate biomechanical properties
  - Severe biomechanical impact from surgery
  - Severe trauma after surgery, such as vigorous eye rubbing in response to allergic conjunctivitis, to cause (possibly unilaterally) post-LASIK keratectasia without other known predisposing risk factors
- **Pathogenesis**
  - Thin residual stroma (< 250)
  - Forme fruste keratoconus (Always read topographies carefully.)
  - Stromal lamellae shift
  - Refraction follow-up
  - Elevation topography (Orbscan) BFS > 55 D, Post Diff > 50 µm
  - The impact from the LVC procedure on the cornea is related to the residual stromal bed (RSB) and to the percentage tissue altered (PTA).
    - PTA higher than 40% is a more sensitive parameter than a fixed value for minimal RSB of 250 µm.
    - The biomechanical impact from surgery is related to the region and number of lamellae that are severed, so that flap thickness and geometry should play a more relevant role, which is in agreement with finite element simulations.

- **Clinical features:**
  - Loss of visual acuity, positive dysphotopsias (eg, glare, halos), and image distortions (eg, multiple images, ghosting)
  - Patients experience increased myopia, with or without increasing astigmatism, and loss of BCVA. On examination, the cornea steepens and thins, as measured by topography and tomography.
- **Randleman** et al. studied patients with **post-LASIK ectasia** and identified five main risk factors for this complication.
  1. Young age at the time of surgery
  2. abnormal preoperative topography,
  3. reduced residual stromal bed thickness
  4. decreased preoperative cornea thickness,
  5. High myopia
- **Ectasia Susceptibility Screening**
  - Anterior corneal curvature topometric asymmetry indices **IHD and ISV** (index of height decentration (IHD) and the index of surface variance (ISV), which provide a more sensitive analysis than keratometry and visual function). A smaller value is indication of cornea normalization (lower IHD, cone less steep and more central; lower ISV, less irregular surface).
  - Qualitative pachymetric asymmetry assessment (normal cornea thickens in circles and smoothly); Scheimpflug, OCT
  - ART-Max = TP/PPI-Max (essentially “steep” cornea pachymetry change)
  - Epithelial map profiles may be the most sensitive tool.
  - Biomechanical measurements-Brillouin may hold promise in the future
  - **Randleman’s Ectasia Risk Scoring System**: of refractive correction, residual stromal bed (RSB), and patient’s age along with corneal topography and CCT
    - Objective quantitative indices, such as the classic **Rabinowitz** inferior-superior dioptric asymmetry value (I-S) and the keratoconus percentage index (KISA), and qualitative pattern of asymmetric bow-tie with skewed radial axes (AB/SRAX)
  - The map pattern, the elevation values at the thinnest point and at maximum elevation within central 4-5 mm zone are the most important characteristics for clinical interpretation.
    - Using the **Pentacam**, the cut-off criteria for the **posterior elevation** value at the thinnest point was 12 µm using the BFS and 8 µm using the BFTE, with respective sensitivity of 96.28% and 95.04% and specificity of 98.79% and 99.09% for detecting keratoconus
    - Using **Galilei Analyzer** (Zeimer Ophthalmic Systems AG; Port, Switzerland), the cut-off values for maximum **posterior elevation** within the central 5-mm diameter obtained by BFTA were 16 µm and 13 µm for keratoconus and mild (forme fruste) keratoconus, respectively.

- The **thinnest point (TP)** is a more accurate parameter than central thickness for screening ectatic corneal diseases, as well as for calculating the PTA and RSB.
- The concept of an **enhanced elevation** has been introduced and implemented on the Pentacam. After calculating the standard BFS for the 8-mm corneal zone, a second "enhanced" best-fit sphere for the same zone excluding the 3.5-mm diameter zone centered at the thinnest point is calculated. The difference map from the standard and enhanced BFS will exaggerate any differences (protrusions) within the excluded zone. More than 5 µm of difference for the front elevation and 12 µm difference for the back elevation are considered suspicious.
- In the Pentacam, **thickness distribution** is described as the average of thickness values in concentric annular circles with increasing diameters centered on the TP. These values are presented in the **corneal thickness spatial profile (CTSP)** and the **percentage of thickness increase (PTI)** graphs, which also contain reference data (mean and 95% confidence intervals) from a normal population.
    - In addition, a **pachymetric progression index (PPI)** is calculated for every 1 degree of meridians of the cornea, starting from the thinnest point outward. This calculation considers the increase in thickness and comparing to the TP at each point of the cornea, referencing to a normal population. The best cut off point is **1.35**, with sensitivity over 92% and specificity of 85%
    - The **Ambrósio relational thickness (ART)** values are calculated as the ratios of the TP and the average of the PPI at all meridians (ART-Ave) and the meridian with maximal PPI (ART-Max).
        - The cut-off criteria for ***ART-Ave*** for clinical and mild (FFKC) keratoconus were, respectively, ***474 µm and 521*** µm, with sensitivity and specificity of 99.59% and 98.19% for keratoconus and 91.49% and 93.05% for FFKC.
        - For ***ART-Max***, ***386 µm and 416 µm*** were the cutoffs, which had, respectively, sensitivity and specificity of 99.17% and 97.28% for keratoconus and 85.11% and 93.05% for subclinical disease.
- **The Belin/Ambrósio Enhanced Ectasia Display (BAD)**
    - comprehensive display that combines the standard and enhanced BFS elevation maps of the front and back surfaces, and the thickness distribution data.
    - anterior and posterior elevation at the thinnest point (8 mm BFS), change in anterior and posterior elevation of the standard and enhanced BFS, thinnest value and location, PPI, ART and maximal curvature (K-max). The BAD-D final parameter is calculated based on a regression analysis to maximize accuracy for detecting ecstatic disease.
    - Software shows five new terms (D values for standard deviation from the mean) representing the front surface (Df), back surface (Db), pachymetric progression (Dp), thinnest point (Dt), and thinnest point displacement (Dy). **A sixth term (D)** is the final overall map reading taking each of the five parameters into account.
    - BAD-D higher than **2.11** was a criteria with sensitivity and specificity of 99.59% and 100% for diagnosing keratoconus, while for detecting mild or

subclinical disease the criteria of higher than **1.22** provided 93.62% sensitivity and 94.56% specificity.

- BAD-D (v3) values turn yellow in the display when higher than 1.6.

- **Prevention of Corneal Ectasia**
  - Detection → phakic IOL for selected cases
  - Beware of enhancement procedures thinning the cornea further, some “regressions” may be early ectasia.
- **Management of Corneal Ectasia**
  - Restoring vision and minimizing symptoms
    - Eyeglasses: Eyeglasses are a mainstay of early or mild ectasia management.
    - Contact lens: Contact lenses are the mainstay of management of corneal ectasia for the purpose of improving visual acuity. CTL options include toric contact lenses, rigid gas permeable lenses, custom wavefront-guided soft contact lenses, hybrid lenses, tandem soft contact lens– rigid gas permeable lenses, and scleral lenses.
    - Intracorneal ring segments (ICRS): Intracorneal rings can be surgically placed in the stroma of the cornea to improve visual acuity by altering the corneal shape.
    - In advanced cases, ALTK, DALK/PK may be required.
  - Preventing ectasia progression
    - CXL: This is a viable, relatively new option for reducing or halting ectasia progression. However, CXL is not without surgical risk. The patient’s degree of ectasia and other eye and health characteristics should be evaluated prior to CXL surgery.
    - Combination of CXL with refractive procedures: CXL is now being combined with procedures to improve UCVA and BCVA and minimize ectasia symptoms, including ICRS and with PRK.
    - Bowman layer transplantation: Transplantation of a Bowman layer tissue to the midstromal bed has been proposed to stabilize corneal ectasia and prevent transplantation.

