## INTRODUCTION
168

Anatomy and physiology 168

Signs of corneal disease 169

Documentation of clinical signs 172

Specular microscopy 172

Corneal topography 173

Principles of treatment 173

### BACTERIAL KERATITIS
175

Pathogenesis 175

Clinical features 175

Investigations 176

Treatment 178

### FUNGAL KERATITIS
180

Introduction 180

Candidal and filamentous keratitis 181

Microsporidal keratitis 183

### HERPES SIMPLEX KERATITIS
183

Introduction 183

Epithelial keratitis 184

Disciform keratitis 186

Necrotizing stromal keratitis 187

Neurotrophic ulceration 188

Indoecytitis 188

Other considerations 188

### HERPES ZOSTER OPHTHALMICUS
189

Introduction 189

Acute shingles 191

Eye disease 191

Post-herpetic neuralgia 194

### INTERSTITIAL KERATITIS
194

Introduction 194

Syphilitic IK 194

Cogan syndrome 196

### PROTOZOAN KERATITIS
197

Acanthamoeba 197

### HELMINTHIC KERATITIS
199

Onchocerciasis 199

### BACTERIAL HYPERSENSITIVITY-MEDIATED CORNEAL DISEASE
199

Marginal keratitis 199

Phlyctenulosis 200

### ROSACEA
201

### PERIPHERAL CORNEAL ULCERATION/THINNING
202

Mooren ulcer 203

Peripheral ulcerative keratitis associated with systemic autoimmune disease 205

Terrien marginal degeneration 205

### NEUROTROPHIC KERATOPATHY
206

### EXPOSURE KERATOPATHY
207

### MISCELLANEOUS KERATOPATHIES
209

Infectious crystalline keratopathy 209

Thygeson superficial punctate keratitis 210

Filamentary keratopathy 210

Recurrent corneal epithelial erosion 211

Xerophthalmia 211

### CORNEAL ECTASIAS
213

Keratoconus 213

Pellucid marginal degeneration 214

Keratoglobus 216

### CORNEAL DYSTROPHIES
216

Epithelial dystrophies 216

Bowman layer/anterior stromal dystrophies 217

Stromal dystrophies 217

Descemet membrane and endothelial dystrophies 223

### CORNEAL DEGENERATIONS
225

Age-related degenerations 225

### METABOLIC KERATOPATHIES
230

Cystinosis 230

Mucopolysaccharidoses 230

Wilson disease 230

Lecithin-cholesterol-acyltransferase deficiency 230

Immunoprotein deposition 230

Tyrosinaemia type 2 230

Fabry disease 230

### CONTACT LENSES
232

Therapeutic uses 232

Complications 232

### CONGENITAL ANOMALIES OF THE CORNEA AND GLOBE
233

Microcornea 233

Microphthalmos 235

Anophthalmos 235

Nanophthalmos 235

Megalocornea 235

Sclerocornea 237

Cornea plana 237

Keratectasia 237

Posterior keratoconus 237
INTRODUCTION

Anatomy and physiology

General

The cornea is a complex structure which, as well as having a protective role, is responsible for about three-quarters of the optical power of the eye. The normal cornea is free of blood vessels; nutrients are supplied and metabolic products removed mainly via the aqueous humour posteriorly and the tears anteriorly. The cornea is the most densely innervated tissue in the body, and conditions such as abrasions and bullous keratopathy are associated with marked pain, photophobia and reflex lacrimation; a subepithelial and a deeper stromal nerve plexus are both supplied by the first division of the trigeminal nerve.

Dimensions

The average corneal diameter is 11.5 mm vertically and 12 mm horizontally. It is 540 µm thick centrally on average, and thicker towards the periphery. Central corneal thickness varies between individuals and is a key determinant of the intraocular pressure (IOP) measured with conventional techniques.

Structure

The cornea consists of the following layers (Fig. 6.1):

- **The epithelium** is stratified squamous and non-keratinized, and is composed of:
  - A single layer of columnar basal cells attached by hemidesmosomes to an underlying basement membrane.
  - Two to three strata of ‘wing’ cells.
  - Two layers of squamous surface cells.
  - The surface area of the outermost cells is increased by microplicae and microvilli that facilitate the attachment of the tear film and mucin. After a lifespan of a few days superficial cells are shed into the tear film.
  - Corneal stem cells are located at the corneoscleral limbus, possibly in the palisades of Vogt. Deficiency may result in chronic epithelial defects and ‘conjunctivalization’ (epithelial instability, vascularization and the appearance of goblet cells). They are thought to be critical in the maintenance of a physiological barrier, preventing conjunctival tissue from growing onto the cornea (e.g. pterygium). Deficiency may be addressed by stem cell auto- or allotransplantation.

