Infectious keratitis

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Purpose of review

Infectious keratitis is a medical emergency. Improper management can lead to marked loss of vision. This review identifies recent trends in the study of infectious keratitis.

Recent findings

A multicountry outbreak of *Fusarium* keratitis emphasizes that contact lens wear is a major risk factor for infectious keratitis. *Acanthamoeba* and fungal keratitis are the most expensive forms of infectious keratitis to treat. Noninvasive methods and molecular techniques have improved diagnosis of infectious keratitis. Fortified topical antibiotics and fluoroquinolones are still the mainstay of bacterial keratitis therapy. Voriconazole and new routes of administration of conventional antifungals appear promising for fungal keratitis. Antivirals and amelioration of host inflammatory response are promising for viral keratitis; the host response is also crucial in pathogenesis of *Pseudomonas aeruginosa* keratitis. Trauma-induced bacterial and fungal keratitis and contact lens-associated keratitis are preventable entities.

Summary

Improved modalities of diagnosis and treatment have improved the outcome of infectious keratitis, but therapy of acanthamoebal, fungal and *P. aeruginosa* keratitis is still a challenge. Effective strategies must neutralize potential risk factors and counter host response overactivity without impairing killing of infecting microorganisms. Trauma-induced bacterial and fungal keratitis can be prevented.

Keywords

corneal ulceration, keratitis aetiology, keratitis bacterial, keratitis fungal, keratitis viral, suppurative keratitis

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Abbreviations

DFA	direct fluorescent antibody test
LASIK	laser in-situ keratomileusis
MRSA	methicillin-resistant *S. aureus*
NTM	nontuberculous mycobacteria
PCR	polymerase chain reaction
PHMB	polyhexamethylene biguanide
PRK	photorefractive keratectomy

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Introduction

Infectious keratitis (microbial keratitis) is characterized by a defect of the corneal epithelium (hence the terms 'infectious keratitis' and 'ulcerative keratitis' are frequently used interchangeably) with inflammation of the underlying corneal stroma caused by replicating organisms including bacteria, viruses, fungi and protozoa [1••]. The presentation is acute, with patients often in significant pain and distress. Infectious keratitis is a medical emergency; rapid initiation of aggressive treatment is needed to halt the disease process and limit the extent of corneal scarring and loss of vision. All clinicians who treat infectious diseases, and not just ophthalmologists, should recognize this sight-threatening condition. This review aims to highlight recent advances in our understanding of this problem.

Epidemiology

The actual prevalence of infectious keratitis is not known. The incidence of corneal ulceration per 100 000 population per year is estimated to vary from 6.3 in Hong Kong [2] and 11 in the USA [3] to 339 in Bhutan and 710 in Burma [4]; the incidence is six-fold higher in contact lens wearers [2]. Routine culture and virological investigations of such corneal ulcers may yield positive results in 55% [1••] to 67% [5•]; the remaining 'sterile' ulcers may occur due to nonmicrobial causes, or may be of infectious origin with negative culture and virological results due to various reasons (see below).

Gender

Infectious keratitis affects both males and females. A male preponderance [1••,5•,6•] has been noted, although this may simply reflect the frequency of antecedent ocular trauma during outdoor work as a risk factor [1••].

Age

Age may influence the aetiological agent and outcome of therapy in infectious keratitis. When patients were categorized into three age-based groups, namely, paediatric ($\leq$16 years), elderly ($\geq$65 years) and control (17–64 years), fungal keratitis was found to occur significantly less frequently in the paediatric group than in other groups; polymicrobial infections were less frequent in controls (5%) than in other groups ($\geq$20%); elderly patients presented with severe central ulcers with a significant risk of a poor visual outcome and non-traumatic predisposing factors (ocular surface disorders, prior ocular surgeries) approached trauma in importance [5•]. In Australia, individuals with contact lens wear as a risk factor tended

to be significantly younger (mean age 30 years) than those with other risk factors (mean age 40–47 years) [1••]. The reasons for these age-based variations need to be elucidated.

Occupation

Agricultural work and outdoor occupations appear to predispose to infectious keratitis [6•]. It is not clear whether certain occupations predispose to specific aetiologies of keratitis, for example agricultural work to fungal keratitis, although fungal keratitis was reported to occur frequently in onion harvesters in Taiwan [7].

Environmental factors

The relative prevalence of filamentous fungal keratitis has been found to increase toward tropical latitudes, possibly due to the influence of wind, temperature and rainfall [8]. Similarly *Curvularia* keratitis along the Gulf of Mexico was found to cluster during the hotter, moister, summer months, possibly reflecting the increase in airborne *Curvularia* spores during these months [9•]. Infectious keratitis due to other aetiological agents, however, does not exhibit such obvious geographical localization or relation to environmental factors.

Risk factors for infectious keratitis

Risk factors for infectious keratitis due to nonviral pathogens include trauma to the eye, overnight or extended wear of conventional contact lenses or orthokeratology lenses, chronic ocular surface disease (including atopic or vernal keratoconjunctivitis and blepharitis), prior ocular surgery, other ocular defects (lagophthalmos), systemic diseases (diabetes mellitus, leprosy, rheumatoid arthritis), use of topical corticosteroids or traditional eye medicines [1••,2,3,5•,6•,7,8,10•–15•,16,17,18•–20•]. Around 10% of individuals with infectious keratitis may not exhibit any risk factor [1••].

