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2.1 Introduction

All forms of infectious keratitis confer a significant personal and economic burden on those afflicted as well as on the society in which they live. While the simple treatment cost for an episode of corneal ulceration varies from less than a US\$ 100.00 in India, above the average monthly wage, to over US\$ 1,000.00 in Australia, the additive costs of significant visual loss and subsequent attempts for visual rehabilitation drives those costs into the thousands of dollars and beyond (Keay et al. 2008; Prajna et al. 2007). Further, the patients most commonly afflicted are working-age men and women in the third and fourth decades of life (Erie et al. 1993; Jeng et al. 2010) where lost wages and productivity not only impact during their treatment but is compounded for decades if profound visual loss results. Very significant differences exist in the incidence of infectious keratitis primarily dependent on a region's economic development which in turn affects a number of known risk factors including rates of contact lens wear, occupation, and domestic and environmental sanitation, among others. Regional incidence in the USA has been

estimated to have risen from .25 to 1.0 per 10,000 person years in Olmsted county Minnesota from 1950 to 1980, although a recent study by Jeng et al. places the incidence at 2.76 per 10,000 person years in Northern California in 1999 (Erie et al. 1993; Jeng et al. 2010). In contrast, the incidence in South India was estimated to be 11.3 per 10,000 in 1993, potentially affecting more than 800,000 individuals yearly (Gonzales et al. 1996). Further, visual outcomes are highly dependent on prompt diagnosis and treatment with relatively dismal rates in regions with limited health-care resources to relatively reasonable outcomes in developed health-care systems where nearly 90 % will maintain a best corrected vision of better than 20/40 and where blindness is uncommon (Burton et al. 2011; Stapleton et al. 2008).

An understanding of associated risk factors is integral to the diagnosis, management, and prevention of infectious keratitis. In developing countries, trauma is the primary risk factor and combined with environmental exposure leads to a predominance of fungal keratitis (Gopinathan et al. 2009). In developed countries, agricultural and work-related trauma is far less common with contact lens-related keratitis comprising approximately 1/3 of all cases (Ibrahim et al. 2009). Consequently, the more favorable prognosis for these cases of bacterial keratitis and, to a lesser extent, *Acanthamoeba* keratitis shifts the predominance of corneal blindness to herpetic

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keratitis in these regions. For nonviral corneal infections, the most important factor in a successful outcome is limitation of corneal scarring through rapid, effective eradication of the offending pathogen and control of inflammation through prompt diagnosis.

2.2 Diagnosis

The most important step in the diagnosis of a potential infectious keratitis is the recognition of the possibility of infection. The history should identify the circumstances of the infection including any specific risk factors that would both suggest an infection as well as a potential etiology primarily for the purpose of identifying the need for special cultures or other diagnostic interventions not routinely performed (Table 2.1). For example, most bacterial infections have a rapid, crescendo clinical course while atypical mycobacterial, fungal, and parasitic infections are usually more slowly progressive but can be more painful in the later stages. Patients with herpes simplex keratitis will often have a history of oral or genital lesions as well as a history of recurrent red eye or keratitis. Failure of prior therapy, especially of antibacterial and antiviral therapy where clinical resistance is uncommon, should direct suspicion to other pathogen classes.

Clinical examination may also be helpful, although acanthamoebal and herpetic infections at various stages may mimic other pathogens as well as noninfectious etiologies of keratitis. Multiple studies have, however, confirmed the pitfalls of basing empiric treatment solely on the history and clinical appearance, but they may offer direction in the absence of positive studies (Dahlgren et al. 2007; Mascarenhas et al. 2012; Dalmon et al. 2012). Prior corticosteroid use will significantly alter the appearance and prognosis of any form of infectious keratitis and should be noted in context to its clinical appearance. Corneal scrapings offer minimal volume for examination and, therefore, need to be apportioned carefully to the studies that offer the highest probability of yield. Standard tests include Gram and Giemsa stains, direct plating of blood

agar and chocolate agar for bacterial species, as well as Sabouraud's dextrose agar (Fig. 2.1) without antifungal additives for fungal isolation and a broth or other media for anaerobic organisms (Bhadange et al. 2013). Superficial scrapings may be obtained either with a moistened calcium alginate swab or metallic instrument such as a platinum spatula or scalpel blade with reasonably equal yields (Benson and Lanier 1992).

2.2.1 Bacteria

The most common type of corneal infections in developed countries is caused by bacteria usually presenting as a single, suppurative lesion with significant pain, photophobia, and intraocular inflammation (Fig. 2.2). A history of ocular surface compromise, chronic corticosteroid use, ocular surgery, and/or contact lens wear should suggest first a bacterial etiology. Besides simple detection of bacteria, a Gram stain should be helpful in directing therapy since the activity of most antibacterials act on the bacterial cell wall type identified by a Gram-positive or Gram-negative result. Unfortunately, numerous studies have shown a poor correlation with subsequent culture results making the Gram stain unreliable in this regard (Sharma et al. 2002). In an untreated ulcer, standard testing methods should yield an organism in about 70 % of cases (Bourcier et al. 2003). Acid-fast stains may be more helpful in detecting atypical mycobacteria in the setting of chronic corticosteroid use in ocular surface disease or, more recently, LASIK surgery (Fig. 2.3). These lesions are minimally necrotic with small raised white lesions that are gritty on corneal scraping. Pain is often significant in these patients. Lowenstein-Jensen media and 7H11 agar slants offer an environment conducive to the isolation of these organisms. *Nocardia*, a filamentous bacterium, is also partially acid fast and is most often detected with Gram or acid-fast stains in about 65 % of cases and grow slowly on charcoal agar with a yeast extract additive (BCYE) (DeCroos et al. 2011). The lesions may have a wreath-like appearance with raised edge