- **The Bowman layer** is the acellular superficial layer of the stroma, and is formed from collagen fibres.

- **The stroma** makes up 90% of corneal thickness. It is arranged in regularly orientated layers of collagen fibrils whose spacing is maintained by proteoglycan ground substance (chondroitin sulphate and keratan sulphate) with interspersed modified fibroblasts (keratocytes). Maintenance of the regular arrangement and spacing of the collagen is critical to optical clarity. The stroma can scar, but cannot regenerate following damage.

- **Descemet membrane** is a discrete sheet composed of a fine lattice of collagen fibrils that are distinct from the collagen of the stroma. The membrane consists of an anterior banded zone that is deposited in utero and a posterior non-banded zone laid down throughout life by the endothelium, for which it serves as a modified basement membrane. It has regenerative potential.

- **The endothelium** consists of a monolayer of polygonal cells. Endothelial cells maintain corneal deturgescence throughout life by pumping excess fluid out of the stroma. The young adult cell density is about 3000 cells/mm². The number of cells decreases at about 0.6% per year and neighbouring cells enlarge to fill the space; the cells cannot regenerate. At a density of about 500 cells/mm² corneal oedema develops and transparency is impaired.

- The existence of a sixth corneal layer between the stroma and Descemet membrane has recently been proposed, though some authorities believe this to be a previously described continuation of the posterior stroma.

Fig. 6.1 Anatomy of the cornea
Signs of corneal disease

Superficial

- **Punctate epithelial erosions (PEE)**, tiny epithelial defects that stain with fluorescein (Figs 6.2A and B) and rose Bengal, are generally an early sign of epithelial compromise. Causes include a variety of stimuli; the location of the lesions may give an indication of aetiology:
  - Superior – vernal disease, chlamydial conjunctivitis, superior limbic keratoconjunctivitis, floppy eyelid syndrome and mechanically induced keratoconjunctivitis.
  - Interpalpebral – dry eye (can also be inferior), reduced corneal sensation and ultraviolet keratopathy.
  - Inferior – chronic blepharitis, lagophthalmos, eye drop toxicity, self-induced, aberrant eyelashes and entropion.
  - Diffuse – some cases of viral and bacterial conjunctivitis, and toxicity to drops.
  - Central – prolonged contact lens wear.

- **Punctate epithelial keratitis (PEK)** appears as granular, opalescent, swollen epithelial cells, with focal intraepithelial infiltrates (Fig. 6.2C). They are visible unstained but stain well with rose Bengal and variably with fluorescein. Causes include:
  - Infections: adenoviral, chlamydial, molluscum contagiosum, early herpes simplex and herpes zoster, microsporidial and systemic viral infections (e.g. measles, varicella, rubella).
  - Miscellaneous: Thygeson superficial punctate keratitis and eye drop toxicity.

- **Subepithelial infiltrates**. Tiny subsurface foci of non-staining inflammatory infiltrates. Causes include severe or prolonged adenoviral keratoconjunctivitis, herpes zoster keratitis, adult inclusion conjunctivitis, marginal keratitis, rosacea and Thygeson superficial punctate keratitis.

- **Superficial punctate keratitis** is a non-specific term describing any corneal epithelial disturbance of dot-like morphology.

Fig. 6.2 Superficial corneal lesions. (A) Punctate epithelial erosions stained with fluorescein in dry eye; (B) high-magnification view of punctate epithelial erosions; (C) punctate epithelial keratitis; (D) filaments stained with rose Bengal; Continued
Filaments. Strands of mucus admixed with epithelium, attached at one end to the corneal surface, that stain well with rose Bengal (Fig. 6.2D). The unattached end moves with each blink. Grey subepithelial opacities may be seen at the site of attachment. Dry eye is by far the most common cause; others include superior limbic keratoconjunctivitis, neurotrophic keratopathy, long-term ocular patching and essential blepharospasm.

• Epithelial oedema. Subtle oedema may manifest with loss of normal corneal lustre (Fig. 6.2E), but more commonly, abundant tiny epithelial vesicles are seen; bullae form in moderate–severe cases (Fig. 6.2F). The cause is endothelial decompensation, including that due to severe acute elevation of IOP.