Risk factors for specific aetiologies of infectious keratitis

These have been described [13•–15•,16,17,18•–20•], but mostly in uncontrolled case series. Such descriptions may be misinterpreted, so that a risk factor is believed to be specific for infection by a specific microorganism. For example, in two recent series describing keratitis due to *Moraxella* [19•] and that due to *Haemophilus influenzae* [20•], multiple ocular risk factors were noted, the most frequent being prior ocular surgery and herpes simplex virus (HSV) keratitis. Thus, case–control studies are needed to elucidate risk factors unique to specific causes of infectious keratitis, but there have hitherto been few such investigations.

Trauma as a risk factor

Trauma to the eye can cause ulceration of the corneal epithelium; once the epithelium is breached, the corneal stroma and deeper part of the cornea are prone to become secondarily infected by bacteria and fungi and, to a lesser extent, by *Acanthamoeba* or other protozoa. This has been reported across different regions [1••,5•,8,14•,15•,16,17,18•] and age-groups [5•]. One case–control study [21] noted antecedent ocular trauma in 35% of fungal and 52% of bacterial keratitis patients while another such study [22] observed that filamentous fungal keratitis was more frequently related to mechanical ocular trauma while bacterial keratitis (principally due to *Pseudomonas aeruginosa*) was less frequently related to trauma. Thus, it is unclear whether trauma *per se*, or specific traumatizing agents, predisposes to specific aetiologies in infectious keratitis.

Wearing of contact lenses or orthokeratology lenses as a risk factor

Contact lens wear is one of the most, if not the most, important risk factor for infectious keratitis in the developed world [1••,2,3,23•] and for *Acanthamoeba* keratitis in China and Turkey [14•,24•]. Increasingly, overnight wear of orthokeratology lenses, which are used for the temporary reduction of myopic refractive error, is being implicated as a risk factor for infectious keratitis in East Asia, where these lenses have become popular [11•,12•].

Type and composition of lens as predisposing factors for contact lens-associated infectious keratitis

One study noted the highest incidence of infectious keratitis in those who wore extended wear lenses, followed by users of daily wear lenses and by users of rigid lenses [2]. The composition of the lens worn may also be a risk factor, with higher numbers of *Acanthamoeba* trophozoites found to attach to first-generation lotrafilcon A silicone hydrogel lenses, compared with second-generation galyfilcon A lenses and conventional (etafilcon A) lenses [25•].

Other factors predisposing to contact lens-associated infectious keratitis

When using conventional contact or orthokeratology lenses, inappropriate lens care procedures, patient noncompliance with practitioner instructions, overnight wear of lenses, smoking and persisting in lens wear despite discomfort, appear to be key risk factors; rinsing the lenses in tap water may predispose specifically to *Acanthamoeba* infection [2,11•,12•,14•,15•]. Contact lens wear may predispose to infectious keratitis because of prolonged hypoxia (experimentally found to augment internalization of *P. aeruginosa* in the cornea) [26•], by causing minor breaks in the corneal epithelium (thereby exposing the underlying stroma to infection), or by other hitherto undefined mechanisms.

An outbreak of contact lens-associated Fusarium *keratitis*

From mid-2005 to around July 2006, a rather unique, multicountry outbreak of contact lens-associated keratitis

due to *Fusarium* species was witnessed, unique because hitherto filamentous fungi have been infrequently implicated in contact lens-associated keratitis [27•]. The outbreak appears to have been first recognized in Hong Kong, but gained attention after reports from Singapore [28•], where more than 60 patients were observed, and the USA [29,30,31•,32•,33••], where more than 160 patients in 33 states were affected. Epidemiological and microbiological studies implicated the use of a specific brand of contact lens multipurpose solution, ReNu with Moisture Loc, in many patients. *Fusarium* was not recovered from the factory, warehouse or solution filtrate, however, or in any unopened bottles of this product, and the *Fusarium* strains isolated revealed high genetic diversity, suggesting that intrinsic contamination of the contact lens solution was not the direct cause of the infection [33••]. The high polymer content of the solution, as well as patient noncompliance (particularly adding fresh solution to left-over solution in the containers), was hypothesized to have facilitated contamination of the solution by *Fusarium* derived from the local environments of the patients. This hypothesis, however, fails to consider the fact that there are numerous microbial species in the environment, and not just *Fusarium*. If contamination had been derived from the patients' environments, one would have expected to see a greater diversity of contaminating organisms.

Ocular surgery as a risk factor

With increasing recourse to refractive surgery such as laser in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), it is natural that corneal surgery is a risk factor for infectious keratitis. LASIK has now become the surgery of choice for correction of errors of refraction between −8 and +3 dioptres, due to various advantages. Although infectious keratitis during the early postoperative period is rare (<1 in 2919) [34], it is a dreaded enough complication to have warranted the publication of a white paper on its management [35•]. Infectious keratitis may also rarely occur following PRK [36•].

Risk factors associated with perforated corneal ulcers

A case–control study in India found significant associations between 11 factors and the occurrence of corneal perforation in infectious keratitis [6•]; of these, the lack of corneal vascularization, delay in starting initial treatment and failure to start fortified antibiotics retained significance on a logistic regression model. The authors themselves identified several limitations of their study.

Aetiological agents of infectious keratitis

The principal organisms isolated from various aetiologies of infectious keratitis are summarized in Table 1 [1••,8,14•,15•,16,17,37,38,39•–45•].

