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■ Anatomy and Physiology of Cornea

Cornea is **avascular and transparent**. Its horizontal and vertical diameters are 12 mm and 11.5 mm, respectively (**Fig. 6.1**). Its thickness at the center and periphery is 0.5 mm and 0.7 mm, respectively. Radius of curvature of anterior surface of cornea (in central region) is 7.8 mm, while that of posterior surface is 6.5 mm. Its refractive index is 1.376 (≈ 1.38). Cornea provides 3/4th of the total refractive power of the eye. Refractive power of anterior convex surface of cornea is +48.8 D; refractive power of posterior concave surface is -5.8 D, so the total refractive power of cornea is 43.0 D. The junction of cornea with sclera is called **limbus**. The corneal curvature is greater than the rest of the globe. Cornea is devoid of lymphatic channels.

■ Histology

Histologically, cornea consists of five layers (**Fig. 6.2**):

1. Epithelium (anterior most).
2. Bowman's membrane.
3. Stroma or substantia propria.
4. Descemet's membrane.
5. Endothelium (posterior most).

Epithelium

It may be regarded as continuation of conjunctiva over cornea. Embryologically, it is derived from surface ectoderm at 5 to 6 weeks of gestation. Characteristic features of epithelium are as follows:

- It is stratified and 4 to 6 cell layers thick.
- The epithelial cells contain microvilli with glycocalyx layer which facilitate adsorption of mucinous portion of tear film and

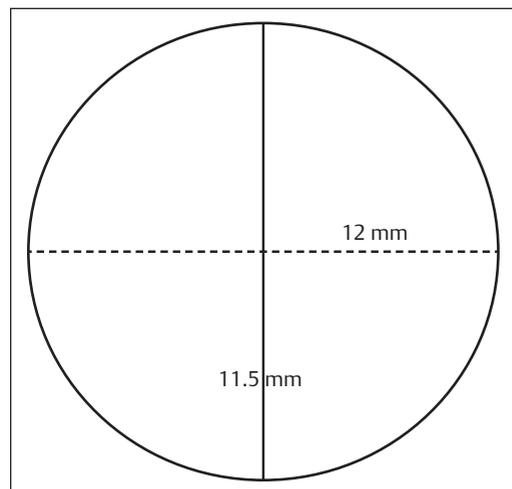


Fig. 6.1 Diameters of cornea.

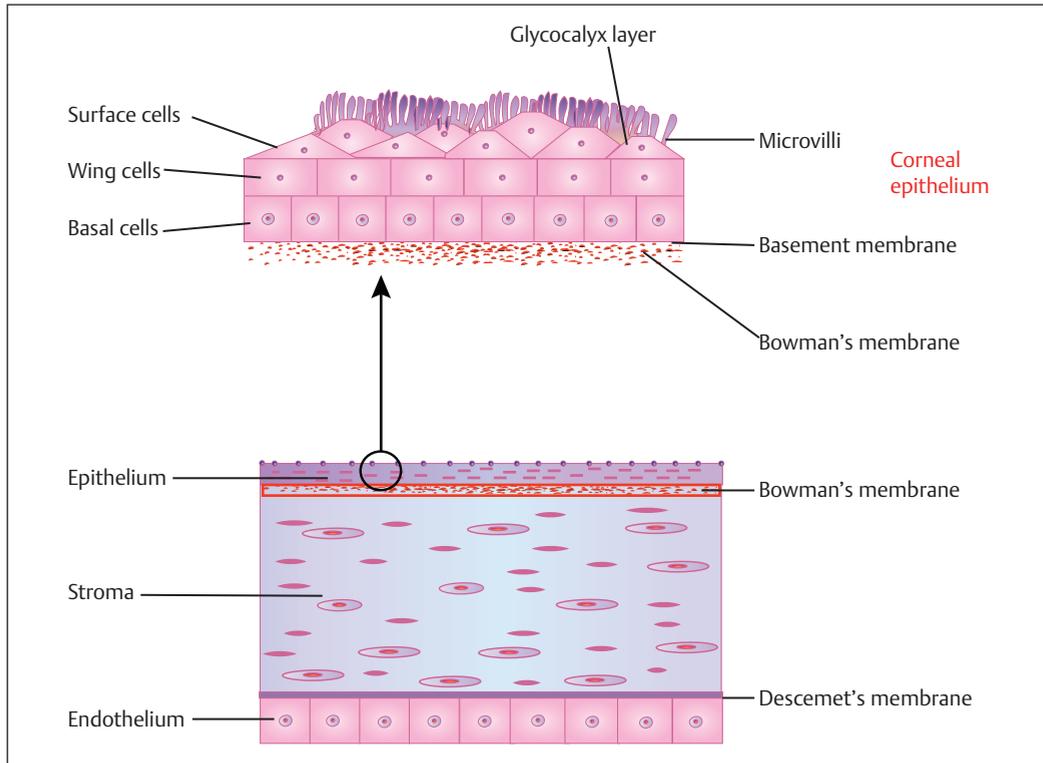


Fig. 6.2 Anatomy of cornea.

hydrophilic spreading of tear film with each eyelid blink. *Loss of glycocalyx from injury or disease results in loss of stability of tear film.*

- Superficial cells undergo desquamation and are replaced by deeper cells of corneal epithelium. *Basal cells are the only corneal epithelial cells capable of mitosis. Because of excellent ability to regenerate, epithelium does not scar as a result of inflammation.*
- Tight junctions between its cells provide *barrier function* and restrict entry of tears into intercellular spaces. *Thus, healthy epithelial surface repels dyes such as fluorescein or Rose Bengal.*
- *Epithelial regeneration:* Epithelial stem cells (undifferentiated pluripotent cells) are principally localized to limbal basal epithelium and serve as an important source

of new corneal epithelium. Junctional barrier prevents conjunctival tissue from growing on the cornea. So, *dysfunction or deficiency of limbal stem cells results in the following chronic epithelial defects:*

- ◇ Overgrowth of conjunctival epithelium onto the corneal surface.
- ◇ Vascularization.

These problems can be *treated by limbal cell transplantation.*

Bowman's Membrane

It is an acellular structure which, once destroyed, does not regenerate.

Stroma (Substantia Propria)

Stroma forms 90% of total corneal thickness. It may be regarded as forward continuation of

sclera. It is composed of collagen fibrils, forming lamellae which are loosely adherent to each other and regularly arranged in many layers. The layers crisscross at approximately right angles to each other. Corneal lamellae become continuous with scleral lamellae at limbus. **The layered structure of stroma results in corneal splitting, as in superficial keratectomy.** Ground substance occupies the space in between lamellae and is composed of glycosaminoglycans (mucopolysaccharides). Corneal cells and **keratocytes** are found between lamellae which are collagen-producing fibroblasts. *Corneal stroma is markedly hydrophilic due to osmotic force of stromal glycosaminoglycans (GAG).*

Descemet's Membrane

It is a thin elastic membrane secreted by endothelium throughout life. It is composed of collagen fibrils and separates corneal stroma from endothelium. Unlike Bowman's membrane, it can regenerate (regenerated by endothelial cells). It is quite resistant to inflammatory process of cornea. Therefore, **descematocele** can maintain integrity of eye for long after all other layers of cornea are destroyed. It fuses with trabecular meshwork. The fusion site is known as *Schwalbe's line* which defines the end of Descemet's membrane and start of the trabecular meshwork.

Endothelium

It is derived from neural crest cells. It consists of single layer of flat hexagonal cells and appears as honey comb mosaic (**Fig. 6.3**). It contains a high-density of $\text{Na}^+ - \text{K}^+$ ATPase pump. It secretes Descemet's membrane throughout life. It cannot regenerate but adjacent cells slide to fill in a damaged area. Endothelial cell density decreases with advancing age and declines from 3,000–4,000 cells/ mm^2 to 2,500 cells/ mm^2 in adults. At a cell density of approximately 500 cells/ mm^2 , corneal edema develops. It is examined by a specular microscope.

The primary physiological role of endothelium is fluid regulation in corneal stroma. This function is most important as it keeps the cornea clear.

Blood Supply of Cornea

Normal cornea is an avascular tissue which gets its nourishment from:

- Capillaries at limbus which are derived from episcleral branches of the anterior ciliary arteries.
- Aqueous by diffusion.
- Oxygen dissolved in tear film.

Nerve Supply of Cornea

Cornea is supplied by the ophthalmic division of the trigeminal nerve (V_1) through *long ciliary nerves* (**Fig. 6.4**).

Course

Long ciliary nerves pierce sclera posterior to limbus and form annular plexus (pericorneal plexus). Branches from annular plexus travel radially to enter the corneal stroma and lose their myelin sheaths. They divide into anterior group, which forms subepithelial plexus, and posterior group, which forms stromal plexus. Branches from subepithelial plexus pierce Bowman's membrane to form intraepithelial plexus. *Due to rich nerve supply, cornea is extremely sensitive structure.* In eyes with corneal abrasions or bullous keratopathy, direct stimulation of these nerve axons causes pain, reflex lacrimation, and photophobia.

Metabolism of Cornea

Energy is needed for normal functions of a tissue. In cornea, energy is needed for maintenance of its

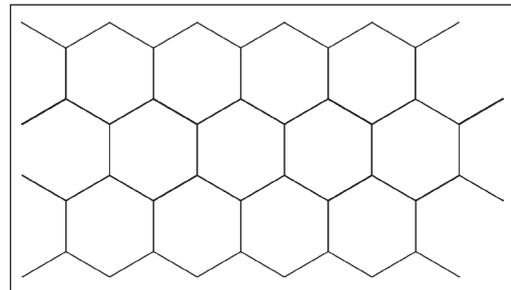


Fig. 6.3 Honey comb mosaic appearance of endothelium of cornea.

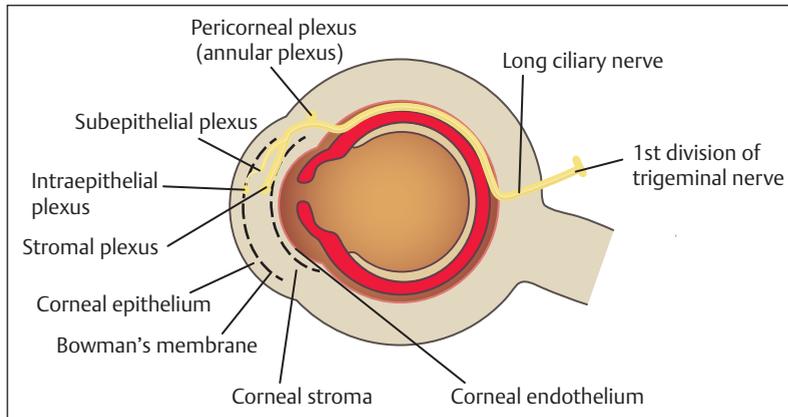
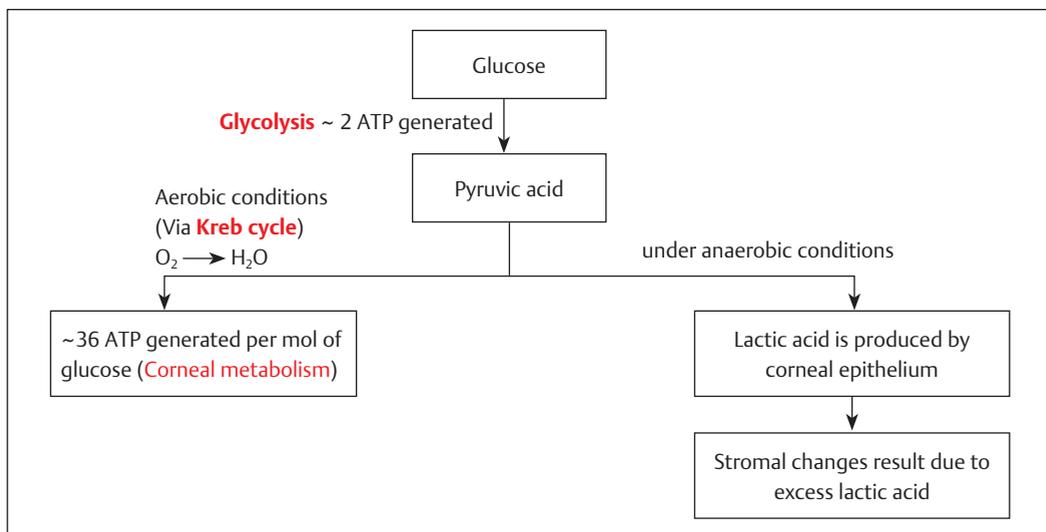


Fig. 6.4 Nerve supply of cornea.



Flowchart 6.1 Metabolism of cornea. Abbreviation: ATP, adenosine triphosphate.

transparency and dehydration. Energy in the form of adenosine triphosphate (ATP) is generated by breakdown of *glucose* and utilization of *oxygen* (**Flowchart 6.1**).

Source of glucose for cornea is aqueous (90%), tears and limbal capillaries (10%).

Source of oxygen for cornea—Most of the O_2 in cornea is consumed by epithelium and endothelium. *Epithelium* gets much of its O_2 from limbal capillaries or precorneal tear film. *Endothelium* gets most of its O_2 from aqueous humor, and the cornea is **mainly aerobic**.

If access of O_2 to epithelium is abolished by tight contact lenses or replacement of air in goggles with N_2 , cornea swells and become cloudy due to production of lactic acid by corneal epithelium under anaerobic conditions.

■ Pathological Changes in Cornea

The pathological changes in cornea can be categorized in (**Table 6.1**) as follows:

- Loss of transparency (corneal edema and corneal opacity).
- Vascularization of cornea.

Table 6.1 Difference between normal and pathological cornea

Normal cornea	Pathological cornea
Transparent	Loss of transparency due to corneal edema and corneal opacity
Avascular	Vascularization of cornea
Absence of pigments	Corneal pigmentation

- Pigmentation of cornea.
- Corneal filaments.
- Prominent corneal nerves.
- Infiltrates.

■ Transparency of Cornea (OP4.3, 4.5)

Normal cornea is a transparent structure. Corneal transparency occurs due to *regular arrangement of collagen fibrils* (corneal lamellae) in stroma, *avascularity* of cornea and *relative state of dehydration*. Water content of normal cornea is approximately 78%. It is maintained at a steady level by a balance between various factors. Disturbance of any of these factors leads to corneal edema.

Corneal Edema (OP4.3, 4.5)

It is the accumulation of fluid in the cornea. Corneal edema may be epithelial or stromal and can affect the entire cornea.

Factors Leading to Corneal Edema

Following factors are responsible for the development of corneal edema:

- Stromal GAG: Osmotic force of stromal GAG plays a role in hydration. *Accumulation of GAG* in the cornea (as in *Mucopolysaccharidoses*) leads to corneal edema.
- Intraocular pressure (IOP): *Raised IOP* (≥ 50 mm Hg) often results in corneal edema due to easy passage of aqueous through corneal stroma but its escape is retarded by epithelium and accumulation of fluid in basal cells of epithelium results in epithelial edema.

- Integrity of endothelium and epithelium: *Damage to epithelium or endothelium* due to any cause results in corneal swelling and loss of transparency. However, *damage to endothelium* is far more serious which can occur during intraocular surgery/postuveitis.
- Corneal endothelial Na^+-K^+ ATPase pump and intracellular carbonic anhydrase pathway in endothelium: Activity in both these pathways produces a net flux from stroma to aqueous. *Inhibition of endothelial Na^+-K^+ ATPase pump*, as in *Fuch's endothelial dystrophy*, leads to corneal edema.

If edema lasts for a long period, epithelium is raised into large vesicles or bullae (vesicular or bullous keratopathy). Bullae periodically burst and symptoms like ocular pain and irritation occur.

Clinical Features

Corneal edema presents with symptoms like impairment of vision, photophobia, watering, ocular discomfort, pain due to periodic rupture of bullae, and halos around light.

On slit lamp examination, corneal thickness is increased with haze. Epithelial edema is visible on retroillumination with slit lamp.

Management

It includes:

- Treatment of primary causes such as lowering of IOP, and control of ocular inflammation.
- Protection of endothelium during intraocular surgery by use of viscoelastics.
- Hypertonic agents:
 - ◇ 5% sodium chloride eye drops \times QID.
 - ◇ 6% sodium chloride eye ointment at bed time.
 - ◇ Anhydrous glycerine.
- Bandage (therapeutic) contact lens to minimize discomfort of bullous keratopathy.
- Penetrating keratoplasty (corneal transplant) is done in long-standing corneal edema which is nonresponsive to medical treatment.

Prognosis

It depends on the status of corneal endothelium. If endothelium is healthy, edema usually resolves completely. Corneas with reduced endothelial cell counts may not be able to recover.

Corneal Opacity (OP4.5)

Corneal opacity occurs in the epithelial breach that involves Bowman's membrane (Fig. 6.5). It may be congenital due to developmental anomalies or birth trauma. The common causes include infection, injury or corneal abrasion. Corneal opacification (loss of transparency) may follow the noninflammatory diseases or inflammation. The term "scar" is reserved for the opacity following inflammation. Scar tissue is white and opaque, and varies in density.

Based on the density of scarring, corneal opacity may be nebular, macular or leucomatous (Table 6.2).

Nebular corneal opacity may be so faint that it could be missed on routine examination. A corneal opacity in pupillary area causes blurring of vision.

- If iris becomes adherent to the back of leucoma in perforated corneal ulcer, it is called adherent leucoma.
- In a sloughing corneal ulcer, where the whole cornea sloughs, prolapse of iris occurs. Exudates which cover the prolapsed iris become organized and form a layer of fibrous tissue over which corneal epithelium rapidly grows, resulting in the formation of pseudocornea. More commonly, iris and cicatricial tissue are too weak to support the IOP. Cicatrix (scar) becomes ectatic. Ectasia of pseudocornea with incarceration of iris tissue is known as anterior staphyloma.

Bowman's membrane does not regenerate. So, some opacity always remains when Bowman's membrane has been destroyed.

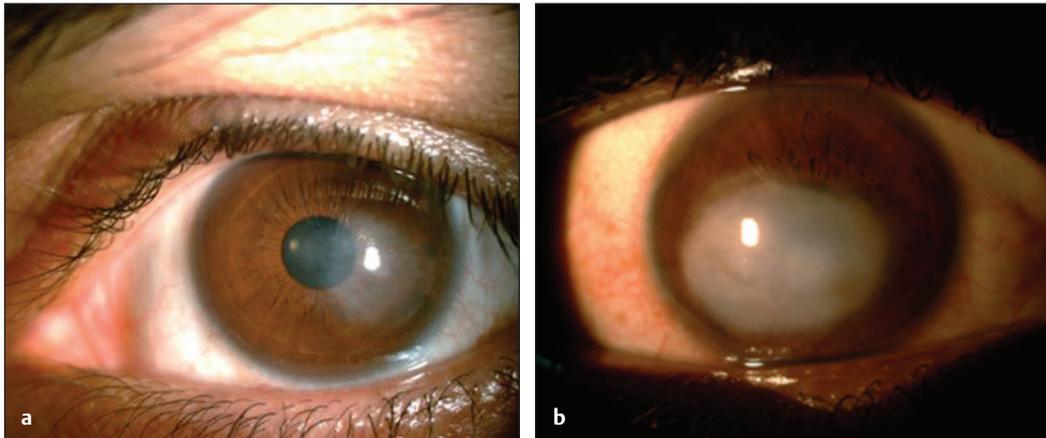


Fig. 6.5 Corneal opacity. (a) Macular grade. (b) Leucoma grade.

