

# Contact lens associated microbial keratitis: practical considerations for the optometrist

Aaron B Zimmerman  
Alex D Nixon  
Erin M Rueff

College of Optometry, The Ohio State University, Columbus, OH, USA

**Abstract:** Microbial keratitis (MK) is a corneal condition that encompasses several different pathogens and etiologies. While contact lens associated MK is most often associated with bacterial infections, other pathogens (fungi, *Acanthamoeba* species, etc) may be responsible. This review summarizes the risk factors, microbiology, diagnostic characteristics, and treatment options for all forms of contact lens-related MK.

**Keywords:** corneal ulcer, fungal keratitis, bacterial keratitis, *Acanthamoeba*, *Fusarium*, *Pseudomonas*

## Introduction

There are approximately 38 million individuals wearing contact lenses in the United States.<sup>1</sup> Contact lens wear significantly increases the risk of ocular complications, specifically microbial keratitis (MK), which is the most severe complication and is vision threatening.<sup>2</sup> MK is a term that includes bacterial keratitis (BK), fungal keratitis (FK), and *Acanthamoeba* keratitis (AK) (Table 1). Geographically, the causes of MK differ. In non-Westernized countries, trauma is the leading cause of MK,<sup>3,4</sup> whereas in Westernized countries, contact lens wear is equal to or often exceeds trauma as the most significant cause.<sup>5-7</sup> This review describes the incidence, risk factors, and pathogenesis of contact lens associated MK and the practitioner's role in properly diagnosing, culturing, and managing these severe complications.

## Incidence

The first large epidemiological study on contact lens-related MK was published in 1989, and the incidence rate of MK among individuals wearing lenses in the daily wear modality was 4.1 per 10,000 individuals per year (Table 2).<sup>8</sup> In 2008, Stapleton et al reported an annual MK incidence rate in daily wear of 1.9 per 10,000 wearers,<sup>9</sup> which is consistent with other studies.<sup>10-12</sup>

Compared with daily wear, overnight (extended wear, EW) use of soft contact lenses is associated with a higher risk of MK. EW, irrespective of material type, has been shown to be the primary factor for corneal infection with an annual incidence of approximately 20 per 10,000.<sup>9,13</sup> Interestingly, sporadic or occasional EW has been shown to be a more significant MK risk factor than continuous wear.<sup>14</sup> The introduction of highly oxygen-permeable silicone hydrogel materials has not provided the anticipated decrease in MK associated with EW. The incidence of MK and corneal inflammatory events<sup>15</sup> with silicone hydrogel EW has been shown to be the same<sup>14,16</sup> or greater<sup>17</sup> than lower oxygen permeability hydrogel materials. While silicone hydrogel materials

Correspondence: Aaron B Zimmerman  
College of Optometry, The Ohio State University, A317 Starling Loving Hall, 338 West 10th Avenue, Columbus, OH 43210, USA  
Tel +1 614 247 6188  
Fax +1 614 247 6626  
Email zimmerman.178@osu.edu

**Table 1** Types of microbial keratitis and the primary risk factors for acquiring these infections in Westernized countries

% MK due to:	Bacterial	Fungal	<i>Acanthamoeba</i>
Contact lens	33.7 <sup>7</sup> –50.3 <sup>5</sup>	25 <sup>124</sup> –29.2 <sup>33</sup>	85 <sup>84</sup> –93 <sup>86</sup>
Trauma	15 <sup>5</sup> –36.4 <sup>7</sup>	8.3 <sup>33</sup> –26 <sup>124</sup>	7 <sup>86</sup> –15 <sup>84</sup>
Ocular surface disease	6.9 <sup>7</sup> –21.3 <sup>5</sup>	29 <sup>24</sup> –41.7 <sup>33</sup>	NR
Other <sup>a</sup>	13.4 <sup>5</sup> –23 <sup>7</sup>	16.7 <sup>33</sup> –20 <sup>124</sup>	NR

**Note:** <sup>a</sup>Other refers to history of ocular surgery, steroids, systemic disease, and unknown risk factors.

**Abbreviation:** MK, microbial keratitis; NR, not reported.

reduce hypoxia-related complications, they do not eliminate exposure to pathogenic organisms. It has been suggested that silicone hydrogel materials may alter epithelial homeostasis, resulting in mechanical stress that makes the cornea more susceptible to inflammatory and/or infectious events.<sup>17</sup>

The incidence of MK with gas-permeable (GP) materials ranges between 0.8<sup>10</sup> and 4.0<sup>8</sup> per 10,000 per year. These reported rates included both daily wear and EW. Orthokeratology, a form of GP lens vision correction, involves wearing lenses overnight to reshape the cornea and correct myopia. The annual rate of MK associated with orthokeratology is estimated to be 7.7 per 10,000.<sup>18</sup> In Asian countries, orthokeratology-related MK has been shown to be most common in areas with more prevalent myopia.<sup>19</sup> It has been suggested that this higher prevalence may be due to poor regulation in these areas.<sup>20</sup> Regardless of wearing soft or GP contact lenses, EW significantly increases the risk of contracting MK compared with daily wear.