Aetiological agents of trauma-associated infectious keratitis

Regional variations in infecting organisms even within defined age groups can be discerned. In Australia, corneal scrapings from patients aged 15–64 years who had sustained ocular trauma yielded no growth of organisms (including *Acanthamoeba*) in 60%, and growth of Gram-positive bacteria (particularly coagulase-negative staphylococci, CoNS) in 31%, Gram-negative bacilli (GNB) in 5% and filamentous fungi in 3.2% [1••]. In contrast, in India, corneal scrapings from essentially the same age-group of patients (many of whom had suffered ocular trauma) yielded no growth in 35%, and growth of filamentous fungi alone in 32.7%, bacteria alone (predominantly *Streptococcus pneumoniae and P. aeruginosa*) in 25% and *Acanthamoeba* in one patient [5•], while in Malaysia, the commonest bacterial causes of keratitis were *P. aeruginosa* and *Staphylococcus aureus* [13•].

Aetiological agents of lens-associated infectious keratitis

Worldwide, aetiological agents of lens-associated infectious keratitis appear to be *P. aeruginosa* and *Acanthamoeba* in wearers of conventional and of orthokeratology lenses [11•,12•,14•,15•]. In Australia, Gram-negative organisms were isolated significantly more frequently in contact lens wearers than in trauma cases [1••].

Aetiological agents of postsurgical infectious keratitis

In post-LASIK infectious keratitis, nontuberculous mycobacteria (NTM), particularly *Mycobacterium chelonae*, are the most commonly cultured organisms [34,39•,40•], followed by staphylococci [including methicillin-resistant *S. aureus* (MRSA) [41•], fungi such as *Exophiala dermatitidis* [42•], streptococci, *Nocardia* [43•] and GNB such as *P. aeruginosa* [44•]].

Other aetiological agents

In a study on infectious keratitis where attempts were made to detect viral pathogens, herpetic keratitis was diagnosed in 6.9% [1••]. Microsporidial keratoconjunctivitis was found to account for 0.4% of suspected infectious keratitis in southern India [45•].

Factors detrimental to isolation or detection of aetiological agents in infectious keratitis

It may not be possible to detect a microorganism in around 35–60% of patients with suspected infectious keratitis, possibly because of scanty sample material, delay in performing investigations, prior use of antimicrobial agents or even the use of certain corneal stains such as rose bengal and lissamine green [46•]. Prior use of topical antibiotics may only delay the time taken to grow organisms in culture without affecting culture-positivity rates [1••,47].

Table 1 Salient features of infectious keratitis

Feature	Gram-positive bacteria	Gram-negative bacteria	Fungi	Protozoa	Viruses
Important corneal pathogens	Gram-positive cocci (GPC): Coagulase-negative staphylococci (CONS) *Streptococcus pneumoniae* *Staphylococcus aureus* Gram-positive bacilli (GPB): Nontuberculous mycobacteria (NTM): *Mycobacterium fortuitum/ Mycobacterium chelonae* Filamentous GPB: *Nocardia* spp. Risk factors: Previous HSV keratitis and *Streptococcus* Trauma and *S. aureus* Age < 50 years. and *S. aureus*	Gram-negative bacilli (GNB): *Pseudomonas aeruginosa* *Enterobacteriaceae* *Moraxella* *Haemophilus* Gram-negative cocci: *Neisseria gonorrhoeae* Risk factors: Contact lens (CL) use and *Ps. aeruginosa* Burn/lagophthalmos and *Acinetobacter* Age > 50 years. and GNB (non-*Pseudomonas*)	Filamentous fungi: *Fusarium* *Aspergillus* *Curvularia* Yeast-like fungi: *Candida albicans* and *Candida* spp. *Cryptococcus spp.* Risk factors: Filamentous fungi: principally trauma *Candida* - Ocular surface disorders - Systemic diseases - CL use	*Acanthamoeba* species Genera of microsporidia Risk factors: *Acanthamoeba* - CL use - Contact with contaminated water - Trauma Microsporidia - Immunosuppression - CL wear	Herpes simplex virus (HSV) type 1 Adenoviruses Varicella -zoster virus (VZV)
Clinical features	(a) GPC: Localised round or oval ulceration Greyish -white stromal infiltrates Distinct borders; minimal surrounding stromal haze (b) *Nocardia*: Multiple small white infiltrates; resembles 'wreath pattern' May have fine filaments extending into surrounding cornea. (c) NTM: 'Cracked wind-shield' type of appearance	GNB: Rapid, inflammatory destructive course Dense stromal suppuration Hazy surrounding cornea 'Immune ring'	(a) Filamentous fungi: Dry elevated slough Stromal infiltrate with hyphate margins Satellite lesions Thick endothelial exudate (b) *Candida*: stromal keratitis resembles bacterial ulcer overlying epithelial defect discrete infiltrate slow progression occurs inferocentrally	*Acanthamoeba:* Epithelial irregularities Single or multiple stromal infiltrates Ring-shaped configuration Severe pain and radial keratoneuritis (b) Microsporidia: punctate epithelial lesions subepithelial scars (mimics atypical adenoviral keratoconjunctivitis)	(a) HSV: Superficial punctate keratitis Coarse epithelial punctate lesions Dendritic ulcer Geographical ulcer Necrotizing stromal keratitis Non-necrotizing (immune, disciform) stromal keratitis (b) VZV: Nummular keratitis (c) Adenoviruses: Keratoconjunctivitis
Diagnosis 1. Microscopy	1. Gram Ziehl–Neelsen, Kinyoun	1. Gram	1. Gram, Giemsa potassium hydroxide (KOH), ink-KOH lactophenol cotton blue (LPCB) acridine orange Gomori methenamine silver (GMS) periodic acid Schiff (PAS) calcofluor white (CFW)	1. (a) *Acanthamoeba*: KOH, ink-KOH, LPCB Gram, Giemsa, acridine orange, GMS CFW (b) Microsporidia KOH+CFW Gram; Giemsa Kinyoun's 1% acid- fast	Vero cell culture Antigen detection techniques