Table 2.1 Diagnostic tests for microbial keratitis

Organism	Stains	Culture media	PCR target	Confocal microscopy
<i>Bacteria</i>				
Aerobic	Gram	Blood	16 s rRNA	No, exc. specific patterns, e.g., infectious crystalline keratopathy
	Giemsa	Chocolate		
	Acridine orange	Broth (thioglycollate, eugonic, etc.)		
Anaerobic	Gram	Blood (anaerobic incubation)	16 s rRNA	No
	Giemsa	Broth (thioglycollate, eugonic, etc.)		
	Acridine orange			
Mycobacteria	Acid fast	Lowenstein-Jensen	16 s rRNA	No
	Ziehl-Neelsen	7H11		
Nocardia	Gram	Buffered charcoal agar with yeast	Hsp65	Yes
	Acid fast	extract (BCYE) Sabouraud's dextrose agar (SDA) slant	16 s rRNA	
<i>Fungi</i>				
Yeasts	Giemsa	SDA with chloramphenicol or gentamicin	18 s rRNA	Yes
	Periodic acid-Schiff	Brain Heart Infusion (BHI)	28 s rRNA	
	Calcofluor white	Blood (25 °C)	ITS	
Filamentous molds	Giemsa	SDA with chloramphenicol or gentamicin	18 s rRNA	Yes
	Calcofluor white	Brain Heart Infusion (BHI)	28 s rRNA	
	Acridine orange	Blood (25 °C)	ITS	
	Gomori methenamine silver KOH prep			
<i>Virus</i>				
Herpes simplex	Direct fluorescence antigen (DFA)	Human cell line (A549, MRC-5, others)	Thymidine kinase	No
	Tzanck	Serotyping	DNA polymerase	
Adenovirus	Indirect immunofluorescence	Human cell line	Hexon	No
		Serotyping	Fiber	
<i>Parasitic</i>				
Acanthamoeba	Giemsa	Non-nutrient agar with bacterial overlay	18 s rDNA	Yes
	Calcofluor white	BCYE		
	Acridine orange KOH Hematoxylin-Eosin	Sabouraud's		
Microsporidia	Giemsa	Cell lines	16 s rRNA	Yes, uncommon
	Calcofluor white	Monkey (Vero)	18 s rRNA	
	Modified trichrome	Rabbit (RK-13)	ITS	
	Gram	Human (MRC-5) Canine (Madin-Darby)		

and an irregular base. Antibiotic sensitivity testing should be performed on all isolates so that the information is available if a patient does not respond appropriately to empiric therapy.

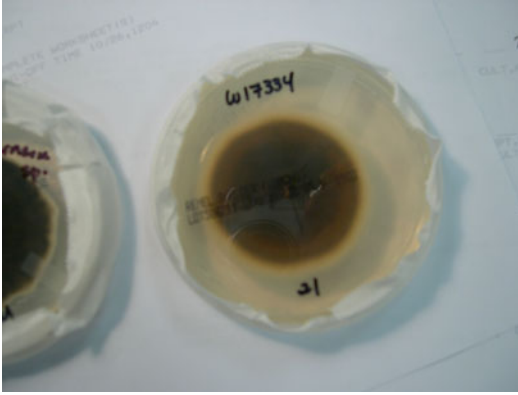


Fig. 2.1 A subcultured colony of an *Alternaria alternata* keratitis isolate on Sabouraud's agar

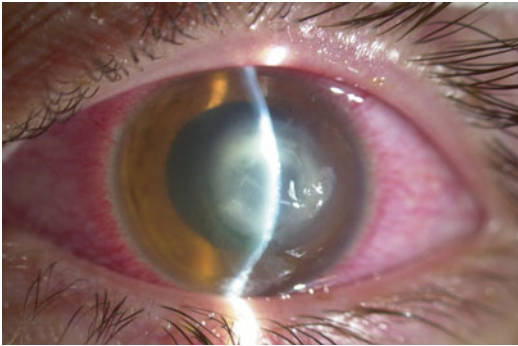


Fig. 2.2 An acutely suppurative contact lens-related *Pseudomonas* corneal ulcer



Fig. 2.3 Atypical mycobacteria after LASIK with limited inflammation sequestered in the corneal interface

2.2.2 Fungi

The presentation of fungal keratitis is species dependent with the most common filamentous mold, *Fusarium*, presenting early with significant pain and proportionally less inflammation than a comparable bacterial ulcer but eventually becoming more infiltrative and characterized by a hypopyon, endothelial plaque, satellite lesions, as well as severe pain and injection (Fig. 2.4). *Fusarium* may rapidly and directly penetrate into the deep stroma and past an intact Descemet's membrane to enter the intracameral space. However, slower-growing species of *Alternaria* or *Beauveria* may be much more indolent with less inflammation, less pain, and a more superficial appearance. *Candida* spp. are the most common overall fungal keratitis pathogen in the more temperate climates of North America and present initially with a creamy-white, superficial infiltrate, but its pseudohyphae may penetrate into deep stroma (Figs. 2.5 and 2.6).