## Risk factors

MK in contact lens wearers is typically associated with non-compliant or unhygienic contact lens practices. Many of these risky behaviors which include EW,<sup>2,8–10</sup> poor storage case hygiene and infrequent case replacement,<sup>9,21,22</sup> smoking,<sup>2,8–10,23</sup> lack of hand washing,<sup>10</sup> and purchasing lenses on the internet<sup>9</sup> are all modifiable. Nonmodifiable risk factors are wearing lenses for less than 6 months,<sup>9</sup> male sex,<sup>8,24</sup> socioeconomic status,<sup>9</sup> and possibly a genetic predisposition.<sup>25,26</sup>

Lens-related MK risk factors include cosmetic lenses, as these lenses are often not prescribed by an eye care professional and therefore, patients have less knowledge of proper lens care.<sup>27</sup> Daily disposable lenses do not eliminate the risk of MK,<sup>9,13</sup> however, there may be a lower risk of vision loss when compared with planned replacement.<sup>9,13</sup> The type of contact lens disinfection system used has been found to modify the risk of MK,<sup>28</sup> and specific brands were responsible for the FK<sup>29</sup> and AK<sup>30</sup> outbreaks.

FK and AK cases have additional risk factors that need to be ruled out when MK is present. FK associated with vegetative trauma and/or ocular surface disease is most common in tropical and subtropical climates.<sup>31,32</sup> Trauma or corneal compromise caused by contact lens wear has also been suggested as a risk factor.<sup>31,33</sup> *Candida* species tend to infect corneas that are comprised due to ocular surface disease and/or systemic immunodeficiency<sup>31,34</sup> and are more common in temperate climates.<sup>31,34</sup>

*Acanthamoeba* associated MK, while relatively rare,<sup>35</sup> often results in severe vision loss due to misdiagnosis.<sup>36</sup> Because of the frequent misdiagnosis of this condition, longer duration of symptoms and history of antibiotic use have been listed as risk factors.<sup>36</sup> As mentioned above, exposure to infected water is a well-known risk factor for *Acanthamoeba* infection.<sup>28</sup> This exposure may occur when contact lenses are cleaned/stored in tap water, or when a patient is exposed to bodies of water that could be infected (lakes, hot tubs, etc).<sup>28,37</sup>

## Pathogenesis

### Inherent protective mechanisms and contact lens-induced alterations

A healthy corneal surface is not susceptible to microbial infection. Chronic ocular surface disease, corneal trauma, ocular surgery, and contact lens wear increase the cornea's susceptibility to infection. The mechanisms of contact lens-related corneal infection are not fully understood; however, several models exist for bacterial, fungal, and protozoan infections.

**Table 2** Annual incidence of contact lens-related bacterial, fungal, and protozoan keratitis

Lens type	Bacterial	Fungal	<i>Acanthamoeba</i>
Overall incidence	4 <sup>9</sup> /10,000	~1/50,000 <sup>119a</sup>	1–33/million <sup>35</sup>
Soft lenses (daily wear)	1.9 <sup>9</sup> –4.1 <sup>8</sup> /10,000	NR	NR
Soft lenses (extended wear)	19.5 <sup>9</sup> /10,000	NR	NR
Hydrogel	9.3 <sup>10</sup> –20.9 <sup>9</sup> /10,000	NR	NR
Silicone hydrogel	20.9 <sup>4</sup> –25.4 <sup>9</sup> /10,000	NR	NR
Gas-permeable (daily wear)	0.8 <sup>10</sup> –4.0 <sup>9</sup> /10,000	NR	NR
Orthokeratology	7.7 <sup>18</sup> /10,000	NR	NR

**Note:** <sup>a</sup>Estimation calculated from Konda et al<sup>119</sup> which stated 5% of all contact lens microbial keratitis is fungal.

**Abbreviation:** NR, not reported.

The non-contact lens exposed cornea easily resists microbes from “sticking” to the ocular surface through several inherent protective mechanisms employed by the tear fluid and corneal epithelium.<sup>38</sup> The tear fluid, along with blinking, clears pathogens from the cornea and contains antimicrobial components such as lysozyme and lactoferrin.<sup>39</sup> The epithelial cells also produce peptides and mucins that are inherently antimicrobial.<sup>40</sup> The epithelial tight junctions serve as a physical barrier to microbes, however, even when the superficial junctions are damaged, *Pseudomonas* cannot traverse the protective anterior limiting lamina (Bowman’s membrane) to the stroma.<sup>41</sup> This suggests that superficial fluorescein staining does not lead to MK.<sup>42</sup>

Contact lens wear disrupts some of these innate defenses and renders the cornea more susceptible to infection. Lens wear, regardless of oxygen transmissibility, has been shown to decrease epithelial mitosis, differentiation,<sup>43</sup> and exfoliation.<sup>44</sup> These processes create a stagnant epithelium and render the cornea more susceptible to infection. Hypoxic conditions have been shown to decrease epithelial exfoliation, but hypoxia alone does not increase *Pseudomonas* binding.<sup>45</sup> Hypoxia can lead to increased *Pseudomonas* corneal binding, but only when a contact lens is also present.<sup>46</sup>