Table 6.2 Types of corneal opacities

	Nebular corneal opacity (nebula)	Macular corneal opacity (macula)	Leucomatous corneal opacity (leucoma)
Density	Less dense +	Moderately dense ++	Very dense +++
Involves	Bowman's membrane and superficial stroma	Less than half the thickness of corneal stroma	More than half the thickness of corneal stroma
Structure seen through opacity	Details of iris can be seen through opacity	Details of iris cannot be seen through opacity	Obscures view of iris and pupil

Treatment

The ideal procedure either involves

- Excimer laser PTK (phototherapeutic keratectomy), or
- Corneal transplantation (keratoplasty).

■ Vascularization of Cornea (OP4.5)

Normal cornea is avascular. Vascularization of cornea is always pathological. Vascularization, which is considered as a defence mechanism (immunological defence) against disease, interferes with corneal transparency. It may be superficial or deep.

Superficial Vascularization

It arises from conjunctival superficial vascular plexus. The vessels are wavy and lie in the epithelial layer. Continuity of vessels can be traced with conjunctival vessels at the limbus. It is seen in the following:

- Trachoma.
- Phlyctenular keratoconjunctivitis.
- Superficial corneal ulcers.
- Rosacea keratitis.
- Contact lens wearers.

Pannus

When superficial vascularization is associated with cellular infiltration, it is termed as **pannus**. It may either be progressive when infiltration is ahead of vessels, or regressive, when infiltration is behind the vessels, that is, infiltration recedes. Pannus may be located superiorly, inferiorly, or generalized. Superior pannus occurs in trachoma and contact lens wearers. Inferior pannus is associated with exposure keratopathy and rosacea. Generalized pannus may be seen in chemical burns, Stevens–Johnson syndrome, and Mooren’s ulcer.

Deep Vascularization

It arises from anterior ciliary vessels. The vessels run a fairly straight course and lie in the corneal stroma. The continuity of vessels cannot be traced beyond the limbus. It is seen in the following:

- Chemical burns.

- Deep corneal ulcers.
- Disciform keratitis.
- Sclerosing keratitis.
- Interstitial keratitis (IK).

Once the cornea has been vascularized, the vessels remain throughout life, but these blood vessels may become empty (“ghost vessels”) when stimulus is eliminated.

Treatment

Vascularization can be prevented by timely and adequate treatment of predisposing conditions. Treatment is usually unsatisfactory. The following treatment regimens may be effective:

- *Topical corticosteroid* causes vasoconstriction and decrease in permeability of vessels.
- *Beta irradiation*.
- *Peritomy* is the surgical treatment of superficial vascularization in intractable cases.

■ Pigmentation of Cornea (OP4.5)

Pigments deposited may be iron, silver, gold, copper, melanin, etc.

Deposition of Iron

In hyphema (blood in anterior chamber), hemosiderin becomes embedded in the corneal stroma. Rise of IOP promotes blood staining of cornea. *Blood staining of cornea simulates dislocation of lens in the anterior chamber.*

In keratoconus, deposition of iron hemosiderin surrounds the base of the cone in the corneal epithelium (**Fleischer’s ring**).

In pterygium, iron is deposited as a golden brown line in front of its head (**Stockers’ line**) in the corneal epithelium.

In filtering bleb, iron is deposited anterior to the filtering bleb (**Ferry’s line**) in the corneal epithelium.

In old age, deposition of iron is seen as a brown horizontal line (**Hudson–Stahli line**) in the corneal epithelium. It is located at the junction of the upper 2/3rd and 1/3rd along the line of lid closure.

Deposition of Silver

Prolonged topical use of silver nitrate causes impregnation of salt in the stroma and Descemet's membrane, resulting in brownish discoloration of Descemet's membrane (**Argyrosis**).

Deposition of Copper

When a copper foreign body is retained in the eye, deposition of copper occurs around the periphery of the cornea in the region of Descemet's membrane and deeper stroma. A gray-green or golden-brown pigmentation of the peripheral corneal stroma is produced (**Chalcosis**).

In Wilson's disease (hepatolenticular degeneration), deposition of copper in the periphery of Descemet's membrane is seen as a golden-brown or green ring just inside the limbus when examined on slit lamp (**Kayser-Fleischer ring**, **Fig. 6.6**).

If viewed in cobalt blue light, the ring appears almost black. The condition is reversible with time, if the disease is treated with penicillamine.

Deposition of Melanin

In pigment dispersion syndrome, uveal pigment (melanin) is deposited on the corneal endothelium in the form of a vertical spindle (**Krukenberg's spindle**). The spindle may be associated with pigment dispersion glaucoma.

Deposition of Gold

Gold is deposited in the epithelium in patients with **chrysiasis**.

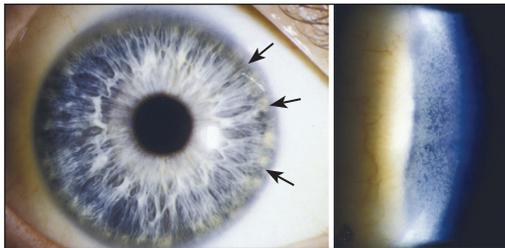


Fig. 6.6 Kayser Fleischer ring (deposition of copper). Source: Wilson disease (hepatolenticular degeneration). In: Biousse V, Newman N, ed. Neuro-ophthalmology illustrated. 3rd Edition. Thieme; 2019.

Corneal Filaments

These are the epithelial threads attached to cornea at one end, and the other unattached end is often club-shaped. These hang over the cornea and move freely with each blink, thereby producing irritation and foreign body sensation.

Prominent Corneal Nerves

These may be associated with—Local ocular disorders, for example,

- Keratoconus.
- Acanthamoebic keratitis.
- Fuch's endothelial dystrophy.
- Congenital glaucoma.

Systemic diseases, for example,

- Neurofibromatosis.
- Refsum syndrome.

Infiltrates

These originate from the limbal vascular arcades and are indicative of active inflammation. These are located usually within the anterior stroma and appear as focal, granular, gray-white opacities. These are composed of leucocytes and cellular debris.

Symptoms of Corneal Diseases

Symptoms of corneal diseases include pain or slight irritation, visual impairment, lacrimation (excessive tear production), photophobia, halos, redness, and foreign body sensation. Specific symptoms pertaining to different pathologies of cornea are listed in **Table 6.3**.

Evaluation of Corneal Diseases

Corneal examination can be done with the following:

- Slit lamp.
- Placido's disc.
- Pachymeter.
- Corneal staining.
- Specular microscopy.
- Confocal microscopy.
- Corneal aesthesiometer.

Table 6.3 Corneal pathology and symptoms

Corneal pathology	Symptoms
<ul style="list-style-type: none"> • Corneal abrasions or bullous keratopathy, resulting in direct stimulation of bare nerve endings 	<ul style="list-style-type: none"> • Lacrimation. • Pain. • Photophobia associated with reflex blepharospasm because of corneal irritation. The reflex blepharospasm is not completely abolished in dark but is greatly diminished by anaesthetization.
<ul style="list-style-type: none"> • Loss of central corneal transparency due to: <ul style="list-style-type: none"> ◊ Stromal edema ◊ Corneal opacity 	Visual impairment.
<ul style="list-style-type: none"> • Epithelial edema resulting in diffraction of light 	Halos around light with blue end of spectrum nearest to light source.
<ul style="list-style-type: none"> • Corneal foreign body or corneal filaments 	Foreign body sensation.

Cornea is examined for the following:

1. Size

- Normal size: Horizontal diameter 12 mm and vertical diameter 11.5 mm.
- Megalocornea (increased size): It may be congenital and due to buphthalmos.
- Microcornea (decreased size): It may occur isolated or as a part of microphthalmos (small eye).

2. Shape:

- Normal cornea: It is like a part of a sphere.
- Flat cornea (cornea plana): It may occur congenitally or in phthisis bulbi.
- Conical cornea: In keratoconus.
- Globular cornea: In Keratoglobus.

3. Surface: Corneal surface and curvature can be evaluated by slit lamp, Placido's disc, Placido keratoscope, corneal topography, and keratometer.

Placido's keratoscopic disc: Kerato means cornea and scopic means visualization. The corneal surface is visualized by a disc painted with alternating black and white circles and contains a hole in the center. Light is kept behind the patient and the examiner looks at corneal image of circles through the hole.

Uniform and sharp image of circles is seen in normal cornea, while irregularities in rings are seen if corneal surface is uneven as in keratoconus, keratoglobus, and corneal astigmatism.

Corneal topography: It is computerized video keratography. It provides an objective record of the condition of anterior corneal surface (optical and anatomical condition) in the form of color-coded maps.

Green color represents normal curvature.

Blue color represents flat curvature.

Red color represents steep curvature.

It is important in preoperative evaluation for refractive surgery, for example, in patient with keratoconus, refractive surgery is deferred.

Orbscan is an improved technology which uses scanning slit technology with Placido disc. It provides information regarding curvature of anterior and posterior surfaces of cornea, and depth of anterior chamber. Curvature of anterior surface of cornea can also be measured by a **keratometer**.

4. Transparency: Cornea is optically transparent, and it becomes hazy in corneal edema, ulcers, opacity, vascularization, dystrophies and degenerations, and corneal deposits. The examination for corneal edema and corneal opacity is carried out with the help of a slit lamp. The corneal opacity is examined for its density (nebular, macular, or leucomatous), sensations, location, and its size.

If keratitis (ulcerative or nonulcerative) is suspected, corneal staining is performed.

5. **Corneal Staining:** Staining of cornea with vital dyes (*Fluorescein* or *Rose Bengal*, **Table 6.4**) is important in evaluating corneal epithelial lesions. It should be performed before corneal sensation is tested and also prior to measurement of IOP.

Alcian blue dye stains mucus selectively, so it stains excess mucus, as in keratoconjunctivitis sicca (**KCS**).

In a geographical herpetic ulcer, peripheral devitalized cells are stained with Rose Bengal dye, while the base of the ulcer (epithelial defect) is stained with Fluorescein dye.

6. **Corneal Vascularization:** The normal cornea is avascular. If corneal vascularization is present, note the following points:

- Whether the vessels are superficial or deep.
- Whether the distribution is localized, circumferential, or peripheral.

7. **Corneal Thickness (Pachymetry):** Corneal thickness indirectly reflects endothelial function. It is measured by with the help of the pachymeter.

Average corneal thickness at center, that is, central corneal thickness (CCT) is about 0.5 mm (490–560 μm). CCT of ≥ 0.6 mm is suggestive of endothelial disease. At periphery corneal thickness is ≈ 0.7 mm.

CCT can alter measurement of IOP: Patients with increased CCT record **high IOP**, while patients with decreased CCT record **low IOP**.

8. **Corneal Sensitivity:** Cornea is richly supplied by nerves. Corneal sensitivity can be tested by:

- Touching cornea with wisp of cotton wool—Normally, there is brisk blink reflex as a response.
- Corneal aesthesiometer provides a more qualitative measurement of corneal sensations. In aesthesiometer, a single horse hair of varying length is used. The longest length which induces blinking is a measure of the threshold of corneal sensitivity. Normally, the cornea is most sensitive in the center.

Corneal sensations are diminished in the following:

- Herpetic keratitis.
- Neuroparalytic keratitis.
- Absolute glaucoma.
- Cerebellopontine angle tumor.
- Leprosy.
- Trigeminal block for neuralgia.

9. **Endothelial Function:** Corneal endothelium can be examined by specular microscopy or confocal microscopy on a slit lamp.

Specular microscopy: Specular microscope photographs the endothelial cells and enables the study of their morphology (their number [count], size and shape).

Average cell count is 2,500 cells/ mm^2 . In adults, it declines with age from 3,500 cells/ mm^2 in children to 2,000 cells/ mm^2 in old age. There is a certain amount of endothelial cell loss after intraocular surgery. Intraocular surgery is deferred in endothelial cell count cases of $<1,000$ cells/ mm^2 .

Table 6.4 Difference between Fluorescein and Rose Bengal dyes

Fluorescein dye 2%	Rose Bengal dye 1%
<ul style="list-style-type: none"> • It remains <i>extracellular</i> and <i>does not stain mucus</i>. It stains tear film and shows up epithelial corneal defects. • It <i>delineates</i> areas denuded of epithelium (abrasions, ulcer) which <i>stains brilliant green</i> when examined under a cobalt blue filter. 	<ul style="list-style-type: none"> • It <i>stains mucus as well as devitalized</i> (dead and damaged) <i>cells red</i> as in superficial punctate keratitis and filamentary keratitis. • It is useful in diagnosis of KCS. • Rose Bengal dye is very irritating, so instill 2% xylocaine (local anesthetic) eye drop before using Rose Bengal.

Abbreviation: KCS, keratoconjunctivitis sicca.

Normally, endothelial cells are hexagonal. Variability in the shape of cells is called **pleomorphism**. *In the presence of 50% nonhexagonal cells, intraocular surgery is contraindicated.* Variation in cell size is called **polymegathism**.

Confocal microscopy: It is performed by a confocal microscope. In cases with corneal edema, endothelium is not adequately visualized by specular microscopy due to edema. *Confocal microscopy may be of value in cases with corneal edema.*

Confocal microscope allows direct visualization of corneal cells. It acquires multiple images of cornea from epithelium to endothelium. Magnified images provide detailed information regarding cell count, shape, and size.

Confocal microscopes are of two types: Confocal slit-scanning microscope and confocal laser-scanning microscope.

■ Inflammation of Cornea

Inflammation of cornea is known as **Keratitis**.

■ Source of Inflammation

Inflammation of cornea may arise from:

- Exogenous source: Cornea is involved by way of exogenous organisms.
- Endogenous source: Inflammation due to endogenous source is typically immunological in nature. *As cornea is avascular, the immunological changes are common near limbal blood vessels close to the corneal margin and called **marginal keratitis**.*
- Contiguous spread (owing to direct anatomical continuity).
- Diseases of conjunctiva spread to corneal epithelium, for example, trachoma and vernal keratoconjunctivitis.
- Diseases of sclera spread to corneal stroma, for example, sclerosing keratitis.
- Diseases of uveal tract spread to corneal endothelium, for example, herpetic uveitis with endotheliitis.

■ Classification

Keratitis can be classified as follows:

- Based on depth:
 - ◇ Superficial keratitis: It is the inflammation involving epithelium and Bowman's membrane.
 - ◇ Deep keratitis: It is the inflammation deep to Bowman's membrane.
- Based on location:
 - ◇ Central.
 - ◇ Peripheral.
- Based on epithelial defect:
 - ◇ Ulcerative.
 - ◇ Nonulcerative.
- Based on etiology:
 - ◇ Infectious.
 - ◇ Noninfectious.

Infectious Keratitis (OP4.1, 4.2)

It is the corneal inflammation caused by bacterial, viral, fungal, or parasitic (protozoal or helminthic) organisms. It can be classified as:

- Depending on depth:
 - ◇ Superficial.
 - ◇ Deep.
- Depending on pus formation:
 - ◇ Purulent (suppurative).
 - ◇ Nonpurulent (Nonsuppurative).
- Depending on epithelial defect:
 - ◇ Ulcerative wherein corneal epithelium shows discontinuity. Loss of epithelium with inflammation in surrounding cornea is called corneal ulcer.
 - ◇ Nonulcerative wherein epithelium is intact (corneal abscess).

Inflammation in cornea is visible as a grayish haze. If it is accompanied by accumulation of leucocytes and cellular debris, this hazy area is called an *infiltration* and appears as gray-white or off-white opacities. *Infiltrates are indicative of active inflammation.*

Noninfectious Keratitis

It is the corneal inflammation with no known infectious cause. It may be:

- Allergic/immune-mediated:
 1. *Localized immune-mediated keratitis*:
 - ◇ Phlyctenular.
 - ◇ Vernal.
 - ◇ Mooren's ulcer.
 - ◇ Marginal.
 - ◇ Atopic.
 2. *Keratitis in systemic immunological disorders*:
 - ◇ Associated with collagen disorders.
 - ◇ Dermatological disorders: Rosacea.
 - Erythema multiforme.
 - Mucous membrane pemphigoid.
- Nonimmune-mediated:
 - ◇ Neurotrophic in Vth cranial nerve (CN) palsy and diabetes.
 - ◇ Neuroparalytic in VIIth CN palsy.
 - ◇ Traumatic:
 - Chemical injury.
 - Thermal injury.
 - Radiation.
 - ◇ Mechanical:
 - Entropion with trichiasis.
 - Lagophthalmos.
 - Exophthalmos.
 - ◇ Nutritional in keratomalacia.
 - ◇ In KCS.
 - ◇ Others:
 - Thygeson's superficial punctate keratitis (SPK).
 - Superior limbic keratoconjunctivitis.

■ Infectious Keratitis

Bacterial Keratitis

The conjunctival sac is never free from organisms. Most of the organisms, normally, present on the ocular surface are:

- Staphylococcus albus or epidermidis.
- Propionibacterium acnes.
- Neisseria catarrhalis.

- Diphtheroids.
- Corynebacterium xerosis, etc.

All these organisms are nonpathogenic commensals. Streptococci, *E. coli*, B proteus, Neisseria gonorrhoeae, Hemophilus aegyptius, Moraxella, etc., are pathogenic and rarely found in normal eyes.

Defence Mechanisms

The following mechanisms help in defending against the microbial invasion of the corneal surface:

1. **Blinking** regularly sweeps away debris trapped in the mucin layer of tears.
2. **Tight junctions between** corneal and conjunctival epithelial cells.
3. **Tears** which contain:
 - Lactoferrin (secreted by lacrimal gland): It inhibits complement activation.
 - Lysozyme, which promotes microbial aggregation and causes lysis of bacterial cell membrane.
 - IgA: It causes bacterial agglutination and inhibits bacterial adherence to corneal and conjunctival surface.
 - β -lysin: It causes bacteriolysis.
4. **Mast cells of conjunctiva**: Stimulation of mast cells cause degranulation of mast cells. It results in vascular dilation and increased vascular permeability. Thus, transudate is produced which is antimicrobial.
5. **Resident normal microbes** produces bacteriocins (high-molecular weight proteins), which inhibit growth of pathogens.

Predisposing Factors

Compromising one or more of the defense mechanisms represent a risk factor in the development of bacterial keratitis. These mechanisms are:

Trauma: Accidental, agricultural or surgical (refractive surgery).