2. Culture	2. For GPC, GPB and *Nocardia*: (a) Solid media at 37°C Sheep blood agar Cystine tryptone agar Brain heart infusion agar (b) Liquid media at 37°C Brain heart infusion broth Thioglycollate broth (c) For *Mycobacterium* Lowenstein-Jensen medium Middlebrook medium	2. (a) Solid media at 37°C Sheep blood agar Cystine tryptone agar Brain heart infusion agar (b) Liquid media at 37°C Brain heart infusion broth Thioglycollate broth	2. Sabouraud glucose neopeptone agar and glucose neopeptone broth (supplemented with antibacterials) at 30°C and 37°C Media used for bacterial culture can be used for fungal culture if antibacterials are added.	2. (a) *Acanthamoeba* (nonnutrient agar with *Escherichia coli* overlay) at 30°C and 37°C (b) Microsporidia: Tissue culture	
Treatment	(a) Initial: cefazolin/cefuroxime + gentamicin/ tobramycin Or fluoroquinolone monotherapy (b) For *S. aureus*, CoNS, *Streptococcus:* same as above (c) For *Mycobacterium chelonae/ M. fortuitum*: topical amikacin + ciprofloxacin (d) For *Nocardia asteroides*: ampicillin + sulphonamides; cotrimoxazole; cefazolin; topical amikacin + erythromycin	(a) Initial: cefazolin/cefuroxime + gentamicin/ tobramycin Or fluoroquinolone monotherapy. (b) For *Haemophilus influenzae, Klebsiella* spp., *Proteus* sp. & other enterobacteria: same as above (c) For *Pseudomonas* ulcers: Ticarcillin/piperacillin (50 mg/ml) + gentamicin (15 mg/ml) + ceftazidime + ciprofloxacin 0.3%	Topical antifungals (a) for filamentous fungi: (i) 1st line: 5% natamycin (ii) 2nd line: 1% itraconazole, 2% econazole (b) For *Candida*: (i) 1st line: 0.15% amphotericin B (ii) 2nd line: fluconazole (b) Oral antifungals (i) Ketoconazole: 200 mg twice daily (ii) Itraconazole: 200 mg once daily (iii) Fluconazole: 50–100 mg once daily (c) Recently topical and oral voriconazole	(a) For *Acanthamoeba*: (i) Dibromopropamidine (ii) Hexamidine (iii) Chlorhexidine 0.02% (iv) Polyhexamethyl-biguanide (PHMB) 0.02% Recommended: Propamidine + Chlorhexidine OR Propamidine + PHMB (b) Microsporidia: (i) debridement (ii) broad-spectrum antibiotic or PHMB or chlorhexidine	(a) HSV keratitis: For epithelial disease: (i) Acyclovir 3% ointment 5 times a day (is able to penetrate intact corneal epithelium) (ii) Idoxuridine 0.1% drops now seldom used (toxicity) (iii) Debridement in dendritic ulcer For necrotizing stromal disease: Oral acyclovir and topical corticosteroids. For nonnecrotizing stromal disease: Topical corticosteroids when lesion involves visual axis. Possibly oral acyclovir (debatable)

Based on references [1••,8,14•,15•,16,17,37,38,39•–45•]). CFW, calcofluor white; CL, contact lens; CoNS, coagulase-negative staphylococci; GMS, Gomori methenamine silver; GNB, Gram-negative bacilli; GPB, Gram-positive bacilli; GPC, Gram-positive cocci; HSV, herpes simplex virus; KOH, potassium hydroxide; LPCB, lactophenol cotton blue; NTM, non-tuberculous mycobacteria; PAS, periodic acid Schiff; PHMB, polyhexamethyl biguanide; VZV, varicella-zoster virus.

Co-infection by multiple aetiological agents

Multiple similar or diverse pathogens may sometimes occur simultaneously or sequentially in an ocular infection. Specific investigations should be done to ensure that such polymicrobial infections are not missed, since the clinical evolution of the disease and the response to treatment may be affected. The reported incidence of polymicrobial keratitis varies from 5 to 22% [5•,13•,48••], even when the same criteria are used to define an organism as a pathogen or contaminant. A recent study [48••] established criteria to define a bacterial co-infection in fungal keratitis. Superinfection by the normal bacterial flora during early keratomycosis was believed to have led to polymicrobial keratitis. *Candida* isolates tended to be coinfected with staphylococci, the risk of polymicrobial infection being approximately three times greater than that with infection by filamentous fungi. Such synergism possibly contributes to the generally poor prognosis for fungal keratitis. *Candida* keratitis, however, actually tends to resolve better than does filamentous fungal keratitis [17], so the importance of bacterial co-infection in filamentous fungal keratitis in tropical regions requires further study.

