Chapter

Contact Lens-Associated Infectious Keratitis: Update on Diagnosis and Therapy

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Abstract

The focus of this chapter is to review the most recent advances in the diagnosis and treatment of contact-lens-related infectious keratitis, the most sight-threatening complication of contact lens wear. In the last decades, contact lenses technology has confronted several challenges, including the need for safer and more comfortable polymer materials. The development of high coefficient oxygen permeability (Dkt) and low-water content disposable contact lens translated into a significant improvement in ocular discomfort related to dry eye and allergic reactions, decreasing biofilm build-up on the external surface of the lens. Additionally, the emergence and boom-effect of corneal refractive surgery have also driven the development of better contact lens manufacturing. Despite these substantial technological advances, contact lens users continue to be at risk for developing corneal infections. We describe recent epidemiologic data, and advances in understanding the complex pathogenesis of the disease, including the clinical characteristics of the infectious process produced by bacteria, fungi, and protozoans. Finally, the recent development of diagnostic techniques and therapeutic regimens are discussed.

Keywords: contact lens, infectious keratitis, bacteria, fungi, Acanthamoeba

1. Introduction

Contact lenses are a useful tool for correcting refractive errors; over 125 million people wear them worldwide [1]. The widespread use of contact lenses is associated with a variable range of complications up to 39–60.99% of contact lens wearers. Complications range from mild superficial punctate keratitis to vision-threatening conditions such as contact-lens-related infectious keratitis. Infectious keratitis is a potentially blinding condition, and it rarely occurs in healthy eyes; it comprises bacterial, fungal, and Acanthamoeba keratitis. Contact lens wear is, in fact, the predisposing factor in up to 50.3% for infectious keratitis [2–4]. Contact lens wear is the most critical risk factor for microbial keratitis in developed countries and the second one in developing countries after trauma [5–8]. Despite different contact lens materials and wearing modalities, infectious keratitis continues to be a sight-threatening condition in contact lens wearers, with a rate of visual loss of up to...
Infectious Eye Diseases - Recent Advances in Diagnosis and Treatment

28.6% [3, 9]. The annual incidence rate for contact lens-related microbial keratitis is 2/10 000 for rigid contact lens users, 2.2–4.1/10 000 for those who use daily-wear soft contact lens, 13.3–20.9/10 000 for extended wear soft contact lens users, and 52/10 000 for patients who wear therapeutic contact lenses [10].

2. Definition

A classical definition of contact lens-associated infectious keratitis (CLAIK) includes a corneal epithelial defect or ulcer, accompanied by a stromal infiltrate, requiring corneal scraping and culturing [11]. However, corneal cultures are not readily available for all practitioners, suggesting a purely clinical definition [11]. Stapleton et al. proposed the following definition: a corneal infiltrate with an overlying epithelial defect and one or more of the following: lesions within the 4 mm of the central cornea, anterior chamber reaction, and pain [12].

3. Epidemiology

The annual incidence of CLAIK per 10 000 wearers ranges from 0.4–4.0 for rigid gas permeable (RGP) contact lenses, 2.2–4.5 for daily use of soft contact lenses, and 9.3–20.9 for overnight soft contact lenses wear [11]. Hence, daily wear of RGP contact lenses continues to have the lowest infectious keratitis rates [12]; however, the incidence of associated microbial keratitis remains unchanged despite the development of new contact lens materials [13].

Orthokeratology (ortho-K) for myopia prevention and cosmetic and decorative lenses have recently gained popularity among young wearers. On the one hand, ortho-K patients are closely monitored during treatment by their practitioners; conversely, cosmetic contact lens wear (color or party) lacks care education and professional supervision. There are reports of microbial keratitis in both wear modalities [14, 15]. In the case of cosmetic lens wear not dispensed by eye care professionals, a report shows an increased risk of infectious keratitis by a factor of 12.3 (OR 95%-CI = 4.8–31.5). Furthermore, lack of lens care education in the same study increased the risk of infectious keratitis by 26.5 times (OR 95%-CI = 10.0–70.2) [16].

4. Etiology

CLAIK is mainly attributed to bacterial pathogens with up to 90% of the cases (Table 1). Moreover, although fungal and protozoal infections are infrequent, they are more severe [24]. The most common bacterial agent involved in CLAIK is Pseudomonas aeruginosa, according to several reports (Figure 1A and B). Gram-negative bacteria are more frequently isolated in tropical climates. Gram-positive bacteria are more commonly identified in regions with temperate climates like Australia and France [2, 3, 11]. Such bacteria include coagulase-negative Staphylococcus (including Staphylococcus epidermidis), Staphylococcus aureus, and Streptococcus pneumoniae. S. aureus is associated with more severe disease and recurrent infections [25].

On the other hand, keratitis caused by Acanthamoeba and fungi has increased in the past few years [26]. In 2006, an outbreak of CLAIK caused by Fusarium was first reported in Singapore [27], followed by multiple reports in the United States [28–30]; these outbreaks were directly linked to a particular contact lens solution formulation reported a decreased antifungal activity [31]. In the same year,
outbreaks of *Acanthamoeba* keratitis were also reported and partly associated with another contact lens solution [32].

It is noteworthy to mention the occurrence of CLAIK associated with multiple microorganisms. A retrospective analysis of CLAIK, performed by Karaca et al., demonstrated that 20% (12 cases) were mixed infections. All of them were mixed bacterium-bacterium infections. *P. aeruginosa* was involved in eight cases [33]. Regarding mixed fungi-bacterial infections, Ahn et al. reported a prevalence of 4.4% (33/757). Ocular trauma (45.5%) and diabetes mellitus (18.2%) were the most frequent associated risk factors for mixed bacterial and fungal keratitis, and *Fusarium* spp. and *Staphylococcus* spp. were the most frequent fungi and bacteria isolated, respectively [34].

### 5. Risk factors

Among the many different risk factors predisposing to CLAIK, overnight wear and poor hygiene are the two most frequent ones, accounting for 43% and 33%
of the cases, respectively [35]. Regarding corneal infection in overnight wear, the risk is higher with increased extended wear and inexperienced patients [36, 37]. Interestingly, in severe keratitis, mishandling of the contact lens case (poor hygiene and lack of replacement) accounts for 63% of the population-attributed risk for bacterial and fungal infection. Moreover, swimming with contact lenses on and traveling are also risk factors for infection. The former for *Acanthamoeba* keratitis, and the latter related to routine wearing changes [3, 38].