• Superficial neovascularization (Fig. 6.2G) is a feature of chronic ocular surface irritation or hypoxia, as in contact lens wear.

Deep

• Infiltrates are yellow– or grey–white opacities located initially within the anterior stroma (Fig. 6.2A), usually associated with limbal or conjunctival hyperaemia. They are stromal foci of acute inflammation composed of inflammatory cells, cellular and extracellular debris including necrosis. The key distinction is between sterile and infective lesions (Table 6.1); ‘PEDAL’ mnemonic: Pain, Epithelial defects, Discharge, Anterior chamber reaction, Location. Suppurative keratitis is caused by active infection with bacteria, fungi, protozoa and occasionally viruses. Non-infectious ‘sterile keratitis’ is due to an immune hypersensitivity response to antigen as in marginal keratitis and with contact lens wear.

Pannus describes superficial neovascularization accompanied by degenerative subepithelial change (Fig. 6.2H).

Fig. 6.2, Continued (E) loss of lustre in mild corneal oedema; (F) corneal oedema with bullae; (G) superficial vascularization; (H) pannus
(Courtesy of Chris Barry – figs E and H)
**Fig. 6.3** Deeper corneal lesions. (A) Infiltration; (B) ulceration; (C) lipid deposition with vascularization; (D) folds in Descemet membrane; (E) descemetocoele; (F) traumatic breaks in Descemet membrane

(Courtesy of C Barry – figs C–D; R Curtis – fig. F)
Table 6.1 Characteristics of infective versus sterile corneal infiltrates

<table>
<thead>
<tr>
<th>Feature</th>
<th>Infective</th>
<th>Sterile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Tend to be larger</td>
<td>Tend to be smaller</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Epithelial defect</td>
<td>Very common when present</td>
<td>Much less common and if present tends to be small</td>
</tr>
<tr>
<td>Pain</td>
<td>Moderate–severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Discharge</td>
<td>Purulent</td>
<td>Mucopurulent</td>
</tr>
<tr>
<td>Single or multiple</td>
<td>Typically single</td>
<td>Commonly multiple</td>
</tr>
<tr>
<td>Unilateral or bilateral</td>
<td>Unilateral</td>
<td>Often bilateral</td>
</tr>
<tr>
<td>Anterior chamber reaction</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Location</td>
<td>Often central</td>
<td>Typically more peripheral</td>
</tr>
<tr>
<td>Adjacent corneal reaction</td>
<td>Extensive</td>
<td>Limited</td>
</tr>
</tbody>
</table>

- **Ulceration** refers to tissue excavation associated with an epithelial defect (Fig. 6.3B), usually with infiltration and necrosis.
- ‘Melting’ describes tissue disintegration in response to enzymatic activity, often with mild or no infiltrate, e.g. peripheral ulcerative keratitis.
- **Vascularization** occurs in response to a wide variety of stimuli. Venous channels are easily seen, whereas arterial feeding vessels are smaller and require higher magnification. Non-perfused deep vessels appear as ‘ghost vessels’, best detected by retroillumination.
- **Lipid** deposition (Fig. 6.3C) may follow chronic inflammation with leakage from corneal new vessels.
- **Folds in Descemet membrane**, also known as striate keratopathy (Fig. 6.3D), may result from corneal oedema exceeding the capacity of the endothelium to maintain normal turgescence. Causes include inflammation, trauma (including surgery) and ocular hypotony.
- **Descemetocoele** (US spelling – descemetocele) is a bubble-like herniation of Descemet membrane into the cornea (Fig. 6.3E), plugging a defect that would otherwise be full-thickness.
- **Breaks in Descemet membrane** (Fig. 6.3F) may be due to corneal enlargement (Haab striae in infantile glaucoma) or deformation such as keratoconus and birth trauma. Acute influx of aqueous into the corneal stroma (acute hydrops) can occur.
- **The Seidel test** demonstrates aqueous leakage. A drop of 1% or 2% fluorescein is applied and the slit lamp with cobalt blue filter is used to detect the change from dark orange to bright yellow–green occurring with localized dilution at a site of leakage.

**Documentation of clinical signs**

Clinical signs should be illustrated with a colour-coded labelled diagram; including lesion dimensions is particularly useful to facilitate monitoring (Fig. 6.4). Slit lamp photography is an increasingly used supplement or alternative, but must be of high quality.