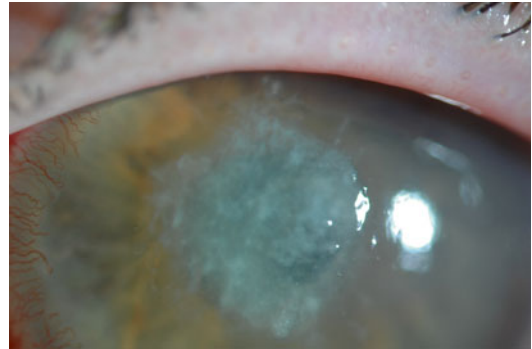


Fig. 2.4 *Fusarium* keratitis in a contact lens wearer

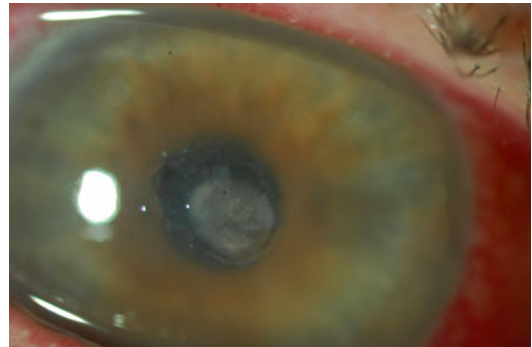


Fig. 2.5 *Candida* ulcer in a patient on chronic topical corticosteroids

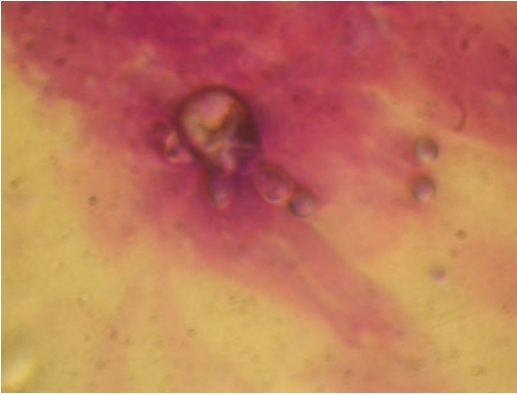


Fig. 2.6 Budding *Candida* sp. on a Diff-Quik smear (original magnification 100×)

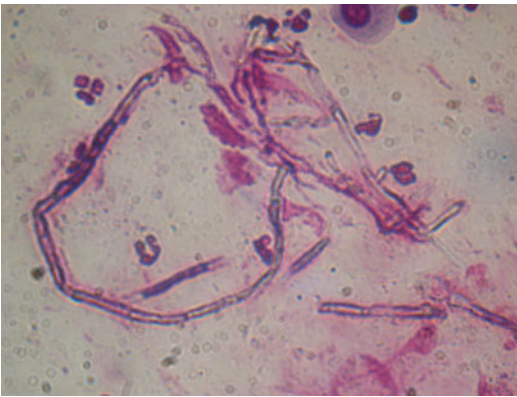


Fig. 2.7 Diff-Quik stain of *Fusarium* sp. hyphae from a corneal scraping (original magnification 100×)

Although yeast and filamentous molds may both be detected on Gram stain, molds are more readily identified on stains that highlight cell walls such as a Giemsa stain and KOH preps where hyphae are easily detected (Fig. 2.7). Similarly, acridine orange and calcofluor white stains have been shown to be more sensitive in detecting larger pathogens like fungi and acanthamoeba but require an epifluorescent microscope to excite the stain (Gomez et al. 1988). The majority of ocular fungal pathogens can be isolated with Sabouraud's dextrose agar or Brain Heart Infusion Agar with non-antifungal additives, e.g., chloramphenicol or gentamicin, since these additives do not affect the saprophytic fungi usually nonpathogenic in other organs (Bhadange et al. 2013). Alternatively, fungal keratitis pathogens will also grow on standard

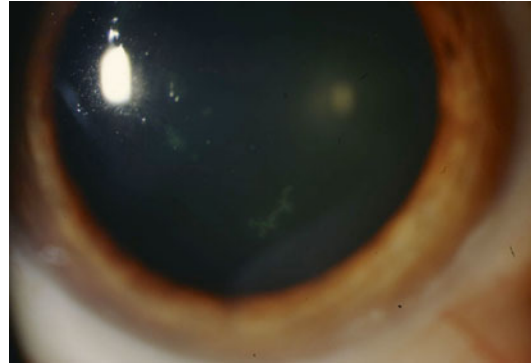


Fig. 2.8 HSV epitheliitis seen in a chronically systemically immunosuppressed chemotherapy patient

blood and chocolate agar plates incubated at 36 °C. Antifungal sensitivities have been poorly reflective, historically, of clinical drug efficacy, but recent refinement of CLSI testing methods and break points have improved correlation of in vitro and in vivo antifungal activity, the knowledge of which can be critical to a successful outcome (Oechsler et al. 2013).

2.2.3 Virus

A diagnosis of herpetic viral disease is most commonly based on the history and clinical appearance. Herpes simplex keratitis is due more commonly HSV 1, associated with above-the-waist disease, but HSV 2 is also commonly isolated (Fig. 2.8). Patients may have a history of oral or genital herpes simplex as well as a past history of vesicular lesions in and around the eye. Although recurrent disease may surface from latency established from a primary infection from any dermatome served by the trigeminal ganglion, recurrences from prior corneal infection is usual. Epithelial HSV keratitis demonstrates a characteristic dendritic pattern with terminal bulbs, leaving an imprint on the anterior stroma after resolution. Geographic lesions may also occur with both stained by Rose Bengal of fluorescein dyes. Primary disease is almost always epithelial, but recurrences may be an epithelial or stromal interstitial keratitis with a conjunctival limbitis, endotheliitis, or

uveitis less common. Patients with atopic keratoconjunctivitis are especially susceptible to severe, bilateral disease. The need for microbiologic confirmation is restricted to neonates and to those patients where the diagnosis is in question. Samples may be obtained through epithelial debridement, swab, or impression cytology of the superficial lesion and submitted for culture, immunofluorescence (IFA), or polymerase chain reaction (PCR) detection. Culture is the least sensitive method while both PCR and IFA have been shown to have similar sensitivities (60–80 %) and high specificities for the detection of HSV-1 in ocular samples (Farhatullah et al. 2004). Serologic testing may be helpful in naïve patients, especially children to rule out HSV as a potential pathogen, but a significant majority of adults have had previous exposure making a positive test unhelpful.