Other risk factors of infectious keratitis in contact lens wearers include being a male, probably related to poor compliance and reluctance to seek regular care attention [39]. Genetic susceptibility related to small mutations of defensins, interleukins, and other inflammatory mediators seems to play a role in CLAIK (Table 2) [43].

### 6. Pathogenesis

The primary vector for bacterial transmission in CLAIK is the contact lens through various contaminants, including the eyelids, hands, storage case, cosmetics, and contaminated water or lens solutions [44, 45]. Contact lenses wear alone alters the normal physiology of the cornea. To a greater or lesser extent, the local hypoxia induced by contact lenses causes a decreased epithelial metabolic rate, resulting in epithelial thinning, loss of tight cell junctions, and hemidesmosomes,
which lead to epithelial abrasions predisposing to opportunistic infections. Other corneal hypoxic effects include vascularization and hypoesthesia.

The understanding of CLAIK pathogenesis has changed over time as contact lens materials evolved. Contact lens wear increased in popularity when soft hydrogel contact lenses were introduced, given a higher comfort for the wearer [46]. However, their intrinsic low-oxygen transmissibility was demonstrated to be problematic. It is well-known that lower oxygen transmissibility is related to a higher rate of bacterial binding to the corneal surface; hypoxic conditions in human corneas increase wild-type cystic fibrosis transmembrane conductance regulator (CFTR) expression, which is the cellular receptor for *Pseudomonas aeruginosa*. Hence a lower bacterial load can induce infectious keratitis and inflammatory responses in this type of contact lenses [47]. Previous reports show that decreasing oxygen permeability of contact lenses is associated with increased desquamation of superficial epithelial cells of the cornea [48–50]. These observations led to development and innovation in contact lens materials to address the problem of hypoxia, which led to the advent of highly oxygen-transmissible, soft silicone hydrogel contact lenses. With the introduction of silicone hydrogel soft contact lenses, a decrease in infectious keratitis cases was anticipated; this was hypothesized because of their increased oxygen permeability and decreased bacterial binding [50]. However, no difference in the incidence of infectious keratitis was observed; clinical characteristics, pathogens, and rate of vision loss also remained unchanged despite the new contact lens material [1].

Because solving the hypoxia mechanism did not result in a reduced incidence rate of microbial keratitis, other alternative pathogenic mechanisms are suggested for corneal infection, including inadequate tear exchange. Deficient tear exchange leads to the entrapment of debris and microbes on the posterior surface of contact lenses and hinders the natural antimicrobial functions of the tear film. In fact, there is a reduction in the antimicrobial activity of the tear film on the posterior surface of silicone hydrogel soft contact lenses after 8 hours of wearing them [51]. This mechanism could explain why soft contact lenses are associated with a higher risk of infectious keratitis than rigid gas permeable lenses, given the inadequate tear exchange in the former [52, 53].

Microbes responsible for infectious keratitis may come from the lid margins, the wearers’ fingers upon contact lens insertion, or removal, directly from the contact lens or indirectly from the storage case or the lens care solution [54]. Contact lens case contamination has been reported in up to 80% of contact lens wearers, despite adequate compliance with care regimens [55, 56]. The formation of bacterial biofilm on the contact lens surface and storage cases has been previously reported, and it may also play a role in the pathogenesis of microbial keratitis [56]. Bacterial cells within a biofilm show increased resistance to antimicrobial agents [57]. Moreover, multiple biguanide-based contact lens solutions have no effect against biofilms of *Serratia marcescens*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* formed in silicone hydrogel contact lenses [58]. Also, outbreaks of keratitis caused by *Acanthamoeba* and *Fusarium spp* have been linked to specific contact lens solutions [26, 27, 32].

Animal models have also been used to improve understanding CLAIK. In mouse and guinea pig models, a corneal erosion must occur to produce infectious keratitis; animals with non-scratched corneas only show non-infectious inflammatory responses [59]. This has led to the hypothesis that a corneal defect or erosion is a prerequisite for CLAIK to occur and not microbial contamination alone [60]. Corneal erosions are known complications in contact lens wearers, especially on extended wear schedules [61, 62].
Several risk factors have been associated with microbial keratitis. The most consistent factor is overnight wear, which increases the risk for microbial keratitis by 10 to 15 times compared to daily wear, irrespective of lens type [9, 12, 50, 63–65]. The extended wear risk of infectious keratitis also increases by 9 times with aphakia correction in elderly patients; 12 times greater in patients misusing daily-wear lenses for overnight wear. Other risk factors include contact lens case hygiene, inadequate or lack of handwashing, infrequent case replacement, and smoking; wearing contact lenses while swimming or showering also increases the risk [27, 17, 66–71]. Contact lens wearers who live or travel to tropical locations also have a higher risk for microbial keratitis [18]. According to the lens type, the risk for microbial keratitis is as follows: daily disposable < rigid gas permeable < daily wear of soft contact lens < extended wear of soft contact lens [3, 35, 72].

Furthermore, contact lens wear results in a decrease in basal cell proliferation on the cornea and vertical migration of differentiated cells to the surface of the epithelium, and an abnormal accumulation of older epithelial cells [73, 74].

The pathogenesis of CLAIK is complex and involves intrinsic lens properties, including lens material and oxygen transmissibility and environmental variables such as bacterial contamination; user behavior, such as schedule wear and poor hygiene coupled with the alteration of normal corneal physiology, loss of epithelial adherence mechanisms and corneal erosions, lead to the development of microbial keratitis [12]. In summary, microbial contamination of the lens is followed by microbial adhesion to the corneal epithelium; then microtrauma or erosion to the epithelium occurs, resulting in the microbial invasion of the corneal stroma (Figure 2) [75].

7. Diagnosis

Proper diagnosis of CLAIK is based on a complete ocular history of contact lens wear, patient’s symptoms, a complete ophthalmological examination, corneal scrape, and culture, including the removed contact lens, the case, and solution [66].

7.1 Symptoms and signs

Symptoms common to microbial keratitis include a rapid onset of ocular pain, red eye, tearing, foreign body sensation, conjunctival mucopurulent discharge, and
photophobia with a variable degree of vision loss. These symptoms are be accompanied by prominent signs including, eyelid swelling, ciliary injection, conjunctival chemosis, a corneal epithelial defect or ulceration, stromal inflammatory/microbial infiltrate, edema, endothelial keratic precipitates (KPs), and anterior chamber reaction (inflammatory cells, flare, fibrin, plasmoid bodies, hypopyon) [11, 76–78].

There are clinical features that may guide the clinician to a possible etiological agent. Bacterial keratitis is characterized by a round, or oval epithelial defect with an underlying stromal infiltrate and anterior chamber reaction or hypopyon (Figure 3A–C) [66].