- **Opacities** such as scars and degenerations are drawn in black.
- **Epithelial oedema** is represented by fine blue circles, stromal oedema as blue shading and folds in Descemet membrane as wavy blue lines.
- **Hypopyon** is shown in yellow.
- **Blood vessels** are added in red. Superficial vessels are wavy lines that begin outside the limbus and deep vessels are straight lines that begin at the limbus.
- **Pigmented lesions** such as iron lines and Krukenberg spindles are shown in brown.

**Specular microscopy**

Specular microscopy is the study of corneal layers under very high magnification (100 times greater than slit lamp biomicroscopy). It is mainly used to assess the endothelium, which can be analysed for cellular size, shape, density and distribution. The healthy endothelial cell is a regular hexagon (Fig. 6.5A) and the normal cell density in a young adult is about 3000 cells/mm².

- **Physics.** When a light beam of the specular photomicroscope passes through the cornea it encounters a series of interfaces between optically distinct regions. Some light is reflected specularly (i.e. like a mirror) back towards the photomicroscope and forms an image that can be photographed and analysed.
- **Indications**
  - Evaluation of the functional reserve of the corneal endothelium prior to intraocular surgery is the most common indication. A clear cornea with normal thickness on pachymetry is not necessarily associated with normal endothelial morphology or cell density.

![Fig. 6.4 Documentation of corneal lesions](image)
Cornea

**Fig. 6.5** Specularmicrograph. (A) Normal cornal endothelium; (B) cornea guttata with marked loss of endothelial mosaic

Corneal oedema is considerably more likely to occur with a cell density below 700 cells/mm² but unlikely above 1000 cells/mm².

- Donor cornea evaluation.
- To demonstrate pathology, particularly cornea guttata (Fig. 6.5B), Descemet membrane irregularities and posterior polymorphous dystrophy.

**Corneal topography**

Corneal topography is used to image the cornea by projecting a series of concentric rings of light on the anterior surface, constituting a Placido image. The reflected light is analysed using computer software to produce a detailed surface map. A major application is the detection and management of corneal ectasia, principally keratoconus; screening for corneal ectasia is especially important prior to refractive surgery. It is used in the management of refractive error, again in relation to refractive surgery as well as sometimes for contact lens fitting, and can be used to measure corneal thickness. Scheimpflug imaging is a newer technology that may offer advantages in topographic imaging. Anterior segment optical coherence tomography (OCT) and ultrasound biomicroscopy can also be used to image the cornea.

**Principles of treatment**

**Control of infection and inflammation**

- Antimicrobial agents should be started as soon as preliminary investigations have been performed. The choice of agent is determined by the likely aetiology according to clinical findings. Broad-spectrum treatment is generally used initially, with more selective agents introduced if necessary when the results of investigation are available.
- Topical steroids should always be used with caution as they may promote replication of some microorganisms, notably herpes simplex virus and fungi, and retard reparative processes such as re-epithelialization. Nevertheless, they are vital in a range of conditions for the suppression of destructive vision-compromising inflammation.
- Systemic immunosuppressive agents are useful in some conditions, particularly autoimmune disease.

**Promotion of epithelial healing**

Re-epithelialization is of great importance in any corneal disease, as thinning seldom progresses if the epithelium is intact.

- Reduction of exposure to toxic medications and preservatives wherever possible.
- Lubrication with artificial tears (unpreserved if possible) and ointment. Taping the lids closed temporarilly (Fig. 6.6A) is often used as a nocturnal adjunct.
- Antibiotic ointment prophylaxis should be considered.
- Bandage soft contact lenses should be carefully supervised to exclude superinfection, and duration kept to a minimum. Indications include:
  - Promotion of healing by mechanically protecting regenerating corneal epithelium from the constant rubbing of the eyelids.
  - To improve comfort, particularly in the presence of a large corneal abrasion.
  - To seal a small perforation (Fig. 6.6B).
- Surgical eyelid closure is particularly useful in exposure and neurotrophic keratopathies as well as in persistent epithelial defects. Lid closure may be used as a conservative method to heal an infective ulcer in selected cases, such as an eye with no visual potential in a patient with severe dementia.
  - Botulinum toxin injection into the levator muscle to induce a temporary (2–3 months) ptosis.
Methods of promoting epithelial healing. (A) Taping the lids temporarily; (B) bandage contact lens in an eye with a small perforation; (C) central tarsorrhaphy; (D) amniotic membrane graft over a persistent epithelial defect; (E) tissue glue under a bandage contact lens in an eye with severe thinning.