Topical steroids (cause impairment of local immune defense).

Trigeminal nerve paralysis causes corneal anesthesia and exfoliation of epithelial cells.

A—Vitamin **A** deficiency.

B—Bullous keratopathy (corneal epithelial problem).

C—Chronic blepharitis.

Contact lens wear, particularly extended wear soft lenses, causing hypoxia and trauma to corneal epithelium.

D—Diabetes mellitus.

Dry eyes (Poor tear production results in reduction of antimicrobial tear component and epithelial desiccation and damage).

E—Entropion with trichiasis (results in breakdown of protective corneal epithelium).

F—Facial nerve palsy (results in exposure keratopathy).

It does not appear that AIDS serves as an independent risk for development of infectious keratitis, but infectious keratitis in AIDS patients might follow a more aggressive course.

Causative Organisms

Bacteria that can penetrate normal (intact) corneal epithelium are *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Corynebacterium diphtheriae*.

However, most other bacteria are capable of producing keratitis with damaged epithelium. Purulent keratitis is usually exogenous due to pyogenic bacteria. The most common pathogens are listed in **Flowchart 6.2**.

Pseudomonas aeruginosa is a frequent cause of contact lens-associated keratitis and found in moist environments.

Pathogenesis of Corneal Ulcer

For a bacterial keratitis to become established, bacterial adherence to cornea requires a defect in the continuity of the corneal epithelium (**Fig. 6.7**). Pathological changes occurring during development of corneal ulcer can be described

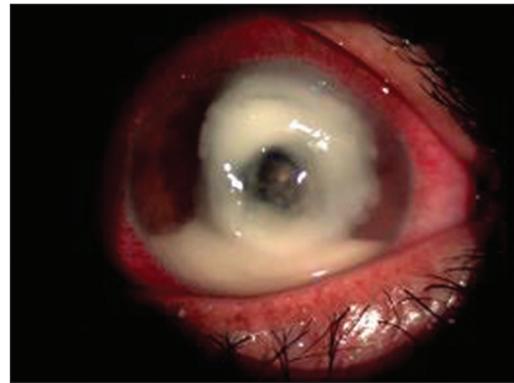
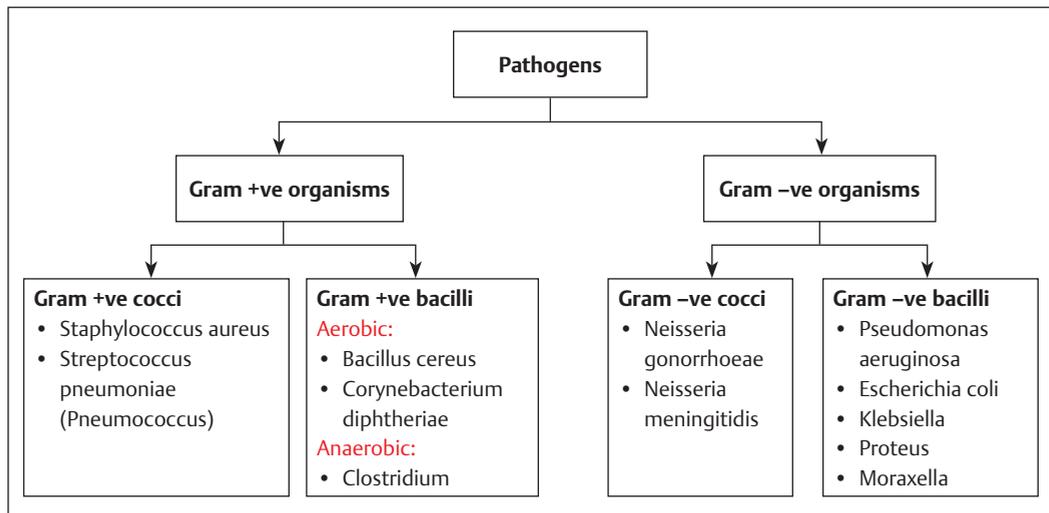


Fig. 6.7 Bacterial corneal ulcer.



Flowchart 6.2 Types of pathogens causing keratitis.

in four stages, namely, infiltration, ulceration, regression and cicatrization (**Fig. 6.8**).

Stage of Infiltration

The bacterial adherence to the cornea on damaged epithelium is facilitated by binding of microbial adhesins and toxins to host cell receptors and glycocalyx coat. The corneal infection and inflammation stimulates immigration of polymorphonuclear leucocytes (polymorphs) via tear film and proliferating limbal blood vessels. The epithelium becomes edematous and is raised at the site of infiltration.

Stage of Ulceration

The stage of infiltration is followed by the necrosis and desquamation of corneal stroma, leading to ulceration. Polymorphs phagocytose bacteria and necrotic stroma. If bacteria overwhelms host defense, necrosis progresses unchecked and corneal perforation takes place.

Stage of Regression

If infection is brought under control, infiltration decreases in size. Superficial vascularization develops from the limbus which supplies antibodies. Immune response increases and epithelium heals over ulcer.

Stage of Cicatrization

Cicatrization, which occurs in vascularized ulcer, involves regeneration of collagen and formation of fibrous tissue. Newly formed fibers are not arranged regularly as in normal corneal lamellae. These refract light irregularly. Scar is, therefore, opaque.

If ulcer is superficial and involves epithelium only, ulcer heals without leaving any opacity behind. **If ulcer involves Bowman's membrane**, some degree of permanent opacification remains, as **Bowman's membrane never regenerates**.

Clinical Features

Clinical features depend on virulence of organism, duration of infection, and use of steroids.

Symptoms

- Pain and photophobia (due to exposure of nerve endings of 1st division of trigeminal [V] nerve).
- Redness.
- Blepharospasm.
- Lacrimation.
- Discharge.
- Blurred vision.

Signs

- Circum corneal (ciliary) congestion of conjunctiva.
- Epithelial defect is associated with gray-white infiltrate around the margin of ulcer. Corneal lamellae imbibe fluid, and margin of ulcer becomes edematous and overhangs above the surface with sloping edges (**saucer-shaped appearance of ulcer**).
- *Corneal ulcer takes a green stain with Fluorescein dye.*
- Lid erythema and edema.
- Anterior chamber inflammation is often present with cells and flare and may produce a hypopyon.

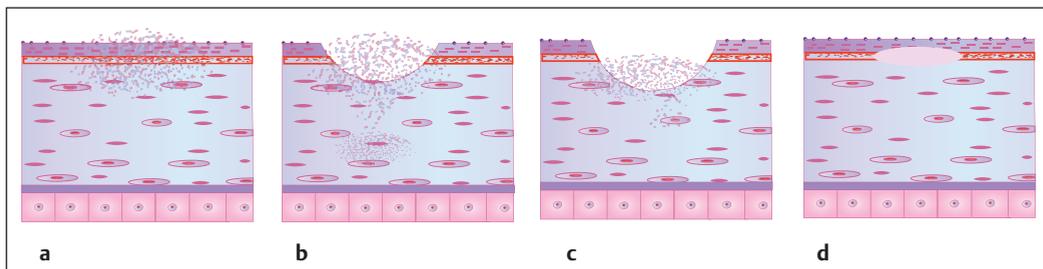


Fig. 6.8 Pathogenesis of corneal ulcer. (a) Stage of infiltration. (b) Stage of ulceration. (c) Stage of regression. (d) Stage of cicatrization.

Hypopyon Corneal Ulcer

Development of hypopyon: Some of the toxins produced by bacteria diffuse into the anterior chamber and irritate the vessels of iris and ciliary body (**keratouveitis**). Polymorphs from vessels are poured into the anterior chamber and thereafter gravitate to the bottom of the anterior chamber to form **hypopyon**. *Hypopyon is sterile since* accumulation of polymorphs is due to toxins, and not to actual invasion by bacteria. Indeed, bacteria and leucocytes are incapable of passing through the intact Descemet's membrane. Such hypopyons are fluid and always move to the lowest part of the anterior chamber with change in the position of the patient's head. Once the ulcerative process is controlled, hypopyon is easily and rapidly absorbed.

Thus, in absence of a full-thickness corneal perforation, hypopyon often represents a sterile accumulation. Development of hypopyon depends on:

- *Virulence of infecting organism:* Pyogenic organisms producing hypopyon are Staphylococci, Streptococci, Gonococci (N-gonorrhoeae), Moraxella, and Pseudomonas.

Pseudomonas and Pneumococcus (*Streptococcus pneumoniae*) are most dangerous and are likely to be present if there is dacryocystitis (inflammation of lacrimal sac).

- *Resistance of tissues:* Hypopyon corneal ulcers are much more common in elderly

individuals, debilitated persons, and alcoholics.

Hypopyon corneal ulcer caused by pneumococci is characteristic and is called **ulcus serpens** because of its tendency to **creep over cornea in a serpiginous fashion**. It starts as a gray-white or yellowish disc-like lesion near the central part of the cornea with shaggy undermined infiltrating edges. One edge of the ulcer, along which the ulcer spreads, shows more infiltration which often looks like a yellow crescent. The tissues breakdown and ulcer spreads (**Fig. 6.9**).

There is violent iritis, leading to hypopyon, which increases in size very rapidly. Massive hypopyon often causes rise in IOP (*secondary glaucoma*).

In severe cases, ulcer spreads rapidly. The entire cornea is affected by the ulcerative process and perforation of ulcer results if there is sudden coughing or sneezing.

Pseudomonas corneal ulcer

Pseudomonas produces destructive enzymes (such as protease, lipase, elastase, and exotoxin) which melt corneal stroma and results in a necrotic soupy ulceration with **greenish-yellow mucopurulent discharge** adherent to the ulcer. The corneal epithelium away from the primary ulcer typically develops a diffuse, semi-opaque **"ground glass" appearance**. The ulcer is associated with marked anterior chamber reaction and hypopyon formation. Rapidly spreading ulcer often extends peripherally, deeply involving the entire cornea and resulting in sloughing corneal ulcer and **perforation**. *If cornea sloughs*, iris is prolapsed and covered by exudates which become organized, resulting in **formation of pseudocornea** (**Fig. 6.10**).

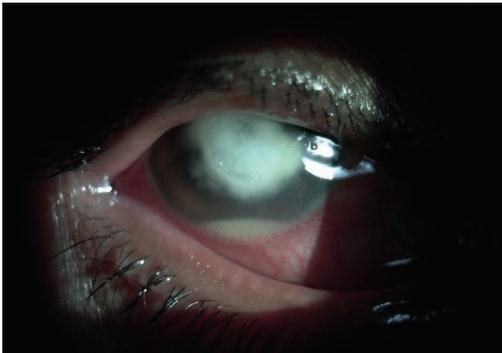


Fig. 6.9 Hypopyon corneal ulcer.

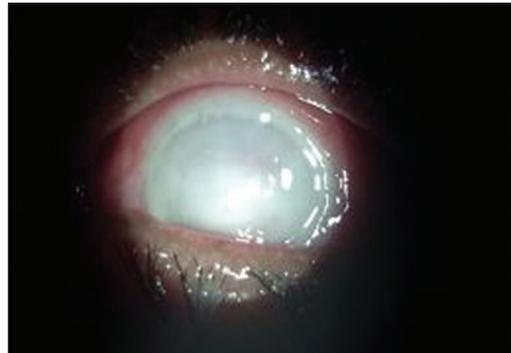


Fig. 6.10 Pseudomonas corneal ulcer.

Management of Corneal Ulcer

It includes identification of organism and treatment. For identifying the causative organisms, corneal scrapings are taken from the margins and base of ulcer for Gram's and Giemsa staining (Table 6.5) and culture and sensitivity (Table 6.6).

Treatment

Fundamental principles for treating corneal ulcer are protection, cleanliness, and specific treatment of infection. Treatment should be initiated before the results of culture and antibiotic sensitivity are available. Treatment includes the use of antibiotics and cycloplegics.

Antibiotics

Commonly used antibiotics are:

- *Aminoglycosides, for example*, Gentamicin, Tobramycin, and Amikacin.
- *Fluoroquinolones, for example*, Ciprofloxacin, Gatifloxacin, Ofloxacin, Moxifloxacin, and Levofloxacin.
- *Cephalosporins, for example*, Cefazolin.
- *Penicillins, for example*, Penicillin G, Methicillin, and Piperacillin.
- *Vancomycin*.

Routes of administration could be topical, sub-conjunctival, or systemic. *Topical administration* is the route of choice because it provides rapid, high-levels of drugs in the cornea and anterior chamber. The infection is controlled by the broad-spectrum antibiotic, while in severe infection, the fortified antibiotic drops are preferred. Fortified drops are not commercially available and are freshly prepared from their injectable preparations.

Treatment Regimen for Topical Antibiotics

Initial therapy should be initiated with a broad-spectrum regimen. Broad-spectrum coverage can be achieved with

- Fluoroquinolone antibiotic alone **or**
- Combination of aminoglycoside + cephalosporin.

Since increasing resistance to fluoroquinolones has been reported, therapy with fluoroquinolones is not a standard practice. *Initial therapy should be a combination of two* fortified antibiotics:

An aminoglycoside (gentamicin or tobramycin) for Gram -ve organisms

+

A cephalosporin (cefazolin is most commonly used for Gram +ve organisms)

Table 6.5 Staining of corneal scrapings

Stain	Organism identified
<ul style="list-style-type: none"> • Gram's and Giemsa: Gram's staining differentiate into Gram +ve and Gram -ve species 	Bacteria, fungi
<ul style="list-style-type: none"> • Potassium hydroxide (KOH) fixation 	Fungi
<ul style="list-style-type: none"> • Calcofluor white (it is a fluorescent dye with an affinity for amoebic cysts and fungi) 	Fungi and acanthamoeba

Table 6.6 Corneal scrapings for culture and sensitivity

Culture media	Organism isolated
<ul style="list-style-type: none"> • Blood agar 	It promotes growth of: <ul style="list-style-type: none"> • Aerobic bacteria except Neisseria, Haemophilus and Moraxella • Saprophytic fungi
<ul style="list-style-type: none"> • Chocolate agar 	It is used to isolate neisseria, hemophilus, and moraxella
<ul style="list-style-type: none"> • Sabouraud's dextrose agar 	Promotes growth of fungi
<ul style="list-style-type: none"> • E. coli plated non-nutrient agar 	For acanthamoeba

Amikacin is useful against Gram -ve organisms resistant to gentamicin and tobramycin. The *instillation frequency* of topical antibiotics is as follows:

- Every 1 hour day and night for 48 hours.
- Every 2 hours during daytime for a further 48 hours.
- 4–6 hourly for another week.

Treatment is continued until epithelium has healed. When combination of two antibiotics is prescribed, drops are given in an alternating fashion every half an hour.

Initial therapy with aminoglycoside and cephalosporin can be changed for effective treatment, if needed, after microbiological investigation (culture and sensitivity) reports. For example, fluoroquinolone treatment is significantly more effective in the treatment of *Neisseria* infection than an aminoglycoside combined with a cephalosporin.

Treatment Regimen for Oral Antibiotics

These are not usually necessary. Systemic antibiotics provide relatively low-level of antibiotic in the cornea because of avascularity. Therefore, these are advised only when keratitis is complicated by scleritis (as in peripheral ulcers with scleral extension) or there is risk of perforation or endophthalmitis.

N. gonorrhoeae should be treated systemically with IM ceftriaxone or IV penicillin G along with topical fluoroquinolone.

N. meningitidis should be treated with i.v. penicillin G along with topical fluoroquinolone.

Treatment Regimen for Subconjunctival Antibiotics

Subconjunctival injections are indicated if there is poor compliance with topical treatment (**Table 6.7**).

Cycloplegics

Atropine 1% as drops or ointment is preferred. Other cycloplegics are homatropine 2% eye drops and cyclopentolate 1% eye drops. These are instilled two to three times a day. Cycloplegics relieves ciliary spasm and reduces pain. These also

prevent posterior synechiae formation as anterior uveitis generally accompanies corneal ulceration.

Treatment of Perforated Corneal Ulcer

If perforation has occurred, the treatment depends upon its size and location. Small perforation in pupillary area is managed with rest, antibiotics, atropine, and pressure bandage. Small perforation over iris results in adhesion of iris to cornea, forming adherent leucoma. In case of perforation, anterior chamber must be restored as quickly as possible. It can be done by use of tissue adhesive (cyanoacrylate glue). It is applied to the area of perforation after careful debridement. Drying of the adhesive may take 5 to 10 minutes. A surgical procedure such as therapeutic penetrating keratoplasty or conjunctival flap can be undertaken thereafter. Persistent anterior stromal scar can be removed by excimer laser phototherapeutic keratectomy.

Topical Corticosteroids in Corneal Ulcer

Steroids are best avoided, since they may retard epithelialization and inhibit repair by fibrosis. If inflammation is severe and persists, it is safest to use steroids when there is evidence of successful antibiotic treatment and cultures become sterile.

Additional therapeutic measures taken for healing of ulcer are as follows:

- Treatment of cause
 - ◇ Dacryocystitis should be treated with dacryocystorhinostomy (**DCR**).
 - ◇ If IOP is raised, it is reduced by antiglaucoma therapy.
 - ◇ Peritomy (excision of 2 mm strip of limbal conjunctiva) is performed for corneal vascularization.

Table 6.7 Dosage of subconjunctival injections for the treatment of corneal ulcers

Drug	Subconjunctival dose
Gentamicin/tobramycin	40 mg
Amikacin	50 mg
Cefazolin	125 mg

Note: Subconjunctival injections are given at 24 hourly intervals for 5 days.

- Removal of necrotic tissue by repeated scraping of the floor of ulcer.
- Cauterization of ulcer with pure (100%) carbolic acid or 10% trichloroacetic acid.
- Conjunctival flaps might be especially useful in peripheral infectious ulceration.

If infection is brought under control, cicatrization occurs in corneal ulcer. The residual scar may cause irregular astigmatism or may be visually debilitating (**Table 6.8**).

Treatment of Nonhealing Corneal Ulcer

If ulcer does not respond to therapeutic measures and continues to progress, a thorough search must be made for the cause, which could be either local or systemic. Local causes include lagophthalmos, trichiasis, raised IOP, dacryocystitis and

Outcome of bacterial keratitis	Treatment
<ul style="list-style-type: none"> • If irregular astigmatism occurs 	<ul style="list-style-type: none"> • It is treated with rigid contact lens.
<ul style="list-style-type: none"> • If scar is anterior stromal 	<ul style="list-style-type: none"> • It is removed by excimer laser phototherapeutic keratectomy.
<ul style="list-style-type: none"> • If scar is deep 	<ul style="list-style-type: none"> • It requires lamellar or penetrating keratoplasty.