The classical findings in *Acanthamoeba* keratitis are severe pain that is disproportionate to the clinical signs, ring-shaped corneal infiltrates, and radial perineuritis [69, 75]. Fungal keratitis may present with a grayish, deep infiltrate with feathery borders and satellite lesions or an endothelial plaque and usually has a more insidious course [27, 66, 69]. However, these clinical findings are often misleading; in fact, cornea specialists distinguish correctly bacterial from fungal keratitis only 66% of the time in a photographic survey [79]. Thus, corneal scrapings and cultures remain the gold standard for microbial identification and the only method for determining antibiotic sensitivity [80].

7.2 Smear staining and culture

Corneal scrapings are obtained in the office under the slit lamp. A topical anesthetic agent is instilled, ideally proparacaine hydrochloride 0.5% or a preservative-free anesthetic [81]. The corneal material is obtained with a sterile platinum spatula, blade, forceps, or a calcium alginate swab moistened in thioglycolate broth. The smear stains helpful in identifying the causative organism are Gram stain, Giemsa stain, and Acridine orange are the most frequently used for detecting bacteria. The Gram stain permits identification of gram-positive and -negative coccus and rods, which is essential to choose the initial antibiotic type before the antibiogram and sensitivity profile of the microorganism in question is available. For example, cephalosporins are more appropriate for gram-positive and aminoglycosides for gram-negative bacteria [82].

In case of presumptive fungal infection, special stains like potassium hydroxide (KOH) and calcofluor white (CFW) are more reliable to initiate antifungal therapy than Gram staining is for bacterial infection (Figure 4A and B) [82, 83].
Mycobacterial or *Nocardia* infection will require the acid-fast or modified Ziehl-Neelsen (1% H$_2$SO$_4$, cold) staining (Table 3).

According to the American Academy of Ophthalmology Bacterial Keratitis Preferred Practice Pattern, cultures and smears should be obtained in cases of suspected microbial keratitis in the following conditions:

- the presence of a large, central infiltrate and/or accompanied with stromal melting
- chronic or unresponsive infection despite broad-spectrum antibiotic therapy
- atypical clinical findings suggestive of fungal, protozoal, or mycobacterial agents
- multifocal infiltrates or a history of corneal surgery [82].

Corneal scrapings should be directly inoculated into the culture media at room temperature and immediately taken to the laboratory for further processing. If culture media are not readily available, scrapings should be inoculated into transport media, including brain-heart infusion media and amies medium with charcoal. Both transport media may be used for aerobic and facultative anaerobic bacteria and, the latter, also for fungi [82]. Standard culture media include blood agar, chocolate agar, Sabouraud dextrose agar, thioglycolate broth, and mannitol salt agar. If *Acanthamoeba* is the suspected pathogen, a non-nutrient agar with *Escherichia coli* overlay must be used (Table 4) [82, 85]. In addition to culturing corneal scrapings, cultures of the contact lens and case can also yield positive results. Corneal scrapings

| Staining technique                  | Visualized microorganisms                        |
|------------------------------------|--------------------------------------------------|
| Gram                               | Bacteria, fungi and *Acanthamoeba*               |
| Giemsa                             | Bacteria, fungi and *Acanthamoeba*               |
| Potassium hydroxide (KOH)          | Fungi                                            |
| Acridine orange                    | Bacteria, fungi and *Acanthamoeba*               |
| Calcofluor white (CFW)             | Fungi and *Acanthamoeba*                         |
| Acid fast (modified Ziehl-Neelsen) | Mycobacteria and *Nocardia* [82, 84]             |

Table 3. Most used microorganism identification staining techniques for the diagnostic confirmation of contact lens-associated infectious keratitis.

Figure 4. A. Potassium hydroxide (KOH) preparation of a corneal smear from a fungal CLAIK patient, showing septate, branched, hyaline hyphae characteristic of filamentous fungus. B. Sabouraud dextrose agar (SDA) plate showing white, cottony colonies consistent with *Fusarium solani*.
culture provides positive results in 34–44% cases [67, 86–88], while cultures of contact lenses are positive in 67–92%, and 80–85% for contact lens cases [66]. Studies have found an association between cultures of corneal scrapings and of contact lenses, with a concordance of up to 84% [67, 89]. Therefore, contact lens culture may guide in the identification of the causative organism in cases in which the corneal scraping culture is negative; however, contact lens cultures do not replace corneal cultures as the gold standard for the etiologic diagnosis of microbial keratitis [67].

7.3 Tissue biopsy

A corneal biopsy may be performed if there is an inadequate response to treatment or if cultures are repeatedly negative, particularly for suspicious *Acanthamoeba* keratitis (Figure 5A–C). It can be performed at the slit-lamp or in the operating room using topical anesthesia and a small 2 or 3-mm dermatologic trephine punch; the tissue obtained is then bisected and sent for culture and histopathologic analysis. A section of the corneal specimen is homogenized with trypticase soy broth and cultured on conventional blood and chocolate agar, anaerobic media, Sabouraud agar, and thioglycolate broth; in specific cases, the corneal specimen may also be plated on a non-nutrient agar with *E. coli* or Lowenstein Jensen media. The specimen section that is sent for histopathologic analysis may be processed with standard stains for bacteria, fungi, acid-fast-bacilli, and *Acanthamoeba* such as Gram and Giemsa stain, potassium hydroxide, calcofluor white and, Ziehl-Neelsen [90]. Several considerations should be taken into account to maximize the diagnostic yield of a corneal biopsy [90–92]:

- To obtain the tissue specimen, topical antibiotics must be suspended at least 24–48 hours before the procedure [90]. Also, appropriate planning and consultation with the microbiologist and pathologist is recommended (i.e., need for special stains for fastidious organisms, appropriate fixatives if electron microscopy is required) [91].