(Courtesy of S Tuft – figs A, B, D and E; S Chen – fig. C)
Common pathogens include:

- *Pseudomonas aeruginosa* is a ubiquitous Gram-negative bacillus (rod) commensal of the gastrointestinal tract. The infection is typically aggressive and is responsible for over 60% of contact lens-related keratitis.
- *Staphylococcus aureus* is a common Gram-positive coagulase-positive commensal of the nares, skin and conjunctiva. Keratitis tends to present with a focal and fairly well-defined white or yellow–white infiltrate.
- *Streptococci*. *S. pyogenes* is a common Gram-positive commensal of the throat and vagina. *S. pneumoniae* (pneumococcus) is a Gram-positive commensal of the upper respiratory tract. Infections with streptococci are often aggressive.

**Risk factors**

- **Contact lens wear**, particularly if extended, is the most important risk factor. Corneal epithelial compromise secondary to hypoxia and minor trauma is thought to be important, as is bacterial adherence to the lens surface. Wears of soft lenses are at higher risk than those of rigid gas permeable and other types. Infection is more likely if there is poor lens hygiene but it can also occur even with apparently meticulous lens care, and with daily disposable lenses.
- **Trauma**, including refractive surgery (particularly LASIK – laser-assisted in situ keratomileusis), has been linked to bacterial infection, including with atypical mycobacteria. In developing countries agricultural injury is the major risk factor, when fungal infection should be considered.
- **Ocular surface disease** such as herpetic keratitis, bullous keratopathy, dry eye, chronic blepharitis, trichiasis and entropion, exposure, severe allergic eye disease and corneal anaesthesia.
- **Other factors** include local or systemic immunosuppression, diabetes and vitamin A deficiency.

**Clinical features**

- **Presentation** is with pain, photophobia, blurred vision and mucopurulent or purulent discharge.
- **Signs**
  - An epithelial defect with infiltrate involving a larger area, and significant circumcorneal injection (Fig. 6.7A and B).
  - Stromal oedema, folds in Descemet membrane and anterior uveitis, commonly with a hypopyon (Fig. 6.7C) and posterior synechiae in moderate–severe keratitis.
  - Chemosis and eyelid swelling in moderate–severe cases.
  - Severe ulceration may lead to descemetocoele formation and perforation, particularly in *Pseudomonas* infection (Fig. 6.7D).
  - Scleritis can develop, particularly with severe perilimbal infection.
  - Endophthalmitis is rare in the absence of perforation.
  - Improvement is usually heralded by a reduction in eyelid oedema and chemosis, shrinking of the epithelial defect, decreasing infiltrate density and a reduction in anterior chamber signs.
  - Subsequent scarring may be severe, including vascularization; in addition to opacification irregular astigmatism may limit vision.
- **Reduced corneal sensation** may suggest associated neurotrophic keratopathy, particularly where there is no other major risk factor. Sensation may also be reduced in chronic surface disease, herpetic keratitis and long-term contact lens wear.
- **IOP** should be monitored.
Differential diagnosis includes keratitis due to other microorganisms (fungi, acanthamoeba, stromal herpes simplex keratitis and mycobacteria), marginal keratitis, sterile inflammatory corneal infiltrates associated with contact lens wear, peripheral ulcerative keratitis and toxic keratitis.

Investigations

- Corneal scraping. This may not be required for a small infiltrate, particularly one without an epithelial defect and away from the visual axis.
  - A non-preserved topical anaesthetic is instilled (preservatives may lower bacterial viability for culture); one drop of proxymetacaine 0.5% is usually sufficient; tetracaine may have a greater bacteriostatic effect.
  - Scrapings are taken either with a disposable scalpel blade (e.g. No. 11 or Bard Parker), the bent tip of a larger diameter (e.g. 20- or 21-gauge) hypodermic needle, or a sterile spatula (e.g. Kimura).
  - The easiest way to 'plate' scrapings without breaking the gel surface is with a spatula. If a fresh spatula is not available for each sample a single instrument should be flame-sterilized between scrapes (heat for 5 seconds, cool for 20–30 seconds). Alternatively, a fresh scalpel blade or needle can be used for each pass. Calcium alginate swabs may also be satisfactory.
  - Loose mucus and necrotic tissue should be removed from the surface of the ulcer prior to scraping.
  - The margins and base (except if very thin) of the lesion are scraped (Fig. 6.8A).
  - A thin smear is placed on one or two glass slides for microscopy, including Gram stain (see below). A surface is provided on one side of one end of the slide (conventionally ‘up’) for pencil labelling. The sample is
Conjunctival swabs may be worthwhile in addition to corneal scraping, particularly in severe cases, as occasionally an organism may be cultured when a corneal scrape is negative. Cotton wool, calcium alginate and synthetic swabs have all been found to have some bacteriostatic effect; calcium alginate may be the best option.