Contact lens wear has also been shown to mechanically damage the epithelium, resulting in punctate epithelial erosions.<sup>47</sup> Interestingly, though the surface damage is worse with a GP, there is increased *Pseudomonas* epithelial binding with soft lenses from reduced tear exchange beneath the contact lens.<sup>47</sup> Planktonic, or free floating, bacteria adhere to the surface of the contact lens and can form virulent biofilms which are less susceptible to the normal antimicrobial defense mechanisms of the tears and epithelium.<sup>42</sup> Biofilms on the posterior contact lens surface place bacteria in close proximity to the epithelium and these microbes cannot be easily cleared away, creating a stagnant tear environment.<sup>48</sup>

## Bacterial keratitis model

The majority of contact lens-related bacterial ulcers are due to *Pseudomonas*,<sup>6,49</sup> and the stagnant post-lens tear environment may allow for *Pseudomonas* to “stick” to the corneal epithelium which must happen in order for an infection to develop.<sup>50</sup> *Pseudomonas* adheres to the corneal epithelium via specific receptors expressed on the outer cell membrane.<sup>51</sup> Specific to *Pseudomonas*, there is an invasive phenotype, exoenzyme S (exoS) gene, and a cytotoxic phenotype, exoenzyme U (exoU) gene. The invasive form enters epithelial cells via lipid rafts, replicates intracellularly, and

eventually causes host cell death.<sup>50</sup> Interestingly, the presence of *Pseudomonas* alone does not trigger lipid raft development, but a low oxygen transmissible lens also is necessary. The cytotoxic phenotype is associated with severe corneal inflammation and tissue damage due to the extracellular injection of a potent cytotoxin.<sup>52</sup> Choy et al suggested that with contact lens wear, the cytotoxic phenotype is isolated more often than the invasive phenotype;<sup>53</sup> however, a recent article suggests otherwise.<sup>54</sup>

Regardless of the phenotypes listed above, *Pseudomonas* species have additional virulence factors such as adhesins,<sup>55</sup> flagella,<sup>56</sup> several forms of toxins,<sup>57</sup> and have even been capable of metabolizing some antibiotics.<sup>58</sup> They also employ auxiliary genetic code in the form of plasmids.<sup>57</sup> These factors allow the bacterium to be extremely dynamic and potentially evade host defense mechanisms which compounds tissue damage and can result in worse visual outcomes.

## Fungal keratitis model

In the United States, FK most often occurs from agricultural related trauma, contact lens wear, and ocular surface disease.<sup>59</sup> Filamentous fungi, such as *Fusarium* and *Aspergillus*, tend to be most often associated with contact lens wear and trauma, while those with ocular surface disease are more prone to yeasts.<sup>59</sup>

Contact lens-related FK likely results from fungal biofilms, which can be firmly attached to the posterior side of the lens or even extend into the lens matrix.<sup>60</sup> Using a murine model, it has been shown that hyphae from *Fusarium* or *Aspergillus* in contact with the corneal epithelium may disrupt epithelial integrity.<sup>61</sup> If the epithelial integrity is affected, then hyphae have the capability of breaching the basement membrane and the anterior limiting lamina and ultimately reaching the stroma.<sup>62</sup> Once in the stroma, the hyphae can continue to extend through the stroma and in some cases can perforate the cornea reaching the anterior chamber.<sup>62</sup> The extending hyphae result in the feathery border appearance that is classically seen with FK.<sup>62</sup> Neutrophils are recruited to the site and release proteolytic enzymes<sup>61</sup> and reactive oxygen species<sup>64</sup> which eradicate the fungus, but can also cause substantial collateral tissue damage. The cumulative inflammation may also trigger the development of a hypopyon and an endothelial plaque.<sup>59,62</sup>

## Acanthamoeba keratitis model

According to the Centers for Disease Control and Prevention, *Acanthamoeba* is commonly found in soil, water, and air.<sup>65</sup> Contact lens-wearing individuals who expose their lenses to water through swimming, hot tubs, trauma with contaminated

water, or care for their lenses with water are at greater risk of infection.

The largest risk factor for contact lens-related AK is poor compliance with lens care which leads to subsequent biofilm formation.<sup>66</sup> These biofilms, such as those formed by *Pseudomonas aeruginosa* provide a nutrient-rich environment for *Acanthamoeba* trophozoites to thrive.<sup>66</sup> Once *Acanthamoeba* is present on the surface of the contact lens, the cornea is at increased risk of infection.<sup>66</sup> Khan et al found that for *Acanthamoeba* to bind to and develop a corneal infection, a previous insult to the epithelial tissue must be present.<sup>67</sup> Omana-Molina et al have recently found that *Acanthamoeba* are actually capable of binding to intact epithelium.<sup>68</sup>