### Table 4.
Respective culture media type used for microorganism isolation in contact lens-associated infectious keratitis.

| Standard media                  | Isolates                                                                 |
|---------------------------------|-------------------------------------------------------------------------|
| Blood agar                      | Aerobic, anaerobic, and facultative anaerobic bacteria. *Pseudomonas*    |
|                                 | *aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*,    |
|                                 | *Streptococcus pneumoniae* Saprophytic fungi and *Nocardia*.             |
| Chocolate agar                  | Aerobic, anaerobic, and facultative anaerobic bacteria. Ideal for isolation |
|                                 | *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Moraxella*.      |
| Sabouraud dextrose agar         | Fungi and *Nocardia*                                                    |
| Mannitol-salt agar              | *Staphylococcus* spp.                                                   |
| Thioglycolate broth             | Aerobic and anaerobic bacteria                                           |
| Supplemental media              |                                                                        |
| CDC anaerobe blood agar         | *Propionibacterium acnes*, *Peptostreptococcus* spp.                    |
| Non-nutrient agar with *E. coli*| *Acanthamoeba* spp.                                                     |
| Transport media                 |                                                                        |
| Brain-heart infusion broth      | Filamentous fungi and yeasts. Aerobic and facultative anaerobic bacteria. |
| Amies medium without charcoal   | Aerobic and facultative anaerobic bacteria. Fungi [66, 82, 84, 85]     |

Table 4. Respective culture media type used for microorganism isolation in contact lens-associated infectious keratitis.
The biopsy must be performed under appropriate magnification at either the operating room or under the slit lamp, with free lamellar dissection using a diamond-sharp blade, set at 0.2 to 0.3 mm depth, or a 3 to 5 mm diameter trephine (skin biopsy punches), cutting to approximately 0.2 to 0.3 mm depth to avoid corneal perforation [92]. After trephination, the base of the tissue block must be gently pulled upward and sideways with a Colibri 0.12 mm tooth forceps to cut it off with a sharp knife (i.e., Grieshaber knife, Beaver blade No.66) or a Vannas scissors, completing the lamellar keratectomy [92].

The tissue biopsy must include a leading edge of the infiltrate or ulcer, including an uninvolved tissue margin [91].

The tissue sample’s processing technique (i.e., electron and light microscopy histopathologic analysis, immunofluorescence, or histochemistry) depends on the clinical features and the amount of tissue available. For small specimens (<3 mm), it is suggested to use only the technique potentially yielding the best result, which must be selected based on a clinical suspicion [91].

If a large sample is obtained, the specimen is divided under sterile technique with a sharp #11 or a 15° knife. Each portion is placed in the appropriate fixative [92].

With a cotton-tipped applicator or a moistened cellulose (Weck-cel) sponge, swab the base of the keratectomy and streak the culture material on plates containing transport media [92].

7.4 Molecular biology techniques

The most common approach to diagnose CLAIK is to culture microorganisms from corneal scrapings. However, more than 99% of the biosphere's microbes are

Figure 5.
Left cornea from a hardware store worker with keratoconus fitted with RGP contact lenses used to wash his face with stagnant water in an open tank deposit. A. Dense ring infiltrate with multiple stromal satellite nummular lesions and anterior chamber reaction. B. A 3 mm diameter corneal biopsy stained with H&E (mag. 40x), showing multiple Acanthamoeba cysts in the corneal stroma. C. Modified Giemsa stain from the same biopsy piece enhancing the presence of multiple Acanthamoeba cysts.
not cultivable using standard laboratory culture techniques [93]. Furthermore, identifying slow-growing bacteria (e.g., atypical mycobacteria) or fungi with atypical phenotypes is tedious and time-consuming [94]. The advent of molecular culture-independent high-throughput sequencing approaches has allowed further identification and characterization of microorganisms that cause CLAIK [95].

7.4.1 Polymerase chain reaction (PCR)

PCR is a highly sensitive technique that allows rapid amplification of tiny samples of DNA. In the context of infection, it may be used to detect the presence of pathogenic DNA of specific microorganisms [96]. The 16S and 18S rRNA are the most frequently used marker genes for assessing bacterial and fungal profiles, respectively. They are found in all respective microorganisms and have enough variation for phylogenetic analysis and sequence conservation for accurate alignment [97]. The 16S rRNA gene sequence is 1,550 bp long, and it is composed of nine variable regions (V1-V9) interspaced in more conserved regions. By amplifying the 16S rRNA region with PCR, the background host contamination encountered in routing culturing techniques is reduced significantly [98].

Kim et al. compared the detection rate of PCR compared with traditional cultures in patients with infectious corneal ulcers [99]. Of 108 samples taken from ulcers, 52% were culture-positive and 89% PCR-positive for fungal primers (18S rRNA), bacterial primers (16s rRNA), or both. Of note, other nonpathogenic organisms (i.e., Ralstonia, Oerksovia, and Leclercia species) were also identified in 60% and 52% of the PCR samples and control swabs, respectively. Airborne contamination and false-positive results for pan-fungal and pan-bacterial PCR constitute a significant limitation of the technique [100]. Moreover, when analyzing culture-positive samples, 24% and 6.5% were PCR-negative for bacteria and fungi, respectively, suggesting that PCR does not replace traditional culturing. PCR, however, accurately distinguishes fungal from bacterial pathogens [99]. In patients with suspected Acanthamoeba keratitis, PCR and in-vivo confocal microscopy (IVCM, see Section 7.5) are preferred over conventional cultures since the latter has a low sensitivity and requires special media and extended incubation periods [101]. Goh et al. compared traditional cultures, PCR, and IVCM in the early diagnosis of Acanthamoeba keratitis. All methods exhibited a specificity and positive predictive value of 100%. However, the diagnostic sensitivities were 100% for IVCM, 71.4% for PCR, and 33.3% for traditional cultures. Since IVCM is an expensive device and requires an experienced operator, PCR is considered as a valuable adjunct to cultures when Acanthamoeba is suspected [101].

7.4.2 Next-generation sequencing (NGS)

NGS encompasses an evolving group of high-throughput sequencing technologies which allow massive sequencing of nucleic acid. The Sanger (1970s), a precursor to NGS, is a first-generation sequencing platform with high accuracy when dealing with one bacterium. In fact, the Human Genome Project (2003) was completed with the automatization of this technique. Isolated bacterial sequencing required multiple reactions with the Sanger platform, and thus, it was complex and time consuming [102]. Second-generation platforms (Illumina HiSeq 2500), although able to generate high sequence throughput data in a single reaction, they only sequenced part of the 16S gene [94, 103, 104]. Current third-generation platforms use nanopore sequencing technology directly from clinical samples to diagnose bacterial keratitis in real time and with higher accuracy [98].
Metagenomic NGS (mNGS) is an emerging approach that analyzes microbial, and host’s genetic material (DNA and RNA) in samples from patients [105]. mNGS may detect all potential pathogens (bacteria, fungi, parasites, and viruses) in a clinical or environmental sample and simultaneously interrogate host responses by performing billions of reads in a single run [105, 106]. Unfortunately, the untargeted nature of this approach most likely results in host-derived reads [102].