Contact lens cases, as well as bottles of solution and lenses themselves, should be obtained when possible and sent to the laboratory for culture. The case should not be cleaned by the patient first!

Gram staining
- Differentiates bacterial species into 'Gram-positive' and 'Gram-negative' based on the ability of the dye (crystal violet) to penetrate the cell wall.
- Bacteria that take up crystal violet are Gram-positive and those that allow the dye to wash off are Gram-negative.

Re-scraping is performed for each medium and samples are plated onto culture media (Table 6.2), taking care not to break the surface of the gel.

Routinely, blood, chocolate and Sabouraud media (Fig. 6.8B–D) are used initially and the samples are placed in an incubator until transported to the laboratory. Refrigerated media should be gently warmed to room temperature prior to sample application.

A blade or needle can be placed directly into bottled media such as brain–heart infusion (BHI). There is evidence that a single scrape, sent in BHI to the laboratory where it is homogenized and plated, provides similar results to the traditional multi-scrape method.

Scraping may be delayed without treatment for 12 hours if antibiotics have previously been commenced.

Fig. 6.8 Bacteriology. (A) Corneal scraping; (B) culture media; (C) S. aureus grown on blood agar forming golden colonies with a shiny surface; (D) N. gonorrhoeae grown on chocolate agar
(Courtesy of J Harry – fig. A; R Emond, P Welby and H Rowland, from Colour Atlas of Infectious Diseases, Mosby 2003 – figs B–D)
Bacterial Keratitis

Table 6.2 Culture media for corneal scrapings

<table>
<thead>
<tr>
<th>Medium</th>
<th>Notes</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood agar</td>
<td>5–10% sheep or horse blood</td>
<td>Most bacteria and fungi except <em>Neisseria, Haemophilus</em> and <em>Moraxella</em></td>
</tr>
<tr>
<td>Chocolate agar</td>
<td>Blood agar in which the cells have been lysed by heating. Does not contain chocolate!</td>
<td>Fastidious bacteria, particularly <em>H. influenzae, Neisseria</em> and <em>Moraxella</em></td>
</tr>
<tr>
<td>Sabouraud dextrose agar</td>
<td>Low pH and antibiotic (e.g. chloramphenicol) to deter bacterial growth</td>
<td>Fungi</td>
</tr>
<tr>
<td>Non-nutrient agar seeded with <em>Escherichia coli</em></td>
<td><em>E. coli</em> is a food source for <em>Acanthamoeba</em></td>
<td><em>Acanthamoeba</em></td>
</tr>
<tr>
<td>Brain–heart infusion</td>
<td>Rich lightly buffered medium providing a wide range of substrates</td>
<td>Difficult-to-culture organisms; particularly suitable for streptococci and meningococci. Supports yeast and fungal growth</td>
</tr>
<tr>
<td>Cooked meat broth</td>
<td>Developed during the First World War for the growth of battlefield anaerobes</td>
<td>Anaerobic (e.g.<em>Propionibacterium acnes</em>) as well as fastidious bacteria</td>
</tr>
<tr>
<td>Löwenstein–Jensen</td>
<td>Contains various nutrients together with bacterial growth inhibitors</td>
<td><em>Mycobacteria, Nocardia</em></td>
</tr>
</tbody>
</table>

- Other stains, generally not requested at initial investigation, are listed in Table 6.3.
- **Culture and sensitivity reports** should be obtained as soon as possible. The type of bacteria alone will generally provide an indication of the antibiotic category to be used. An indication of resistance on standard sensitivity testing does not necessarily extrapolate to topical antibiotic instillation, where very high tissue levels can be achieved.

**Treatment**

**General considerations**

- **Hospital admission** should be considered for patients who are not likely to comply or are unable to self-administer treatment. It should also be considered for aggressive disease, particularly if involving an only eye.
- **Discontinuation of contact lens wear** is mandatory.
- **A clear plastic eye shield** should be worn between eye drop instillation if significant thinning (or perforation) is present.
- **Decision to treat**
  - Intensive treatment may not be required for small infiltrates that are clinically sterile and may be treated by lower-frequency topical antibiotic and/or steroid, and by temporary cessation of contact lens wear.
  - It is important to note that the causative organism cannot be defined reliably from the ulcer’s appearance.
  - Empirical broad-spectrum treatment is usually initiated before microscopy results are available.