Aetiological agents of infectious keratitis and financial implications

An interesting study tried to assess the financial burden of infectious keratitis [1••]. *Acanthamoeba* keratitis was the most expensive to treat, followed by fungal and herpetic keratitis and lastly by culture-proven bacterial keratitis or culture-negative cases.

Clinical features

Early signs and symptoms of infectious keratitis include redness, tearing, pain, sensitivity to light, discharge, decreased vision and a white corneal infiltrate. Certain signs have been described as being unique to specific presentations of infectious keratitis (Table 1). Again, the specificity of such findings requires simultaneous study of multiple presentations of infectious keratitis.

Clinical features of fungal keratitis

Serrated margins, raised slough and colour other than yellow were found to be independently associated with fungal keratitis in a logistic regression model [49•]. The probability of fungal infection was 63% if one clinical feature was present, increasing to 83% if all three features were present. A drawback of this study was that clinical presentation was not stratified based on duration of symptoms nor were infecting bacteria or fungi arranged by genus.

Clinical features of less frequent causes of infectious keratitis

Microsporidial keratitis may mimic atypical or unusual adenoviral keratoconjunctivitis [45•] while keratitis due to NTM is indolent in evolution and mimics herpetic, mycotic and *Nocardia* keratitis or even crystalline keratopathy [34,39•]. Nonulcerative stromal keratitis, a complication of late congenital syphilis that typically begins during childhood or adolescence, may mimic viral interstitial keratitis [50•].

Diagnosis

In recent years, there have been notable advances in noninvasive techniques for diagnosis of infectious keratitis and in molecular techniques for diagnosis of viral and fungal keratitis.

Noninvasive methods

Noninvasive methods of diagnosis include confocal microscopy and impression cytology.

Confocal microscopy

The confocal microscope allows in-vivo examination of the cornea. First-generation confocal microscopes have yielded to the advanced tandem scanning confocal microscope and the Heidelberg retina tomograph II (HRT-II) with cornea module. These two confocal microscope models have been used for diagnosis of *Acanthamoeba* keratitis [14•,15•,51•] by direct visualization of *Acanthamoeba* cysts in the corneal stroma, while HRT-II demonstrated inflammatory necrotic cells in the corneal stromal and anterior chamber cell reaction in bilateral infectious ulcers due to *Streptococcus sanguis* [10•]. This facility is valuable in regions where cost is no constraint to the investigation of infectious keratitis.

Impression cytology

Impression cytology can be used for diagnosis of ocular diseases, including infectious keratitis. A cellulose acetate filter is applied to the ocular surface to remove the most superficial layers of the ocular surface epithelium, the cells obtained then being subjected to histological, immunohistological or molecular analysis; deeper cells can also be accessed by repeated application over the same site [52•]. Impression cytology has permitted the diagnosis of superficial infections due to HSV, varicella-zoster virus and adenoviruses [53], and of *Acanthamoeba* keratitis [54].

Conventional method of specimen collection

To identify the aetiological agent in infectious keratitis, samples (usually scrapings) are obtained from the infected cornea; a biopsy or (in LASIK patients) material from the stromal bed after lifting the flap may sometimes be needed; material from the anterior chamber or a corneal endothelial plaque is an infrequent sample [17,37,39•,40•,45•]. The material thus obtained is used for microscopic examination, using various stains, or inoculated onto appropriate culture media (Table 1).

Diagnosis of viral keratitis

This is done by cell culture using Vero cell lines, the direct fluorescent antibody test (DFA) or the polymerase chain reaction (PCR). In diagnosis of HSV keratitis, DFA was found to be more sensitive than PCR, which was in turn more sensitive than culture; DFA had better sensitivity and negative predictive values while PCR had better specificity and positive predictive values [55•]. Demonstration of antibodies to HSV and varicella-zoster virus in samples from the anterior chamber may help to diagnose recurrent herpes keratitis in patients presenting with intraocular inflammation and neovascularization [56]. Recently, a fully automated molecular assay using an automated extraction system and a real-time PCR protocol successfully detected human adenoviral DNA in conjunctival smears, the results coinciding with those obtained using an immunofluorescent test kit [57•].

Diagnosis of fungal keratitis

A sensitive and rapid PCR-based method using single-stranded conformation polymorphism was recently described for diagnosis of fungal keratitis in four patients [58•]. This approach may yield positive results when the conventional approach proves negative. Interestingly, in this study, a clinical diagnosis of fungal keratitis had been made in all four patients, and the PCR results only confirmed the diagnosis.

Treatment

Conventional lines of therapy for infectious keratitis are outlined in Table 1. The efficacy of povidone-iodine (betadine) in reducing the microbial load of corneal ulcers before patients were given antibiotics was recently assessed [59•]. A single application of 5% betadine was not found to reduce the bacterial load of corneal ulcers more than just scraping and rinsing alone, possibly due to lack of penetration deep into the corneal stroma and the number of organisms present, as well as other factors.