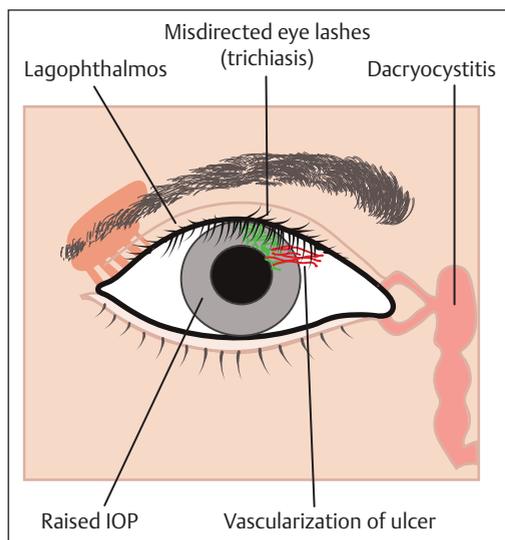


Fig. 6.11 Local causes of nonhealing corneal ulcers.

vascularization of ulcer, while systemic causes include diabetes mellitus and systemic steroid administration (**Fig. 6.11**).

Complications

Following are the complications of corneal ulcers:

1. **Ectatic cicatrix** (secondary keratectasia): Deep ulcer may lead to marked thinning of cornea which may bulge under normal IOP. The corneal scar (cicatrix) becomes consolidated with permanent bulging as secondary keratectasia.
2. **Secondary glaucoma**: Corneal ulcer causes absorption of toxins in the anterior chamber, leading to the formation of toxic iridocyclitis. This further causes blockage of an angle of the anterior chamber with fibrinous exudates leading to secondary glaucoma.
3. **Descemetocele**: Some ulcers become adequately deep (due to virulent organisms) to involve the whole thickness of cornea except *Descemet's membrane*. Descemet's membrane being elastic offers resistance to inflammation and is unable to support IOP and herniates. The herniation of Descemet's membrane through the ulcer is known as descemetocele.
4. **Perforation of corneal ulcer** (perforated corneal ulcer, **Fig. 6.12**).

Descemetocele is a sign of impending perforation which may convert into perforation on



Fig. 6.12 Perforated corneal ulcer.

coughing, sneezing, straining at stool, or spasm of orbicularis muscle. Pain is alleviated after perforation. Perforation of ulcer is accompanied by sudden escape of aqueous and fall in IOP. The iris lens diaphragm moves forward and cicatrization of corneal ulcer results (**Fig. 6.13**).

Factors responsible for preventing perforation are as follows:

- Forced expiration (blowing the nose, coughing, etc.) must be avoided.
- IOP is reduced by oral acetazolamide and/or i.v. mannitol and topical IOP-lowering eye drops.

Sequelae and complications of perforation: The effect of perforation largely depends on its size and position. These include the following:

- **Endophthalmitis** or **panophthalmitis:** Due to perforation of ulcer, organisms gain access to the interior of the eye, leading to the development of endophthalmitis or panophthalmitis.
- **Intraocular/expulsive hemorrhage:** Sudden perforation of large ulcer causes sudden lowering of IOP, hence there is dilatation of intraocular blood vessels. This leads to the development of intraocular/expulsive hemorrhage (profuse bleeding along with extrusion of contents of globe).
- **Anterior synechiae:** If perforation is small and opposite the iris, anterior synechiae develop, leading to leucoma adherens.

- **Iris prolapse:** If perforation is large and opposite the iris, iris prolapse occurs. There is deposition of exudates on the iris surface which becomes organized. Iris and cicatricial tissue are too weak to support IOP, hence anterior ectasia of cicatrix with incarceration of iris, which is called **anterior staphyloma**, develops.
- **Anterior capsular cataract:** If perforation is opposite the pupil (central perforation), the lens comes in contact with the ulcer-causing anterior capsular cataract. **If perforation is not plugged by iris but exudates fill the gap**, the repeated ruptures of exudates fill the gap, causing the opening to become permanent and leading to the formation of **corneal fistula**.

Fungal Keratitis (Mycotic Keratitis)

For clinical purpose, fungi are of the following two types:

- Filamentous fungi.
- Nonfilamentous fungi (**yeasts**).

Risk Factors

The following risk factors are involved in the development of fungal keratitis:

- **Trauma** with vegetable matter or animal tail.
- **Systemic immunosuppression** by use of corticosteroids or immunosuppressives.
- Diabetes.

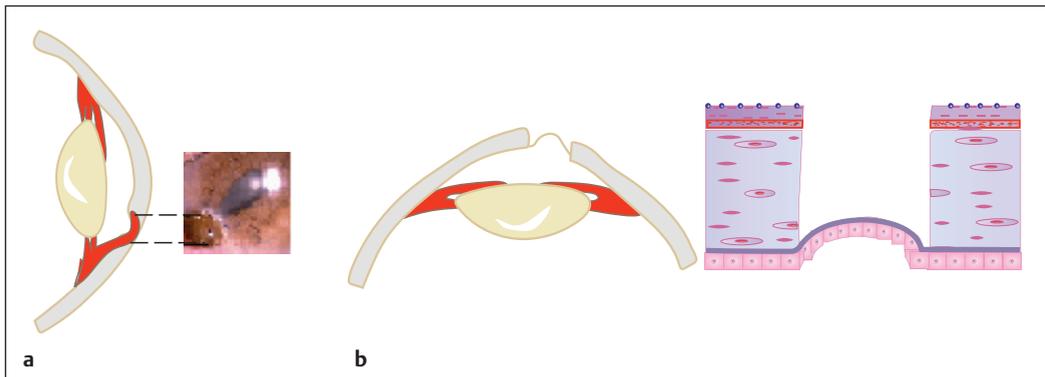


Fig. 6.13 (a) Perforation. (b) Descemetocoele.

- *Hydrophilic contact lens wear.*
- *Corneal surgery* (fungal infection at lamellar interface has been described following LASIK).

Etiology

Fungal keratitis is rare in temperate countries but common in tropical countries, warm and humid climates, rural areas, and immuno-compromised individuals. It is most prevalent in agricultural areas and typically preceded by ocular trauma with vegetable matter. It is commonly due to infections with *Aspergillus*, *Fusarium*, and *Candida albicans*.

Clinical Features

The onset is gradual and slowly progressive. Symptoms are relatively minimal, much milder than clinical signs, and include foreign body sensation, photophobia, blurred vision, and discharge.

Clinical signs of filamentous fungi are:

- Organism adherence results in *gray-white, elevated infiltrate*. Epithelium over *infiltrate may be elevated* above the remainder of the corneal surface.
- Invasion into corneal lamellae and extension along corneal lamellae results in *feathery borders* and *satellite lesions*.
- Penetration of intact Descemet's membrane by filamentous fungi results in thick and immobile *hypopyon* with upper convex border (**Fig. 6.14**). Infection in anterior chamber is difficult to eradicate.
- Sometimes, a white immune ring (**Wessely ring**) may be seen around the ulcer due to deposition of immune complexes.

In case of nonfilamentous fungi (*candida*), keratitis is characterized by a yellow-white stromal infiltrate, associated with dense suppuration, which appears as a collar-button abscess without feathery edge.

Diagnosis

History of trauma with vegetable matter, wood, animal tail, or chronic use of steroid is present.

Investigations helpful for coming to a diagnosis include:

- Scrapings from the floor of ulcer are stained with 10% KOH.
- Scrapings are also plated on Sabouraud dextrose agar for culture and sensitivity. Cycloheximide should not be included in the medium since it inhibits fungal growth.

Treatment

As *most antifungals are only fungistatic*, topical treatment should be continued for several weeks. Removal of epithelium over the lesion enhances penetration of antifungal agents.

Topical treatment includes the following considerations:

- Infection due to *filamentous fungi* is treated with natamycin 5%, amphotericin B 0.15%, or miconazole 1% drops. Voriconazole eye drops are more effective against *Aspergillus*. The drops are instilled initially every 1 hour and tapered gradually.
- ***Candida infection* (yeast)** is usually treated with amphotericin B. Nystatin eye ointment applied five times a day is only effective against *candida*.

If infection fails to respond to single agent therapy, amphotericin B and natamycin can be used alternatively on an hourly basis.

Systemic antifungal drugs (itraconazole or voriconazole) may be required in endophthalmitis.

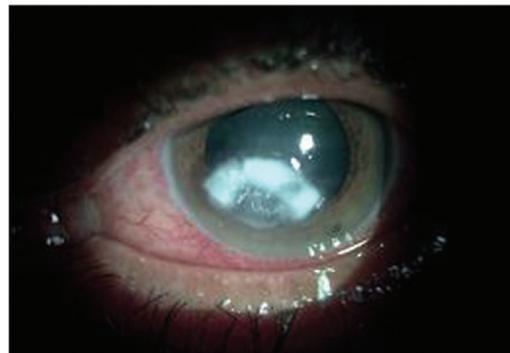


Fig. 6.14 Fungal keratitis with satellite lesions and hypopyon.

If medical treatment fails, surgical intervention may be required. **Penetrating keratoplasty** should be performed sooner to minimize the risk of endophthalmitis or infectious scleritis. Clear margins should be included in excised cornea. Corticosteroid use is not recommended in management of fungal keratitis.

Viral Keratitis

Viruses are obligate, intracellular parasites. Viruses that cause corneal disease include:

- Herpes simplex virus (**HSV**).
- Varicella zoster virus (**VZV**).
- Epstein–Barr virus (**EBV**).
- Adenovirus.
- Cytomegalovirus (**CMV**): It is a more common entity in association with AIDS.

Herpes Simplex Keratitis

HSV is a DNA virus and is of two types: HSV-1 and HSV-2. HSV-1 causes infection above waist and affects face, lips and eyes, while HSV-2 is associated with genital infection (genital herpes). HSV infection can be categorized into neonatal, primary, and recurrent infections.

Neonatal Infection

It is the infection of newborns by maternal genital herpes.

Fetus passes through the birth canal, so *neonatal HSV infection occurs by way of Type-2 virus (Fetus)*. It may affect the central nervous system (CNS) or can remain localized to the eye. Neonatal ocular HSV infection can present as conjunctivitis, keratitis, iridocyclitis, iris atrophy, cataract, chorioretinitis, or optic neuritis (**Fig. 6.15**).

Primary Infection (i.e., no previous virus exposure)

Neonates are usually protected by maternal antibodies against HSV infection during the first 6 months of life. So, primary infection by HSV-1 is uncommon during the first 6 months of life. Transmission occurs by droplet transmission via contaminated adult saliva. So, children under 3 years of age are more prone to get HSV infection, owing to close contact, that is, it typically occurs between 6 months to 5 years of age.

Primary infection remains *often subclinical* and may cause mild fever, malaise, upper respiratory tract symptoms, and local lymphadenopathy. Oral mucosa is more commonly involved than eye in primary infection.

Children may develop **follicular keratoconjunctivitis**. **Epithelial punctate keratitis** may be found in nearly 50% of the cases. Primary

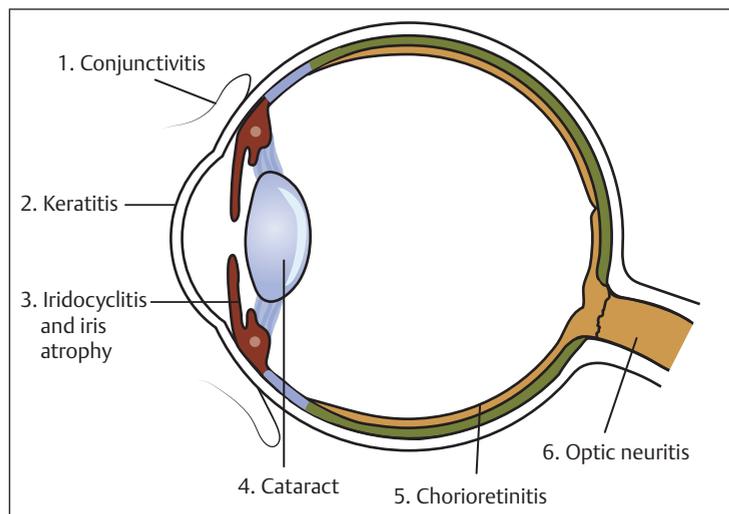


Fig. 6.15 Presentation of neonatal ocular HSV. Abbreviation: HSV, herpes simplex virus.

herpetic infection is usually *benign and self-limited*. An attack does not produce lasting immunity and recurrences are frequent, particularly associated with upper respiratory tract infection (URTI). A person once infected frequently becomes a carrier.

Recurrent Infection (i.e., reactivation in presence of cellular and humoral immunity)

After primary infection with HSV-1, the virus reaches the sensory ganglion, where it may lie dormant for many years. Risk factors for recurrence are fever, stress, trauma, malnourishment, measles, and use of corticosteroids and other immunosuppressive.

The above stimuli (risk factors) may cause a clinical reactivation and replication of the virus. The virus travels down the sensory ganglion (e.g., trigeminal ganglion) and result in recurrent ocular HSV disease. Fortunately, ocular HSV disease tends to be a form of unilateral disease.

Clinical Features

Clinical features depend upon the part affected. Recurrent ocular HSV infection can affect lids, conjunctiva and cornea (epithelium, stroma and endothelium).

Note: Epithelial lesions are caused by replicating live virus. Stromal and endothelial lesions involve both live virus activity and immune reaction to viral antigen.

I. Involvement of lids causes lid vesicles and blepharitis.

II. Involvement of conjunctiva manifests as severe follicular conjunctivitis.

III. Involvement of corneal epithelium by way of HSV results in **epithelial keratitis**.

Symptoms include mild discomfort, foreign body sensation, redness, watering, blurred vision, and photophobia.

Following are the clinical signs of involvement of corneal epithelium due to recurrent HSV infection:

- Characteristic epithelial lesion of recurrent HSV infection is **dendritic ulcer** (Fig. 6.16).

Virus replication results in opaque epithelial cells on the cornea, arranged in a row or group. Central desquamation of these results in linear branching ulcer (dendritic ulcer). *The ends of the ulcer have characteristic terminal knobs which are pathognomonic. The central ulcerated area stains with Fluorescein dye, while the peripheral cells at the margin containing live virus stain with Rose Bengal dye.* Indiscriminate use of topical steroids results in progressive enlargement of dendritic ulcer to an amoeboid or geographical configuration known as **geographical ulcer**.

- Corneal sensation is *reduced*. The ulcer may resolve spontaneously or with treatment over 1 to 2 weeks. A nonhealing epithelial defect after live virus disappears with prolonged topical treatment is referred to as **“metaherpetic” ulcer**. It is caused by basement member damage, resulting in failure of reepithelialization. It is not caused by reactivation of virus (viral replication). *Margins of these ulcers do not stain with Rose Bengal.*

IV. Involvement of corneal stroma: Stromal lesion might be an immunological reaction, be infectious, or may involve combined mechanism. Stromal lesions in herpetic disease include disciform

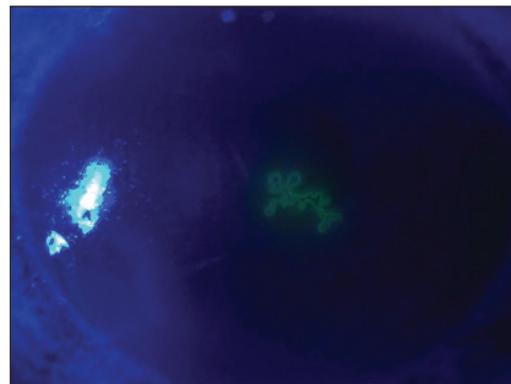
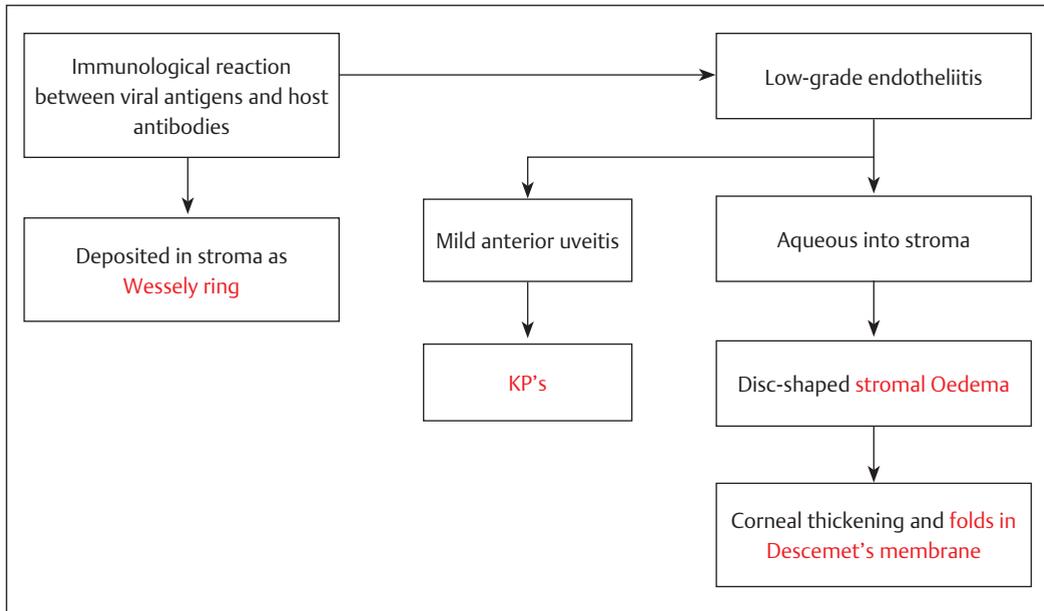


Fig. 6.16 Dendritic ulcer. Source: Uveitis. In: Glass L, ed. Ophthalmology Q&A Board Review. 1st Edition. Thieme; 2019.



Flowchart 6.3 Signs of disciform keratitis.

keratitis and stromal necrotizing keratitis.

Disciform keratitis: It is a *hypersensitivity reaction* to HSV antigen in the cornea. Symptoms include blurred vision and halos around lights. Following are the clinical signs of disciform keratitis due to recurrent HSV infection (**Flowchart 6.3**):

- Disc-shaped *stromal edema*, often with overlying epithelial edema, is a dominant feature.
- Folds in Descemet's membrane.
- Mild anterior uveitis with keratic precipitates (KPs).
- A ring of stromal haze may be present surrounding the stromal edema called the **Wessely ring**. It signifies deposition of viral antigen and host antibody complexes.
- Corneal sensations are reduced. There is no stromal neovascularization or necrosis.

Stromal necrotizing keratitis: It is caused by *active viral invasion*. The infiltration of cornea by polymorphs, lymphocytes, macrophages, and plasma cells mediate tissue destruction and stromal necrosis.

Typical lesion has a cheesy, yellow–white necrotic appearance. There may be associated anterior uveitis with KPs. Scarring, vascularization, and lipid deposition are common.

- In advanced disease, corneal stromal melting results in descematocele formation and perforation.
- If peripheral cornea is involved, inflammation and necrosis spread to sclera, resulting in *sclerokeratitis*.

V. Involvement of corneal endothelium (endotheliitis) results in corneal edema, anterior uveitis, which in turn leads to hypopyon and synechiae formation, and trabeculitis resulting in elevated IOP.