Other herpesviruses including herpes zoster (HZV), Epstein-Barr virus, and cytomegalovirus have been described to cause keratitis. Herpes zoster may manifest as pseudodendritic lesions (poorly branching, absent terminal bulbs), mucoid plaques, stromal keratitis, and/or uveitis characteristically leaving sectoral iris atrophy. Whether some or all of these entities represent immune response or active viral disease is controversial, but virus has been detected in late dendritic disease of HZV which are highly responsive to antiviral therapy (Pavan-Langston et al. 1995). Epstein-Barr virus more commonly causes a nummular keratitis but may also manifest as subepithelial infiltrates or a deep stromal keratitis. Acute and convalescent titers of Epstein-Barr-related IgM and IgG and EBV early antigen may be helpful in this setting. Monoclonal antibodies and PCR of corneal scrapings have been reported but are rarely done (Pflugfelder et al. 1990). Adenoviral epidemic keratoconjunctivitis may similarly be isolated and genotyped from swabs of the ocular surface but is seldom performed except in the setting of tracking large outbreaks of disease. A rapid in office antigen test has been available with a reasonable sensitivity (88 %) and specificity (91 %) to guide treatment and isolation of certain patients (Sambursky et al. 2006).

2.2.4 Parasitic

A number of different parasitic organisms can cause corneal disease. Parasites that are primarily spread to the cornea from endogenous sources include *Onchocerca*, *Leishmania*, and *Trypanosoma* are a devastating source of corneal blindness worldwide. They manifest as peripheral stromal interstitial keratitis at their site of entry, although frank corneal ulceration may sometimes occur. *Acanthamoeba* represents the most common ocular parasitic pathogen in Western world. Contact lens wear (>90 %) is the strongest risk factor for *Acanthamoeba* keratitis in that region with nearly 20 cases per million contact lens wearers per year afflicted in the UK with similar numbers now in the USA (Tu and Joslin 2010). Additional risk factors include exposure to contaminated domestic or environmental water while wearing or caring for the lenses and other hygiene related factors (Tu and Joslin 2010). The infection presents in many forms including a diffuse or pseudodendritic epitheliopathy, anterior stromal keratitis, interstitial keratitis, a ring infiltrate, and/or perineural infiltrates leading to confusion with other infectious and noninfectious processes (Fig. 2.9). Pain in the early stages is minimal but increases with the presence of perineural disease or deep stromal keratitis. Corneal scrapings can be subject to Giemsa stain, acridine orange, KOH preps, and calcofluor white for diagnosis with reasonable sensitivity and specificity (Fig. 2.10). Culture on non-nutrient agar with a bacterial overlay

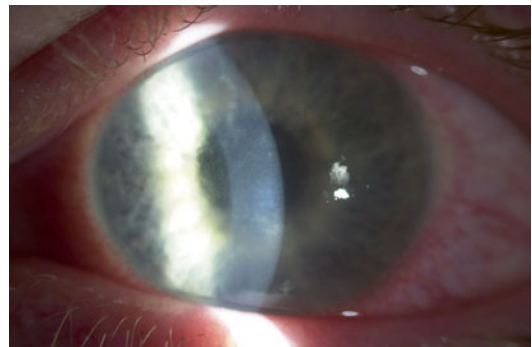


Fig. 2.9 Acanthamoebal epitheliopathy with perineuritis

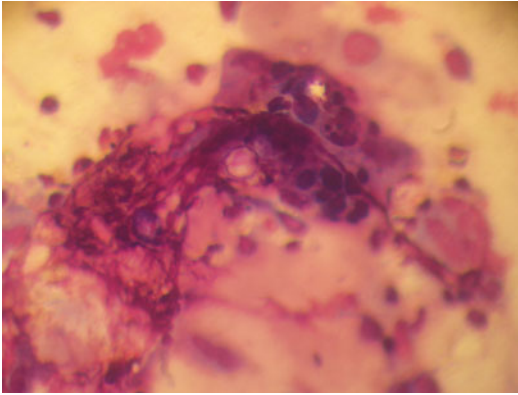


Fig. 2.10 Acanthamoebal cysts on Diff-Quik stain demonstrating classic “pores” in the cyst wall (original magnification 100×)



Fig. 2.11 Confocal microscopy of *Acanthamoeba* exhibiting the classic paired “coffee-bean” appearance on a slit-scanning instrument

(higher yields obtained with *Enterobacter* than *E. coli*) or charcoal agar is relatively simple, but sensitivities are generally low between 35 and 50 %. *Microsporidia* keratitis has been increasingly described in immunocompetent individuals as causing an epithelial/subepithelial keratitis and a stromal interstitial keratitis. These patients usually have some history of exposure to soil or water and have been predominantly described in South Asia. Because it is an obligate intracellular organism, culturing microsporidia is difficult, requiring canine kidney cells for growth. Histologic stains have, therefore, been relied upon to make the diagnosis.