Acanthamoeba keratitis

In *Acanthamoeba* keratitis, propamidine or hexamidine, in combination with polyhexamethylene biguanide (PHMB) or chlorhexidine, is the recommended line of treatment [14•,15•]. A combination of PHMB and hexamidine diisethionate exerted a synergistic effect and was more effective than PHMB, hexamidine diisethionate or miltefosine alone in a rat model of chronic *Acanthamoeba polyphaga* keratitis [60•]. The advent of effective antiamoebic therapy has permitted a redefining of the goal of therapeutic penetrating keratoplasty in *Acanthamoeba* keratitis, from a mere salvaging of the affected cornea to restoration of useful vision after the infection has completely resolved. A study on a small series of patients showed that when penetrating keratoplasty was undertaken at least 3 months after discontinuation of antiamoebic therapy, with a negative preoperative confocal microscopy examination, there were no recurrences [61•]. Here, the 'waiting period' of at least 3 months was identified as being crucial to success so that when the corneal limbus was affected, there was a longer waiting period. In some instances of very refractory infection, a combination of conjunctival flap surgery, corneal cryo treatment and penetrating keratoplasty may be needed [62•].

Bacterial keratitis

While treatment of *P. aeruginosa* keratitis requires special antibiotics, other forms of bacterial keratitis continue to be treated either by a combination of fortified topical antibiotics, using a cephalosporin and an aminoglycoside, or by fluoroquinolone monotherapy (Table 1). When combined therapy with cephalothin and gentamicin was used to treat patients with infectious keratitis, there was a clinical lack of response in 13% and treatment failure in 4%, whereas when ciprofloxacin monotherapy was used there were no treatment failures [63•]. Treatment groups were nonrandomized, however, and the differential outcomes possibly reflected a desire to treat milder cases with monotherapy. The use of fluoroquinolone monotherapy (possibly in an inadequate frequency) and the delay or failure in starting fortified antibiotics were reported to be risk factors for perforation in patients with infectious keratitis [6•]. There have also been concerns regarding the safety of fluoroquinolone use in keratitis. Fluoroquinolones, however, continue to be considered as useful alternatives, due to inherent problems in preparation and storage of fortified antibiotics [5•,6•,63•]. Use of fluoroquinolones such as ofloxacin may be associated with corneal precipitates and poor wound healing due to impaired epithelialization [64]; fortunately these effects resolve when treatment is stopped.

Fourth-generation fluoroquinolone therapy

Gatifloxacin, was found to be superior to ciprofloxacin in treatment of bacterial keratitis, particularly that due to Gram-positive cocci [65•], while gatifloxacin and moxifloxacin were found effective in *M. chelonae* keratitis, in varying combinations with amikacin, clarithromycin or other fluoroquinolones [39•,40•]. MRSA keratitis, however, was reported in a patient who was receiving gatifloxacin after LASIK, while *P. aeruginosa* keratitis developed in a patient receiving moxifloxacin after PRK; both cases resolved only after topical aminoglycoside therapy and surgical intervention [41•]. Therefore, overuse of these advanced fluoroquinolones should be avoided to prevent development of widespread resistance.

Therapy of keratitis due to nontuberculous mycobacteria, Moraxella *and* Haemophilus

The course of post-LASIK infectious keratitis due to NTM is often protracted because of delayed diagnosis,

the advent of resistance to monotherapy, the inadvertent use of corticosteroids, inadequate penetration of drugs into the cornea and slow response to therapy. More than 25% of patients with *Moraxella* keratitis were reported to have a poor visual outcome, which was attributed to both the nature of the infection and the predisposing factors [19•]. Fortunately, *H. influenzae* keratitis appears to have a favourable outcome, with a good response to medical antibiotic therapy being noted in all 10 patients in a recently reported series of patients with this condition [20•].

Subpalpebral lavage therapy

The technique of subpalpebral lavage therapy was devised to provide continuous irrigation of the eye so as to improve scleral penetration by antibiotics, such as tobramycin (100 mg/ml) and levofloxacin (500 mg/100 ml) [66•]. This technique also allows the cleaning of necrotic debris, causes a decrease in the free bacterial load, reduces likelihood of recurrences and is ideally suited for patients who may resist frequent nursing care.

Defensins

Defensins are small cationic peptides with broad in-vitro antimicrobial activity. They also offer potential as wound healing agents. Their efficacy in treating ocular microbial infections, however, may be affected by the presence of tears [67•].

Fungal keratitis

Filamentous fungal keratitis continues to be difficult to treat despite the use of topical and systemic antifungal agents and adjuvant surgery, such as corneal transplantation. Few prospective studies have evaluated the effectiveness of different therapeutic approaches for fungal keratitis [17].

Medical therapy of fungal keratitis

Medical therapy has been boosted by the use of voriconazole, given topically or by other routes [68•,69•]. In addition, new ways of administering established drugs have been tried, for example intrastromal corneal injection of amphotericin B (5 μg per 0.1 ml) [70•], subconjunctival fluconazole (0.5–1.0 ml of a 2% solution) [71•,72•], and topical fluconazole with oral ketoconazole [73•]. It should be noted that the amphotericin B paper dealt with a single case, while in the fluconazole papers, there was insufficient detail regarding the severity of the keratitis in the patients.

Amniotic membrane transplantation for fungal keratitis

When amniotic membrane transplantation (AMT) was used to treat acute, culture-proven fungal keratitis in 23 eyes (23 patients), complete epithelialization was achieved in 75% of patients with active disease and in all patients with inactive disease. [74•]; importantly, antifungal agents were administered throughout the entire duration of hospitalization, and repeated cultures were done immediately before AMT.

Viral keratitis

While antivirals continue to be important in therapy of viral keratitis, there is increasing emphasis on methods to ameliorate the effects of an overactive host inflammatory response (Table 1).