*Acanthamoeba* trophozoites are likely present during epithelial binding, because the cystic form shows minimal binding capability.<sup>69</sup> The trophozoites adhere to the epithelium using mannose-binding protein<sup>70</sup> and other laminin-binding proteins.<sup>69</sup> Contact lenses have been shown to stimulate glycoprotein expression,<sup>71</sup> and the mannose-binding protein may have greater tendency to bind to the epithelium.<sup>72</sup> Once bound to the corneal epithelium, the trophozoites use phagocytosis for nutrition and secrete toxins, such as serine proteases, collagenases, and stimulate the activity of cytotoxic matrix metalloproteinases, which creates a cytopathic effect.<sup>73</sup> The cytopathic effect includes killing host cells by phagocytosis, apoptosis, or cytolysis, followed by degradation of the epithelial basement membrane and anterior limiting lamina, and subsequent migration into the corneal stroma. Interestingly, *Acanthamoeba* does not typically breach the corneal endothelium<sup>74</sup> and this is thought to be due to an intense response from neutrophils.<sup>75</sup>

When the trophozoites experience a change in pH, temperature, lack of nutrition, or chemicals they can form double-walled cysts.<sup>76</sup> Cysts are very difficult to treat and have been found in postinfected corneas 31 months after onset and in some cases likely longer.<sup>77</sup> The corneal infection is not truly gone until all the trophozoites and cysts have been removed from the cornea.<sup>77</sup>

## Diagnosis

### Patient history

Proper diagnosis of MK is based on a combination of patient symptoms, pertinent ocular history, clinical examination, and culturing. The patient's history and symptoms provide us valuable clues regarding the etiology of the keratitis. Trauma due to vegetative debris often is associated with

FK while a history of hot tub use or contact with stagnant water suggests AK. Patients with a history of contact lens wear are at risk for any form of MK and should be further questioned to elucidate potential risk factors such as overnight wear, poor contact lens, or case hygiene, swimming in contact lenses, or using water for cleaning, disinfection, or storage.

### Bacterial keratitis

Individuals with BK will often experience significant pain, photophobia, and likely enter the clinic with reduced visual acuity (Table 3). The onset of symptoms often occurs quickly. There are several common slit lamp characteristics found with BK. A corneal infiltrate, or multiple corneal infiltrates are found in every case, while the size of the infiltrate can vary dramatically.<sup>5</sup> An infiltrate that is greater than or equal to 1 mm in width is often considered infectious.<sup>78</sup> Depending on the severity of the infection, infiltrate depth can vary with the majority (77%) being confined to the anterior one-third of the stroma.<sup>5</sup> The epithelium overlying the infiltrate is often absent, and the tissue may appear slightly excavated.<sup>79</sup> A noninfectious ulcer often has an overlying staining area that is smaller than the infiltrate diameter.<sup>79</sup> Anterior chamber inflammation may be present with hypopyon developing between 6.1%<sup>5</sup> and 55%<sup>36</sup> of the time. The bulbar conjunctiva is often diffusely injected, and the discharge can range from a watery to a mucopurulent consistency.<sup>79</sup> In addition to the ocular surface changes, the eyelids may also be edematous.<sup>79</sup>

### Fungal keratitis

The patient history and onset of symptoms is essential when diagnosing FK. Fungi need time to grow, so symptoms may be delayed for 5–10 days.<sup>62</sup> AK and BK typically will have a faster onset of symptoms.

The clinical appearance of FK depends on whether the infection is due to filamentous fungi such as *Fusarium* and *Aspergillus* or a yeast such as *Candida*. Corneal infections due to *Candida* often resemble BK as there is a round or ovalish epithelial defect with surrounding inflammation.<sup>80</sup> Mycotic keratitis due to *Fusarium* or *Aspergillus* will be associated with “feathery” edges, elevated slough,<sup>62,81</sup> and satellite infiltrates.<sup>82</sup> A hypopyon can develop<sup>81</sup> as can an endothelial plaque.<sup>83</sup> Thomas et al compared the slit lamp signs of patients with fungal and BK, and found that serrated margins, raised slough, and satellite lesions were more often associated with FK, whereas BK had a greater frequency of hypopyon and anterior chamber flare.<sup>81</sup>