Complications

Complications of herpetic eye disease include:

- Secondary infection.
- Secondary glaucoma.
- Cataract (secondary to inflammation or prolonged use of steroids).
- Iris atrophy (secondary to keratouveitis).

Diagnosis

Diagnosis of ocular HSV disease is based on a constellation of:

- Assessment of *corneal sensations*.
- *Staining characteristics* with Fluorescein and Rose Bengal dye.
- Enzyme-linked immunosorbent assay (ELISA) test identifying viral antigens.
- Polymerase chain reaction (PCR) which detects HSV viral DNA in tissues, aqueous, and tears.

Treatment

Treatment of HSV ocular disease depends on the nature of ocular involvement. Ocular HSV disease is treated by antiviral agents. These are purine or pyrimidine analogues that are incorporated to form abnormal viral DNA.

To define the role of oral antiviral agents and topical corticosteroids in the treatment and prevention of recurrent HSV ocular disease, a study termed **Herpetic Eye Disease Study (HEDS)** was conducted. According to HEDS:

1. **Oral acyclovir:** Provides no extra benefit over topical steroids and topical antiviral agents in treatment of stromal keratitis. It provides benefit in HSV iridocyclitis. So, concurrent administration of oral acyclovir is recommended in HSV iridocyclitis. It does not seem to prevent recurrent stromal keratitis or iridocyclitis.
2. **Topical steroids:** In absence of accompanying HSV epithelial keratitis, topical steroids along with topical antiviral agents reduce progression of stromal inflammation and shorten the duration of stromal keratitis (i.e., stromal keratitis improves more rapidly).

- Treatment of **epithelial keratitis without stromal involvement** includes the following considerations:

1. Debridement of the edges of dendritic ulcer with cotton-tipped applicator to reduce infected (virus-laden) epithelial cells.
2. Antiviral agents:
 - ◇ TFT (Trifluorothymidine) 1% drops every 2 hours
 - or

- ◇ Vidarabine (Ara - A) 3% ointment 5 times daily.

TFT and acyclovir both are active against HSV-1 and HSV-2.

Early IDU (Idoxuridine) 0.1% drops and 0.5% ointment were used, but due to the relative toxic effect on epithelium (punctate keratopathy), it is seldom used now. The most frequently used drug is Acyclovir 3% ointment. Recently, Ganciclovir 0.15% gel 5 times daily is effectively used. Antiviral agents are used until the epithelial ulcer has healed.

3. Lubricants are also given.
4. Cycloplegics, if required.
5. Topical antibiotics to prevent secondary bacterial infections.
6. Topical steroids are contraindicated in epithelial HSV keratitis because of the presence of active viral replication in HSV epithelial keratitis.

Advantages of acyclovir over IDU, TFT, and Vidarabine.

1. It has less epithelial toxicity.
2. It penetrates intact corneal epithelium and stroma, achieving therapeutic levels in aqueous humour.
3. It acts preferentially on virus-laden epithelial cells and has low-toxicity for host cells.

• Treatment of metaherpetic ulcers

(*postinfectious ulcer*): If ulcer is truly metaherpetic, that is, persistent epithelial defect after live virus disappears with topical treatment; antiviral agent serves no purpose and most likely will only inhibit epithelial regeneration. Treatment is directed toward encouraging epithelial healing and includes:

- ◇ Lubrication of eye with preservative free drops.
- ◇ Therapeutic (bandage) soft contact lens.
- ◇ Temporary tarsorrhaphy (if above measures fail) (OP4.7).
- ◇ Conjunctival flap.

- **Treatment of stromal keratitis:** It is treated with topical steroids and topical antiviral

agents. Important points of consideration are:

- ◇ Topical Prednisolone (1% drops) is used 4 to 5 times daily and gradually tapered. It reduces inflammation.
- ◇ Acyclovir 3% ointment is recommended five times daily. It penetrates intact corneal epithelium and stroma and can therefore be used to treat stromal herpetic keratitis.

Oral acyclovir provides no extra benefit over topical steroids and topical antiviral agents in treatment of stromal keratitis.

- Treatment of patients with **HSV iridocyclitis**: HSV endotheliitis, trabeculitis, and iridocyclitis are treated with topical steroids (Prednisolone 1% drops tapered gradually) plus topical antiviral agent (Acyclovir 3% ointment five times daily) and oral Acyclovir (400 mg five times daily for 7–10 days).
- To reduce rate of **recurrent herpetic eye disease**: Low-dose oral Acyclovir 400 mg BD for 6 to 12 months reduces the rate of recurrent HSV ocular disease but this effect reduces or even disappears when the drug is discontinued. So, long-term prophylactic treatment should be considered in patients with frequent recurrences and at the risk of visual loss, particularly involving an only eye.
- Patients with **stromal scarring and opacity** can be treated by penetrating keratoplasty (PKP). Recurrence of active herpetic infection in corneal grafts is often a problem. Since long-term oral antiviral treatment can reduce recurrence rate, oral Acyclovir 400 mg BD should be given to patients undergoing PKP for herpetic eye disease to improve the survival of corneal grafts.

Varicella-Zoster Virus Keratitis (VZV Keratitis)

Varicella-zoster virus causes **varicella** (chickenpox) on *initial infection* and **zoster** or shingles on *recurrence* (herpes zoster). Thus, herpes zoster is caused by same virus that causes chicken pox. After initial varicella (chicken pox) infection in childhood or youth, the virus remains latent in a sensory ganglion (like herpes simplex virus). It can reactivate to cause shingles (herpes zoster) after depressed cellular immunity. Depressed cellular immunity can occur with age, AIDS, immunosuppressives, blood dyscrasias, neoplasms, and radiotherapy. Thus, herpes zoster represents a form of recurrent disease.

The virus travels via sensory nerve to skin dermatome or eye where peripheral inflammation develops. *Trigeminal nerve infection is second in frequency as a site of recurrence after the thoracic region.*

Herpes zoster ophthalmicus (HZO) is a consequence of Gasserian ganglion (trigeminal nerve) involvement. Involvement of ophthalmic (1st) division occurs far more commonly than involvement of 2nd or 3rd divisions of trigeminal nerve. Of the 1st division, frontal nerve is the most commonly involved branch. The virus travels via branches of ophthalmic division of trigeminal nerve to the skin, eye, and adenexae (**Fig. 6.17**).



Fig. 6.17 Herpes zoster ophthalmicus. Source: The diagnosis of binocular diplopia. In: Bioussé V, Newman N, ed. Neuro-ophthalmology illustrated. 3rd Edition. Thieme; 2019.

Pathology

There is prominent *vasculitis with granulomatous or lymphocytic infiltration*. Tissue damage caused by zoster infection is due to both inflammation and vasculitis-induced ischemia.

Clinical Features

Prodromal stage of HZO precedes the appearance of rashes (eruptive stage) and lasts 3 to 5 days. The disease starts with fever, malaise, and headache followed by neuralgic pain along the distribution of the 1st division of the trigeminal nerve.

Eruptive stage follows the prodromal stage and lasts for approximately 3 weeks. The vesicles appear on one side of the forehead of the scalp along the distribution of the ophthalmic division of the trigeminal nerve and does not cross the midline. The pain sometimes diminishes after the appearance of vesicles but may persist for months or years.

The skin of lid and affected area becomes red and edematous. The vesicles suppurate before they crust and leave behind pitted scars. Anesthesia of skin follows as the eruptions subside.

Postherpetic neuralgia is the pain that persists for months to years after the skin lesions (rashes) have healed.

Contact with nonimmune or immunosuppressed individuals should be avoided until the crusting is complete.

Ocular involvement: Ocular complications arise as the eruptions subside. The eye is frequently affected if the vesicles appear on the tip and the side of the nose due to *involvement of the nasociliary branch of the trigeminal nerve (Hutchinson sign)*. The eye involvement may rarely occur when disease affects maxillary nerve (2nd division of trigeminal nerve) (**Table 6.9**).

Table 6.9 Ocular manifestations in HZO

Structure involved	Ocular manifestation
• <i>Involvement of lid</i>	• Lid scarring may result in cicatricial entropion or ptosis.
• <i>Involvement of conjunctiva</i>	• Conjunctivitis is common. It can be follicular or necrotizing.
• <i>Involvement of sclera</i>	• Scleritis may become chronic and frequently recurrent, leading to staphyloma.
• <i>Involvement of cornea</i>	<ul style="list-style-type: none"> • Corneal involvement in acute phase can manifest as: <ul style="list-style-type: none"> ◇ Punctate epithelial keratitis. ◇ Dendritic lesions (<i>in contrast to HSV dendrites, these have tapered ends without terminal bulbs</i>). ◇ Nummular keratitis. ◇ Disciform keratitis. ◇ Sclerokeratitis. ◇ Kerato uveitis. • Chronic corneal lesions that follow HZO are: <ul style="list-style-type: none"> ◇ Mucous plaque keratitis. ◇ Neurotrophic keratitis. ◇ Exposure keratitis.
• <i>Involvement of uvea</i>	• Anterior uveitis is frequently associated with sector iris atrophy.
• <i>Involvement of trabecular meshwork</i>	• <i>Trabeculitis</i> may cause secondary glaucoma.
• Occlusive vasculitis	• It may cause ARN and anterior segment ischemia.
• <i>Involvement of optic nerves</i>	• Optic neuritis is rare and a late complication.
• <i>Involvement of motor nerves</i>	• HZO affecting 3rd, 4th, and 6th CN results in extraocular muscle palsy, while facial N (7th CN) involvement results in facial palsy (Bell's palsy).

Abbreviations: ARN, acute retinal necrosis; CN, cranial nerve; HSV, herpes simplex virus; HZO, herpes zoster ophthalmicus.

Treatment

A. Treatment of acute systemic herpes zoster.

1. Systemic antiviral agents: Oral Acyclovir – 800 mg five times daily $\times 7$ to 10 days and initiated within 72 hours of the onset of symptoms.

It accelerates healing of skin lesions. It reduces period of viral shedding, severity of acute pain, incidence of episcleritis, keratitis, and iritis. Other antivirals are oral Famciclovir 500 mg TDS $\times 7$ to 10 days **and** oral Valaciclovir 1000 mg TDS $\times 7$ to 10 days.

2. Systemic steroids are used in combination with antiviral agents. These are not only recommended to reduce acute pain but also used in the treatment of inflammatory complications of HZO such as severe scleritis, uveitis or orbital inflammation.
Dose: 60 mg/day and then reduced gradually.

B. Treatment of postherpetic neuralgia.

Nonsteroidal anti-inflammatory drugs (NSAIDS) are ineffective in postherpetic neuralgia. Initially, it is treated with:

Topical Lidocaine 5% gel (local anesthetic) or topical Capsaicin cream (depletes substance P). If it is ineffective, then the following drugs are given:

- Amitriptyline (a tricyclic antidepressant)—12.5 to 25 mg at night and increased gradually to 75 mg/day, or
- Carbamazepine 400 mg daily to reduce pain.

C. Local ocular treatment of HZO.

For cutaneous lesions, antibiotic–corticosteroid skin ointment is applied on skin and lids. **Calamine lotion is better avoided** as it promotes crust formation. In the eye itself:

- Topical antivirals are not effective.
- Topical antibiotics are instilled to prevent secondary bacterial infection in acute stage of disease.

- Topical steroids and antiviral eye ointment are given if there is scleritis, sclerokeratitis, or iridocyclitis to reduce inflammation. Steroids are tapered gradually.
- Major complication of HZO, neurotrophic ulceration, is treated with bandage contact lens, tarsorrhaphy (OP4.7), and cyanoacrylate glue/penetrating keratoplasty (in case of corneal perforation).

Parasitic Keratitis

Acanthamoeba Keratitis

It is caused by *Acanthamoeba* (a protozoan) found in soil and water environments such as ponds, swimming pools, contact lens solutions, and tap water.

Source of infection

- Contact lens solutions are the usual source of infection. Once contact lens is contaminated, risk of infection is established, since the organism can adhere to and penetrate an intact epithelium.
- Swimming or bathing in contaminated water may be the source in noncontact lens wearers.

Acanthamoeba exists in dormant cystic form and active trophozoite form. Trophozoite produces a variety of enzymes and binds to corneal epithelium, resulting in thinning and necrosis of corneal epithelium. Early infection can be confined to the epithelium, but in advanced cases, the organism can enter the stroma and anterior chamber.

Clinical Features

Symptoms of *acanthamoeba keratitis* include severe ocular pain, blurred vision, photophobia, and lacrimation.

Clinical signs of *acanthamoeba keratitis* include the following:

- Early infection is confined to the epithelium which shows irregular surface as well as infiltrates and pseudodendrites mimicking

H simplex keratitis. The epithelium is intact initially and later breaks down.

- Deep linear stromal infiltrates might be seen around corneal nerves (radial keratoneuritis) and are pathognomonic.
- The infiltrates coalesce to form a ring abscess in stroma and resemble stromal herpetic disease. Scleritis may develop. In spite of severe inflammation, corneal vascularization is typically absent.
- Corneal melting may occur at the periphery of the area of infiltrates. Satellite lesions can appear. Anterior chamber inflammation can cause anterior uveitis and hypopyon.

Differential Diagnosis

This condition should be differentiated from herpetic keratitis and fungal keratitis. Patients with acanthamoeba keratitis are younger than patients with bacterial keratitis or fungal keratitis, and have a longer duration of symptoms before being treated. In terms of clinical signs, acanthamoeba keratitis is more likely to have disease confined to the epithelium and ring infiltrate.

Diagnosis

- *Staining of corneal scrapings* with calcofluor white stain. It is a fluorescent dye with an affinity for amoebic cysts which demonstrates the walls of the cysts but requires a fluorescent microscope.
- Polymerase chain reaction (PCR) to detect acanthamoebic DNA.

Nonsuppurative keratitis in a contact lens wearer is a high-index of suspicion, and treatment should be as for acanthamoeba infection.

Treatment

It includes the following considerations: Debridement to remove infected epithelium for early disease. Topical anti-amoebics which include:

- **Cationic antiseptics** (inhibit membrane function) include Chlorhexidine and PHMB (polyhexamethylene biguanide).

- **Azoles** (destabilize cell walls) include Clotrimazole, Fluconazole, Ketoconazole, and Miconazole.
- **Aminoglycosides** (disrupt plasmalemma of organism) include Neomycin and Paromomycin.
- **Aromatic diamidines** (inhibit DNA synthesis) include Propamidine isethionate, Hexamidine, and Pentamidine.

Topical amoebicides are given as dual therapy (diamidines + cationic antiseptics) with:

- Propamidine isethionate + PHMB drops

or

Hexamidine + Chlorhexidine

Topical neomycin and miconazole are quite effective. The diseases may require a prolonged treatment for several months. Since cysts are difficult to eradicate, stromal relapses are common, as treatment is tapered.

- Topical steroids should be avoided, if possible.
- Persistent corneal inflammation occurs due to necrotic protozoa (acanthamoeba antigen) rather than viable organism and may result in scarring and impaired vision. PKP is needed for residual scarring.

■ Noninfectious Keratitis

Interstitial Keratitis (IK)

It is an inflammation of the corneal stroma without primary involvement of epithelium or endothelium.

Etiology

It is most often associated with congenital syphilis but may also be seen in acquired syphilis, tuberculosis, leprosy, and viral infections (**Table 6.10**). **Cogan's syndrome** (IK and deafness) is a rare cause affecting both eye and ear.

IK due to congenital syphilis occurs via *transplacental route*, usually *bilateral*, and affects children between the ages of *5 and 25 years*.

In IK, the uveal tract is almost always affected. The disease is fundamentally uveitis and keratitis is secondary. **Keratitis is the result of immune-mediated reaction.** *Treponema pallidum* is not seen in cornea even during the acute phase.

Course of the Disease

It is divided into three stages: Progressive, florid, and regressive stages.

Progressive Stage

The cellular infiltration in deeper layers of cornea (just anterior to Descemet's membrane) occurs after anterior uveitis with ciliary congestion. The stromal cloudiness involves the whole cornea, giving it a ground glass appearance in 2 to 4 weeks. Anterior uveitis may be obscured by corneal clouding.

Florid Stage

In this stage, deep vascularization of stroma occurs. The vascular growth begins at the limbus and grows in a brush-like manner. Since these vessels are covered by hazy cornea, vessels look dull reddish pink, resulting in a characteristic **salmon patch**. There is superficial vascularization but it never extends far over the cornea. Conjunctiva may heap up at the limbus.

Regressive Stage

In this stage, stromal vessel become nonperfused and remain as fine opaque lines (empty or ghost vessels), which indicates the previous occurrence of the disease. The cornea clears slowly from periphery toward center. If cornea does not clear within 18 months, visual prognosis is poor.

Clinical Features

Symptoms include pain, blurring of vision, photophobia, and watering of eyes.

Following are the clinical signs of IK:

- Signs in *progressive stage*: Keratic precipitates, ciliary congestion, and ground glass appearance of cornea with stromal edema.
- Sign in *florid stage*: Deep vascularization with salmon patch.
- Sign in *regressive stage*: Ghost vessels. Since infiltration of cornea is almost limited to deeper layers, ulceration of corneal surface is rare.

Diagnosis

It depends on:

- Other evidences of congenital syphilis include:
 - ◇ Frontal eminence.
 - ◇ Flat nasal bridge.
 - ◇ Hutchinson's teeth (notching of two upper central incisors in permanent dentition).
 - ◇ Vestibular deafness.
 - ◇ Rhagades at the angles of the mouth.
- **Hutchinson's triad** includes IK, Hutchinson's teeth, and vestibular deafness. Coagan's syndrome include non syphilitic IK and deafness.
- **Serological tests**: All patients with IK should have treponemal serology including rapid reagin test, FTA-ABS (fluorescent treponemal antibody absorption) test, **and** venereal disease research laboratory (VDRL) test.

Table 6.10 Differentiating features of syphilitic and tubercular IK

	Syphilitic IK	Tubercular IK
Laterality	Usually bilateral	Usually unilateral
Involvement	Involves whole cornea	Frequently sectorial involving lower sector of cornea
Treatment (Systemic)	Antisyphilitic	Antitubercular
(Topical treatment is same in both)		

Abbreviation: IK, interstitial keratitis.

Treatment

Active IK is dealt with the help of:

- Systemic treatment with penicillin and systemic steroids tapered gradually.
- Topical treatment with topical steroids (as IK is a hypersensitivity reaction), and cycloplegics for uveitis.
- Lubricating eye drops.
- PKP in cases with dense corneal opacity.

Immunologically Mediated Keratitis

Immunologically mediated keratitis includes the following:

- Keratitis secondary to conjunctival diseases, for example, phlyctenular keratitis and vernal keratitis.
- Marginal ulcer (catarrhal ulcer).
- Mooren's ulcer.
- Keratitis associated with collagen vascular disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), polyarteritis nodosa, and Wegener's granulomatosis.