**Local therapy**

Topical therapy (Table 6.4) can achieve high tissue concentration and initially should consist of broad-spectrum antibiotics that cover most common pathogens. Initially instillation is at hourly intervals day and night for 24–48 hours, and then is tapered according to clinical progress.

- **Antibiotic monotherapy** has the major advantage over duotherapy of lower surface toxicity, as well as greater convenience.
  - A commercially available fluoroquinolone is the usual choice for empirical monotherapy and appears to be about as effective as duotherapy.
  - Ciprofloxacin or ofloxacin are used in countries where widespread resistance to earlier-generation fluoroquinolones has not been identified. Activity against some Gram-positive organisms, particularly some streptococci, may be limited.
Fig. 6.9 Ciprofloxacin corneal precipitates

- Resistance to fluoroquinolones has been reported in some areas (e.g. *Staphylococcus* spp. in the USA and *Pseudomonas* in India). Moxifloxacin, gatifloxacin and besifloxacin are new generation fluoroquinolones that largely address this, and also have better activity against Gram-positive pathogens. Moxifloxacin has superior ocular penetration. Novel drug preparations, with higher concentrations or modified vehicles, have been introduced to enhance antibacterial activity.
- Ciprofloxacin instillation is associated with white corneal precipitates (Fig. 6.9) that may delay epithelial healing.
  - **Antibiotic duotherapy** may be preferred as first-line empirical treatment in aggressive disease or if microscopy suggests streptococci or a specific microorganism that may be more effectively treated by a tailored regimen (see Table 6.4).
- Empirical duotherapy usually involves a combination of two fortified antibiotics, typically a cephalosporin and an aminoglycoside, in order to cover common Gram-positive and Gram-negative pathogens.
- The antibiotics are not commercially available and must be specially prepared (Table 6.5). A standard parenteral or lyophilized antibiotic preparation is combined with a compatible vehicle such that the antibiotic does not precipitate. Optimally, constitution should take place in the sterile preparation area of a pharmaceutical dispensary.

### Table 6.4 Antibiotics for the treatment of keratitis

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Antibiotic</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical treatment</td>
<td>Fluoroquinolone monotherapy or cefuroxime + 'fortified' gentamicin duotherapy</td>
<td>Varies with preparation 5% 1.5%</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>Cefuroxime vancomycin or teicoplanin</td>
<td>0.3% 5% 1%</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>'Fortified’ gentamicin or fluoroquinolone or cefazidime</td>
<td>1.5% Varies with preparation 5%</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td>Fluoroquinolone or ceftriaxone</td>
<td>Varies with preparation 5%</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Amikacin or clarithromycin</td>
<td>2% 1%</td>
</tr>
<tr>
<td>Nocardia</td>
<td>Amikacin or trimethoprim + sulfamethoxazole</td>
<td>2% 1.6% 8%</td>
</tr>
</tbody>
</table>

- Disadvantages of fortified antibiotics include high cost, limited availability, contamination risk, short shelf-life and the need for refrigeration.
- **Subconjunctival antibiotics** are usually only indicated if there is poor compliance with topical treatment.
- **Mydriatics** (cyclopentolate 1%, homatropine 2% or atropine 1%) are used to prevent the formation of posterior synechiae and to reduce pain.
- **Steroids**
  - Steroids reduce host inflammation, improve comfort, and minimize corneal scarring. However, they promote replication of some microorganisms, particularly fungi, herpes simplex and mycobacteria and are contraindicated if a fungal or mycobacterial agent is suspected (beware prior refractive surgery and trauma involving vegetation)
  - By suppressing inflammation, they also retard the eye’s response to bacteria and this can be clinically significant, particularly if an antibiotic is of limited effect or bacteriostatic rather than bactericidal.
  - Evidence that they improve the final visual outcome is mainly empirical, but the recent Steroids for Corneal Ulcers Trial (SCUT) found no eventual benefit in most