Obtaining a rapid, real-time diagnosis of the causative microbe in bacterial keratitis will allow the ophthalmologist to initiate prompt and adequate antibiotic therapy; thus, improving the visual outcome and reducing antibiotic resistance [107]. However, test validation, reproducibility, high costs, among others, are significant drawbacks for the routine use of NGS and mNGS in clinical settings. Nevertheless, they must be considered in refractory difficult-to-identify cases of infection.

7.5 In vivo confocal microscopy (IVCM)

IVCM is a non-invasive imaging technique that allows dissection of the corneal architecture at a cellular level, providing real-time images equivalent to those obtained from ex-vivo histopathological techniques (tissue biopsy) [108]. It is currently used to evaluate corneal nerves in healthy eyes and those affected by ectatic corneal diseases, neurotrophic keratopathy, corneal dystrophies, ocular surface inflammation, contact lens wear, and infectious keratitis [108–110].

The role of IVCM in CLAIK relies on the identification of fungal hyphae and Acanthamoeba cysts; bacteria are too small to be visualized by IVCM [111]. Chidambaram et al. evaluated the IVCM cellular features in patients with bacterial, fungal, and Acanthamoeba keratitis [112]. A honeycomb-like distribution of anterior inflammatory cells in the corneal stroma was distinctive of fungal keratitis. Aspergillus and Fusarium ulcers were also associated with stromal dendritiform cells and interconnected cell processes with a stellate appearance, respectively. Bacterial keratitis was significantly associated with anterior stromal bullae and basal dendritiform cells. Normal keratocyte-like morphology was found in most eyes with both bacterial and fungal keratitis. Distinguishing features of Acanthamoeba included double-walled cysts, bright spots, and clusters after topical steroid use. While the keratocyte morphology was altered in 82% of bacterial (82%) and 77% of fungal keratitis, it was only abnormal in 39% of Acanthamoeba cases [112].

Although IVCM may be used in culture-negative cases or when the clinical diagnosis is unclear, this technique requires an experienced examiner. The rearmost since cellular features exhibited in microbial keratitis may be easily confused with nerve fibers, activated stromal keratocytes, and Langerhans cells [111]. Moreover, its small field of view precludes fair dismissal of Acanthamoeba cysts [113].

8. Differential diagnosis

8.1 Microorganism profile

According to the clinical features of the infectious/inflammatory process seen in CLAIK, specific differences, although not compelling, help identify the infectious agent involved in the process. For example, Gram-negative bacteria are usually associated with a significant anterior chamber reaction and larger ulcers compared to Gram-positive ones. Also, Pseudomonas aeruginosa tends to produce larger stromal inflammatory infiltrates [2, 40]. A study analyzing the causative microorganism involved in CLAIK found moderate positive prediction for Acanthamoeba annular
stromal infiltrate at 89% (95% CI = 52–100) and *Pseudomonas* larger ulcer at 65% (95% CI = 43–84) [114]. On the other hand, pseudo-dendrites, epitheliopathy, and stromal infiltrate found in *Acanthamoeba* keratitis may confuse herpetic keratitis [115]. Serrated (feathery) ulcer margins with raised and dry texture infiltrate and satellite lesions are common features of fungal keratitis [116].

### 8.2 Infectious versus inflammatory keratitis

One of the first dilemmas confronted by professionals taking care of patients wearing contact lenses is to know if the corneal lesion is infectious or inflammatory (Figure 6A and B). The difficulty arises because the ocular immune response to foreign stimuli, including microbes and their products, foreign bodies, trauma, allergic and toxic reactions, is non-specific inflammation, which may be indistinguishable from infection in that respect [78, 117, 118]. A study asking ophthalmologists to identify sterile from culture-proven CLAIK found good predictability (76%, 95% CI = 67–84) with 79 cases classified correctly [114].

Some key clinical features help to differentiate between sterile from infectious keratitis. In sterile inflammation, the absence of eyelid edema, no conjunctival discharge, peripheral location of the lesion, and minimal or no anterior chamber reaction contrast with significant eyelid edema, abundant mucopurulent discharge, central/paracentral lesions, and severe reaction and hypopyon formation in infectious keratitis [78].

### 9. Management

First and foremost, efforts should be focused on the prevention of CLAIK. Wearers should be educated on the proper use of contact lenses. They should be counseled to avoid overnight wear and exposure to water and be educated on appropriate hygiene practices when handling contact lenses and timely contact lens replacement [35].

To make the right management decisions, recognizing the risk factors for CLAIK, its different clinical infectious patterns, and getting the causal microorganism identification/isolation are critical to obtaining an optimal therapeutic response, avoiding sight-threatening severe complications.
9.1 Bacterial keratitis

An early diagnosis and appropriate treatment of infectious keratitis are essential. Broad-spectrum topical antibiotics are the first-line therapy for bacterial keratitis and should be initiated immediately after cultures are obtained, while waiting for the results. Antibiotics should be indicated, taking into consideration the local epidemiological data, frequency of specific pathogens, and antibiotic sensitivities (Table 5) [82, 119]. Severe keratitis should be treated with an initial loading dose every 5 to 15 minutes for the first hour, followed by hourly instillation for 24 to 48 hours; a topical fortified antibiotic or fluoroquinolone may be used [119].

In a recent meta-analysis, no difference in effectiveness, defined as complete corneal re-epithelialization, was observed between the use of commercially available fourth-generation topical fluoroquinolones and aminoglycoside-cephalosporin fortified combinations; there was no difference in time to resolution either. However, symptoms of ocular discomfort and toxic conjunctivitis were more frequent when using fortified aminoglycoside-cephalosporin combinations (see Appendix 1) [119].

Treatment should be tapered according to response to a minimum of four times a day, avoiding toxicity from prolonged and unnecessary use of antibiotics [112]. If no clinical stabilization or improvement is observed after the first 48 hours of treatment, the therapeutic regimen should be modified; culture results and antibiotic sensitivity should guide the clinician under these conditions. Good therapeutic response features include decreased pain, conjunctival discharge, eyelid edema, reduced corneal stromal edema, a decreased anterior chamber response, and signs of re-epithelialization. Patients with severe keratitis should be followed daily until clinical improvement is observed. Cycloplegic agents may be indicated in cases of severe keratitis with significant anterior chamber reaction to prevent the formation of irissynechiae and reduce the pain [63].