PTK: Phototherapeutic Keratectomy

- **Phototherapeutic keratectomy (PTK)** represents an interesting application of excimer laser, and it progressively proved to be an interesting alternative to penetrating or lamellar keratoplasty. Due to its high ablation precision, the excimer laser is now an ideal tool for focal removal of corneal irregularities.
- FDA approval:
  - PRK: 1995
  - PTK: 1995

- LASIK: 1998
- Advantage
  - Precision: 0.25 µm of tissue, or about 1/2000 of the corneal thickness.
  - shape of the laser spots can be adjusted
  - allows the surgeon to remove superficial corneal abnormalities
- Disadvantage
  - does not discriminate between abnormal and normal tissue

- **FDA-approved indications for PTK**
  - Superficial corneal dystrophies (including granular, lattice, and Reis-Bücklers dystrophies),
  - Epithelial basement membrane dystrophy and irregular corneal surfaces (e.g. secondary to Salzmann's nodular degeneration, keratoconus nodules or other irregular surfaces), and
  - Corneal scars and opacities (e.g. due to trauma, surgery, infection, and degeneration)
- **Contraindications**
  - Immunocompromised host, uncontrolled ocular disease such as uveitis, blepharitis or dry eyes, and any condition thought to adversely affect corneal healing.
- Laser should not remove greater than one-third of the corneal thickness and should leave at least 250 µm of tissue after the procedure.
- **Side Effects and Complications**
  - Pain
  - Poor epithelial healing
  - Haze/scar
  - Infection
  - Induced hyperopia (common)
  - Induced myopia
  - Induced regular and irregular astigmatism
  - Decreased uncorrected and best-corrected vision
  - Recurrence of herpes simplex virus infection
  - Recurrence of the condition (especially stromal dystrophies, Salzmann's nodular degeneration, keratoconus nodules)
  - Graft rejection/failure

Corneal Epithelium Mapping & Its Application

- **Alfred Vogt** in 1921: corneal epithelium has the ability to alter its thickness profile to compensate for changes in stromal surface curvature in order to try and re-establish a smooth, symmetrical optical surface. Understanding this epithelial compensatory

mechanism is crucial to fully understand how the cornea will respond to different conditions and surgical procedures. As the refractive index of epithelium and stroma are sufficiently different (1.401 vs. 1.377), the epithelial-stromal interface constitutes an important refractive interface within the cornea, with a mean power contribution estimated at approximately -3.60 D.

- **Epithelial thickness measurement**
  - 1979: Brian Holden using optical pachometry
  - 1993: high-frequency digital ultrasound, 3 mm map
  - 2000: high-frequency digital ultrasound, 10 mm map
  - 1997: Confocal microscopy, Torben Moller-Pedersen
  - 2001: OCT
  - 2008: Haque, Epithelial thickness maps in an 8 mm diameter using OCT
  - 2012: David Huang, RTVue
- **Behavior of the Corneal Epithelium**
  - Epithelium is not a layer of homogeneous thickness
  - Non-uniformity seems to provide evidence that the epithelial thickness is regulated by eyelid mechanics and blinking
  - 5.7 µm thicker inferiorly than superiorly, and 1.2 µm thicker nasally than temporally, with a mean central thickness of 53.4 µm
- **Compensatory epithelial thickness changes can be summarized by the following rules:**
  - The epithelium thickens in areas where tissue has been removed or the curvature has been flattened (eg, central thickening after myopic ablation or radial keratotomy and peripheral thickening after hyperopia ablation).
  - The epithelium thins over regions that are relatively elevated or where the curvature has been steepened (eg, central thinning in keratoconus, ectasia and after hyperopic ablation).
  - The more irregular the topography, the more epithelial remodelling will have occurred.
  - The amount of epithelial remodelling is defined by the rate of change of curvature of an irregularity; there will be more epithelial remodelling for a more localized irregularity. The epithelium acts as low-pass filter, smoothing small changes almost completely but only partially smoothing large changes.
- **Applications of Epithelial Thickness Mapping**
  - **Keratoconus Screening**
    - Distinctive epithelial donut pattern, characterized by a localized central zone of thinning surrounded by an annulus of thick epithelium, demonstrating that the epithelium compensates for the underlying stromal cone by thinning over the cone and thickening around the cone
    - Potential to exclude the appropriate patients by detecting keratoconus earlier or confirming keratoconus in cases where topographic changes may

be clinically judged as being “within normal limits”. Secondly, epithelial thickness profiles may be useful in excluding a diagnosis of keratoconus despite suspect topography; epithelial thickening over an area of topographic steepening implies that the steepening is not due to an underlying ectatic surface.

- **Assessment of Progression of Ectasia**
  - The stromal surface curvature in a case of post-LASIK ectasia is very similar to that of a keratoconic cornea; there is a localized region where the stroma bulges forward resulting in increased curvature and associated corneal thinning.
  - Over this region, the epithelium becomes thinner, surrounded by an annulus of thicker epithelium, in exactly the same manner as in keratoconus. Given the predictable nature of epithelial remodeling, the amount of central thinning and paracentral thickening is caused by the rate of change of curvature of the stromal surface, and therefore the epithelial thickness profile can be used to assess the severity of the ectasia and also to monitor the progression over time.
  - Following the introduction of corneal collagen cross -linking, the consequences of post-LASIK ectasia have been significantly reduced now that we have a procedure available that can halt the progression, particularly if it can be identified in its earliest stages. As with keratoconus, the corneal epithelium acts to partially mask from front surface topography the extent of the changes to the stromal surface in ectasia. Therefore, an epithelial thickness map is able to pick up ectasia at a very early stage as the epithelial thickness profile of ectasia is distinctive from the expected thickness profile after a myopic ablation. We have previously described a severe case of ectasia where the epithelial thickness profile demonstrated a reduction in the extent of the stromal cone following a corneal cross-linking procedure.
- **Trans-epithelial PTK / Stromal Surface Topography-guided Custom Ablation**
  - 1994: Reinstein’s Law of Epithelial Compensation for irregular astigmatism, Irregular astigmatism results in irregular epithelium. If a patient presents with stable irregular astigmatism, by definition the epithelium has reached its maximum compensatory function by thinning over peaks and thickening over troughs in the stromal surface.
  - Trans-epithelial PTK is an excellent treatment option in irregularly irregular astigmatism.
  - The only disadvantage of trans-epithelial PTK is that it is limited to treat only the proportion of the stromal irregularities compensated for by the epithelium (as defined by the rate of change of curvature of the stromal irregularity), so more than one procedure is often required.
  - Artemis VHF digital ultrasound : Digital Subtraction Pachymetry (DSP) is used for Artemis assisted trans-epithelial PTK procedure
- **Limits for hyperopic steepening**

- It is currently assumed that hyperopic LASIK should be limited according to postoperative curvature, as too much steepening can result in epitheliopathy or apical syndrome; it is generally accepted that the postoperative curvature should not exceed 49.00 to 50.00 D.
- central epithelial thickness may be a more useful indicator, as it is a direct measurement of the potential risk of apical syndrome which occurs once the epithelium is too thin (less than 25 µm).

- **Improved IOL power calculation after corneal refractive surgery**
  - Given the lenticular nature of epithelial remodeling after corneal refractive surgery, the postoperative epithelium will make a contribution to the refractive effect of the cornea.
  - However, the epithelial thickness profile after a myopic ablation will have the opposite effect as that after a hyperopic ablation, while also being correlated to the amount of correction—and studies have demonstrated this exact result of undercorrection in post-myopic eyes and overcorrection in post-hyperopic eyes.

Mitomycin C in Corneal Refractive Surgery

- The main complication associated with laser surface ablation was the loss of corneal transparency (corneal haze) that appeared most frequently associated with deep ablations.
- The efficacy of the MMC in reducing the incidence of this complication has led to its widespread use in most refractive surgery practices.
- **Mechanism**
  - First isolated from cultures of Streptomyces caespitosus by Hata in 1956
  - Genotoxic antibiotic because of its alkylating action: once it becomes activated by enzymes such as the cytochrome p450 reductase, it produces cross-linking of the DNA molecules between adenine and guanine, thereby blocking DNA synthesis and secondarily inhibiting cell mitosis, causing cell cycle arrest
  - Primarily acts during the late G1 and S phases, it is non-cell cycle specific
  - Cytotoxic:
    - Upregulation of IL-8 and MCP-1
    - Fas-mediated apoptosis
    - Mitochondrial dysfunction
    - T-lymphocytes mediated cell lysis • Reactive oxygen radicals
    - Amplification of TNF
- **Effect on Cornea**
  - During surface ablation, both the de-epithelialization and the laser ablation incite keratocyte apoptosis → migration of the surrounding keratocytes → TGF-beta causes differentiation of keratocytes into myofibroblasts causing corneal haze. Myofibroblasts participate in extra-cellular matrix remodelling, resulting in a denser

and more disorganized extracellular matrix, with abundant collagen type III, which contributes to the loss of corneal transparency.