2.2.5 Corneal Imaging and Corneal Biopsy

Confocal microscopy refers to the precise timing of illumination and imaging at a specific focal point or plane to achieve high degrees of magnification, minimizing motion blur and light scatter. The cornea is ideal for this type of imaging because of its relative clarity and lack of reflective elements, to highlight areas of abnormality. Resolution of these instruments are in the 1–2 μm range, making it impossible to image most bacteria and viruses, but specific patterns, e.g., infectious crystalline keratopathy where a biofilm insinuates itself through cornea lamellae, owl eye

cells in CMV endotheliitis, and filamentous bacteria (*Nocardia*) can be recognized (Elmallah et al. 2006; Vaddavalli et al. 2006;. Kobayashi et al. 2012). The greatest utility of the instrument in corneal infectious disorders has been to detect larger pathogens which do not cause dense supuration such as fungi, acanthamoeba, and, to a lesser extent, *Microsporidia* (Sagoo et al. 2007). Both cysts and trophozoites can be seen, but the cysts are most characteristic observed as a double-walled cyst or a paired “coffee bean” appearance isolated or in chains (Fig. 2.11). The detection of *Acanthamoeba* keratitis has been shown in some centers to have a high sensitivity (>90 %) and high specificity (100 %) when compared to culture and other microbiologic methods (Tu et al. 2008a) but has also been reported to be significantly lower in other facilities (Hau et al. 2010). Similar results have been reported in the detection of the slender, septate branching of corneal fungal pathogens (Vaddavalli et al. 2011; Tu and Park 2007) as well as yeast. Confocal microscopy is invaluable in imaging deeper lesions without easy access for scraping such as *Candida* interface keratitis after endothelial keratoplasty (Lee et al. 2011).

Although confocal microscopy has largely supplanted corneal biopsy in many institutions, it remains a relevant technique for refractory or deep keratitides that otherwise defy identification. A number of techniques have been described,

but all involve dissection of a sample of solid corneal tissue either from the anterior lamellae or from mid- to deep stroma using a flap created manually or via a femtosecond laser (Kim et al. 2008). Specimens are sent for histopathology and microbiologic studies with a success of greater than 40 % in identifying a causative organism in a recent review (Younger et al. 2012). Corneal scarring or perforation can be significant risks to corneal biopsy.

2.2.6 Molecular Diagnosis

Molecular diagnosis refers to identification of pathogens from their molecular signature, primarily DNA or RNA which by definition is unique to each organism. Utilizing primers either specific to an organism, a class of organisms, or universal primers, a single copy of DNA can be multiplied a million times over a period of hours, allowing its easy sequencing. Once its sequence has been determined, it can be matched fully or partially to previously sequenced organisms for identification. Because of its high sensitivity, however, false-positive results can be seen because of contamination at any stage of specimen recovery or with organisms that may be present or nonviable but not pathogenic. Extraneous compounds such as topical anesthetic or fluorescein can decrease the sensitivity of the assays (Goldschmidt et al. 2006). Quantitative and real-time PCR with appropriate validation can reduce the number of false-positive test results. It is most useful in detecting organisms not normally present in the eye and/or is difficult to confirm by other means. For example, PCR of tears or corneal scrapings directed toward the HSV polymerase gene has largely supplanted culture for herpes simplex ocular disease because of culture's low sensitivity for an organism which is not normally found in the eye (Farhatullah et al. 2004; Satpathy et al. 2011). Identification of bacterial pathogens is based on their 16 s ribosomal DNA sequences (Prabhasawat et al. 2010), while a more significant experience with the 18 s ribosomal RNA region for the diagnosis of fungal keratitis has

proven its utility (Vengayil et al. 2009; Ferrer and Alio 2011). Recent development of acanthamoebal PCR should lead to its increasing study and validation (Thompson et al. 2008; Goldschmidt et al. 2009).

2.3 Management

Unlike many other organ systems, comparatively small alterations in corneal structure and clarity can profoundly affect lifelong visual function. This combined with the relative inability of the corneal immune response to limit corneal infection makes it imperative to rapidly eliminate pathogens and modulate the corneal immune response to retain as much vision as possible. Empiric therapy is, therefore, directed not only against the most likely responsible pathogens but also against those pathogens most rapidly destructive of the corneal stroma specifically Gram-positive and Gram-negative bacteria. Although other pathogens may be more common in certain regions and mechanisms of injury, atypical bacteria, acanthamoeba, microsporidia, filamentous molds, and yeast are all comparatively slow growing, whereas bacteria may destroy the cornea in a matter of hours.

Since the availability and success of single-drug empiric therapy in the early 1990s, corneal scrapings for culture and smear are no longer routinely employed as part of the initial management of a routine bacterial corneal ulcer. However, microbiologic yields are highest before initiation of any antimicrobial therapy and should be strongly considered in large or deep ulcers, ulcers near the visual axis, ulcers failing prior therapy, and ulcers with either an atypical appearance or history at presentation. Suspicion for a larger, atypical organism at any stage should prompt consideration of confocal microscopy, although corneal biopsy should be reserved for later in the process because of its more invasive nature and higher risk of complication. Ongoing therapy should be directed by initial response or lack of response to initial therapy and directed by microbiologic examination when available.

2.3.1 Bacteria

Since the commercial availability of broad-spectrum fluoroquinolones in the early 1990s, single-drug therapy of presumed bacterial keratitis has been shown to have similar outcomes to multiple, fortified drug therapy (O'Brien et al. 1995; Constantinou et al. 2007). Single-drug therapy has the advantage of availability, easier compliance, and less time off of work, but some studies have pointed to a higher rate of corneal perforation presumably related to its activation of matrix metalloproteinases (Constantinou et al. 2007; Mallari et al. 2001). Although they are considered broad spectrum, having activity against both Gram-positive and Gram-negative bacteria, fluoroquinolones are commonly divided into second (ciprofloxacin, ofloxacin), third (levofloxacin), and fourth (moxifloxacin, gatifloxacin, besifloxacin) generations which predicts their specific antibacterial efficacy. Of these, only besifloxacin has pursued the FDA indication, but more extensive clinical studies of infectious keratitis have sufficiently established the particular spectrums of efficacy of the other fluoroquinolones in bacterial corneal ulceration. In general, the best Gram-negative activity, including *Pseudomonas*, is seen with the second-generation fluoroquinolones, while the fourth-generation fluoroquinolones have added some Gram-positive and atypical mycobacterial coverage. Other antibiotics need to be "fortified" to achieve effective corneal concentrations and combined together to afford the broad-spectrum coverage needed for empiric therapy. This usually consists of topical vancomycin or cephalosporin prescribed with an aminoglycoside like gentamicin or tobramycin.