**Table 3** Clinical characteristics of the different forms of microbial keratitis

Clinical characteristics	Bacterial keratitis	Fungal keratitis	Acanthamoeba keratitis
Onset of symptoms	Rapid	Several days <sup>62</sup>	Rapid
History	Contact lens wear, trauma, and ocular surface disease	Vegetative trauma, contact lens wear, and ocular surface disease	Water exposure and contact lens wear; may have been treated prior as herpes simplex
Key differentiating slit lamp findings <sup>a</sup>	Round or oval shaped lesion, and anterior chamber flare <sup>81</sup>	Feathery borders, satellite lesion, and necrotic slough <sup>81</sup> *Yeast infection mirrors bacterial ulcers <sup>62</sup>	Early: <sup>85</sup> epithelial disruption without stromal disease and perineural infiltrates Late: <sup>85,86,103</sup> ring infiltrate
Treatments	Fluoroquinolones, chloro-fluoroquinolones, and fortified antibiotics	Natamycin, voriconazole, and amphotericin	Polyhexamethylene biguanide, chlorhexidine, propamidine, neomycin, and oral voriconazole
Healing time (days)	3.5–6.8 <sup>98,b</sup>	31–40 <sup>102</sup>	140–547 <sup>103,127,129</sup> Steroid: <sup>103</sup> 163±50 <sup>c</sup> No steroid: <sup>103</sup> 94±45 <sup>c</sup>
Percentage with visual acuity worse than 20/30	13.9 <sup>9</sup>	30 <sup>129</sup>	0 (early diagnosis) <sup>85</sup> 44.4 (late diagnosis) <sup>85</sup> Prior steroid use equaled worse outcome <sup>86,103</sup>
Percentage requiring penetrating keratoplasty	0 <sup>9</sup> –13 <sup>131</sup>	16.8 <sup>124</sup>	20–32 <sup>87</sup>
Cost <sup>7</sup> (US\$)	1,200–1,800	4,648	5,697

**Notes:** <sup>a</sup>All conditions will likely have redness, photophobia, discharge, and significant pain. <sup>b</sup>For ulcers ranging from >1 mm<sup>2</sup> to <4 mm<sup>2</sup>. <sup>c</sup>Data presented as mean ± standard deviation.

## Acanthamoeba keratitis

The classic clinical signs of AK are a ring infiltrate and perineuritis;<sup>84–86</sup> however, the clinician must understand that these signs are not always present. Two recent retrospective studies have found that perineuritis was present in 20.7%<sup>85</sup> and 21.6%,<sup>86</sup> whereas the ring infiltrate was found in 27.6%<sup>85</sup> and 29.3%.<sup>86</sup> The early clinical signs tend to be a nonspecific epitheliopathy, pseudo-dendrites, subepithelial infiltrates, and in some cases perineurial infiltrates.<sup>84,85</sup> As the disease progresses, the progression to a ring infiltrate and uveitis are more likely to be identified.<sup>84</sup> If the disease is diagnosed early, usually within the first few weeks, the disease can be confined to the epithelium or anterior stroma and visual outcomes are substantially better compared with a late diagnosis.<sup>85</sup>

Confocal microscopy is a technique that has been shown to assist with diagnosing the condition.<sup>86</sup> Hau et al presented confocal microscopy images from culture positive specimens to cornea specialists masked to the tissue diagnosis and asked them to provide a clinical diagnosis.<sup>87</sup> Relying on confocal microscopy alone resulted in a sensitivity range of 27.9%–55.8% and specificity range of 42.1%–84.2%.<sup>87</sup> When using confocal microscopy in addition to clinical characteristics and objective findings, Tu et al found the sensitivity to be 90.6% and a specificity of 100%.<sup>88</sup> Confocal microscopy alone is not reliable enough to diagnose AK, but when combined with clinical findings and culturing (positive culture rates are as high as 88%), it can aid in properly diagnosing the condition.<sup>86</sup>

## Treatment Bacterial keratitis

Due to the inherent delay in accessing culture results, the clinician must initiate treatment empirically. Studies have shown that a single fluoroquinolone is as effective as fortified preparations in treating BK.<sup>89–91</sup> It should be noted that only ciprofloxacin 0.3%, ofloxacin 0.3%, and levofloxacin 1.5% have US Food and Drug Administration approval for treating BK<sup>92</sup> although use of fourth generation fluoroquinolones as monotherapy is quite common.<sup>89</sup> Due to increased microbial resistance to fluoroquinolones,<sup>93</sup> specifically with methicillin-resistant *Staphylococcus aureus*,<sup>94</sup> some advocate for initial empirical monotherapy use of the chlorofluoroquinolone, besifloxacin 0.6%.<sup>95,96</sup> If methicillin-resistant *Staphylococcus aureus* is identified through culturing or Gram stain, the treatment may be modified to include a more potent agent such as fortified vancomycin.<sup>97</sup>

The antibiotic must be applied to the ocular surface frequently. In two studies, the initial treatment consisted of a drop every hour around the clock.<sup>4,89</sup> With severe ulcers the eye drops can be instilled every 5–15 minutes for first hour followed by hourly or half-hourly application.<sup>92</sup> BK resolution depends on the initial size of the ulcer, but most re-epithelialize within 3.5–7 days.<sup>98</sup>

In addition to an antibiotic, a cycloplegic agent can be used to minimize photophobia and risk of posterior synechiae.<sup>92</sup> The role of corticosteroids with BK is more controversial and



the Steroids for Corneal Ulcer study found no improvement in clinical outcome in the steroid group versus the placebo group.<sup>99</sup> Although there was no overall benefit, there was also no evidence of a reduced visual outcome.<sup>99</sup> When limiting the sample to only the most severe cases, steroids did provide a slight clinical benefit.<sup>99</sup> For the clinician, if BK is suspected, the application of a steroid should only commence if clinical signs are improving, which suggests that the selected antibiotic is effective against the offending microbe.