### Table 6.5 Preparation of fortified antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Method</th>
<th>Concentration</th>
<th>Shelf-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins: cefazolin, cefuroxime, or cefazidime</td>
<td>500 mg parenteral antibiotic is diluted with 2.5 ml sterile water and added to 7.5 ml of preservative-free artificial tears</td>
<td>50 mg/ml (5%)</td>
<td>24 hours at room temperature; at least 4 days if refrigerated</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 ml parenteral antibiotic (40 mg/ml) is added to 5 ml commercially available gentamicin ophthalmic solution (0.3%)</td>
<td>15 mg/ml (1.5%)</td>
<td>Up to 14 days if refrigerated</td>
</tr>
</tbody>
</table>
cases, though severe cases (counting fingers vision or large ulcers involving the central 4 mm of the cornea) tended to do better; a positive culture result was an inclusion criterion, and steroids were introduced after 48 hours of moxifloxacin.
- Epithelialization may be retarded by steroids and they should be avoided if there is significant thinning or delayed epitheal healing; corneal melting can occasionally be precipitated or worsened.
- Many authorities do not commence topical steroids until evidence of clinical improvement is seen with antibiotics alone, typically 24–48 hours after starting treatment.
- Others delay their use at least until the sensitivity of the isolate to antibiotics has been demonstrated, or do not use them at all.
- Regimens vary from minimal strength preparations at low frequency to dexamethasone 0.1% every 2 hours; a reasonable regimen is prednisolone 0.5–1% four times daily.
- Early discontinuation may lead to a rebound recurrence of sterile inflammation.
- The threshold for topical steroid use may be lower in cases of corneal graft infection, as they may reduce the risk of rejection.

Systemic antibiotics

Systemic antibiotics are not usually given, but may be appropriate in the following circumstances:
- **Potential for systemic involvement**, when microbiological/infectious disease specialist advice should optimally be sought but should not delay treatment:
  - *N. meningitidis*, in which early systemic prophylaxis may be life-saving. Treatment is usually with intramuscular benzylpenicillin, ceftriaxone or cefotaxime, or oral ciprofloxacin.
  - *H. influenzae* infection should be treated with oral amoxicillin with clavulanic acid.
  - *N. gonorrhoeae* requires a third-generation cephalosporin such as ceftriaxone.
- **Severe corneal thinning** with threatened or actual perforation requires:
  - Ciprofloxacin for its antibacterial activity.
  - A tetracycline (e.g. doxycycline 100 mg twice daily) for its antocollagenase effect.
- **Scleral involvement** may respond to oral or intravenous treatment.

Management of apparent treatment failure

It is important not to confuse ongoing failure of re-epithelialization with continued infection. Drug toxicity, particularly following frequent instillation of fortified aminoglycosides, may give increasing discomfort, redness and discharge despite the eradication of infection.
- If no improvement is evident following 24–48 hours of intensive treatment, the antibiotic regimen should be reviewed, including contact with the microbiology laboratory to obtain the latest report.
- There is no need to change the initial therapy if this has induced a favourable response, even if cultures show a resistant organism.
- If there is still no improvement after a further 48 hours, suspension of treatment should be considered for 24 hours then re-scraping performed with inoculation on a broader range of media (see Table 6.2) and additional staining techniques requested (see Table 6.3). Consideration should be given to the possibility of a non-bacterial causative microorganism.
- If cultures remain negative, it may be necessary to perform a corneal biopsy for histology and culture.
- Excisional keratoplasty, penetrating or deep lamellar, may be considered in cases resistant to medical therapy, or for incipient or actual perforation (see below).

Perforation

A small perforation in which infection is controlled may be manageable with a bandage contact lens; tissue glue is often adequate for slightly larger dehiscences. A penetrating keratoplasty or corneal patch graft may be necessary for larger perforations, or in those where infection is extensive or inadequately controlled. Occlusive surface repair techniques may be appropriate in some circumstances, such as an eye with no useful visual potential.

Endophthalmitis

No clear protocol exists for the management of this rare complication, but a similar approach to postoperative endophthalmitis should be considered, whilst continuing specific management of the corneal infection. Secondary sterile intraocular inflammation should not be mistaken for intraocular infection.

Visual rehabilitation

- Keratoplasty (lamellar may be adequate) may be required for residual dense corneal scarring.
- Rigid contact lenses may be required for irregular astigmatism but are generally only introduced at least 3 months after re-epithelialization.
- Cataract surgery may be required because secondary lens opacities are common following severe inflammation. Even in the absence of severe corneal opacification, surgery may be hampered by corneal haze, posterior synechiae and zonular fragility.

**FUNGAL KERATITIS**

**Introduction**

**Pathogenesis**

Fungi are a group of microorganisms that have rigid walls and a distinct nucleus with multiple chromosomes containing both...