- First hours: increases keratocyte apoptosis
- 24h: less keratocyte repopulation
- 4 weeks: lower density of keratocytes and myofibroblasts, less deposit of collagen and extracellular matrix: less haze and regression

- **First use of MMC in Corneal Refractive Surgery**
  - Talamo in 1991, post operative MMC in surface ablation (Rabbit study)
  - Schipper et al observed that intraoperative 0.04% MMC for 5 minutes
  - Majmudar et al pioneered its use to treat corneal scars secondary to refractive procedures and applied 0.02% MMC intraoperatively for 2 minutes
  - Carones et al: MMC reduced the incidence and severity of haze after surface ablation for high myopia
- **Uses**
  - Primary Surface Ablation Procedures: Moderate to high myopia, thin cornea
  - Advanced Surface Ablation Procedures: LASEK and Epi-LASIK
  - Surface Ablation After Other Corneal Surgical Procedures: Post RK or PK, Post Lasik Flap complications, Residual refractive errors
- **Preparation and Duration:**
  - 5 ml of balanced salt solution (BSS) or distilled water are added to 2mg of MMC, to obtain a 0.4 mg/ml dilution of MMC. Using an insulin syringe, we take 0.5 ml of this solution and we add 0.5 ml of BSS or distilled water, thus obtaining 1 ml with 0.2 mg of MMC that is, an MMC concentration of 0.2 mg/ml (0.02%).
  - 0.02% for 2minutes over the ablated stroma (as per multiple studies)
- **How to Apply:**
  - use a round cellulose sponge approximately 7--9 mm in diameter. This is soaked in the MMC solution and placed carefully over the ablated stroma. This technique results in the release of good amount of MMC.
  - Jain et al proposed the use of a ring instead of a complete disk, in order to diminish the exposure of the central cornea
  - A small piece of cellulose sponge soaked in MMC may be used to apply brushstroke
- **Adverse Effects**
  - Epithelium:
    - dose-dependant delay in re-epithelialization
    - no difference in the epithelial migration rate (once the re-epithelialization began)
    - development of epithelial hyperplasia
  - Stroma:

        - keratocyte depletion but minimal (controversial)
        - no case of ectasia or corneal melting after surface ablation with MMC
    - Endothelium
        - decrease in corneal endothelial cell density and little change in morphology (controversial)
        - Dose dependant transient edema
    - Ciliary body and IOP: No effect

Collagen Shrinkage

- Lanz: dutch medical student
- Terrian: cautery to correct astigmatism
- Gasset and Kaufmann: thermokeratoplasty, 1975

Laser Thermokeratoplasty

- 1990s: holmium:yttrium-aluminum-garnet (Ho:YAG) laser → FDA approved
- Noncontact Sunrise Hyperion system was approved by the FDA in 2000.

Conductive Keratoplasty

- Lans in the 1880s.
- Can steepen the central cornea approximately 1 to 1.5 D
- Treating residual astigmatism after previous surgery and for creating monovision in presbyopes 2002, the FDA approved the ViewPoint CK system
- Radiofrequency waves
- Presbyopic patient with an endpoint of -1.00 to -2.00 D
- The number and location of spots determine the amount of refractive change, with an increasing number of spots and rings used for higher amounts of hyperopia.

C3R CXL Corneal Collagen Cross Linking

- **Collagen cross-linking (CXL or C3-R)** is the most recent addition to the surgical armamentarium and may slow or halt the progression of keratoconus by using a photo-oxidative treatment to increase the rigidity of the corneal stroma.
- **History**
    - 1970s: Siegel, formation of crosslinking aldehydes in collagen and elastin
    - 1990s: Spoerl (1997), corneal application
    - 2003: Wollensak, Seiler, 22 eyes with keratoconus, 1-year results (Dresden)

- K-max reduced at all follow-up periods
- Average decrease in K-max: 1.45 D at 12 months

- **CXL occurs naturally with aging**
  - Chronic exposure to UV light
  - Keratoconus tends to stabilize in patients after middle-age (30-35 years of age)
- **3 main Effect and Evidence of Cross-linking**
  - ***Biomechanical stabilization***
    - Cross-linked cornea is stiffer by factor 1.8 than normal cornea
    - Cornea's shrinking temperature is raised from 63°C to 70°C.
    - Cross-linked collagen shows significantly less tendency for swelling
    - The diameter of collagen lamellas increases by 12% in the anterior stroma and by 4.5% in the posterior
    - 4-fold increase of stiffness of the anterior cornea leads, in the majority of cases, to a halt of the progression of the keratoconus
    - **2.68 D reduction** in corneal power at 1 year postoperatively. Three years after the treatment, the BCVA improved one line in 58% of 33 eyes and remained stable in 29% of eyes
    - Most beneficial for patients with mild progressive keratoconus
  - ***Biochemical stabilization***
    - Enhanced resistance against proteolytic enzymes
    - Crosslinks are produced in the outer surface of the collagen molecule, blocking the docking stations for enzymes, and therefore the enzymatic activity is blocked for days.
    - Apoptosis of keratocytes in the anterior stroma is seen after cross-linking. new keratocytes move in from the limbus.
    - 328.9% increase in corneal rigidity
    - Clinical Application in Melting: A melting process indicates that the equilibrium between synthesis and catalysis of collagen inside the cornea is distorted, and the catalysis obviously is stronger than the synthesis. Now making the collagen more resistant against enzymes may bring this equilibrium into the opposite direction, and therefore melting can be stopped.
  - ***Cytotoxic effect***
    - Killing keratocytes up to 350 µm deep in the cornea, which, it is believed, happens due to the cytotoxic activity of the radicals. Now this cytotoxic activity could be also used to kill germs (in PACK-CXL)
- **Riboflavin**
  - Micronutrient with a key role in humans and animals
  - Precursor of two coenzymes known as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).

- pKa =9.888
- Molecular weight (376,36 Da+Ph-)
- Negative charge in physiological pH
- High solubility in water
- Fluorescent
- Type of riboflavin
  - **With enhancer → epi-on:** Riboflavin is a hydrophilic compound and cannot easily cross the intact epithelial barrier. So an enhancer is needed:
    - Trometamol (Tris-[hydroxymethyl]aminometane)
    - Sodium ethylenediaminetetraacetic acid (EDTA)
    - Benzalkonium chloride
  - **Without enhancer → epi-off**
    - With dextran
    - Without dextran
    - Hypo-osmolar

- **Methods**
  - **Standard procedure**: 30 minutes riboflavin soak + 30 min UV irradiance 2.
  - **Accelerated procedure**
    - Shorter UV treatment time + higher intensity UV exposure: Results equivalent to standard procedure ?
- **Dresden Technique** (as developed at University of Dresden)
  - Theo Seiler, MD, PhD, of Switzerland, was the first to suggest in **2003** applying this principle to ophthalmology, more specifically cross-linking corneal collagen fibers.
  - The principal effects of cross-linking are localized to the **anterior 300 *µ*m** of the stroma.
  - Corneal stroma should be greater than **400 *µ*m thick** (for thin corneas with storms less than 400 microns, **Hypotonic Riboflavin** can be used)
  - Riboflavin is a vitamin (vitamin B2), nontoxic and available as a drug. It has two important functions: the absorption of the UV-irradiation and as photosensitizer the generation of reactive oxygen species (singlet oxygen). **Riboflavin (0.1% in 20% dextran)** is then administered topically every 2 minutes for a total of 30 minutes. Following riboflavin administration, riboflavin absorption throughout the corneal stroma and anterior chamber is confirmed on slitlamp examination.
  - Molecular weight (376 g/mol) → so epithelial debridement needed
  - **Lambert-Beer's-law**: 400 µm-thick cornea the concentration at the endothelium reaches a level where the absorption of the UV-light is high enough to protect endothelium and intraocular structures
  - Two absorption maxima: 365 nm and 430 nm. **365** nm → higher energy, so it is used with an irradiance of 3 mW/cm^2 an optimal irradiation time of 30 minutes was found

- Damage threshold for the endothelium of 4 mW/cm2 and it gets only 0.18 mW/cm2. no risk for lens and retina.
- UVA-radiation source: UV-X (Fa. Peschke) → homogenous irradiance of 3 mW/cm^2 in a distance of 5 cm within a diameter of 8 mm of the central cornea

- **Indications**
  - ***Keratoconus Disease progression*** by Serial assessment of disease progression (every 4-6 months)
    - Kmax ≥ 1D increase
    - Kmax-Kmin ≥1D increase
    - Mean ≥0.75D increase
    - Pachymetry ≥2% decrease in CCT
    - Corneal apex power >1D increase
    - MRSE >0.5D
    - Decrease ≥ 0.1 mm in back optical one radius RGP
- **Contraindications**
  - Corneal thickness < 400µ
  - Herpetic eye infection
  - Corneal scarring or opacification
  - Poor corneal wound healing
  - Severe ocular surface disease
  - Autoimmune disease
- ***Other uses of C3R***
  - Athens Protocol
  - Bullous keratopathy
  - Corneal ulcer and melt
  - LASIK Xtra
  - Prophylaxis in myopic LASIK
  - Hyperopic LASIK (!!.. Yes this is to prevent regression..!!)