## Fungal keratitis

The only US Food and Drug Administration approved ophthalmic antifungal medication is 5% natamycin, which is commercially labeled as Natacyn (Alcon Inc., Fort Worth, TX, USA). A recent worldwide survey on FK treatment practice patterns found that natamycin is the most frequently used antifungal for filamentous fungi.<sup>100</sup> Amphotericin and voriconazole were the next most common. For infections caused by yeast, amphotericin was the most common followed by natamycin.<sup>100</sup> Overall, respondents reported use of oral antifungals “always” (10%), “most of the time” (27%), “sometimes” (55%), and “never” (8%).<sup>100</sup>

Natamycin and amphotericin are polyenes which irreversibly bind to ergosterol and increase fungal cell wall permeability.<sup>101</sup> Voriconazole is a triazole, and this inhibits ergosterol synthesis.<sup>100</sup> The Mycotic Ulcer Treatment Trial compared the performance of these two medications and found that natamycin overall had better visual outcomes and faster resolution when compared with voriconazole.<sup>102</sup> For *Fusarium* keratitis, natamycin significantly improved vision outcomes and reduced the risk of perforation. For non-*Fusarium* FK, the two medications performed similarly.<sup>102</sup>

## Acanthamoeba keratitis

There are no approved amoebicidal agents at this time.<sup>84</sup> The typical medications used for AK can include biguanides or diamidines. The two biguanide agents are polyhexamethylene biguanide 0.02%–0.06% and chlorhexidine 0.02%–0.2%.<sup>84</sup> Biguanides damage the cytoplasmic membrane which results in a loss of cellular components.<sup>84</sup> The diamidines induce structural changes to the cellular membrane altering permeability,<sup>84</sup> and the typical agents are propamidine 0.1% and hexamidine 0.1%. Some centers still use neomycin, but not as monotherapy.<sup>85,103</sup> The vast majority of corneal specialists (93.9%) use a combination of agents.<sup>104</sup> Oral voriconazole, an antifungal, can have an amoebicidal effect by binding ergosterol – which is present in the cell membrane of fungi and *Acanthamoeba*.<sup>105</sup> Steroids are reportedly used

during the course of *Acanthamoeba* treatment, but their role is controversial.<sup>104</sup>

Nonpharmaceutical treatments for MK cases that are not responding to topical medication can include penetrating or lamellar keratoplasties of the infected cornea,<sup>106</sup> which are known as “hot corneal grafts”. The use of corneal cross-linking for MK is becoming more common<sup>107–109</sup> and can be effective in eradicating offending microbes. Amniotic membranes can also be used to augment pharmaceutical treatment.<sup>110</sup>

## Culturing

Knowing when to culture a corneal lesion often times is not intuitive. Some advocate for culturing any corneal lesion, whereas the majority of ophthalmologists reserve culturing for lesions meeting specific criteria.<sup>111</sup> According to the 2013 American Academy of Ophthalmology (AAO) Preferred Practice Patterns for Bacterial Keratitis, culturing only needs to be performed for ulcers that are deep, large, an atypical presentation, having questionable history or unresponsive to initial treatment.<sup>92</sup> A recent survey, performed by Park et al, provides a glimpse of corneal culture procedures performed by ophthalmologists in the United States.<sup>111</sup> Only 8.6% of ophthalmologists felt that it was necessary to always culture a lesion.<sup>111</sup> Fifty-eight percent of the cases seen by corneal specialists are cultured versus 22% by noncorneal specialists.<sup>111</sup> Overall, corneal specialists were more likely to culture, and all respondents were more likely to culture with unresponsive lesions, deep infiltrates, or atypical lesions. The practice patterns identified in the Park survey align well with the AAO corneal culturing guidelines.

Tertiary referral centers<sup>36,93,112</sup> likely will have complete culturing supplies which include chocolate agar, blood agar, thioglycolate broth, brain–heart infusion broth, Sabouraud’s dextrose agar, and nonnutrient agar with overlying *Escherichia coli*<sup>113</sup> (Table 4). For nontertiary referral centers, having access to transport swabs for culturing may be more prudent. The ESwab (Copan Diagnostics, Murrieta, CA, USA) uses a flocked nylon tip (Figure 1) which allows for increased fluid uptake and enhances specimen release.<sup>114</sup> ESwabs have a shelf life of 18 months without refrigeration and they provide enhanced microbial uptake and release when compared with traditional swabs.<sup>115</sup> ESwabs were compared with direct plating<sup>115</sup> and found to provide positive cultures 69% of the time while direct plating yielded positive cultures 70% of the time.

Once a swab is used to collect microbes, the swab needs to be delivered to a microbiology lab for processing.