Phlyctenular Keratitis

Cornea is often involved in phlyctenular keratoconjunctivitis, which is essentially a conjunctival disease.

Phlyctens are commonly found at the limbus but may occur within the corneal margin (*corneal phlycten*).

Etiology

It is thought to be delayed hypersensitivity (Type IV and cell-mediated) to an endogenous microbial antigen, mostly staphylococcal or tubercular.

Clinical Features

Symptoms include photophobia, lacrimation, blepharospasm, and pain. *Corneal phlyctens* cause much pain and photophobia.

Clinical signs of phlyctenular keratitis include:

- Phlycten appears as a gray nodule at the limbus, which is associated with superficial vascularization.

- A limbal phlycten may extend onto the cornea and appear as slightly raised above the corneal surface. The overlying epithelium breaks down and a triangular yellowish ulcer is formed with prominent vascularization known as **fascicular ulcer**.

As the disease is essentially conjunctival, so the epithelium and superficial layer of cornea are involved. The ulcer remains superficial and seldom perforates. A healed corneal phlycten leaves a triangular scar associated with superficial vascularization and thinning.

Treatment

Treatment includes use of topical steroids, topical antibiotics, and cycloplegics, in case of corneal involvement.

It is also essential to treat associated staphylococcal blepharitis.

Vernal Keratitis

Cornea can be involved in up to 50% of cases with vernal keratoconjunctivitis. It is more frequent in palpebral type of disease. Several types of corneal lesions may be produced such as:

- Punctate epithelial keratitis which begins as discrete micro erosions in the superior cornea (punctate epithelial erosions).
- Epithelial macro erosion due to continued epithelial loss.
- **Shield ulcer** (vernal ulcer): A vernal ulcer is noninfectious, horizontally oval, shallow, nonvascularized, and indolent ulcer of the superior cornea. It is associated with sub-epithelial scarring and mild corneal opacity. Chronic inflammation in the absence of ulcer may develop peripheral superficial vascularization, especially superior.

Treatment

- Punctate epithelial keratitis responds to usual treatment of vernal keratoconjunctivitis.
- For persistent epithelial defects with ulceration, amniotic membrane graft with lamellar keratoplasty is carried out to enhance reepithelialization.

Marginal Ulcer (Catarrhal Ulcer)

Marginal ulcer is a *superficial* ulcer situated *near the limbus* and frequently seen in *old people*.

Etiology

It is thought to be caused by immune reaction to exotoxins produced by *Staphylococcus aureus*. These ulcers may also be caused by *Moraxella* and *Haemophilus*. They are often associated with Staphylococcal blepharitis in which an immune reaction occurs in the toxins produced by staphylococcus. This antigen-antibody complex is deposited in the peripheral cornea with secondary lymphocytic infiltration.

Clinical Features

Symptoms include mild irritation, lacrimation, photophobia, and pain. The subepithelial marginal infiltrates, *separated from limbus by a clear zone of cornea*, are typically located at the point of contact of eyelids with cornea (i.e., at 4, 7, 10, and 2 o'clock positions). The infiltrates coalesce with the circumferential spread which is accompanied by the breakdown of overlying epithelium. The ulcer formed is *shallow* and frequently become *vascularized*. Resolution occurs but *recurrences are common* and ulcer runs a chronic indolent course (**Fig. 6.18, Table 6.11**). Differentiating features between marginal keratitis and bacterial keratitis can be remembered by the mnemonic, PEDAL.

Lesions are culture negative, but *S. aureus* can frequently be isolated from lid margins.

Treatment

Treatment includes topical antibiotic + steroid drops. Treatment of coexisting blepharitis is done to prevent recurrences.

Mooren's Ulcer

It is a rare peripheral ulcerative keratitis also known as **chronic serpiginous ulcer** or **rodent ulcer**.

Etiology

Its exact etiology is unknown but autoimmune mechanism appears to be involved. It can be triggered in genetically susceptible individuals by trauma.

It may be unilateral or bilateral and affects males more commonly than females. Unilateral involvement affects older patients, is slowly progressive and responds better to treatment; bilateral involvement affects younger patients and is more aggressive.

Clinical Features

Symptoms include severe pain, lacrimation, photophobia, and blurred vision due to irregular astigmatism.

It begins as gray infiltrates near the margin of the cornea which breakdown, forming peripheral ulcer. The ulcer spreads circumferentially and toward the center of the cornea. Typically, advancing edge of ulcer undermines the corneal epithelium and superficial stroma. The base of the ulcer soon becomes vascularized. Healing takes place behind the active margin of the ulcer, but the healed area remains thin, vascularized and opaque. It rarely perforates. Spontaneous perforation is rare; however, minor trauma may lead to perforation.

Differential Diagnosis

It includes the conditions that are characterized by peripheral corneal ulceration and/or melting. Patients with bilateral Mooren's ulcer must be investigated for collagen vascular disorders.

Treatment

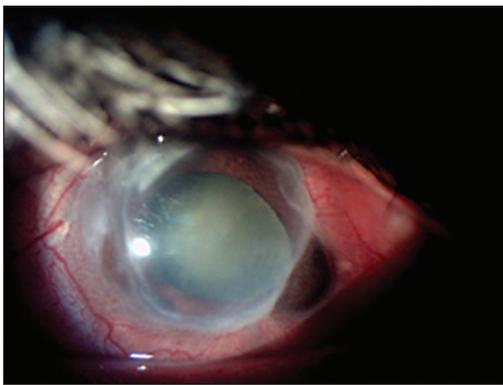
Treatment for Mooren's ulcer is difficult and disappointing as ischemia is the underlying cause.

Stepladder approach to manage this aggressive disease includes local, systemic, and surgical therapy.

- **Local treatment** includes: *Topical* treatment with corticosteroids, cyclosporine, and Acetylcysteine 10% (collagenase inhibitor). *Conjunctival resection* is done if inflammation is not controlled. It eliminates conjunctival sources of collagenase, proteoglycanase, and other inflammatory mediators.
- **Systemic treatment:** Systemic immunosuppression with cyclophosphamide, cyclosporine, steroids, or methotrexate may be

Table 6.11 Comparison between marginal and bacterial keratitis (i.e., distinction between noninfectious and suppurative infiltrates)

	Marginal keratitis	Bacterial keratitis
Pain	Less	More
Epithelial defect	Small or absent (<1 mm)	Present (>1 mm)
Discharge	Watery	Purulent
Anterior chamber reaction (uveitis)	–	+
Location	Peripheral	Central

**Fig. 6.18** Peripheral ulcerative keratitis (PUK).

initiated if the treatment with conjunctival resection fails.

- **Surgical treatment:** It includes lamellar keratoplasty and cyanoacrylate glue to treat small perforations.

Lamellar keratoplasty with systemic immunosuppression may reduce the risk of recurrence; without systemic immunosuppression, recurrence rate is high.

Conditions causing peripheral corneal ulceration and thinning:

- Marginal ulcer.
- Mooren's ulcer.
- Systemic collagen vascular disorders:
 - ◊ Rheumatoid arthritis.
 - ◊ Polyarteritis nodosa.
 - ◊ SLE.
 - ◊ Wegener's granulomatosis.
- Oculo-dermatologic conditions:
 - ◊ Rosacea keratitis.
- Corneal degenerations:
 - ◊ Terrien's marginal degeneration.
 - ◊ Pellucid marginal degeneration.

■ Miscellaneous Keratitis

Superficial Keratitis

It involves corneal epithelium, Bowman's membrane, and superficial corneal stroma. It is divided into:

- Superficial punctate keratitis (SPK).
- Superior limbic keratoconjunctivitis.
- Filamentary keratitis.
- Recurrent corneal erosions.
- Photophobia.

Superficial Punctate Keratitis (SPK)

It is characterized by multiple, punctate lesions in the superficial layers of the cornea (**Fig. 6.19**). It is caused by:

- **Viral infections:** Most common causes are: adenovirus, H-simplex, and H-zoster.
- **Chlamydial infections:** Trachoma and inclusion conjunctivitis.
- **Toxic:** It may be due to staphylococcal toxins in blepharoconjunctivitis.
- **Dry eye syndrome:** In KCS.
- **Idiopathic:** Thygeson's SPK.

Location

Location of lesions may serve as a clue to the etiology of SPK.

Superior location of SPK: The probable etiology may be vernal keratoconjunctivitis (VKC), superior limbic keratoconjunctivitis (SLK), and trachoma.

Inferior location: The probable etiology is Staphylococcal blepharitis, trichiasis, entropion, and lagophthalmos.

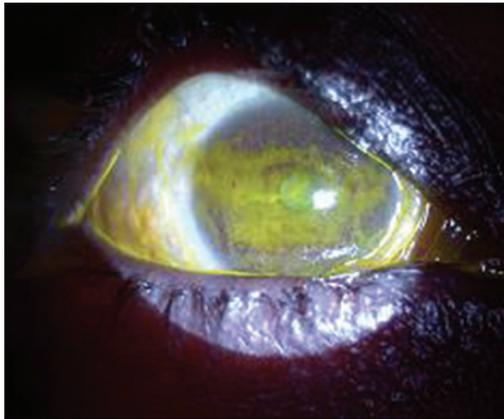


Fig. 6.19 Superficial punctate keratitis.

Interpalpebral location: The probable etiology is seborrheic blepharitis and KCS.

Clinical Features

Symptoms include mild ocular discomfort, photophobia, and lacrimation. It is characterized by punctate epithelial lesions which stain with Fluorescein dye. Subepithelial lesion may be present which do not stain with Fluorescein dye.

It is usually associated with conjunctivitis. One of the most characteristic features of Thygeson's SPK is lack of associated conjunctival inflammation (conjunctivitis). All other disease entities have associated conjunctivitis.

Treatment

It is treated with topical steroids with gradual tapering, lubricants, and treatment of cause.

Superior Limbic Keratoconjunctivitis (SLK)

As the name suggests, it is superior, limbic, corneal and conjunctival inflammation. It typically affects those belonging to the middle age group, with a greater affinity for females than males. It is usually bilateral. It is associated with abnormal thyroid dysfunction, usually hyperthyroidism. Its exact etiology is unknown. It appears to be the result of blink-related mechanical trauma which is supported by increased lid apposition of exophthalmic thyroid patients, who are known to have an increased incidence of SLK. SLK runs a

chronic course with remissions and exacerbations. *Thyroid function tests* should be performed due to strong association with thyroid disease.

Clinical Features

Symptoms include foreign body sensation, burning, irritation, redness, watering, and photophobia.

Characteristic signs are seen in cornea and conjunctiva:

- Conjunctiva: Hyperemia of superior bulbar conjunctiva and opposing superior tarsal (palpebral) conjunctiva with papillary reaction is marked.
- Cornea shows filamentary keratitis of the superior cornea and limbus.
 - ◇ SPK in the superior part of cornea which stains with Fluorescein and Rose Bengal.
 - ◇ Superior corneal pannus.
- KCS in 25 to 50% of cases.

Treatment

Treatment is symptomatic as the condition is usually self-limiting and include the following:

- Topical lubricants to reduce friction between lid and bulbar conjunctiva. Lubricant must be preservative-free.
- Topical steroids to reduce inflammation.
- Topical Acetyl Cysteine drops (10%) for filamentary keratitis.
- Topical retinoic acid to prevent keratinization.
- Punctal occlusion as 25 to 50% patients with SLK also have KCS (dry eyes).
- Soft contact lenses which intervene between lid and superior bulbar conjunctiva and may be useful.
- Resection of superior limbal conjunctiva and Tenon's capsule.

Filamentary Keratitis

It is a superficial keratitis associated with formation of corneal filaments.

Etiology

KCS is the most common cause. Other causes include recurrent corneal erosions, H. simplex

keratitis, prolonged eye patching, neurotropic keratitis, and SLK.

Clinical Features

Symptoms include irritation and foreign body sensation. Filaments consist of the core of mucous strands lined with epithelium. One end of the filament is attached to the corneal epithelium, while the other is unattached (free), moves with each blink, and causes foreign body sensation. They *stain well with Rose Bengal* (**Fig. 6.20**).

Treatment

Treatment includes the following:

- Mechanical removal of filaments.
- Hypertonic 5% saline drops to encourage adhesion of loose epithelium.
- A topical mucolytic agent such as Acetyl Cysteine (10%).
- Bandage contact lens.
- Treatment of underlying cause.
- Short-term topical steroids.

Recurrent Corneal Erosions

It is characterized by recurrent breakdown of epithelium. The basic cause is abnormalities in the underlying basement membrane microstructure. The condition may be associated with trauma, epithelial basement membrane or anterior stromal dystrophy, and diabetes.

Pathogenesis

Trauma or epithelial basement membrane dystrophy results in microscopic derangement in the epithelial basement membrane (such as thickening and discontinuity). It leads to abnormally weak attachment between basal cells of epithelium and basement membrane. Thus, epithelial layers are prone to separation and frequent erosions.

Minor injuries such as opening the eyes after sleep can cause shearing forces, resulting in tearing of epithelium.

Clinical Features

Symptoms often occur on wakening and include severe pain, blurring, photophobia, foreign body sensation, blepharospasm, and watering.

Characteristic Signs of recurrent corneal erosions include the following:

- Frank epithelial defects, particularly in the lower part of cornea.
- Signs of epithelial basement membrane dystrophy (intraepithelial microcysts and finger print lines) may be present in both eyes.

Typically, onset of corneal erosion occurs upon awakening in the morning, although it may occur at any time. Sleep causes relative anoxia, leading to edema of corneal epithelium. Vulnerable epithelium is easily rubbed off on sudden opening of eyelids upon awakening.

Treatment

Treatment includes the following:

- Lubricants: Eye drops during waking hours and gel or ointment at night.
- Therapeutic soft contact lenses (bandage contact lens).
- Topical antibiotics and cycloplegics.
- If erosions are severe or frequent, *excimer laser phototherapeutic keratectomy can be performed*.
- Anterior stromal micropunctures over and surrounding the erosions not involving the visual axis.

Photophthalmia

It is caused by exposure to ultraviolet (UV) rays in the range of 290 to 311 nm. UV damage to cornea is both wavelength- and intensity-dependent.

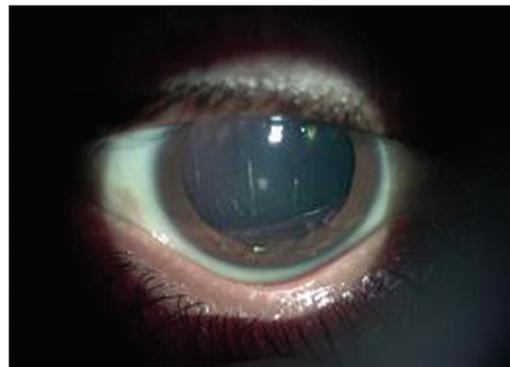


Fig. 6.20 Filamentary keratitis.

For short wavelength, a very small amount of UV energy may produce a corneal lesion. Nucleic acids of corneal epithelium maximally absorb these wavelengths. *Sources of UV rays* are welding flashes, germicidal lamps, and snow surface.

Most damaging range of wavelength is 260 to 290 nm but absorbed by ozone layer. So, radiation of these wavelengths rarely penetrates the Earth's surface.

Pathology

After 4 to 6 hours of exposure to UV rays damaged epithelial cells desquamate and multiple erosions result, which produces characteristics punctate Fluorescein staining (superficial punctate keratitis).

Symptoms

Symptoms include burning pain, lacrimation, photophobia, and blepharospasm.

Prophylaxis consists of wearing dark glasses made of crooks glass which cuts off nearly all infrared and UV rays.

Treatment

Treatment includes cold compression, lubricant drops, and bandaging both eyes for a day.

■ Trophic Keratitis

Neurotrophic Keratitis

Sensory innervation is vital for the health of corneal epithelium and stroma. Neurotrophic keratitis occurs in an anesthetic cornea, that is, it *results from damage to the trigeminal nerve* which supplies the cornea. Following are the causes of neurotrophic keratitis:

1. Damage to trigeminal nerve: It may occur due to surgery for trigeminal neuralgia, injection of alcohol in gasserian ganglion for trigeminal neuralgia, and tumors: acoustic neuroma and neurofibroma.
2. Ocular disease such as the following:
 - Herpes simplex keratitis.
 - Herpes zoster keratitis.

3. Systemic diseases such as diabetes (peripheral neuropathy may result in decreased corneal sensation) and leprosy.

Pathogenesis of neurotrophic keratitis is explained in **Flowchart 6.4**.

Clinical Features

Symptoms include red eye, **absence of pain**, decreased aqueous tear production, mild foreign body sensation, and blurred vision.

Following are the clinical signs of neurotrophic keratitis:

- Presence of ciliary congestion.
- Decreased corneal sensation.
- Persistent epithelial defects. The ulcer is typically found in the interpalpebral area, and the cornea appears dull. It is followed by stromal edema and melting (**Flowchart 6.5**).

Treatment

- Decreased aqueous tear production in neurotrophic keratitis is treated with:
- Topical lubricant eye drops (**preservative-free**).
- Punctal occlusion abolishes drainage of tears.
- Tarsorrhaphy to prevent drying and reduce exposure. It is a good alternative and kept for at least 1 year (OP4.7).
- Amniotic membrane transplantation.

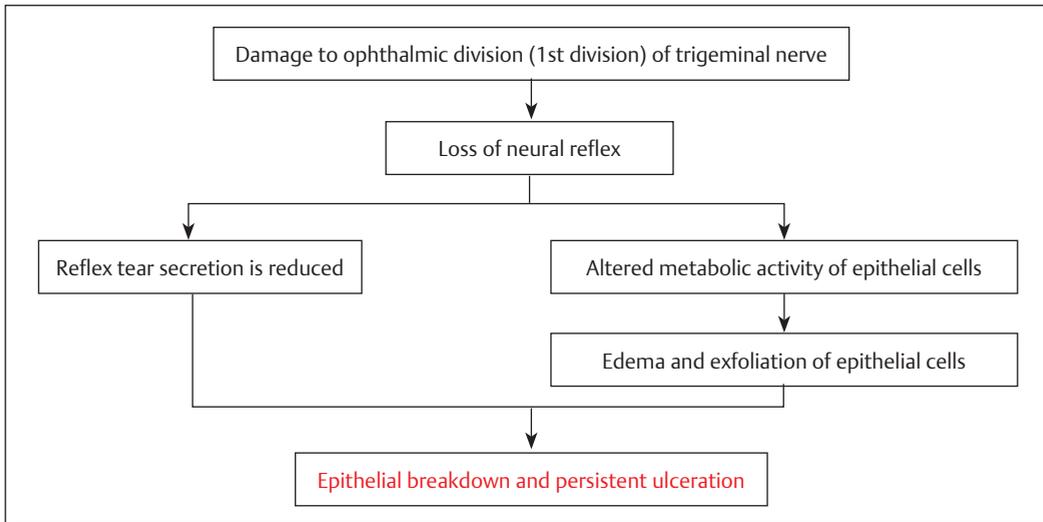
Exposure Keratitis

Lids resurface the cornea with the help of precorneal tear film at each blink and keep the cornea moist. Exposure keratitis is caused by improper wetting of corneal surface by precorneal tear film despite the presence of normal tear secretions.