CXL Modifications

- **“Epithelial-on” CXL**
  - Advantages of epithelial-on CXL over epithelial-off CXL: Avoiding complications caused by epithelial removal
  - The major limitation: an inadequate and inhomogeneous riboflavin penetration
  - To increase the concentration gradient across the epithelium, with an aim to enhance its penetration and achieve higher UVA absorption, 0.5% Hypotonic Riboflavin is used.
- **Accelerated crosslinking (aCXL)**

- The Bunsen-Roscoe Law of photochemical reactions predicts that under certain circumstances the product of radiation intensity and radiation time is a constant dose. Based on this law, the idea arose to develop a high-intensity crosslinking device using a shorter radiation time, thus quickening the treatment procedure.
  - 5 mW/cm2 x 18 min = 5.4 J/cm2
  - 10 mW/cm2 x 9 min = 5.4 J/cm2
  - 30 mW/cm2 x 3 min = 5.4 J/cm2
  - [3 mW/cm2 x 30 min = 5.4 J/cm2 (standard Dresden treat ment protocol)]
- "Pulsed protocol" (i.e. a blinking UV-light that alternates between being switched on for 1 second and then switched off for 1 second) lets the oxygen necessary for the photochemical reaction to replenish during the "off times."5,6 All these different protocols with different exposure times are now grouped under the term "accelerated crosslinking" (aXCL), but they may show different outcomes, biomechanical changes, and side effects to the corneal tissue.
- The corneal epithelium is removed (7-8 mm in diameter) with a hockey knife under local anesthesia using proxymetacain eye drops (eg, Proparakain-POS 0.5%). Then, 1 eye drop of 0.1% riboflavin (VibeX Rapid) with saline and hydroxypropylmethyl cellulose (HPMC) is applied every 2 minutes for 10 minutes.
- After rinsing with BSS, the cornea is treated with a 365-nm UV-light (KXL, Avedro Inc.; Waltham, MA, USA) radiation of **30 mW/cm2 for 4 minutes**. Since the "pulsed protocol" with the UV-light is used, 1 second "on" and then 1 second "off," the total treatment time increases to 8 minutes. At the end of the procedure after rinsing again with a BSS, a therapeutic contact lens is placed on the corneal surface for 3-4 days until full epithelial healing.
- The KXL System for ***Accelerated Cross-linking achieves speed by increasing the UVA power and reducing the exposure time***, thereby maintaining the same energy on the eye as standard cross-linking while reducing crosslinking time by an order of magnitude.
- Avedro's new procedures made possible with its KXL System, can restore the strength of the cornea with a 5-minute treatment that accompanies LASIK, according to a company news release.
- Faster or accelerated, based on **Bunsen-Roscoe law** of reciprocity so that the constant radiant exposure is 5.4 J/cm2
- "Lasik Xtra helps patients avoid the risk of ectasia after LASIK, which has become a troublesome and unpredictable unpredictable problem," David Muller, PhD, President and Chief Executive Officer of Avedro, said in the news release. "In addition, our accelerated KXL procedure offers a much more acceptable treatment for patients with keratoconus and for those already suffering from post-LASIK ectasia."

CA-CXL

- Contact Lens-Assisted Crosslinking for Thin Corneas

- Thin corneas where the thickness of the corneal stroma after epithelial removal is less than 400 microns
- Works on Beer-Lambert principle
- Performed in thin corneas by utilizing a soft contact lens soaked in riboflavin solution. This contact lens, when placed on the cornea, attenuates the UV irradiance to safe levels by increasing the functional thickness of the cornea. The contact lens that is used should not have an in-built UV filter (e.g. B&L Hilafilcon B daily disposable)
- A soft lens design has advantages of adding a thickness of 90 microns to the functional corneal thickness.
- Intraoperative dehydration can be avoided by the use of riboflavin in HPMC (Vibex Rapid, Avedro, Inc.). It may also be decreased by performing accelerated crosslinking (CLUVR Rapid, Appasamy Associates; Chennai, India).

CXL Combinations

- **PRK with CXL**
  - The **Athens Protocol**:
    - Combining Topography-Guided Partial PRK With Corneal Crosslinking (CXL)
    - The management of keratoconus and post-LASIK ectasia by means of combined, same-day, topography-guided partial PRK and collagen cross-linking.
    - Therapeutic intervention in highly irregular corneas with keratoconus and progressive post-LASIK ectasia.
    - **4 steps**
      - 1: Topo guided Partial PRK
      - 2: PTK @ 50micron
      - 3: MMC 0.02% for 30 seconds
      - 4: CXL 6mW/m^2
  - **Montreal protocol**: One-year results show improvements in corneal curvature, visual acuity, and refractive error
- **LASIK Xtra:** Combining LASIK and CXL
  - Technique
    - Laser ablation
    - Riboflavin under flap
    - Flap repositioned
    - UV light on flap surface
- **PTK with CXL**
  - Mechanism: Differentially ablates peak of cone using epithelium to mask.

- **Cretan protocol** – trans-epithelial PTK
  - Better outcomes than mechanical PTK
- Up to 5-year results show improvement in corneal curvature, visual acuity, and refractive error.

- Prophylactic CXL In Situ Femtosecond Laser–Assisted Treatment of **Corneal Ectasia**
- Prophylactic CXL in Attempting Corneal Deturgescence in **Bullous Keratopathy**
- **Photorefractive Intrastromal Crosslinking (PiXL)**
  - Customizable patterns for predictable refractive changes
  - The epithelium-on CXL results in a significantly weaker biomechanical effect in comparison to the epithelium-off CXL.
  - Addressing keratoconus with PiXL
- CXL and **Intrastromal Corneal Ring Segments (ICRS)**
  - Flattens cone
  - Improves VA and corneal topography
  - Improves biomechanical stability
  - Intacs + CXL: Variable results – improvement?
  - Keraring, Ferrara ring + CXL: effective results
- **Phakic IOLs** After CXL
  - Toric, posterior chamber P-IOL or iris claw P-IOL
  - Mechanism: Correcting high refractive error
  - Used after CXL stabilization
- CXL in Infectious Keratitis (PACK CXL)

PACK-CXL: Cross-linking for Infectious Keratitis

- In **2008**, a proof of concept study showed photoactivated riboflavin to be beneficial in cases of therapy-resistant infectious keratitis.
- Iseli HP, Thiel MA, Hafezi F at Zurich, Switzerland
- **Mechanisms of action**
  - UVA light directly damages DNA and RNA in micro-organisms and inhibits them from replicating.
  - Riboflavin also has its own microbicidal effect.
  - When Riboflavin is photoactivated, it releases reactive oxygen species (ROS) that interact with the nucleic acids and cell membranes of the microbe.
  - Additionally, CXL interferes with the enzymatic digestion caused by the pathogenic micro-organisms that induces corneal melting.
  - New term adopted: **PACK-CXL** photo-activated chromophore for keratitis CXL
- **Actions against different infectious keratitis**

- Significant action of UVA-Riboflavin treatment was demonstrated against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.
- On the other hand, the effect of CXL against fungi has been controversial, with poor results against *Candida* in vitro but good efficacy against *Fusarium solani* in vivo
- CXL treatment in experimental studies with Acanthamoeba keratitis have been much less encouraging, showing a poor antitrophozoite and cysticidal effect

- PACK-CXL seems promising in the management of infectious keratitis, notably bacterial keratitis, and is not indicated in herpetic corneal disease. More evidence regarding its efficacy against fungal and parasitic infections and a better standardization of the procedure are needed to confirm its clinical relevance in the treatment of corneal infection.
- **PACK-CXL at Slit Lamp**
  - C-Eye© device
  - Basile Salmon
  - Gravitational influence on the riboflavin distribution was observed only after 60 minutes of vertical positioning. Given that a PACK-CXL treatment typically lasts for 3 to 30 minutes, this difference can be considered not clinically relevant.