**Table 4** Culture yields obtained from the cornea and contact lens paraphernalia

Type of microbe	Positive cultures from cornea (%)	Positive cultures from lens case (%)	Positive cultures from lenses (%)	Preferred culture media
Bacteria	37 <sup>123</sup> –63 <sup>120</sup>	80 <sup>119</sup> –83 <sup>5</sup>	67 <sup>118</sup> –92 <sup>119</sup>	Chocolate agar Blood agar Thioglycollate broth Brain–heart infusion broth Sabouraud's dextrose agar
Fungal	76 <sup>93</sup> –94 <sup>8</sup>	70 <sup>124</sup> –84 <sup>59</sup>	57 <sup>124</sup>	Sabouraud's dextrose agar
Protozoan	23 <sup>93</sup> –88 <sup>87</sup>	23 <sup>30</sup>	23 <sup>30</sup>	Nonnutrient agar with <i>Escherichia coli</i>

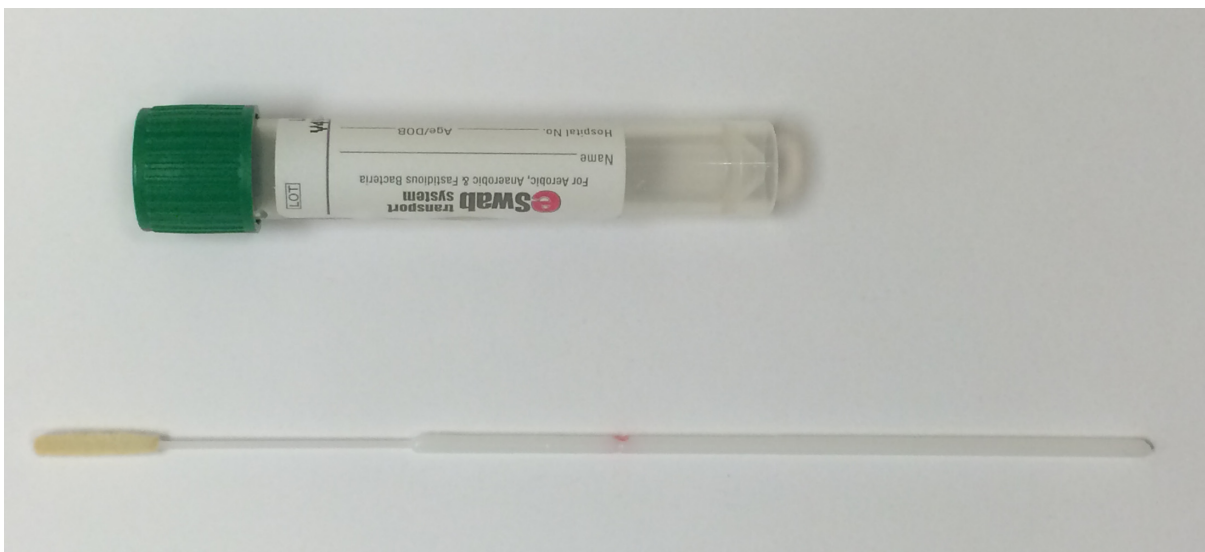
The ESwabs have been shown to provide viable specimens for several microbes even after 48 hours.<sup>116</sup> Refrigeration of the sample improves the recovery viability for *Neisseria gonorrhoeae* at 48 hours. *Pseudomonas*, the most common isolate in contact lens-related BK, can be recovered with or without refrigeration at 48 hours.<sup>116</sup>

Not all cultures yield positive results (Table 4), and the information obtained from cultures is not instantly available, so the clinician must begin treatment empirically. Once the culture is obtained, the topical therapy can be adjusted if the prescribed antimicrobial is ineffective against the offending microbe. If the corneal lesion is unresponsive to therapy, a referral to a corneal specialist should be initiated. The corneal specialist may need to obtain additional corneal scrapings for Gram stains or perform a corneal biopsy to be sent for culture and histopathological analysis.<sup>92</sup> Gram stains obtained from corneal scrapings have been shown to be more sensitive than culturing for detecting fungus and protozoans in infectious keratitis cases.<sup>117</sup> Scrapings should occur for both suspected FK, AK, and nonresolving BK. Specific to *Acanthamoeba*, scraping should occur, regardless of whether it is early or late in the disease process.<sup>85</sup>

In addition to culturing the cornea, contact lenses and their storage cases can provide positive cultures (Table 4). Positive culture yields from the contact lenses of patients with MK range from 67%<sup>118</sup> to 92%,<sup>119</sup> while positive yields from storage cases are as high as 80%–85%.<sup>119,120</sup> Culture positive cases are common in healthy contact lens wearers and do not always lead to MK. However, studies have shown a high species concordance between the cultures obtained from the corneas, contact lenses, and storage cases of patients with MK. Martins et al found that when the corneal cultures were positive, the species concordance with lens paraphernalia was 100% for FK, 80% for AK, and 74.5% for BK.<sup>121</sup> Konda et al also demonstrated that when corneal cultures were negative, but microbes were obtained from the lens paraphernalia, that the isolated microbe likely was the infectious agent.<sup>119</sup>

## Microbiology

Although culture yields vary among studies, often times the identified isolates are the same. For contact lens-related BK, the most frequently isolated organism tends to be the Gram-negative species, *P. aeruginosa*<sup>5,10,122</sup> (Table 5).