Inducible antibiotic resistance is increasingly seen in both systemic and ocular infections. For corneal isolates specifically, methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly reported in postsurgical corneal ulceration, and the laboratory resistance of *Pseudomonas* sp. to fluoroquinolones is rising secondary to both local and systemic use (Ray et al. 2013; Fintelmann et al. 2011). Despite laboratory resistance, topical ophthalmic anti-

otics generally deliver sufficient concentrations of drugs to be clinically effective, but infections may be slower to resolve (Wilhelmus et al. 2003). While MRSA demonstrates high levels of fluoroquinolone resistance, vancomycin still remains almost universally effective against ocular pathogens. Vancomycin-resistant enterococcus is a rare but increasingly reported pathogen for infectious keratitis but may be sensitive to newer antibiotics like linezolid (Tu and Jain 2013). Similarly, 4th-generation fluoroquinolones have some activity against atypical mycobacteria, but primary therapeutic options remain topical fortified amikacin or clarithromycin with recent reports of linezolid sensitivity. *Nocardia* spp. are sensitive to fluoroquinolones but may also respond to amikacin and topical sulfamethoxazole-trimethoprim.

Topical corticosteroids should reduce inflammatory damage by modulating corneal damage in infectious keratitis but theoretically has the potential to worsen infections that require an intact immune response for clearance of the pathogen. Multiple studies have demonstrated a worsening of outcomes in vitro and in vivo when corticosteroid administration precedes effective antibacterial therapy but were less definitive when administered with or after initiation of antibiotics (Wilhelmus 2002). A recent prospective, randomized trial of corticosteroid administration 48 h after antibiotic initiation demonstrated no increase in complications with a trend toward improved visual acuity in those patients presenting with severe visual loss (Srinivasan et al. 2012). Future studies should help define the optimal indications and timing for administration of corticosteroids for bacterial keratitis.

2.3.2 Fungi

The treatment of fungal keratitis is significantly more challenging than bacterial keratitis because of the nature of fungal infections of the cornea and the limited options for topical and systemic therapy. The recognition of fungal keratitis is usually delayed, and fungal pathogens are often more deeply infiltrative which further hampers

sufficient delivery of poorly penetrating antifungals to the deeper cornea (Table 2.2). Natamycin, an ophthalmic suspension of the polyene class drug pimarinic, is the only commercially available antifungal in commercial production. It is most efficacious against filamentous molds and was recently shown to be superior to voriconazole in the treatment of *Fusarium* keratitis, the most common fungal corneal pathogen, and similarly effective for other molds (Prajna et al. 2013). Topical amphotericin B 0.15 %, a compounded polyene antifungal, is effective against most fungi and was considered the drug of choice for yeast pathogens. Both drugs are associated with considerable ocular surface toxicity and irritation with topical use. Systemic use of amphotericin

B, 1st- and 2nd-generation triazoles such as ketoconazole, fluconazole, and itraconazole have been described, but penetration into ocular tissues for the azoles is limited and severe side effects from all of the drugs limit their utility in all but the more refractory cases, especially amphotericin B. More recent preparations are much better tolerated. Compounded topical formulations of clotrimazole, itraconazole, and fluconazole have also been described for specific uses (Tu 2009). Because of the long turnaround time from order to result, all suspected fungal ulcers should be isolated, definitive identification pursued and antifungal sensitivities obtained without regard to the initial clinical response so that therapeutic options are available if and when treatment fails.

Table 2.2 Current antifungal drugs utilized for ocular infections

Drug	Topical concentration (common dosage)	Intrastromal concentration	Subconjunctival concentration	Intracameral concentration	Systemic dosing	Spectrum of activity
<i>Polyenes</i>						
Natamycin	5 %	N/A	N/A	N/A	N/A	Filamentous molds Minor activity against yeasts
Amphotericin B	0.1–0.5 % (0.15 %)	5 mcg/0.1 cc	1 mg/0.5 ml	5–10 ug/0.1 cc	0.1–1.5 mg/kg daily dosage slow IV infusion	Broad-spectrum activity against both molds and yeasts
<i>Imidazoles</i>						
Ketoconazole	5 %				2–400 mg po daily	
Clotrimazole	1 %	N/A	N/A	N/A	N/A	Broad spectrum
Miconazole	10 mg/ml	N/A	5 mg/0.5 cc	N/A	N/A	Broad spectrum
<i>Triazoles</i>						
Itraconazole	1 %	N/A	N/A	N/A	200 mg po bid	Broad spectrum
Fluconazole	2 mg/ml	N/A	N/A	N/A	200 mg po QD	Broad spectrum
Voriconazole	1 %	50 mcg/0.1 cc	N/A	50–100 mcg/0.1 cc	200 mg po bid	Broad spectrum
Posaconazole	200 mg/5 ml	N/A	N/A	N/A	400 mg po bid	Broad spectrum
<i>Echinocandins</i>						
Caspofungin	0.5 %	N/A	N/A	N/A	N/A	Yeasts, selected molds
Micafungin	0.1 %	N/A	N/A	N/A	N/A	Yeasts, selected molds