Complications

- **Corneal Infiltrates**
  - Phototoxic effect on the corneal stroma may be the main mechanism that triggers these infiltrates
  - Alterations in antigenicity that occur in native proteins after CXL could result in the body recognizing the proteins as nonself and mounting an immune response
- **Corneal Haze**
  - More extensive stromal wound healing response that is proportional to the level of stromal cell death and associated with the generation of corneal fibroblasts with decreased intracellular corneal crystalline production and alterations in the regular structure of the stromal matrix that is responsible for optical transparency of the cornea
  - Haze after CXL is usually seen starting at 2-3 weeks postoperatively. In contrast to haze after PRK, CXL-associated haze is deeper, but it usually also dissipates after 2-5 months. While excessive, visually disabling haze is rare after epithelium-off CXL, it seems to be more common when CXL is combined with wavefront-guided surface ablation. In these cases, epithelial healing is also delayed and may take up to several weeks instead of the typical 3-4 days
- **Endothelial Damage**
  - Endothelial damage was reported a number of times in the literature. After examining the protocols used in all these cases, it was found that the technical properties of UV irradiation were not respected. The most common error was not measuring stromal thickness immediately before irradiation because the cornea may thin by up to 100 µm due to evaporation during riboflavin instillation.

- **Massive Remodelling**
  - Massive remodelling was first observed in 2010 when clinical researchers in Zurich analyzed their first 1000 CXL procedures and noted that massive remodelling occurred in 1:200 eyes. Massive remodelling may start as early as 10 days after CXL and can lead to a flattening effect of up to 11 D. In all cases, flattening is accompanied by a distinct, permanent deep stromal haze. In these highly irregular corneas, the flattening effect of the haze leads to an increase in corrected distance visual acuity. This advantage outweighs the negative effect of increased glare caused by the haze. In other words, this haze, which would have been a major nuisance in a healthy eye, came with an added benefit in a keratoconus cornea.
- **Ongoing Flattening and Thinning**
  - Rare postoperative remodeling effect
- **Sterile Melting**
  - This complication was reported in a number of cases; all cases were associated with prolonged use of NSAR, which may increase MMP-9 expression and induce corneal melting.
- **Infectious Keratitis**
  - CXL with photoactivated chromophore for infectious keratitis (PACK-CXL) is seen as a potential new tool to combat infectious keratitis. PACK-CXL shares the same irradiation settings as CXL for keratoconus, so at the end of every CXL procedure for keratoconus, the surface of the cornea should, as a side effect, be free of all pathogens. Thus, any infection occurring in the postoperative period is due instead to poor handling of the

INTRACOR

- Done on TECHNOLAS Femtosecond work station. (Previously (Victus Femtosecond Laser Platform; Bausch + Lomb/TPV)
- The first Intracor procedures were performed in patients in 2007 by Dr.Luis Ruiz, Bogotá, Colombia.
- It applies energy inside the cornea without bringing it to the surface
- No incision of epithelium, endothelium or Bowman's or Descemet's membrane and thus ensure better healing with minimal risk of infection.
- The pulses are placed on 5 concentric intrastromal circles centered about visual axis and extended at least up to 100 microns from the surface.
- The concentric patterns of cut fibers shift the centre of cornea slightly anteriorly and create a hyperprolate shape.
- At present myopia up -3D and astigmatism up to 2D have been tried. However the results are not very accurate.

- Also its role in presbyopia has been emphasized as it causes a biomechanical change in cornea that shifts centre slightly forward creating a pattern of hypersphericity thus allowing some near vision while retaining distance vision.
- A good solution for presbyopic hyperopes (+0.5 D to +1.25 D), where patients normally gain 4-5 lines of near vision with a potential slight impact on distance vision and few side effects.

Intraocular Surgery

Phakic IOLs

(To be Read from LENS Book of same series)

Bioptics

- Term suggested by **Zaldivar** in the late 1990s
- PCPIOL implantation followed at a later time by LASIK to treat patients with extreme myopia and/or residual astigmatism
- Term adjustable refractive surgery (ARS), is also used

Refractive Lens Exchange

- Considered only if alternative refractive procedures are not feasible
- May be preferable to a PIOL in the presence of a lens opacity that is presently visually insignificant but that may soon progress and cause visual loss
- Risk of intraocular surgery present

All FemtoSecond Laser LASIK

FLEX

- Femtosecond lenticule extraction or FLEx
- VisuMax femtosecond laser (Carl Zeiss Meditec; Jena, Germany) in 2007
- Femtosecond laser creates two cuts, a refractive and a nonrefractive as a single step. The first cut is made at the bottom of the refractive lenticle while the second one at its roof. Once the cuts are made, flap is lifted and refractive lenticule is removed.
- The flap is reposited in usual manner. It is important to make manipulation at correct plane between flap & lenticule and separate lenticule edge.

SMILE

- SMall Incision Lenticular Extraction
- Less invasive where by the entire lenticule can be extracted through a small incision without lifting up the flap.
- Following FLEx, new procedure called small-incision lenticule extraction (SMILE) was developed. This procedure involves passing a dissector through a small, 2-3 mm, incision to separate the lenticular interfaces and allow the lenticule to be removed, thus eliminating the need to create a flap.
- Small-incision lenticule extraction (SMILE) has become increasingly popular. While visual and refractive outcomes and safety in terms of the change in distance corrected visual acuity (DCVA) have been shown to be similar to those achieved with LASIK, there are some ***expected benefits of using the small incision instead of a hinged flap***:
    - Less postoperative dry eye after SMILE because the anterior corneal nerves are less affected
    - Lower biomechanical impact with increased biomechanical stability due to the absence of a flap
    - More accurate and repeatable tissue removal independent of prescription treated
    - Potential marketing advantage
    - Smaller external incision size
- **The main characteristics of the VisuMax system are as follows:**
    - The VisuMax coupling contact glass interface with the cornea is curved, thus leading to very little corneal distortion when securing full corneal surface contact.
    - Corneal coupling of the contact glass is achieved with very low suction force applied though specifically designed suction ports that are applied to the peripheral cornea/limbus, but not the corneal conjunctiva/sclera. This low suction coupling force minimizes corneal distortion.
    - Each contact glass is individually calibrated by a built-in optical coherence imaging system, thus compensating for individual differences in contact glass geometry that are inevitable in serial production.
    - The optical beam path system coupled to the contact glass is suspended on a fulcrum. The fulcrum, together with a continuous force-feedback servo control for patient bed height, produces a system delivering a constant force of the contact glass onto the cornea. This constant force minimizes changes in corneal distortion that may occur with patient head movement during the femtosecond cutting process.
    - The optical system delivering the femtosecond beam is designed with very high numerical aperture optics, thus allowing for very tight concentration of femtosecond energy, very little collateral energy dissipation and high femtosecond spot placement accuracy.
    - The laser-tissue interaction dynamics are optimized for speed with a repetition rate of 500 kHz, which minimizes treatment time and achieves the critical refractive cuts in a short enough time to reduce the chances of eye or patient movements during this phase of the cutting.

- **SMILE Procedure**
  - The VisuMax is prepared for the procedure by the attachment of a disposable curved contact glass onto the laser aperture cone. It is useful to select the smallest possible treatment pack. If the selected suction ring is too large, it may cause suction pressure on the conjunctiva, resulting in premature abortion of the treatment due to loss of suction.
  - The contact glass has a curved surface designed to couple with the cornea. Before coupling, the VisuMax system selfcalibrates the contact glass. Also, the eye's keratometry data are entered into the VisuMax to account for the difference between the relaxed cornea and the contact glass curvature. This allows the system to calculate the ratio between the intended clinical treatment and cap diameter on the relaxed eye and the technical incision diameter when cutting the eye coupled to the contact glass. The patient bed is moved using a joystick which controls x-y and z so that the eye is brought up into contact with the contact glass, while the patient is fixating on a flashing green light.
  - Once contact is made between the cornea and the contact glass, the patient is able to see the flashing fixation target in clear focus, as it uses the manifest refraction of each individual eye. This aligns the eye in the primary position, allowing the bed to be raised vertically while the surgeon observes the alignment of the contact glass application through the operating microscope and the side screen.
  - Then the cornea applanates in a self-entering way on the corneal vertex followed by application of suction, the eye is immobilized by low corneal suction, where the IOP increases with the VisuMax is low enough for the patient to see throughout the procedure, and the laser is activated by the surgeon pressing on a foot pedal.
  - Then the patient is moved to the observation microscope and manual dissection is performed, starting with the upper surface dissecting the cap from lenticule first, then we dissect the lenticule from the stromal bed. Then the lenticule is removed with a forceps through a 3-4 mm incision.
- **Potential Intraoperative Challenge**
  - During laser
    - Suction loss
    - Decentration
    - Obstructive OBL or black spots
  - During dissection
    - Incisional or central abrasion
    - Difficult or incomplete dissection
    - Torn or perforated cap
  - During extraction: Torn or partially retained lenticule
- **Pearls for Success**
  - Valium and verbal reinforcement calm the patient during the laser application.
  - Patient fixation on green light is key to centration (do many flaps before SMILE).