**Figure 1** Copan E-swab.

**Table 5** Common microorganisms responsible for contact lens-related microbial keratitis

Common microorganisms associated with contact lens microbial keratitis	
<b>Bacteria (71%–88%)</b> <sup>8,119</sup>	
Gram-positive	
<i>Staphylococcus</i> spp. <sup>11</sup>	20%
Coagulase-negative <i>Staphylococci</i> <sup>5,112,123</sup>	<b>16.8%–49%</b>
<i>Staphylococcus aureus</i> <sup>112</sup>	5.9%
<i>Staphylococcus epidermidis</i> <sup>119</sup>	4.8%
Gram-negative	
<b><i>Pseudomonas</i></b> <sup>5,10,11,112,119,122,123</sup>	<b>19%–73.5%</b>
<i>Serratia</i> <sup>5,11,119,122</sup>	4.8%–23%
<b>Fungal (2.6%–5%)</b> <sup>6,8,10,119</sup>	
Filamentous	
<b><i>Fusarium</i></b> <sup>124</sup>	<b>51%<sup>a</sup>–68%<sup>b</sup></b>
<i>Aspergillus</i> <sup>124</sup>	9.2% <sup>a</sup> –11% <sup>b</sup>
Yeast	
<i>Candida</i> <sup>124</sup>	2% <sup>b</sup> –12% <sup>a</sup>
<b>Acanthamoeba (0.9%–4%)</b> <sup>8,119</sup>	
<b><i>Acanthamoeba castellanii</i></b> <sup>125,126</sup>	<b>38%–66%</b>
<i>Acanthamoeba polyphaga</i> <sup>126</sup>	30%

**Notes:** The specific microbes that are in bold text indicate the most common species. Percentages do not add up to 100 as sterile keratitis cases can also be found. <sup>a</sup>non-*Fusarium* outbreak<sup>124</sup> (January 2001–September 2004 and October 2006–December 2007); <sup>b</sup>*Fusarium* outbreak<sup>111</sup> (October 2004–September 2006).

Another commonly identified Gram-negative organism is *Serratia* spp. Rivaling *Pseudomonas* for the most commonly isolated bacteria associated with contact lens-related BK is the Gram-positive commensal organism, coagulase-negative *Staphylococci*.<sup>5,112,123</sup> Gram-negative species tend to be more virulent and are associated with worse visual outcomes compared with Gram-positive microbes.<sup>7</sup>

FK accounts for approximately 5% of all contact lens-related MK.<sup>6,10</sup> The most common isolates are the filamentous organisms, *Fusarium* and *Aspergillus*. These two species account for between 62% and 77% of cases with the majority of cases due to *Fusarium*.<sup>124</sup> Yeast, or molds, such as *Candida* spp, make up approximately 10% of contact lens-related FK cases.

AK comprises between 0.9% and 4% of contact lens-related MK.<sup>7,11,119</sup> There are eight *Acanthamoeba* species that have been identified in patients with keratitis. The most common species related to keratitis are *Acanthamoeba castellanii*<sup>125</sup> and *Acanthamoeba polyphaga*.<sup>84,126</sup> Although it is important to attempt to identify the offending amoeba, regardless of the species, the treatment will be the same.<sup>84</sup>

## Morbidity/visual outcomes/cost

Of the three forms of MK, AK is the most worrisome and costly (Table 3). Key et al estimate that the average cost of treatment (in 2006) was over US\$5,500<sup>7</sup> with the

mean duration of treatment lasting between 140 days and 18 months.<sup>103,127,128</sup> The worst visual outcomes tend to be cases with delayed diagnosis or those exposed to topical steroids.<sup>85,86</sup> If diagnosed and treated early, visual outcomes are substantially better than a delayed diagnosis.<sup>85,86</sup>

About 30% of resolved contact lens FK result in visual acuity of worse than 20/30.<sup>129</sup> In a multicenter analysis of FK in the United States, those with contact lens-related FK had a penetrating keratoplasty rate of approximately 17%.<sup>124</sup> Fortunately, if diagnosed early, there are effective medications, and time to resolution is approximately 1 month.<sup>130</sup>

BK tends to have less severe outcomes compared with AK or FK, but certainly can be visually devastating with one study showing a penetrating keratoplasty rate of approximately 13%.<sup>131</sup> Most studies show PK rates of less than 13%<sup>9</sup> and visual acuity loss (worse than 20/30) associated with contact lens-related BK has been reported to be around 14%.<sup>9</sup>

## Conclusion

The incidence of contact lens-related MK has not significantly changed since 1989. Some believe the incidence of MK, particularly AK is increasing.<sup>132,133</sup> Eye care practitioners play an important role in diagnosing and managing cases of MK. While it is unlikely that an optometrist or a general ophthalmologist will be actively treating severe MK, it is important to recognize the clinical signs and symptoms early in the course of these diseases in order to refer for appropriate care quickly.

When fitting or evaluating contact lenses, the eye care practitioner must discuss the risks of contact lens wear and the need for proper lens replacement and disinfection with their patients. Improved and persistent patient education will hopefully help to decrease the incidence of MK.

## Disclosure

The authors report no conflicts of interest in this work.

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