Treatment of herpes simplex virus epithelial keratitis

Acyclovir is currently the drug of choice [75•]. In a small series of patients, topical ganciclovir gel 0.15%, given every 6 h, was helpful in the treatment of herpetic epithelial keratitis; when given twice daily, it was effective prophylaxis for patients with herpetic keratitis who were undergoing penetrating keratoplasty [76•], while perioperative prophylaxis with oral valacyclovir and topical acyclovir ointment was found to prevent reactivation of latent HSV keratitis in a small series of patients who underwent LASIK [77•]. These encouraging results require further confirmation in a larger series of patients, using controls.

Treatment of herpes simplex virus stromal keratitis

For nonnecrotizing (disciform) stromal keratitis, topical corticosteroids are predominantly applied. Topical corticosteroid use has many undesired side-effects and response to such therapy may be limited in some patients, hence other modalities of treatment have been tried. In a recent study [78•], 10 of 12 patients with HSV nonnecrotizing stromal keratitis, who had failed to respond to 4 weeks of 1% topical prednisolone acetate therapy, were found to respond to 1 month of topical cyclosporine 0.05% twice daily; unfortunately, the keratitis recurred in four patients when therapy was discontinued. Oral acyclovir therapy, in conjunction with corticosteroids, might ameliorate the deep corneal inflammation of disciform keratitis. For necrotizing stromal keratitis, oral acyclovir is given to control the viral invasion and replication in corneal tissue, while topical corticosteroids are given twice daily to control inflammation. Recently, attempts have been made to apply protective cytokines topically, either as naked DNA or in plasmids, to mitigate the course of experimental herpes stromal keratitis [75•]. Other methods of applying the DNA have also been tried [79•].

Treatment of adenoviral keratitis

Two new compounds, namely N-chlorotaurine [80•] and a topical cobalt chelate, CTC-96 [81•], were found to be effective against adenovirus in tissue culture and in Ad5/NZW rabbit ocular model. Clinical trials with these compounds are awaited.

Pathogenesis

Infectious keratitis arises from an interplay between organism factors (e.g., invasiveness, toxins) and host

Table 2 Recent advances in understanding pathogenesis/resistance in infectious keratitis

References	Putative virulence/resistance factor	Important findings
[83,84•]	IL-8 (not normally found in cornea; present in certain pathological conditions)	IL-8 production by corneal and conjunctival stromal cells caused chemoattraction of neutrophils leading to corneal ulceration and marked angiogenesis
[85]	Toll-like receptors (TLRs) and common adapter protein MyD88	Activation of TLR2 and TLR4 caused chemokine secretion and neutrophil infiltration into corneal stroma, causing keratitis. This mechanism may be relevant to pathogenesis of Gram-positive and Gram-negative bacterial keratitis, respectively
[86,87•]	IL-1; NFκB;	IL-1 stimulated (a) collagen degradation by cultured corneal fibroblasts (this effect is mediated by NF-κB) (b) synthesis or activation of matrix metalloproteinases. Sulfasalazine inhibited these effects.
[26•]	Prolonged hypoxia (> 3 days) of cornea due to contact lens wear/eyelid suturing	Physical effects of contact lens wear found to direct localization of lipid-raft associated *P. aeruginosa* internalization on corneal surface.
[88•]	Nitric oxide causes bacterial killing/stasis	Absence of IFNα and reduced nitric oxide synergistically increased proinflammatory cytokines, neutrophil number and bacterial load after corneal infection with *P. aeruginosa*
[89••]	Matrix metalloproteinase (MMP)-9	MMP-9 found to regulate immune function in cornea by proteolysis, degrade collagen IV in corneal basement membrane and to upregulate chemotactic cytokines/chemokines IL-1 beta and MIP-2, thereby promoting corneal perforation in B6 mice with *P. aeruginosa* keratitis.
[90••]	Toll-like receptor (TLR) 4	In *P. aeruginosa* keratitis in mice, TLR4 deficiency caused increased neutrophil infiltration and proinflammatory cytokines, decreased induced nitric oxide synthase (iNOS) and beta-defensin-2 production, and impaired bacterial killing
[91•]	Single immunoglobulin IL-1R-related molecule (SIGIRR)	In *P. aeruginosa* keratitis in mice, inhibition of SIGIRR led to increased corneal opacity, stromal damage and bacterial load; significant upregulation of corneal mRNA levels of proinflammatory and type 1 cytokines; significant upregulation of protein levels for IL-1 beta and MIP-2
[92•]	20-kDa polysaccharide (PS) antigen of *Staphylococcus epidermidis* (slime-producing strain)	Active immunization with the antigen and passive immunization with anti20 kDa PS antibodies resulted in high levels of antibodies in serum and aqueous and significantly less corneal damage than in unimmunized rabbits
[93]	Toll-like receptor (TLR)-2	Cultured corneal epithelial cells exposed to *Staphylococcus aureus* peptidoglycan produced proinflammatory cytokines, chemokines and antimicrobial peptide
[94•]	Vitronectin	This extracellular matrix protein promoted and enhanced in-vitro infection of human corneal epithelium by adenovirus serotype 19
[95•]	Nitric oxide (NO)	In primary HSV keratitis, NO was neuroprotective without antiviral effect. In recurrent HSV keratitis, inhibition of NO did not affect virus shedding or clinical disease. Therefore, NO may not have a significant role in evolution of recurrent HSV keratitis
[96•]	IL-6	IL-6 played a key role in angiogenesis in HSV keratitis by stimulating production of vascular endothelial growth factor (VEGF). This effect was reversed by antibody to IL-6
[97,98••]	Herpes simplex virus (HSV) type 1 immediate early protein ICPO	HSV1 ICPO found in virus-free tears from rabbit eyes acutely infected with HSV1. Using ex vivo confocal microscopy to scan rabbit corneas infected with a HSV1-derived strain expressing ICPO, this protein was found expressed in corneal epithelial and stromal cells of acutely infected corneas. HSV 1 ICPO possibly excites the immune response in herpes stromal keratitis
[99]	Protease activities of *Acanthamoeba*	Protease patterns in *Acanthamoeba polyphaga* and *Acanthamoeba castellanii* found to be complex (17 bands ranging from 30 to 144 kDa). Aprotinin inhibited crude extract protease activity in cell culture.
[100••]	Anterograde axonal spread of HSV1	HSV mutant was able to produce keratitis even when anterograde axonal spread was not possible
[79•]	IL-10 and IL-4	After gold particle-mediated gene transfer to mouse corneas 2 days before HSV1 infection, IL-10 and IL-4 were expressed in cornea, leading to reduced expression of IL-6 and milder clinical course of keratitis
[101•]	Mannose-binding protein (MBP) of *Acanthamoeba*	Trophozoites of *A. castellanii* bound strongly to cultured corneal epithelial cells in a mannose-inhibitable manner (cysts did not). Trophozoites of other *Acanthamoeba* strains that bound strongly to corneal cells and produced marked CPE robustly expressed MBP
[102••]	Recombinant mannose-binding protein (rMBP) of *Acanthamoeba*	Oral immunization with rMBP ameliorated *Acanthamoeba* keratitis in a hamster model. This protection was associated with elevated levels of anti-MBP IgA in tear fluid of immunized animals.