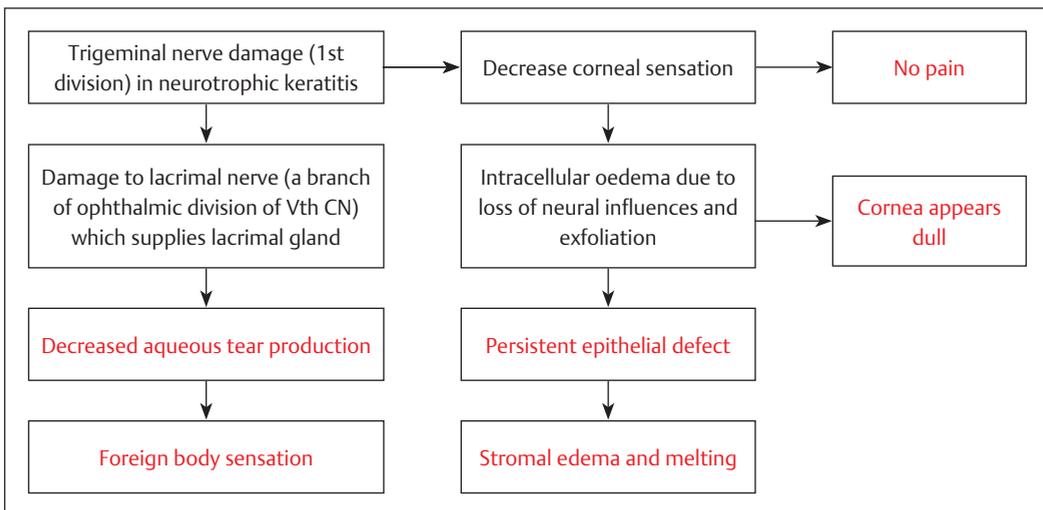
Etiology

It is caused by the conditions that lead to exposure of cornea, that is, due to incomplete closure of lids. Causes of exposure keratitis (**lagophthalmos**) are:

1. Facial nerve palsy (**neuromyolytic keratitis**): VIIth nerve palsy may be idiopathic or can follow surgery for



Flowchart 6.4 Pathogenesis of neurotrophic keratitis.



Flowchart 6.5 Clinical features in neurotrophic keratitis.

acoustic neuroma/parotid tumor. It results in the paralysis of orbicularis muscle and incomplete closure of lid.

2. Severe proptosis due to thyroid ophthalmopathy and orbital tumor.
3. Eyelid scarring associated with cicatricial pemphigoid, burns, and trauma.
4. Reduced muscle tone as in coma.

Occasionally corneal exposure during sleep may occur in normal healthy individuals if there is poor Bell's phenomenon.

Pathogenesis

Incomplete closure of lids results in desiccation of cornea. The epithelium is cast off, and invasion of cornea by infective organisms may occur.

Clinical Features

Because of lagophthalmos, cornea is exposed in lower part. So, initial desiccation occurs in the lower part of cornea, leading to inferior punctate epithelial keratitis followed by epithelial breakdown, stromal melting, infection, and even perforation (Fig. 6.21).

Treatment

- Tear substitutes (preservative-free lubricants) during day time.
- At night, application of eye ointment and closure of lids by tape or bandage.
- Treatment of the cause of exposure, but in the meantime, tarsorrhaphy may be required by suturing lids together (OP4.7).

Combined neurotrophic (Vth CN damage) and neuro-paralytic (VIIth CN palsy) keratitis is difficult to manage.

Nutritional Deficiency (Vitamin A Deficiency)

Ocular manifestations caused by vitamin A deficiency are referred to as **xerophthalmia**. **Cornea in vitamin A deficiency shows the following changes:**

1. Corneal xerosis: Earliest changes in cornea involve loss of corneal luster due to xerosis and bilateral punctate corneal epithelial erosions.
2. Keratomalacia: It reflects very severe vitamin A deficiency, often as early as the first year of life. Night blindness and conjunctival signs of vitamin A deficiency precede keratomalacia. The condition is usually bilateral. Bilateral melting of cornea is associated with conjunctival xerosis, and vitamin A deficiency is referred to as **keratomalacia**.

In *keratomalacia*, cornea becomes dull, insensitive, and hazy. The ulcer is formed with yellow infiltrates. Typically, it is devoid of usual inflammatory reaction and is a **characteristic**

feature. The lesion rapidly involves full-thickness of cornea. Finally, whole tissues undergo necrosis and melt away (corneal melting by liquefactive necrosis).

Treatment

Systemic treatment involves oral or IM administration of vitamin A. Locally, intense lubrication and topical antibiotics are advised.

Atheromatous Corneal Ulcer

It occurs in old leucoma undergoing degenerative changes or it may start after a minor trauma. It is readily vulnerable to infection, as cornea is devitalized and insensitive. It is treated with the usual treatment, conjunctival flap, or keratoplasty. The amniotic membrane transplantation may be effective for the treatment of deep ulceration.

■ Keratitis Associated with Skin Diseases

Rosacea Keratitis

Acne rosacea is a skin disease characterized by erythema of cheeks and nose in butterfly configuration, progressing to telangiectasia, hypertrophy of sebaceous glands, papules and pustules. Rosacea keratitis is usually associated with seborrheic blepharitis. It is generally seen among elderly women.

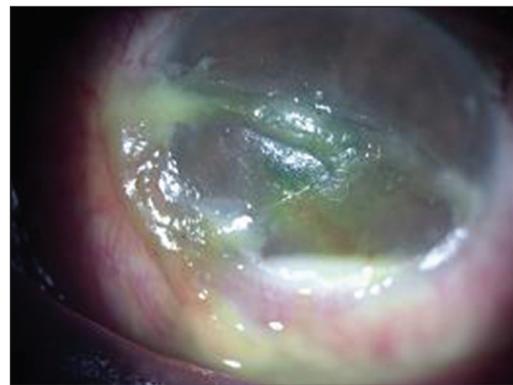


Fig. 6.21 Exposure keratitis.

Clinical Features

Symptoms include irritation, mild redness, and lacrimation.

Clinical signs of rosacea keratitis are:

- Seborrhic blepharitis and recurrent chalazia.
- Conjunctival vessels in the interpalpebral region are dilated.
- Yellowish-white infiltrates are seen in the cornea near the limbus which may ulcerate and then corneal vascularization takes place.
- Punctate epithelial keratopathy involving lower cornea.

Treatment

Local treatment: Topical *corticosteroids* as drops or ointment.

Systemic treatment: The essential treatment involves treating the skin condition with *systemic tetracycline* 250 mg 4 times daily for 3 weeks and then once daily for 6 months or *doxycycline* 100 mg twice daily for 3 weeks.

■ Corneal Degenerations (IM24.15)

There is marked distinction between degeneration and dystrophy. Degenerations are nonhereditary and usually unilateral, while dystrophies are hereditary and usually bilateral.

■ Etiology

Degenerations could arise due to age-related changes like arcus senilis, Vogt limbal girdles and Hassell–Henle bodies or pathological changes like lipid degenerations, amyloid degeneration, band keratopathy, Salzmann's nodular degeneration, Terrien's marginal degeneration, and spheroidal degeneration.

■ Classification

Corneal degenerations can be divided into:

- Primary degenerations.
- Secondary degenerations due to some compromising factors, for example,

trauma, chemicals, systemic diseases, or inflammation.

- Infiltration associated with lipid and mucopolysaccharide metabolisms.

■ Arcus Senilis (Gerontoxon)

It is a lipid infiltration of peripheral corneal stroma. It begins in the superior and inferior perilimbal cornea as a crescent and gradually progresses circumferentially to form a circle. It is approximately 1 mm wide and does not affect vision. It is seen among the elderly population. It has a diffuse central border and a sharper peripheral border. It is separated from limbus by a clear zone which is known as the lucid interval of Vogt.

Arcus juvenilis (anterior embryotoxon): If the arcus appears in young persons (below 40 years of age), it is known as arcus juvenilis. It may be associated with familial lipidemia.

■ Vogt Limbal Girdle

It is an age-related change characterized by bilateral, chalky white crescentic lines in the interpalpebral area along both nasal and temporal limbus.

■ Hassell–Henle Bodies

These are the excrescences of hyaline material present in peripheral Descemet's membrane and are part of normal aging process.

■ Terrien's Marginal Degeneration

It is an idiopathic, noninflammatory thinning of peripheral cornea. It is usually bilateral, but may be unilateral. It is more frequently seen in males. It is most frequent in middle-aged to elder persons.

Signs: It starts with fine yellow–white punctate stromal opacities and superficial vascularization, usually superiorly. The lesion spread circumferentially and separated from the limbus by a clear zone. Progressive circumferential thinning results in peripheral gutter. Astigmatism develops from associated corneal flattening which may

be irregular and results in visual deterioration. Usually, there is no pain or inflammation. Perforation may rarely occur following blunt trauma.

■ Band Shaped Keratopathy (Calcific Degeneration)

Band keratopathy is characterized by deposition of calcium salts in the subepithelial layers (Bowman's layer, epithelial basement membrane, and anterior stroma) of the cornea. Calcium is deposited as hydroxyapatite salt.

Etiology

1. Ocular causes: It occurs in eyes with chronic diseases, particularly chronic uveitis, glaucoma, chronic keratitis, Pthisis bulbi, and silicone oil in anterior chamber, that is, in aphakic eyes which have undergone vitrectomy with silicone oil.
2. Increased serum calcium or phosphate.
3. Systemic associations like sarcoidosis, hyperparathyroidism, vitamin D toxicity, and metastatic neoplasms to bone. All these conditions are associated with elevated serum calcium.

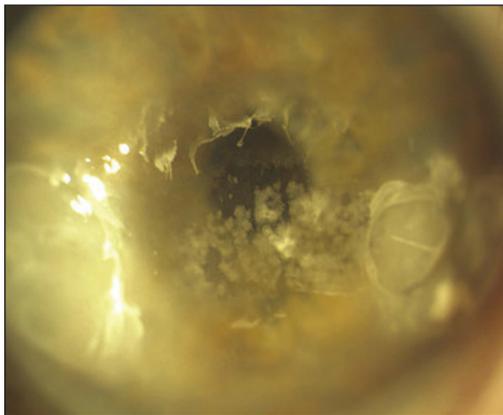


Fig. 6.22 Band-shaped keratopathy. Source: Band-shaped keratopathy. In: Gulani A, ed. *The art of pterygium surgery: mastering techniques and optimizing results*. 1st Edition. Thieme; 2019.

4. Juvenile rheumatoid arthritis (Still's disease): Chronic uveitis in Still's disease causes band-shaped keratopathy.
5. Chronic renal failure (CRF).

Clinical Features

Calcium is deposited as a horizontal band in the interpalpebral area of the cornea. Calcification starts near the corneal periphery which is separated from the limbus by a clear zone of cornea as in so many degenerative conditions, probably owing to better nutrition close to blood vessels. Calcium deposition gradually progresses toward the center to form a band-like chalky plaque (**Fig. 6.22**). The calcium plaque contains clear holes where Bowman's membrane is traversed by nerve endings and the surface of this opaque band appears stippled. Epithelium usually remains intact as deposition is beneath it.

Treatment

It is indicated if the vision decreases or persistent discomfort occurs. Central deposits may be removed by:

- **Chelation**—It involves removal of epithelium over deposits followed by application of 0.01 molar solution of **EDTA** (ethylene diamine tetra acetic acid), which is a chelator of calcium. It removes most of the deposited calcium. Pad and bandage for reepithelialization is taken care of.
- Treat any underlying systemic conditions or persistent uveitis to prevent recurrences.
- **PTK** with excimer laser to remove band keratopathy.
- Lamellar keratoplasty may be performed.

■ Spheroidal Degeneration (Climatic Droplet Keratopathy)

It is also called oil droplet keratopathy or actinic droplet keratopathy.

Etiology

It is thought to be a result of UV light exposure and occurs most often in men who work outdoor in

the sun and in areas that have sunlight reflection off snow or sand.

Clinical Features

It is always bilateral and characterized by the presence of subepithelial, golden or yellow, fine droplets in the interpalpebral area of peripheral cornea and advance toward the center. Droplets appear oily although they are not of lipid origin. These globules are made up of a protein material with elastotic features. As the condition advances, droplets become larger and form large corneal nodules with elevated corneal epithelium.

Treatment

Majority of cases are asymptomatic. In cases with central lesions affecting vision, PTK with excimer laser or lamellar keratoplasty can be carried out.

■ Salzmann Nodular Degeneration

Etiology

It occurs in persons with previous chronic keratitis, particularly associated with trachoma, phlyctenular keratitis, vernal keratitis and IK.

It is characterized by bluish-white, avascular nodules in superficial stroma and Bowman's membrane that elevate the epithelium and may be associated with recurrent corneal erosions. The base of the nodule may be outlined by epithelial iron deposits.

Treatment

Most of the cases are asymptomatic and require no treatment. If nodules encroach the central cornea, affecting vision, PTK with excimer laser or lamellar keratoplasty can be done.

■ Corneal Dystrophies (OP4.5)

Corneal dystrophies are a group of opacifying disorders of cornea which are progressive, bilateral, symmetrical, hereditary, non inflammatory and nonvascularized. *All corneal dystrophies are*

autosomal dominant except macular dystrophy which has autosomal recessive inheritance.

■ Classification

On the basis of corneal layer primarily involved, corneal dystrophies are classified into (**Fig. 6.23**).

- Epithelial dystrophies:
 - ◇ Epithelial basement membrane dystrophy.
 - ◇ Meesmann dystrophy.
- Bowman layer dystrophies:
 - ◇ Reis-Buckler dystrophy.
 - ◇ Thiel-Behnke dystrophy.
- Stromal dystrophies:
 - ◇ Lattice dystrophy.
 - ◇ Granular dystrophy.
 - ◇ Macular dystrophy.
 - ◇ Gelatinous drop-like dystrophy.
- Endothelial dystrophies:
 - ◇ Fuch's endothelial dystrophy.
 - ◇ Posterior polymorphous dystrophy.
 - ◇ Congenital hereditary endothelial dystrophy.

Epithelial Dystrophies

Epithelial dystrophies include:

- Epithelial basement membrane dystrophy (*Cogan's microcystic dystrophy* or *map-dot-fingerprint dystrophy*).
- Meesmann's dystrophy (juvenile epithelial dystrophy).

Epithelial Basement Membrane Dystrophy

Onset: In the second decade, the condition is asymptomatic. In a few patients, recurrent corneal erosions develop in the third decade.

Clinical features: It is characterized by bilateral, intraepithelial lesions which are best visualized by retroillumination. The pattern of lesions may be: dot-like opacities, epithelial microcysts, fingerprint-like lines or map-like gray patches. Simultaneous bilateral recurrent corneal erosions suggest epithelial basement membrane dystrophy.

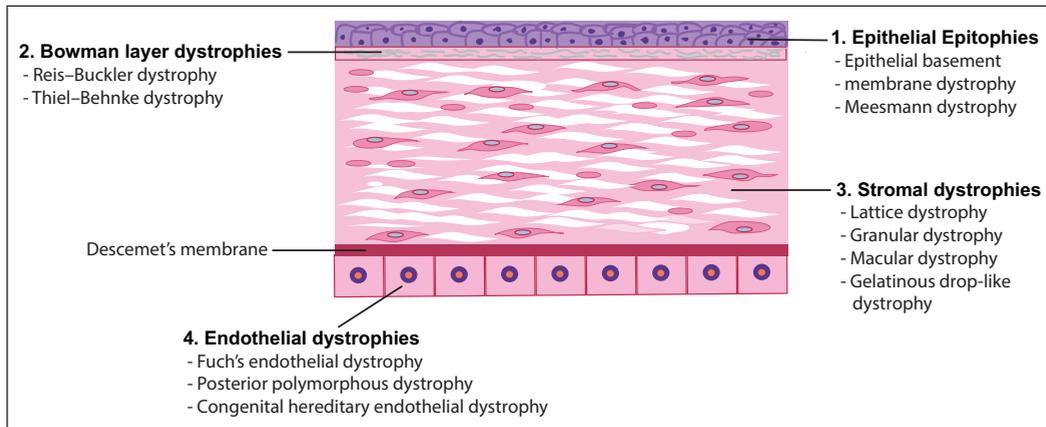


Fig. 6.23 Classification of corneal dystrophies.

Histology: It shows thickening of basement membrane and deposition of fibrillar material between basement membrane and Bowman's membrane.

Meesmann's Dystrophy (Juvenile Epithelial Dystrophy)

Onset: It is in the first 2 years of life, and has autosomal dominant inheritance.

Clinical features: It is characterized by multiple, tiny intraepithelial vesicles which are maximum centrally. The patient remains asymptomatic until middle age, then vesicles break through the anterior epithelial surface and cause intermittent irritation and decrease in visual acuity. Corneal sensations are reduced.

Bowman Layer Dystrophies

These include:

- **Reis-Buckler dystrophy** (corneal dystrophy of Bowman's layer type I or granular corneal dystrophy).
- **Thiel-Behnke dystrophy** (Honey comb dystrophy or corneal dystrophy of Bowman's membrane Type II).

Characteristics of both types of Bowman layer dystrophies:

Inheritance: Autosomal dominant.

Clinical features: These are characterized by gray-white, round opacities in the central cornea. Over time, these result in a reticular pattern in the Reis-Buckler dystrophy and assume a honeycomb pattern in the Thiel-Behnke dystrophy. Patients have recurrent corneal erosions which are painful initially. Later, the pain diminishes, as corneal sensitivity decreases. Vision is impaired due to fibrosis at Bowman's layer.

Histology: It shows destruction of Bowman's membrane and fibrous tissue, replacing Bowman's layer in both dystrophies.

Treatment: Symptomatic for **recurrent erosions**. Excimer laser keratectomy for visual disturbance. Lamellar keratoplasty is associated with relatively rapid recurrence of dystrophy on the graft and penetrating keratoplasty (PKP) may become necessary in both dystrophies.

Stromal Corneal Dystrophies

- These include: Granular corneal dystrophy.
- Macular corneal dystrophy.
- Lattice corneal dystrophy.
- Schnyder crystalline dystrophy.

Granular Dystrophy

Inheritance: Autosomal dominant.

Onset: In first decade of life.

Clinical features: Opacities are dense, white and granular in the anterior stroma of central cornea, sparing the peripheral cornea. The intervening cornea between the opacities also remains clear (Fig. 6.24).

Histopathology: The opacities are formed due to the hyaline degeneration of collagenous protein and stain with Masson trichrome.

Effect on vision: Glare is present but the vision is good. The opacities coalesce into various irregular shapes and vision is impaired.

Treatment: PKP is usually required by the fifth decade.