A number of new antifungals from the triazole (voriconazole, posaconazole, ravuconazole) and echinocandin (casposungin, micafungin, anidulafungin) classes have been recently introduced. The triazoles are better absorbed, achieve higher tissue levels, and have a broader spectrum than previous azoles. Multiple reports of clinical resolution of keratitis and consecutive intracameral fungal endophthalmitis have been reported with systemic administration of these drugs (Tu and Park 2007; Tu et al. 2007). Although topical voriconazole was shown to be inferior to natamycin in *Fusarium solani* keratitis, it has been reported to be successful in a number of atypical fungal keratitides highlighting the utility of antifungal sensitivity testing for individual isolates. Since it is highly aqueous soluble, voriconazole as well as amphotericin B has been delivered intrastromally in recalcitrant fungal ulcers with sometimes dramatic resolution after a single injection (Garcia-Valenzuela and Song 2005; Prakash et al. 2008). Unlike bacterial keratitis, a certain number of fungal corneal infections will not be amenable to medical cure either due to pan-resistance to antifungals or because of the extent of infection. Circumscribable lesions which are responding poorly to medical therapy should be considered for early corneal transplantation. The lack of highly effective antifungals and the potentiation of fungal proliferation makes the use of corticosteroids at any point during routine treatment inadvisable. For this reason, alternative immune suppressants such as topical cyclosporine have been utilized post-keratoplasty.

2.3.3 Virus

In immunocompetent individuals, herpes simplex epithelial keratitis is a self-limited disease. Visual disability from a single episode is uncommon but increases significantly with reactivation of the virus from its latent state in the trigeminal ganglia resulting in repeated episodes epithelial keratitis, stromal or endothelial involvement, and/or uveitis (Young et al. 2010). Therapy is, therefore, directed against primary involvement of the cornea, although infection in any dermatome of CN V may result in corneal recurrence and prevention of recurrent disease. Although topical and systemic therapy is often prescribed to patients with periocular outbreaks, avoidance of direct inoculation is critically important. For corneal epithelial disease, commercially available ophthalmic treatments include topical trifluridine, the most epithelially toxic, and ganciclovir in the USA and topical acyclovir abroad which can reduce the duration of epithelial disease by 1–2 days (Table 2.3). Use of topical drugs should be limited to a 10-day period before reassessment for potential toxicity simulating active disease. The Herpetic Eye Disease Study did not find that a 3-week course of oral acyclovir (400 mg 5×/day) prevented progression of an epithelial HSV keratitis to stromal keratitis or iritis, but did find a suggestion that oral acyclovir may be beneficial in treating HSV iritis. Although topical corticosteroids did not affect final outcome, resolution of HSV keratitis symptoms was significantly more rapid when used in conjunction with an antiviral. Importantly, the study did find that long-term prophylaxis with oral acyclovir

Table 2.3 Current antiviral drugs utilized for ocular infections

Drug	Topical concentration	Systemic dosing HSV	Systemic dosing HZV
Acyclovir	3 % 5×/day	400 mg po 5 ×/day	800 mg po 5×/day
Famciclovir	N/A	250 mg po 3/day	500 mg po 3×/day
Valacyclovir	N/A	500 mg po tid	1 g po tid
Ganciclovir	0.15 % 5×/day	N/A	N/A
Trifluridine	1 % 9×/day	N/A	N/A
Idoxuridine	0.1 (soln)–1.0 (ointment)%	N/A	N/A
Vidarabine	3 % 5×/day	N/A	N/A
Valganciclovir	N/A	CMV – 900 mg po bid	

(400 mg 2×/day) reduced by half the number of recurrences of HSV ocular disease. This benefit has been confirmed in subsequent series (Young et al. 2010). Valacyclovir is a prodrug which is converted to acyclovir in vivo and demonstrates oral absorption ~5 times greater than oral acyclovir. This results in lower-frequency dosing which may be better tolerated and improve compliance with long-term prophylaxis. Long-term prophylaxis, however, may select for acyclovir-resistant strains, already high in patients with HSV keratitis, which would also be resistant to the common systemic alternatives of valacyclovir, famciclovir, or ganciclovir (van Velzen et al. 2013). The development of Herpes simplex vaccines has the potential to reduce both primary infection as well as suppress viral reactivation but has yet to be realized.

Herpes zoster keratitis is also usually self-limited and is not as prone to frequent recurrences, although chronic stromal keratitis can be blinding. Topical antivirals are usually unnecessary except in late pseudodendritic disease or mucoid plaques. Inflammatory stromal keratitis can be treated with topical corticosteroids. Both herpes simplex and herpes zoster keratitis, however, may develop blinding complications related to neurotrophic keratitis and/or chronic stromal inflammation. Persistent epithelial defects may lead to corneal melting and scarring, metaherpetic lesions may mimic persistent infection but require corticosteroids for resolution, and chronic stromal keratitis may lead to vascularization and corneal opacification. Because the prognosis for corneal transplantation is dismal in this setting, every effort should be taken to preserve sufficient clarity of the patient's cornea with adequate immunosuppression, treating the corticosteroid side effects of cataract formation and glaucoma as needed. The effect of the increasing use of herpes zoster vaccines on recurrent ocular disease is yet unknown, but selective application of the vaccine may have unintended consequences in increasing reactivations in patients currently excluded from vaccination windows.