The use of topical corticosteroids is controversial but may have a role in treating certain bacterial keratitis to reduce corneal scarring. According to a subgroup analysis of the Steroids for Corneal Ulcers Trial (SCUT) in non-Nocardia bacterial keratitis, topical corticosteroids within two to three days of topical antibiotic therapy resulted in a one-line improvement in visual acuity compared to placebo [120]. However, topical corticosteroid use in Nocardia ulcers was associated with larger scars at 12 months, and therefore, it is not recommended for these cases [121]. Other well-designed randomized clinical trials are necessary to confirm these findings [122].

9.2 Fungal keratitis

Fungal keratitis is often more aggressive than bacterial keratitis. However, there is no consensus on standard treatment, and randomized clinical trials on this subject are scarce [122]. Most antifungal medications available for ocular infections have significant limitations, including low bioavailability and limited ocular penetration in deep-seated lesions (Table 6) [123–125]. Furthermore, antifungal susceptibility testing has limited availability and is rarely used in ordinary contact lens and cornea clinics [126]. The Mycotic Ulcer Treatment Trial I (MUTT I) showed that topical natamycin is superior to topical voriconazole treating fungal keratitis in general, particularly in those caused by Fusarium [127]. According to the MUTT II results, there is no difference in perforation rate or need for therapeutic penetrating keratoplasty in fungal ulcers treated with oral voriconazole combined with topical antifungal agents compared to oral placebo and equal antifungal topical therapy. However, systemic adverse events were more frequent in the oral voriconazole group.
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## Drug top 7.

| Drug | Topical concentration | Subconjunctival dose | Activity |
|------|-----------------------|----------------------|----------|
| Cephalosporins: Inhibit bacterial cell wall formation by disrupting the synthesis of peptidoglycans. Less susceptibility to β-lactamases compared with penicillins. |
| Cefazolin<sup>1</sup> | 50 mg/mL | 100 mg in 0.5 mL | Gram-positive cocci |
| Ceftriaxone | 50 mg/mL | 100 mg in 0.5 mL | Gram-negative cocci<sup>2</sup> |
| Cefazedime | 50 mg/mL | 100 mg in 0.5 mL | Gram-negative cocci / rods |
| Fluoroquinolones<sup>1</sup>: Inhibit bacterial DNA gyrase and topoisomerase IV, enzymes required for bacterial DNA synthesis. |
| Ciprofloxacin | 3–6 mg/mL | Not available | Gram-negative cocci / rods |
| Ofloxacin | 3–6 mg/mL | Not available | Gram-negative cocci / rods |
| Levofloxacin | 5–15 mg/mL | Not available | + gram-positive cocci |
| Moxifloxacin | 5–6 mg/mL | Not available | + gram-positive cocci and NTM |
| Gatifloxacin | 5–6 mg/mL | Not available | |
| Besifloxacin | 5–6 mg/mL | Not available | |
| Aminoglycosides: Bind to ribosomal subunits, resulting in defective mRNA translation and inhibition of protein biosynthesis. |
| Gentamicin<sup>1</sup> | 9–14 mg/mL | 20 mg in 0.5 mL | Gram-negative rods |
| Tobramycin<sup>1</sup> | 9–14 mg/mL | 20 mg in 0.5 mL | Gram-negative rods |
| Amikacin | 20–40 mg/mL | 20 mg in 0.5 mL | NTM / *Nocardia* |
| Penicillins: Inhibit bacterial cell wall formation by disrupting the peptidoglycan synthesis. |
| Penicillin G | 100,000 U/mL | 1,000,000 U/mL | Nonpenicillinase producing gram-positive organisms |
| Methicillin | 50 mg/mL | 200 mg/mL | Penicillinase-producing gram-positive organisms |
| Piperacillin | 7 mg/mL | 200 mg/mL | Gram-positives and some gram-negatives, including *Pseudomonas* |
| Glycopeptides: Inhibit cell wall formation of gram-positive bacteria |
| Vancomycin<sup>1</sup> | 15–50 mg/mL | 25 mg in 0.5 mL | Gram-positive cocci |
| Macrolides: Inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. |
| Erythromycin<sup>4</sup> | 5 mg/gram | Not available | Gram-positive bacteria |
| Clarithromycin | 10 mg/mL | 20 mg in 0.5 mL | NTM |
| Bacterial folic acid inhibitors: Folic acid, used in DNA synthesis is required by bacteria for growth and replication. |
| Sulfacetamide<sup>5</sup> | 100 mg/mL | 20 mg in 0.5 mL | *Nocardia* |
| TMP-SMX<sup>6</sup> | 16 mg/mL | 20 mg in 0.5 mL | *Nocardia* |

*Adapted and modified from Mannis MJ and Holland EJ (Eds.). (2017). *Cornea*. Elsevier.*

<sup>1</sup>Also used when no organism or multiple types or organisms are identified.

<sup>2</sup>Systemic therapy is required for suspected gonococcal infection.

<sup>3</sup>Potent activity against methicillin-resistant *Staphylococcus aureus*; used for resistant *Enterococcus* species and penicillin allergy. Must not be used as single therapy against bacterial keratitis due to poor gram-negative activity.

<sup>4</sup>Mostly used in ointment presentation for the management of blepharitis, rarely used in keratitis due to poor corneal penetration.

<sup>5</sup>Active against gram-negative and -positive bacteria; however, used because bacteria become highly resistant during therapy.

<sup>6</sup>Rarely used in bacterial keratitis due to poor corneal penetration when intact epithelium.

### Table 5.

**Topical and subconjunctival antibiotics and their indication for microbial keratitis.**

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Table 5.

**Topical and subconjunctival antibiotics and their indication for microbial keratitis.**
According to a metaanalysis of the available randomized clinical trials, there is still limited evidence to support using any particular drug or combination of drugs to treat fungal keratitis [129]. In general, topical treatment may include natamycin 5%, amphotericin-B 0.15% to 0.5 %, or voriconazole 1% or 2% [122].

### 9.3 Acanthamoeba keratitis

There is no consensus on the standard treatment for *Acanthamoeba* keratitis. Trophozoites are sensitive to a variety of antibiotics, antifungals, antiseptics, and antineoplastic agents. In contrast, cysts are highly resistant to a number of these drugs [113]. Effective topical treatment for *Acanthamoeba* cysts may include diamines and biguanides such as propamidine-isethionate 0.1%, hexamidine-diisethionate 0.1%, dibromopropamidine 0.1%, polyhexamethylene-biguanide 0.02%, or chlorhexidine 0.02% [130]. A combination therapy of a biguanide and a diamidine is often used initially on an hourly schedule for the first 48 hours; treatment is then tapered according to the clinical response and potential epithelial toxicity and may be continued for several months. The objective is to eradicate *Acanthamoeba* trophozoites and cysts, with the resolution of the corneal inflammatory response [113].