- Define cap and lenticule interface in the same region (lenticule is often tough to find).
- Dissect the cap first, then the lenticule with anchor tags to stabilize lenticule till complete.
- A drop-on dissector makes tissue less sticky.

SMILE Complications

- **Suction Loss**
  - The femtosecond cutting is the most critical part of the procedure. While a suction loss rarely leads to the patient not receiving a complete treatment, it is obviously better if a suction loss can be avoided. The VisuMax software is programmed to handle a suction loss; this is known as the Restart treatment module. This wizard-style software system will provide a recommendation for continuing the procedure following a suction loss.
    - Lenticule interface, first 10%: Restart SMILE with the same settings.
    - Lenticule interface, 10%-100%: Convert to LASIK with flap thickness equivalent to the planned cap thickness.
    - Lenticule side cut: Restart SMILE from the lenticule side cut with the same settings.
    - Cap interface: Restart SMILE from the cap interface with the same cap thickness.
    - Small incision: Restart SMILE from the small incision.
  - However, there are some scenarios where following the actions provided by the internal software is not recommended. One important scenario to consider is when it is possible that femtosecond cutting was continued as suction was lost and the eye moved away from the contact glass. This will result in the interface tracking upward through the cornea, thus increasing the risk of tissue slivers or false plane creation during interface separation if further interfaces are created. Therefore, whether conversion to LASIK may be a better option should be carefully considered.
- **Black Spots in Femtosecond Bubble Pattern:** Dark spots represent areas where there may not have been effective femtosecond cutting, which can be more difficult to separate. Significant manual separation can lead to irregularities in the lenticule that manifest as irregularly irregular astigmatism after surgery.
  - Dark spots can be associated with the following:
    - Very low energy
    - Stromal geometry
    - Debris or fibers on the contact glass or in the tear film (eg, meibom). If there are black spots or translucent lines affecting the bubble pattern, especially within the pupil borders and on the lenticule cut, it is highly recommended that you consider switching to LASIK.

- **False Plane Creation:** Creating a false plane, even when the bubble pattern is normal, was more common in the early years of SMILE, before SMILEspecific instruments were designed. Even with blunt instruments it is important to monitor interface creation intently at all times. If a false plane is created, the procedure should be aborted and layered corneal imaging should be obtained to create a plan for subsequent removal/treatment to decrease the chances of incomplete lenticule removal.
- **Opaque Bubble Layer (OBL)**
- **Lenticule Remnants:** Another possible complication of SMILE is leaving a lenticule remnant in the interface. A lenticule remnant is most likely to occur in cases where the separation was difficult, and it is more likely when extracting thinner, more delicate lenticules. However, these can also occur after lenticule separations that appear routine. Lenticule remnants can cause distortions and irregular astigmatism on topography, and consequently cause issues with quality of vision. Therefore, every care should be taken during surgery to ensure that the entire lenticule has been removed.
  - Lenticule recovery techniques include the following:
    - Sweeping the circumference of the lenticule border using the Separator bulb
    - Using the built-in slit-lamp feature within the operating microscope
    - Creating an air pocket by lifting the instrument to raise the cap away from the stromal bed to improve visibility of the stromal bed
    - Using a reserve incision to improve instrument manipulation or change direction of force to help aid in removal
    - Flooding the interface with an opaque suspension (eg, Kenalog-10) to demarcate the contours within the interface
  - Once removed, the lenticule remnant should be placed on the cornea together with the main body of the lenticule to check that the pieces of the puzzle fit together. If the pieces do not fit perfectly, then further investigation of the interface might be performed.
- **Cap Tears and Perforations:** As in LASIK, there is the possibility of the separating instrument perforating the cap and creating a tear. These tears are most likely to occur at the small incision, with the most common cause being manipulation of the surgical instrument. When the instrument is fully inserted into the interface, it is important to rotate the shaft so the elbow does not stress the wound, as opposed to making lateral movements of the instrument. A small, or even large, incision tear very rarely has any effect on the final outcome as long as it is carefully replaced and repositioned in the same manner as any corneal incision or LASIK flap.
- **Cap Folds:** The management of the cap starts during the initial slit-lamp evaluation by the surgeon directly after the procedure. The cap should be smoothed using heavy fluorescein staining to aid visualization of even the subtlest annular or linear nanofolds by evaluation of the negative staining pattern.2 This slit-lamp technique can be repeated if necessary at the day 1 examination.
- **Atypical DLK: Sterile Multifocal Inflammatory Keratitis After SMILE**
  - Diffuse lamellar keratitis (DLK) can occur after SMILE with the same classic presentation as after LASIK. However, inflammation can also present after SMILE

with a unique appearance not typically seen after LASIK, appearing as small focal infiltrates scattered throughout the interface with or without a diffuse component.

- This presentation is usually seen on day 1 after SMILE and can be alarming, given the focal appearance. So the index of suspicion for infection needs to be very high, and these cases need extremely close monitoring during the perioperative period.
- This cases are managed similarly to classic DLK, with increased steroids and antibiotic coverage.
- However, focal infiltrates are still more likely to cause localized melting; thus the threshold for performing an interface washout should be lower than with classic DLK.

- **Epithelial Ingrowth/Implant:** Epithelial ingrowth after SMILE can sometimes present as an "implant" rather than an "ingrowth," caused by stray epithelial cells being drawn into the interface. The ingrowth tends to be very small and rarely visually significant. Epithelial implants can be treated by washout and or cap scrape. For implanted islands that become elevated over time, focal Nd:YAG laser has been shown to speed absorption in most cases.

Retreatment after SMILE

- **PRK:** Considered the simplest procedure to correct a residual refraction after SMILE, but pain, slow recovery, and postoperative haze are the major concern.
- **D. Reinstein: LASIK** is still the best solution for an enhancement after a primary SMILE procedure.
- **CIRCLE Enhancement After Myopic SMILE**
  - In contrast to LASIK, which can be retreated by a flap re-lift, enhancement after small-incision lenticule extraction (SMILE) using a re-SMILE is currently neither approved nor commercially available in the VisuMax platform (Carl Zeiss Meditec AG; Jena, Germany), and only very sparse experimental data on its safety and efficacy exist.
  - Multiple alternative enhancement options have been proposed and established, including surface ablation, cap-to-flap conversion using the CIRCLE program, and thin-flap LASIK.
  - **Surgical Technique**
  - The CIRCLE software is integrated into the VisuMax platform. (However, it is currently not available in the United States.) It has been specifically developed for enhancements and can convert the SMILE cap into a full flap for secondary excimer laser enhancement.
  - Four CIRCLE patterns available from which pattern D is the easiest to lift in a study.
  - For pattern D, the first step is the creation of a lamellar ring around the original cap cut at the same depth as cap.
  - Secondly, a side cut is created around the new incision plane, with exception of an area used as hinge.
    Thirdly, a junction cut parallel to the side cut is created to establish a connection between the planes of the primary cap and the secondary lamellar ring around it,

creating one large joint plane. Rotation of the flap has to be preprogrammed in such a fashion that the planned new flap hinge area does not overlap with the former side cut incision (eg, SMILE incision at 130° and CIRCLE flap at 50°).