Although adenoviral disease is normally of minimal visual impact, the sheer number of sufferers and the uncommon moderate visual

disability caused by EKC attracts attempts at treatment. Several promising antiviral compounds have been found to be of limited benefit and have been abandoned. Topical betadine corticosteroid combinations are currently being studied. Despite the availability of topical ganciclovir, no specific justification for its use in this disorder has yet surfaced.

2.3.4 Parasitic

The management options for *Acanthamoeba* keratitis are limited, and visual outcomes are highly dependent on early recognition and initiation of effective therapy (Tu et al. 2008b). A high index of suspicion should be held in all atypical keratitides especially in contact lens wearers. Once a diagnosis is made, debridement of all involved epithelium to debulk the infection is performed both for therapeutic and diagnostic purposes. The mainstay of therapy are the biguanides, either chlorhexidine 0.02 % or polyhexamethylene biguanide (PHMB) 0.02 % administered hourly for the first several days followed by a slow taper usually over several months based on clinical response (Table 2.4) (Dart et al. 2009). Adjunctive use of diamidines, propamidine or hexamidine, can be helpful in the early stages of treatment to inhibit encystment and kill active trophozoites but exhibit cumulative toxicity over several weeks. A minority of cases may be recalcitrant requiring increased biguanide concentrations, increased frequency of administration, and/or the addition of systemic medications. Topical neomycin and clotrimazole have also been described. Other previous generation azoles have been added systemically with limited evidence of benefit. The successful adjunctive use of topical and the sole use of oral voriconazole have been reported in the cure of *Acanthamoeba* keratitis (Tu et al. 2010; Bang et al. 2010). *Acanthamoeba* keratitis may also cause adnexal disease consisting of limbitis, scleritis, and dacryoadenitis as well as late complications of glaucoma, cataract, and permanent mydriasis. Corneal melting, persistent epithelial defects, and persistent stromal disease can severely complicate treatment. No definitive evi-

Table 2.4 Current antiparasitic drugs utilized for ocular infections

Drug	Topical dosing	Systemic dosing
<i>Aminoglycosides</i>		
Neomycin	15 mg/cc Q1h	N/A
<i>Diamidines</i>		
Propamidine	0.1 % Q1h	N/A
Hexamidine	0.1 % Q1h	N/A
<i>Biguanides</i>		
Chlorhexidine	0.02–0.6 % Q1h	N/A
Polyhexamethylene biguanide	0.02–0.06 % Q1h	N/A
<i>Triazoles</i>		
Itraconazole		200 mg po bid
Voriconazole	1 % Q1h	200 mg po bid
<i>Anti-microsporidial</i>		
Fumagillin	0.3 % qid	N/A
Albendazole	N/A	400 mg po bid × 1 week then 200 mg po bid × 2 weeks then 200 mg po daily × 1 week
Fluoroquinolones	Q1h tapered according to response	N/A
Mechanical debridement	As needed	

dence yet exists for a detrimental effect of corticosteroid therapy on *Acanthamoeba* keratitis, and many of the corneal and extracorneal complications are immune in nature but still should be avoided if not needed. Selected cases may benefit from immune suppression either with corticosteroids or other systemic drugs to preserve ocular function (Dart et al. 2009). Similarly, the prognosis for corneal transplantation in active corneal disease has improved significantly with the use of effective anti-acanthamoebal therapy and should be considered a well-circumscribed, recalcitrant disease (Kitzmann et al. 2009). Microsporidial disease remains rarely described in the USA. Increased incidence of disease in Asia is a considerably different disease entity than previously described in immunosuppressed patients, occurring in immunocompetent individuals and responding to various commercially available topical antibacterials as well as observation only (Tu and Joslin 2012). Some patients will still progress to corneal transplantation, however.

Collagen cross-linking, a therapeutic intervention designed to “harden” the cornea with riboflavin-assisted UV irradiation for cases of corneal ectasia, has been recently described for a number of cases of infectious keratitis of varying

etiologies. In vitro studies, however, show no effect on acanthamoebal cysts or fungi and a variable effect on most bacteria with the concentrations of riboflavin and UV exposures utilized for cross-linking. The depth of penetration of standard treatments is also limited to the anterior cornea. Recent studies have demonstrated a reduction in corneal necrosis and overall improvement in bacterial ulcers and some acanthamoebal ulcers as an adjunctive treatment to medical therapy with fungal ulcers being the least responsive (Price et al. 2012; Makdoui et al. 2010; Alio et al. 2013). There is little agreement on the mechanism, indications, or complications for collagen cross-linking and will be the continued subject of studies for the near future.

Conclusions

Infectious keratitis can lead to significant ocular morbidity and loss of overall function and represents both a diagnostic and management challenge. Prevention and prompt diagnosis relies on an understanding of the prevalent risk factors for corneal infection which vary from contact lens wear in more economically developed areas to trauma in less developed areas. Common pathogens will vary based on

these risk factors as well as climate, local immunosuppression, and mechanism of injury. While almost all initial empiric therapy for infectious keratitis must target common bacterial pathogens because of their propensity for rapid corneal destruction, a high index of suspicion should be held for unresponsive or atypical appearing keratitides. All of these patients should be subject to culture and sensitivity testing. With all forms of infectious keratitis, final visual outcomes are highly dependent on minimizing delay in the administration of effective antimicrobial treatment. Topical ophthalmic administration provides a highly concentrated route of drug delivery. Treatment efficacy should be judged by frequent observation regardless of culture results and changed if found to be ineffective. A flexible approach to utilizing available diagnostic techniques and treatment options alongside innovative drugs, alternative routes of administration, and judicious use of immunosuppressants will improve long-term visual outcomes.

Compliance with Ethical Requirements Elmer Tu declares that he has no financial interests in the subject matter of the manuscript.

No animal or human studies were carried out by the authors for this article.

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