### 9.4 Topical corticosteroids in infectious keratitis

The use of topical corticosteroids in infectious keratitis remains controversial [131]. Some authors advocate their use suggesting corticosteroids minimize corneal

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Table 6.

**Topical antifungals formulations for the treatment of mycotic keratitis.**

| Drug                  | Topical concentration | Coverage                                      |
|-----------------------|-----------------------|------------------------------------------------|
| **Polyenes**          |                       | Polyenes: bind to ergosterol in the fungal cell wall; disruption of cell wall |
|                       | Dose: initial dose of one drop every 30 minutes with tapering to every 3 to 6 hours |
| Amphotericin B        | 0.05%–0.50%           | First-line therapy for *Candida*; good activity against *Aspergillus* and *Fusarium*. |
| Natamycin             | 2.5%–5%               | *Aspergillus*, *Fusarium*; moderate for *Candida* |
| **Azoles**            |                       | Azoles: inhibit the synthesis of ergosterol through the cytochrome P-450-dependent enzyme |
|                       | Dose: undetermined    |                                               |
| Clotrimazole          | 1%                    | *Candida*, *Aspergillus*                      |
| Econazole             | 0.02%–2%              | *Fusarium*, *Aspergillus*, *Candida*          |
| Voriconazole          | 1%–2%                 | *Candida*, *Aspergillus*                      |
| Itraconazole          | 1%                    | *Candida*, *Aspergillus*                      |
| Fluconazole           | 0.5%–1%               | *Candida* and other yeasts                    |
| Ketoconazole          | 1%–2%                 | *Candida* and *Aspergillus*                   |
| **Echinocandins**     |                       | Echinocandins: block beta-glucan synthesis    |
|                       | Dose: undetermined    |                                               |
| Caspofungin           | 0.5%                  | *Candida*, *Aspergillus*                      |
| Micafungin            | 0.1%                  | *Candida*, *Aspergillus*                      |
| **Allylamines**       |                       | Allylamines: block ergosterol biosynthesis by inhibition of squalene epoxidase |
|                       | Dose: undetermined    |                                               |
| Terbinafine           | 0.25%                 | *Aspergillus*, *Fusarium* and *Candida*       |

*Adapted and modified from Mannis MJ and Holland EJ (Eds.). (2017). Cornea. Elsevier.*
inflammation, opacification, and neovascularization. Others oppose their use, claiming that they might exacerbate microbial replication, delay epithelial healing, accelerate stromal melting, and increase the risk of perforation [132]. Several authors have demonstrated in non-controlled studies that prior corticosteroid use in bacterial keratitis significantly increases the risk of antibiotic failure and corneal ulceration [132, 133]. A Cochrane review of three small randomized trials found no benefit in healing times or visual acuity outcomes with adjuvant corticosteroid treatment [134]. The Steroids for Corneal Ulcers Trial (SCUT), the largest randomized controlled trial to date, showed no overall benefit of steroid use in visual acuity, scar size, or perforation rate at 3-months follow-up [121]. Of note, steroids (prednisolone sodium phosphate 1%) or placebo were started after 48 hours of topical 0.5% moxifloxacin. The SCUT also demonstrated that adjuvant corticosteroids, compared to placebo, resulted in one-line improvement in visual acuity in non-Nocardia ulcers and more extensive scars in Nocardia ulcers at one year [121]. In a recent report by the American Academy of Ophthalmology, authors suggest using topical corticosteroids after 48 hours of antibiotic therapy in culture-positive non-Nocardia bacterial keratitis [122].

Similar results were described by Wouters et al. in eyes with Acanthamoeba keratitis [135]. Topical corticosteroid use was associated with a delay in diagnosis (23 vs. 62 days, p < 0.001), increased disease severity, worst visual outcomes (≤20/80, p = 0.03), and the need for an urgent corneal transplant [135].

In a recent murine model of Candida albicans, topical 0.1% dexamethasone exacerbated fungal keratitis by increasing the aggressivity of the pathogen, reducing the neutrophil infiltration, and inhibiting the formation of neutrophil extracellular traps [136].

9.5 Corneal collagen crosslinking (CXL)

Corneal CXL is a therapeutic modality consisting of photoactivation of a chromophore, riboflavin (vitamin-B$_2$), by ultraviolet (UVA) light at a wavelength of 370 nm. This technique is mainly used for stabilizing the corneal curvature and vision in patients with keratoconus and ectatic disorders [137, 138]. Studies suggest that guanine oxidation of nucleic acids and reactive oxygen species generation by activated riboflavin results in nucleic acid destruction with subsequent microbial proliferation. In 2013, the term photoactivated chromophore for infectious keratitis-corneal collagen crosslinking (PACK-CXL) emerged [137].

Price et al. performed the first prospective study assessing the efficacy of CXL in infectious keratitis [139]. PACK-CXL was deemed more effective for bacterial keratitis involving the superficial layers of the corneal stroma [139]. Another prospective clinical trial randomized 40 eyes to receive either PACK-CXL in addition to antimicrobial therapy or antimicrobial therapy alone [140]. Although PACK-CXL did not shorten the corneal healing time compared to the control group, it did result in an absent incidence of corneal perforation or recurrence of infection (0% vs. 21%) [140]. A recent meta-analysis performed by Ting et al., including four randomized-control trials, demonstrates that adjuvant PACK-CXL results in shorter mean healing times and quicker resolution of infiltrates when comparing with antimicrobial treatment alone. Despite the latter, high-quality randomized controlled trials are required to establish PACK-CXL’s efficacy in infectious keratitis fully [141].

9.6 Rose bengal photodynamic antimicrobial therapy (RB-PDAT)

RB-PDAT is an emerging therapeutic modality for the management of infectious keratitis [142]. It was first introduced by Amescua et al. in 2017 for the management
of a patient with multidrug-resistant *Fusarium keratothlasticum* keratitis [143]. In this therapeutic modality, rose bengal, a routinely used dye in ophthalmology, is excited with a green light at a wavelength of 500–550 nm to generate reactive oxygen species [144]. Rose bengal is a type II photosensitizer that, when activated, induces cellular apoptosis by converting triplet oxygen to singlet oxygen [142]. A pilot study performed by Naranjo et al. including *Acanthamoeba* keratitis (10 cases), *Fusarium spp.* (4 cases), *Pseudomonas aeruginosa* (2 cases), and *Curvularia spp.* (1 case), evaluated the clinical outcomes of RB-PDAT. One patient had no microbiological diagnosis [144]. Most individuals (14/18, 79%) were contact-lens wearers. Successful therapy, defined as avoiding therapeutic keratoplasty, was achieved in 72% of the cases. Although adequately powered randomized controlled trials are required to ascertain the efficacy of RB-PDAT, preliminary results are promising.