CL, contact lens; CPE, cytopathic effect; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; iNOS, induced nitric oxide synthase; MBP, mannose-binding protein; MIP-2, macrophage inflammatory protein-2; MMP, matrix metalloproteinase; NF, nuclear factor; PS, polysaccharide; rMBP, recombinant mannose-binding protein; SIGIRR, single Ig IL-1R-related molecule; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor.

factors (e.g., polymorphonuclear leucocyte infiltration). Initially, much of the focus was on contribution of organism factors to pathogenesis of infectious keratitis; in recent years, there is increasing realization of the importance of host factors such as Toll-like receptors [82••]. Recent advances in our understanding of the pathogenesis of, and resistance to, infectious keratitis are summarised in Table 2 [82••,83,84•,85,86,87•,88•,89••,90••,91•, 92•,93,94•–96•,97,98••,99,100••,101•,102••].

Prevention

There have been advances in prevention of trauma-associated and contact lens-associated infectious keratitis and in development of vaccines for some types of infectious keratitis.

Prevention of trauma-associated infectious keratitis

If posttraumatic infectious keratitis is initiated following infection of a breach in the corneal epithelium, then application of antimicrobials to the abraded cornea soon after trauma should reduce the incidence of infectious keratitis. Proof that this hypothesis is correct has been provided by two studies at the village level, one in Bhutan [103••], and the other in Burma [104••]; application of 1% chloramphenicol ointment or 1% chloramphenicol–clotrimazole ointment soon after detection of trauma-induced corneal abrasion effectively prevented bacterial and fungal keratitis respectively. These reports stressed the importance of committed grassroots workers (volunteer or otherwise), a fairly extensive rural health network and a campaign (either official or by word of mouth) to publicize the fact that individuals with abrasions could seek treatment with the health workers. Interestingly, neither of these papers dwelt on the importance of traditional healers in these defined populations, and whether it was necessary to solicit their cooperation.

Prevention of contact lens-associated infectious keratitis

General measures include proper storage, disinfection and cleaning of contact lenses and their cases; overnight contact lens wear should be avoided, and the contact lenses promptly removed at the onset of ocular irritation [27•]. To prevent contact lens-associated *Acanthamoeba* keratitis, patients should be informed of the possible danger of wearing first-generation silicone hydrogel lenses when exposed to sources of the organisms while swimming or in showers and hot tubs, since such lenses are very sticky for *Acanthamoeba* trophozoites and may increase the chances of infection [25•]; use of these lenses on a trial basis, or use of second-generation lenses could be advised. Infectious keratitis should not be treated with a corticosteroid in the absence of appropriate antimicrobial therapy since it may aggravate an unrecognized fungal keratitis.

Prevention of infectious keratitis by using vaccines

Vaccines for *S. epidermidis* and *Acanthamoeba* are at an experimental stage [92•,102••]. Much progress has been made, however, in developing vaccines to prevent HSV keratitis, and the routine use of such vaccines may become a reality one day [75•,105•].

Conclusion

While infectious keratitis is a well recognized cause of visual loss in the developing world, the recent outbreak of contact lens-induced *Fusarium* keratitis has heightened the awareness of the international community about this problem. Hopefully, this will lead to increased recognition of potential risk factors predisposing to the condition, as well as improvements in diagnosis and therapy. An overactive host response is detrimental to the resolution of infectious keratitis, so methods need to be devised to check this overactivity without, however, impairing the elimination of pathogens. There should be increased emphasis on the prevention of infectious keratitis by prompt recognition of trauma-induced corneal abrasions, and by eliminating potential predisposing factors.

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