- To facilitate surgical manipulation, the outer diameter of the CIRCLE procedure should be programmed to extend beyond the SMILE interface (eg, 8.2 mm over 7.9 mm or larger, depending on the white-to-white diameter). The inner diameter should be smaller than the lenticule (eg, 6.2 mm within 6.5 mm). CIRCLE flaps can be lifted using a blunt spatula like regular LASIK flaps. The postoperative application of mitomycin C is not necessary in routine cases due to the low potential for postoperative haze.
- Advantage
  - CIRCLE is easy to use and requires less complex preoperative planning than thin-flap LASIK above the SMILE interface.
  - Painless nature so appealing to many patients than surface ablation, especially in conjunction with the aspect of a quicker visual recovery.
- Disadvantage
  - CIRCLE sacrifices the idea of a flap-free approach, separating the anterior stroma above the flap from the posterior corneal structures, and thus induces more biomechanical weakening than surface ablation or thin-flap LASIK.
  - This will be especially pronounced in deep caps, eg, >160 µm. In these cases, thin-flap LASIK anteriorly to the SMILE interface might provide better outcomes

- **SubCap-LE**
  - Sub-cap-lenticule-extraction" (SubCap-LE)
  - Retreatment performed with modified SMILE technique after a primary SMILE surgery
  - The aim of this new technique is to **leave the cap of the primary SMILE** procedure untouched to conserve the benefits associated with SMILE.
  - It has no new superior lenticule cut to avoid the risk of a multiple dissection plane. The interface of the primary SMILE procedure became the superior plane of the new lenticule; and the laser cut, the inferior plane and the side cut of the new lenticule.
  - The surgeon stops the treatment after the laser cut the new lenticule and the side cut. The new lenticule was removed through the original corneal incision.
  - Feasible, successful and efficient option

Future Cornea based Laser Vision Corrections

- Advanced Customized Photoablation with LASIK
- Next Generation Photodisruption with SMILE
- No Touch and No Aberrations with Transepithelial PRK
- Stromal Laser Induced Refractive Index Change (LIRIC)

- Epithelial Refractive Index Change with Nanodrops
- Tissue Addition with Lenticular Implantation Keratoplasty (LIKE)

PTA as a Risk factor for Ectasia

- PTA: Percent Tissue Altered
- **Santhiago** et al coined the term and first investigated and consistently determined the association of a high value of PTA and ectasia risk
- Percent tissue altered (PTA) determines the relative amount of biomechanical modification that has occurred after excimer laser refractive surgery.
- For LASIK, PTA is described as:
  - ***PTA = (FT + AD)/CCT,*** where FT = flap thickness, AD = ablation depth, and preoperative CCT = central corneal thickness.
- **The Concept of PTA**
  - As corneal strength is not uniform throughout the central cornea, with a progressive weakening in the posterior two-thirds, we hypothesized that the relative extent of tissue alteration would play a more representative role on the postoperative weakening than the same cut-off of residual bed for all patients. There is an integrated relationship between preoperative CCT, AD, and flap thickness in determining the relative amount of biomechanical change that has occurred after a LASIK procedure, and PTA better describes this interaction during excimer laser refractive surgery.
  - One of our first studies in this context investigated changes in novel biomechanical descriptors after different levels of myopic femtosecond LASIK in normal eyes, and revealed the PTA as a much stronger predictor of LASIK-induced biomechanical change compared to AD or residual stromal bed (RSB). These findings were an important background to specifically investigate the relationship between PTA and the risk of ectasia after LASIK.
- **Association Between PTA and Ectasia in Eyes With Normal Topography**
  - In order to remove bias and better understand the potential, and specific, association between PTA and ectasia risk, we conducted a comparative case-control study including eyes that developed ectasia after LASIK for myopia and myopic astigmatism with strictly normal bilateral preoperative Placido diskbased corneal topography. With a high odds ratio, the study revealed that in eyes with normal preoperative topography, a PTA of 40% or higher is, by definition, a risk factor for ectasia after LASIK for myopia. PTA presented not only a higher odds ratio value in eyes that developed ectasia compared to traditional risk factors such as RSB, CCT, high myopia, AD, or age, but also a higher prevalence.
  - As well as in the original study, the validation study published this year also revealed mean values of previously recognized risk factors such as RSB, CCT, and age that would place this average patient at low risk for post-LASIK ectasia, except for the mean high PTA value. Endorsing the presence of similar characteristics in these previously regarded low-risk eyes (except for the high PTA) that otherwise did develop ectasia. These findings, concurrently with the high odds ratio value,

validate a high PTA as a risk factor and possibly explain why ectasia occurred in corneas with RSB and thickness values within acceptable safety standards, even with normal topography before LASIK, if the combination of these factors resulted in a high percentage of altered tissue.

- The main explanation for this scientific finding most likely lies in the relative percentage contribution of the anterior stroma to the total corneal strength, which is modified after excimer laser refractive surgery. As corneal tensile strength presents an inhomogeneous distribution throughout the central corneal, removing the anterior part of the stroma may induce corneal weakening in increasing proportion as the threshold of 40% is reached and crossed. As compared to specific RSB or CCT cutoff values, PTA likely provides a more individualized measure of biomechanical alteration because it considers, at the same time and in one metric, the relationship between thickness, tissue altered through ablation and flap creation, and ultimate RSB thickness.
- In a recent computational study, Dupps and Seven also provided indirect validation of PTA as a risk factor for ectasia. They investigated the biomechanical strain as a structural susceptibility metric for corneal ectasia in a large-scale computational trial and found that PTA more strongly correlated to the change in mean maximum principal (MPS) strain and that PTA presented a stronger relationship with surgically induced strain change after myopic refractive surgery compared to RSB. MPS represents the maximum amount of tensile strain at that material point under the modeled loading conditions, and higher strains are associated with a higher risk of material failure when subjected to tensile deformations.
- The main advantage of the PTA method lies in its simplicity as it incorporates the information about flap thickness, AD, and CCT. It should be highlighted that PTA already considers the optical zone in each calculation—as ***Munnerlyn's equation*** for AD is *[(optical zone)2 x diopters]/3*—and indirectly informs about the residual stroma that is left not altered, all in one single variable.

Role of PTA in Eyes With Suspicious Topography

- PTA will obviously have a different impact in eyes with topographic irregularities, since those corneas are by definition already showing evidence of weakening prior to any tissue removal. Previous studies have arguably demonstrated that abnormal corneal topographic patterns are the most significant risk factor for postoperative ectasia. In a study specifically conducted on eyes with suspicious topography, we showed that less tissue alteration, or a lower PTA value, was necessary to induce ectasia in eyes with more remarkable signs of topographic abnormality. PTA again provided better discriminative capabilities than RSB for all study populations.

PTA for PRK

- The relationship between PTA and ectasia after PRK was not the scope of our studies simply because the ideal scientific context to specifically investigate this association would include eyes that developed ectasia after PRK with strictly preoperatively bilateral normal topography. However, the vast majority of these specific cases of ectasia after surface ablation occurred in eyes with suspicious, or abnormal, topography preoperatively.
- However, although we should not easily transpose the findings obtained investigating eyes submitted to LASIK to eyes submitted to PRK, if the preoperative

topography is genuinely healthy, the limits may be potentially higher in PRK because of its surgical structural differences, as there is no flap cut or peripheral impairment of corneal fibers. For PRK, PTA can be described as *PTA: (epithelium thickness + AD)/CCT*. The epithelial thickness could be estimated at 50 microns in healthy eyes. Average epithelial thickness does not vary significantly by overall corneal thickness, so the relative stroma altered in any PTA measurement will change only slightly (less than 1%) with the standard variation of epithelial thickness.

- PTA is a risk factor for ectasia after LASIK and not a screening method. A risk factor determines a relationship and has nothing to do with symptoms, whereas a screening detects disease in asymptomatic individuals.

Miscellaneous

Topical Hematopoetic Therapies for Dry Eyes

Autologus Serum Tears (AST)

- *Serum* is the fluid component of full blood that remains after clotting. *Plasma* is obtained when clotting is prevented by mixing a full blood donation with an anticoagulant and removing all corpuscular elements by centrifugation
- Initially used as a preservative free tear
- First described by **Fox** et al in 1984 to be used as a tear substitute.
- **Tsubota** recognized that it had various growth factors (EGF, TGF, NGF,IGF-1)
- As has been found to be beneficial in neurotrophic ulcers, epithelial defects, keratitis sicca, recurrent erosions
- Risk of infection as non-preserved
- **Rationale**:
  - vitamin A, epitheliotrophic and neurotrophic growth factors, immunoglobulins and fibronectin
  - lacks antigenicity
  - without preservatives and hence toxicity due to additives is not an issue.
- **Production Process (Phases: CCDS)**
  - Clotting phase: 10 ml blood kept 2 hours at room temperature
  - Centrifugation: 15-min centrifugation at 3,000 *g* results in good separation of serum and blood clot, without inducing haemolysis
  - Dilution: 20%, 33%, 50% or 100%, BSS rather than saline should be used
  - Storage: drops can be refrigerated or stored frozen. 3 months if stored at –20 °C and for 1month if stored at 4 °C.
- **Difference from Artificial Tear Substitutes**
  - Normal artificial tears serve to lubricate the ocular surface.
  - Autologous serum tears, or ASTs
  - ASTs contain a host of epitheliotrophic factors such as growth factors, immunoglobulins, vitamins, and substance P (Matsumoto et al., 2004 ; Geerling, et al., 2004).
  - ASTs also lack preservatives.
- **Indications**
  - Severe dry eye (idiopathic, graft versus host disease, etc.)
  - Superior limbic keratoconjunctivitis
  - Recurrent erosions
  - After ocular surface reconstruction
  - Persistent epithelial defects including neurotrophic ulcer

Umbilical Chord Serum: prepared like autologous serum (5 min centrifugation at 1,500 rpm), diluted to a 20% concentration in 0.9% saline and used as an alternative treatment for promoting corneal epithelial wound healing.