9.7 Future drug-delivery systems

Despite the high efficacy and broad spectrum of the antimicrobials used in infectious keratitis, their insolubility in water, low precorneal residence time on the ocular surface, inadequate control of drug release and penetration, nasopharyngeal drainage, and toxicity hinders their performance [145]. To overcome such limitations, recent developments on drug-delivery systems are emerging.

Chhonker et al. developed amphotericin-B-loaded lecithin/chitosan nanoparticles with enhanced mucoadhesive properties for the prolonged ocular application [145]. The nanoparticles sized 161.9 to 230.5 nm improve drug bioavailability by approximately 2.04 fold and precorneal residence time by 3.36 fold in rabbit eyes [145]. Guo et al. developed self-assembled micelles of poly(ethylene glycol)-block-poly(glycidyl methacrylate) (PEG-b-PGMA) to deliver natamycin [146]. The sustained drug release from micelles allows reducing the frequency of natamycin application from 8 to only 3 times per day in rabbits with fungal keratitis. The use of contact lenses as drug carriers or sustained-release deposits has also been evaluated to improve antimicrobial efficacy. Huang et al. developed a hybrid hydrogel-based contact lens, loaded with voriconazole, comprised of quaternized chitosan, graphene oxide, and silver nanoparticles [147].

Another strategy employs carbon dots, which are small, highly fluorescent non-toxic element nanoparticles that measure less than 10 nm and are considered to replace metal-based quantum dots [148]. Zhao et al. demonstrated that nitrogen-doped carbon quantum dots sized 2–5 nm can destroy the cell structure of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) [149].

There is a paucity of studies evaluating the efficacy of drug-delivery mechanisms to manage infectious keratitis in humans. Such mechanisms may enhance drug penetration, better compliance, and reduced toxicity, thus improving patient outcomes.

9.8 Surgical procedures

Surgical management must be considered to maintain the globe integrity in patients with unresponsive keratitis associated with severe stromal melt with impending perforation risk. Zhong et al. demonstrated that full-thickness conjunctival flap covering surgery with amniotic membrane transplantation might represent a viable option to save the eyeball for eyes with severe fungal keratitis without corneal perforation [150]. In their series, most eyes (15/17, 88%) achieved complete conjunctival re-epithelization. Seven of them achieved a mean best-corrected visual acuity of ~20/100, remaining disease-free at least one month after
sclerokeratoplasty [150]. However, melting of the conjunctival flap, with subsequent endophthalmitis requiring evisceration, occurred in two eyes.

Therapeutic keratoplasty (TKP) should be reserved for patients who are not candidates for other therapies, and if possible, after quiescent infection [151]. In *Acanthamoeba* keratitis, TKP is recommended in cases of corneal perforation unresponsive to repeat gluing, severe corneal abscess, or significant cataract [113]. Because of the risk of rejection with large grafts in *Acanthamoeba* keratitis, corneal grafts must be kept to the minimum size required [113]. In cases of fungal keratitis, Selver et al. demonstrated that smaller grafts (≤ 8 mm) were associated with lower rejection rates, but higher recurrence rates possibly related to incomplete removal of infected tissue [151, 152].

10. Conclusions

Despite significant technological development in contact lens materials resulting in remarkable improvement in safety and comfort, microbial keratitis continues to be a severe sight-threatening complication in contact lens wearers. Overnight extended contact lens wear and deficient lenses and case hygiene continue to be the primary risk factors for CLAIK worldwide; hence improvement in contact lens hygiene, education, and handling is necessary to reduce this potential complication.

The clinician must be able to promptly recognize the condition and identify the causative microorganism through corneal scraping, smear, and culture in case of severe keratitis, and treat the disease according to the suspected etiological agent; Empirical treatment must be initiated in every case and modified according to the clinical response and microbiology laboratory results.

Appendix

**Fortified topical antibiotic formulations and mode of preparation**

| Tobramycin 14 mg/mL or gentamicin 14 mg/mL |
|-------------------------------------------|
| 1. Withdraw 2 mL of either drug from an injectable vial (40 mg/mL). |
| 2. Add 2 mL to an ophthalmic solution (5 mg) of either drug to give a 14 mg/mL solution. |
| 3. Refrigerate and shake prior to instillation. |

| Cefazolin 50 mg/mL or ceftazidime 50 mg/mL |
|------------------------------------------|
| 1. Add 9.3 mL of lubricant eyedrops to a vial of either drug, 1 g (powder for injection). |
| 2. Dissolve. Take 5 mL and add it to 5 mL of lubricant eyedrops. |
| 3. Refrigerate and shake prior to instillation. |

| Amikacin 10–40 mg/mL |
|----------------------|
| 1. Dilute intravenous formulation (80 mg/2 mL ampules) with lubricant eyedrops or 0.9% sodium chloride for injection USP to the desired concentration. |
| 2. Refrigerate and shake prior to instillation. |

| Vancomycin 15 mg/mL, 25 mg/mL, or 50 mg/mL |
|-------------------------------------------|
| 1. Add either 33 mL, 20 mL, or 10 mL of 0.9% sodium chloride for injection USP, or artificial tears, to a vial of 500 mg of vancomycin to produce a solution of 15, 25, or 50 mg/mL, respectively. |
| 2. Refrigerate and shake prior to instillation. |
Linezolid 2 mg/mL (for methicillin-resistant Staphylococcus aureus)

1. May be used directly from parenteral linezolid intravenous infusion available as 200 mg/100 mL.

Colistin 0.19% (for multiple drug-resistant Pseudomonas aeruginosa)

1. Add 1 million UI / 75 mg of parenteral colistimethate sodium powder to 10 ml of distilled water to obtain 75 mg/mL.
2. Withdraw 1 mL of the above solution and add to 3 mL of distilled water to obtain a 0.19% concentration

Trimethoprim (16 mg/mL) - sulfamethoxazole (80 mg/mL)

1. Commercial intravenous preparation may be used as topical solution without preparation.

Imipenem – cilastin (1%)

1. Add 10 mL of sterile water to parenteral imipenem (500 mg) – cilastin (500 mg) to create a 50 mg/mL solution.
2. Withdraw 1 mL of the above solution and add 4 mL of sterile water to make topical 1% imipenem to obtain 1 mg/mL
3. Storage in amber-colored bottles

Data retrieved from [153].

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