Macular Dystrophy

Inheritance: Autosomal recessive.

Onset: In the first decade of life (6–9 years).

Clinical features: Opacities assume a discrete granular form in the central cornea which spreads to the periphery. There is no clear space between the opacities.

Histopathology: The opacities are composed of glycosaminoglycans (GAG) and stain with alcian blue.

Effect on vision: Vision is affected at an early age.



Fig. 6.24 Granular dystrophy. Source: Corneal disorders. In: Narang P, Trattler W, ed. Optimizing sub-optimal results following cataract surgery. 1st Edition. Thieme; 2018.

Treatment: Penetrating keratoplasty is indicated but recurrence in graft may occur.

Lattice Dystrophy

Inheritance: Autosomal dominant.

Onset: During the second decade.

Clinical features: It is characterized by presence of branched, crisscross lines along with punctate opacities in between.

Histopathology: Histopathology reveals that it is a form of amyloidosis, that is, amyloid is deposited in the corneal stroma and stain with Congo red.

Effect on vision: The crisscross lines form an irregular lattice work and cause impairment of visual acuity.

Treatment: PKP is the treatment of choice when acuity decreases significantly.

Schnyder Crystalline Dystrophy

It is a disorder of corneal lipid metabolism associated with systemic hypercholesterolemia (raised serum cholesterol).

Inheritance: Autosomal dominant.

Features: It is caused by central subepithelial corneal crystals, often in a ring pattern, initially in the first decade of life. With advancing age, central corneal haze becomes evident.

Histology: Shows accumulation of cholesterol and phospholipids throughout stroma.

Treatment: Excimer laser keratectomy is advised.

Endothelial Corneal Dystrophies

- These include: Fuch's endothelial dystrophy.
- Posterior polymorphous dystrophy.

Fuch's Endothelial Dystrophy

It is bilateral and associated with increased incidence of primary open-angle glaucoma.

Inheritance: It is autosomal dominant.

Age: It occurs after 50 years.

Sex: It is more common in females.

Stagings: It is characterized by progressive loss of corneal endothelial cells, resulting in reduced vision, and the severity of disease varies as follows (**Flowchart 6.6**):

Stage 1: Earliest finding in Fuch’s dystrophy is the presence of excrescences (irregular warts) of Descemet’s membrane called guttae in the central corneal endothelium (**corneal guttata**) which involve the corneal periphery as well with time. The confluence of guttae produces a roughened surface with beaten metal appearance. Stroma and epithelium are uninvolved and patient’s vision is normal at this stage.

Stage 2: Disruption of normal endothelial mosaic takes place with endothelial dysfunction. It results in stromal edema which is significant upon awakening and clears later in the day due to evaporation. Stromal edema results in Descemet membrane’s folds with increase in corneal thickness.

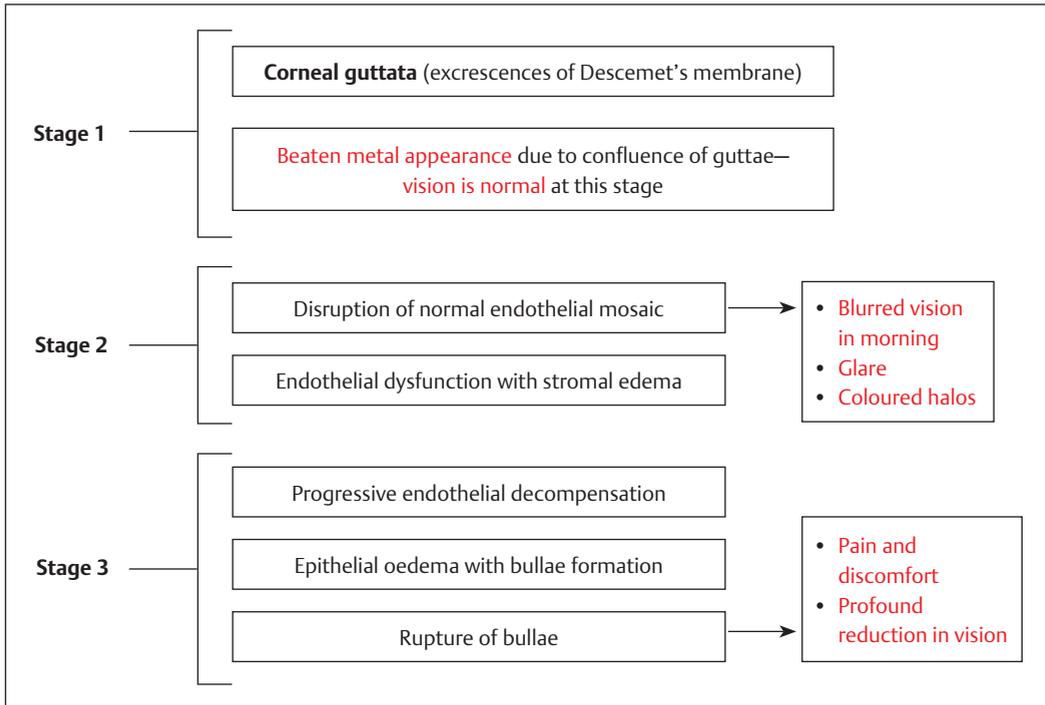
Patient complains of blurred vision in morning that improves during the day, Glare and colored halos around lights in the morning.

Stage 3: Due to progressive endothelial decompensation, epithelial edema with bullae formation takes place (**bullous keratopathy**). The periodic rupture of bullae causes:

- Pain and discomfort due to exposure of naked nerve endings, and eye is prone to secondary infection.
- Profound reduction in vision.

Diagnosis—It is diagnosed by:

- Specular microscopy: It is done for endothelial cell count (**Fig. 6.25**).
- Corneal pachymetry: It is done to document increased corneal thickness.
- Confocal microscopy: It is done to image endothelium in the presence of corneal edema (corneal opacification precludes specular microscopy).



Flowchart 6.6 Staging of Fuch’s endothelial dystrophy.

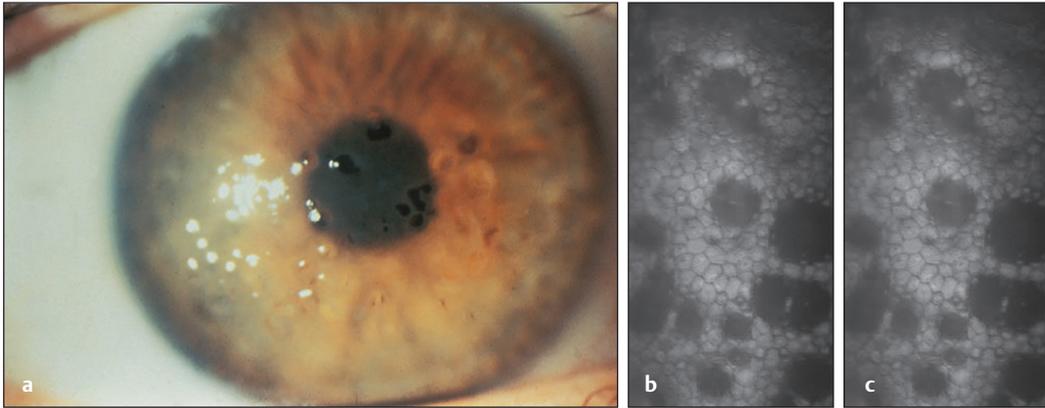


Fig. 6.25 Fuch's dystrophy. **(a)** On slit lamp. Source: History. In: Singh K, Smiddy W, Lee A, ed. Ophthalmology review: a case-study approach. 2nd Edition. Thieme; 2018. **(b)** Moderate type. **(c)** Advanced type with endotheliopathy (on specular biomicroscopy). Source: Specular microscopy and pachymetry. In: Narang P, Trattler W, ed. Optimizing suboptimal results following cataract surgery. 1st Edition. Thieme; 2018.

Differential diagnosis—It includes:

- Posterior polymorphous dystrophy.
- Congenital hereditary endothelial dystrophy.
- Aphakic/pseudophakic bullous keratopathy (**Fig. 6.26**).
- Hassell–Henle bodies.

Treatment

- Topical Sodium Chloride as drops (5%) and ointment (6%).
- Lubricating eye drops.
- Bandage contact lenses to relieve pain caused by rupture of bullae.
- PKP.
- If IOP is >20 mm Hg, reduce it. Lowering of IOP may reduce the force that drives the fluid into stroma.

Cataract surgery and Fuch's endothelial dystrophy

Cataract surgery may accelerate endothelial cell loss. Extra precautions during intraocular surgery (such as intraoperative soft shell viscoelastics technique) should be taken to protect the endothelium from surgical trauma:

- In eye with corneal epithelial edema or corneal thickness >640 μm by pachymetry, consider triple procedure, that is, cataract surgery + IOL implantation + keratoplasty.
- If corneal thickness is <640 μm , good visual outcome is expected.

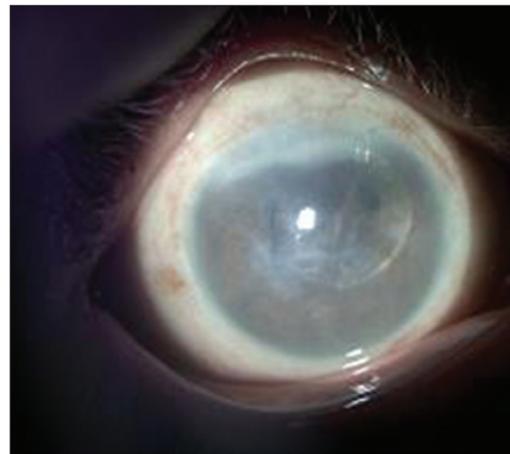


Fig. 6.26 Pseudophakic bullous keratopathy.

Posterior Polymorphous Dystrophy

Inheritance: Usually autosomal dominant.

Clinical features: It occurs early in life and is characterized by the presence of multilayered endothelium. The single cell layer of endothelium is transformed into a multilayered epithelium-like tissue. The posterior surface of cornea shows vesicular pattern, band-like lesions of diffuse opacities.

Treatment

It is usually asymptomatic and treatment is not required. Those with corneal opacification require PKP.

Ectatic Conditions of Cornea

Disorders of corneal shape include:

- Keratoconus.
- Keratoglobus.
- Pellucid marginal degeneration.

Keratoconus (Conical Cornea) (OP4.5)

It is a progressive steepening of cornea secondary to stromal thinning whereby it assumes a conical shape. The apex of cone always being slightly below the center of cornea. It occurs around puberty with slow progression. It is usually bilateral but the patients have asymmetrical involvement.

Etiology

It is unknown but seems to be multifactorial. It may be:

- Due to congenital weakness of the cornea.
- Secondary to trauma.
- Associated with Down syndrome.
- Due to repeated rubbing of the eyes.

Clinical Features

Symptoms include progressive bulging of cornea which induces myopic astigmatism and subsequently becomes irregular. It causes marked visual impairment and the patient may complain of frequent changes in spectacle power and decreased tolerance to contact lens wear.

Ocular manifestations of keratoconus are limited to cornea and include:

- Conical protrusion of cornea with apex of cone slightly below the center of cornea (**Fig. 6.27a**).
- Bulging of lower eyelid by cone of cornea on down gaze (**Munson's sign**).
- With direct ophthalmoscope at 1 m distance, a ring of shadow concentric with

the margin of cone is seen in red reflex "oil droplet" reflex which alters its position on moving the ophthalmoscope (**Fig. 6.27b**).

- Retinoscopy shows irregular "scissor" reflex.
- A ring of iron deposition occurs in the epithelium at the base of cone (Fleischer ring). It is best seen with a cobalt-blue filter.
- Presence of vertical striae in deep stroma (Vogt striae) may be noticed. These deep stromal stress lines disappear with external pressure on the globe (**Fig. 6.27c**).
- Distortion of corneal reflex is best seen with Placido disc or corneal topography.
- When light beam is focused from the temporal side across the cornea, a conical reflection is seen on the nasal cornea (**Rizutti's sign**).

Sometimes, rupture in Descemet's membrane develops, which causes influx of aqueous into cornea (**acute hydrops**) and sudden stromal edema with opacification. It results in sudden impairment of visual acuity. Break usually heals within 6 to 10 weeks, corneal edema clears, and stromal scarring may develop.

Keratoconus can be graded by keratometry, as depicted in **Table 6.12**.

Associations

Systemic associations: Keratoconus may be associated with:

- Down's syndrome.
- Marfan's syndrome.
- Ehlers Danlos syndrome.
- Apert's syndrome.
- Atopy.

Ocular associations—These include:

- Vernal keratoconjunctivitis.
- Leber's congenital amaurosis.
- Retinopathy of prematurity.
- Fuch's dystrophy.
- Blue sclera.
- Aniridia.
- Ectopia lentis.

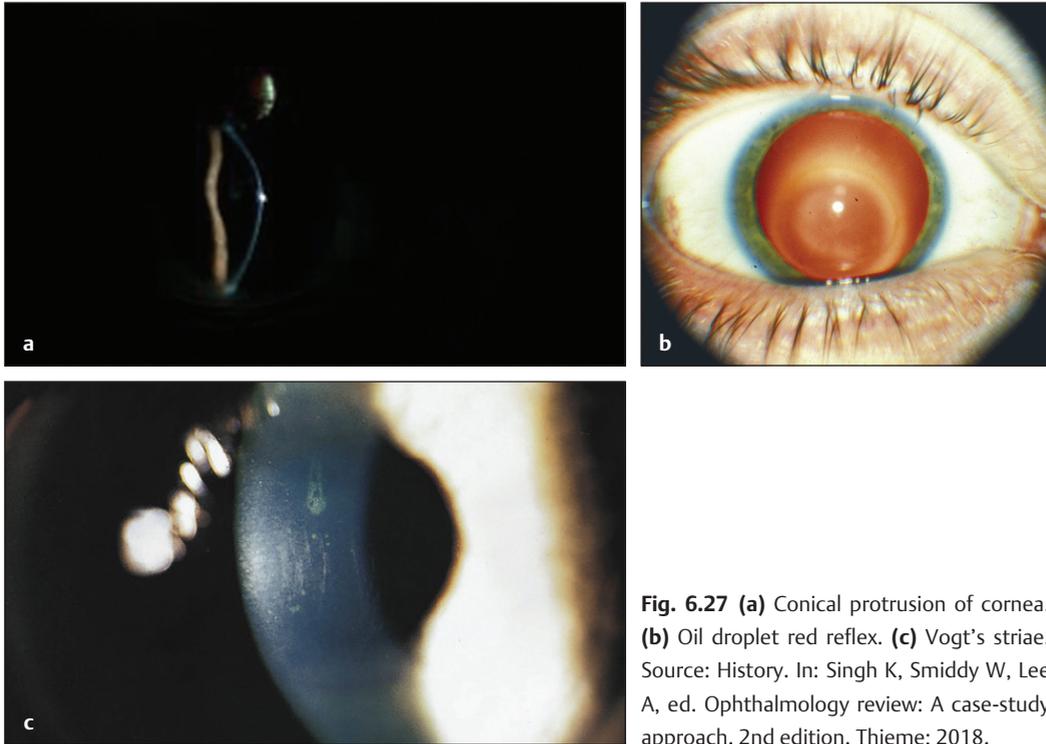


Fig. 6.27 (a) Conical protrusion of cornea. (b) Oil droplet red reflex. (c) Vogt's striae. Source: History. In: Singh K, Smiddy W, Lee A, ed. Ophthalmology review: A case-study approach. 2nd edition. Thieme; 2018.

Posterior keratoconus

In posterior keratoconus, the posterior corneal surface protrudes into the stroma. Frequently, scarring occurs in stroma, anterior to Descemet's bulge. It is congenital, nonprogressive, and usually unilateral.

Treatment

- Spectacles in early stages to correct refractive errors.
- Rigid gas permeable contact lenses to eliminate irregular corneal curvature. So, these are required to correct higher degree of astigmatism.
- Intracorneal rings in low to moderate keratoconus.
- **Corneal collagen cross linking (CCC)**: It is a new technique to arrest progression of keratoconus. In this procedure, corneal epithelial is removed and *riboflavin 0.1% eye drops* are instilled over cornea till cornea is adequately saturated, which is exposed to UV radiation. Riboflavin triggers increased

Table 6.12 Grading of keratoconus

Grade of keratoconus	Keratometry reading
Mild	< 48 D
Moderate	48–54 D
Severe	> 54 D

cross-linking of corneal collagen fibrils by formation of intrafibrillary and interfibrillar covalent bonds and stabilizes the corneal stroma. Bandage soft contact lenses are prescribed to permit the epithelium to heal.

- **Corneal transplantation (Keratoplasty)**: It is done if disease progresses despite all measures and in case of acute hydrops.

PKP or deep lamellar keratoplasty is currently becoming procedure of choice. It removes entire corneal stroma, sparing the host's Descemet membrane and endothelium. It reduces the risk of rejection and the donor cornea with low endothelial cell count can be used.

Table 6.13 Differentiating features between keratoglobus and buphthalmos

	Keratoglobus	Buphthalmos
Corneal transparency	Clear cornea	Hazy
IOP	Normal	Increased
Angle of anterior chamber	Normal	Angle anomaly present
Optic disc	No cupping	Cupping present

Abbreviation: IOP, intraocular pressure.

■ Keratoglobus

It is congenital, nonprogressive, and bilateral. It is inherited as an autosomal recessive trait. It is characterized by hemispherical (globular) corneal protrusion due to thinning of entire cornea (i.e., limbus-to-limbus corneal thinning). In contrast, keratoconus shows central stromal thinning. It may be associated with blue sclera and systemic connective tissue abnormalities. *Vogt striae and Fleischer's ring are absent*. It must be differentiated from buphthalmos (**Table 6.13**).

Corneal topography shows generalized steepening, and cornea is more prone to rupture on relatively mild trauma in keratoglobus. It is treated with scleral contact lenses because results of surgery are very poor.

■ Pellucid Marginal Degeneration

It is a progressive, bilateral peripheral corneal thinning typically affecting the inferior cornea (usually 4 to 8 o'clock positions).

The following clinical signs helps in diagnosing pellucid marginal degeneration:

- Area of thinning is 1 to 2 mm inside the inferior limbus and measures approximately 2 mm in width and 6 to 8 mm in horizontal extent (4–8 o'clock).
- Cornea above the crescent-shaped band of thinning protrudes with flattening in vertical meridian. Therefore, there is a marked against-the-rule astigmatism and reduced visual acuity.
- Epithelium is intact.
- Vogt striae (deep stromal stress lines) and Fleischer's ring do not occur.
- Acute hydrops is rare.
- **Corneal topography** shows a classical "butterfly" pattern.

Treatment

- Contact lenses are prescribed for correction of astigmatism. Spectacles usually fail due to increasing irregular astigmatism.
- Surgery includes:
 - ◇ Large eccentric penetrating keratoplasty.
 - ◇ Crescentic lamellar keratoplasty.
 - ◇ Thermocauterization.