PRP Platelet Rich Plasma

- Platelet-rich plasma (PRP) has been used for over a decade in different clinical areas like orthopedics, oral and maxillofacial surgery, reconstructive surgery, cardiovascular surgery, and plastic surgery, but only recently has PRP been brought to ophthalmology, showing very promising results.
- PRP obtained from total unclogged blood is very rich in platelets and growth factors.
- Platelets are known to secrete some of these factors from alpha granules, such as platelet-derived epidermal growth factor, transforming growth factor β (TGF-β), plateletderived angiogenesis factor, platelet-derived growth factor, and platelet factor IV.
- In 2007, Alio et al demonstrated that the use of autologous PRP promotes the healing of dormant corneal ulcers, even in eyes threatened by corneal perforation, and was accompanied by a reduction in pain and inflammation.
- The advantage of PRP over autologous serum is that PRP has a higher presence of ***vitamins and growth factors.***
- Autologous PRP has a large quantity of growth factors that are released from the platelets; then the growth factors act directly on the ocular surface.
- In the PRP preparation, the platelets are intact and can adhere to the ocular surface and improve the biochemical and biological mechanism.

Tissue Adhesives

- There are two basic types of tissue adhesives available:
  - Synthetic: Cyanoacrylate glue.
  - Bioadhesives : Fibrin glue.
- **Cyanoacrylate glue**
  - There are two variants of cyanoacrylate glues:
    - **N Butyl 2 cyanoacrylate** which is mainly used in ophthalmology.
    - **2-octyl cyanoacrylate (Dermabond)** used mainly for external wound closure in plastic surgery, and dermatology. It is available in Indian Market as Dermabond (Ethicon Inc., Somerville, NJ). It is used in ophthalmology with paraben as a liquid bandage.
  - Uses
    - Corneal thinning
    - Corneal perforation
    - Corneal laceration

- Cyanoacrylate tissue glue has a long track record of success in the treatment of corneal thinning and small perforations.
- Numerous application techniques work well.
- Problems
  - Difficult application process
  - Immediate polymerization
  - Unfavorable mechanical
  - Properties (stiff/abrasive): low tolerance in wound
  - Toxic (lens, retina): formaldehyde, cyanide

- **Fibrin glue/Tisseel**
  - In India, it is available as Tisseel Fibrin Sealant (Baxter AG Vienna, Austria), and as reliseal (from Relince life-sciences).
  - The kit contains the following in separate vials.
    - Large Blue Bottle: Sealer protein concentrate (human), Freeze dried, vapour treated, containing:
      - Clottable protein-75-115 mg
      - Fibrinogen-70-110 mg
      - Plasma fibronectin-2-9 mg
      - Factor XIII-10-50 IU
      - Plasminogen-40-120 µg (microgram)
    - Small blue bottle: Aprotinin solution, bovine 3000 KIU/ml
    - White bottle: Thrombin 4 (bovine), freeze dried reconstituted contains 4 IU/ml
    - Large black bottle: Thrombin 500 (bovine), freeze dried reconstituted contains 500 IU/ml
    - Small black bottle: Calcium chloride solution, 40 mmol/L
  - Forms solid coagulum within 3–5 min of delivery
  - 70% of ultimate strength attained in the first 10 minutes; full strength reached in about 2 hours
  - Biocompatible, with minimal inflammation or FB reaction, and no tissue necrosis
  - Uses
    - Pterygium surgery
    - Conjunctival surgery
    - Strabismus surgery for conjunctiva closure
    - Corneal surgery: Perforation, AMT, Lamellar grafts, PKP, Limbal cell transplantation
    - Refractive surgery: treating epithelial ingrowth, as a temporary basement membrane,

Cynoacrylate	Fibrin Glue
Synthetic	biologic
Immediately available	Must be reconstructed
Polymerises rapidly especially with fluids	Polymerises very slowly
Rigid and uncomfortable	Soft
Toxic	Non-toxic
Bacteriostatic or bacteriocidal	Theoretical risk of disease transmission
Long termepithelium growing under dislodges the glue	Rapidly degraded

- **Novel Ocular Bandage Technology**
  - Ocular Therapeutix hydrogel (PEG) technology has been proven safe in other applications
  - 100% Synthetic and Biocompatible (non-toxic and non-exothermic)
  - Easy application
  - Localised persistence: stays where you need
  - Protects the incision from the external environment and lid movement
  - Flexible and transparent to enhance patient comfort
  - **ReSure Kit and Applicator**
    - Founded 11/2006
    - Used for clear corneal incisions
  - **OcuSeal Liquid Ocular Bandage**
    - Founded 3/2003
    - BD (licensee) OcuSeal
    - HyperBranch Medical (manufacturer)
    - Synthetic, dendritic hydrogel activated at time of use
    - Unique applicator applies ocular bandage in liquid form
    - Crosslinks in 30 seconds
    - Creates low profile protective barrier film: smooth, soft and transparent

PED: Persistent Epithelial Defects

- A persistent epithelial defect (PED) can be loosely defined as an epithelial defect that has not healed in the expected period of time. However, in accordance with the literature, when a defect has been treated for approximately 2 weeks without resolution, the cornea is said to have a PED.
- PEDs have been reported to occur in 16.4% of eyes after penetrating keratoplasty and in 22.8% of eyes after corneal epithelial debridement during diabetic vitrectomy surgery.

Given that improvements in techniques of vitrectomy surgery have dramatically reduced surgical time, the need to debride the corneal epithelium has decreased, and the number of eyes developing PED in this situation has decreased as well. However, the rates of PED occurring after other events, such as ocular surface burns, post-photorefractive keratectomy, and postinfectious keratitis, are unknown. A conservative estimate may place the figure for the number of PEDs in the United States annually at 40,000.

- **Potential Complications**
  - Although PED is uncommon, management of patients with PED can be quite challenging and requires intensive and sometimes extensive follow-up to ensure resolution. Complications from PED include infection (usually bacterial, but it can be fungal
  - in etiology), corneal melting, and perforation. Less commonly thought of, but just as important, is the development of subepithelial haze and scarring from long-standing defects that can ultimately limit final visual outcome. Evidence in the literature suggests that the longer an epithelial defect is left open, the longer it will take to heal, and therefore the higher the chance of complications. As such, it is advisable to treat PED aggressively, and potentially even earlier in the course of the disease process if it is anticipated that difficulty with healing may be the case.
- **Etiologies**
  - There are numerous possible etiologies for PED, and the more common ones include dry eye, exposure keratopathy, diabetic keratopathy, herpetic keratopathy, neurotrophic keratopathy (for example, after keratoplasty or keratorefractive surgery), and limbal stem cell deficiency (for example, after chemical burns).
  - It is imperative to identify the possible causative etiologies for PED because for some of these situations, treatment of the PED should be first aimed at the underlying cause; the definitive management of PED secondary to exposure keratopathy from thyroid eye disease, for example, may be vastly different from that for a patient with limbal stem cell deficiency (LSCD) from an alkali burn. In the former condition, a tarsorrhaphy or even orbital decompression surgery may be warranted, whereas in the latter condition, limbal stem cell transplantation or Boston keratoprosthesis implantation may be the indicated treatment. In eyes with herpetic keratopathy, sometimes a PED is present because inflammation or persistent viral infection persists, precluding closure of the epithelial defect. Treatment targeted toward the inflammation (with corticosteroids) or toward the persistent viral infection (with antivirals) can sometimes cure the PED. A careful examination of the eyelids, tear film, and ocular surface are required in order to make the correct diagnosis.
- **Management**
  - Medical management strategies
    - Aggressive lubrication
    - Discontinuation of medications
    - Punctal occlusion
    - Bandage soft contact lens placement
    - Pressure patching
    - Autologous serum

- Scleral contact lenses

- Surgical management strategies
  - Epithelial debridement
  - Tarsorrhaphy
  - Amniotic membrane grafting
  - Conjunctival flap
  - Limbal stem cell transplantation
  - Boston keratoprosthesis