Contact Lens-Related Infections
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As the use of therapeutic and cosmetic contact lenses becomes more widespread, the incidence of contact lens-related microbial infections is also increasing. Simple preventative measures can be implemented by wearers to avoid infection, corneal ulceration, and compromised vision. Ophthalmologists and optometrists must be vigilant in providing the necessary education to patients when prescribing contact lenses and ensure that patients understand the risks of noncompliance.

Approximately 41 million adults in the United States, representing almost 17% of the adult population, wear contact lenses to correct refractive errors in vision. In addition, children are being prescribed orthokeratology lenses at an increasing rate to reduce myopic progression. The yearly incidence of infectious keratitis is estimated to be 1 in 1 in 10,000 in daily wear rigid gas permeable lens wearers and 3-4 in 10,000 in daily wear soft contact lens wearers. Extended wear soft contact lenses confer the highest risk of infection, irrespective of lens material, with an incidence of 20 in 10,000 individuals. Newer silicone hydrogel contact lenses with higher oxygen transmissibility aimed at reducing the deleterious effects of hypoxia on the corneal epithelium have not been shown to reduce the risk of microbial keratitis compared to older hydrogel materials, as was initially anticipated. In addition, we are not only seeing an increase in the incidence of contact lens-related microbial keratitis, but also an increase in the severity of infections with greater risk of vision loss.

Pathogenesis of contact lens-associated infections

The pathogenesis of contact lens-associated microbial keratitis is multifactorial. For starters, corneal infection requires microbial contamination. Microbes can gain access to the ocular surface easily from hand contamination during lens insertion and removal, from the lens surface, or from contaminated storage cases and care solutions. However, given the robust mechanisms of the ocular defence system, access alone is not sufficient for corneal infection.

Contact lenses can interfere with the cornea’s inherent protective mechanisms against infection. In vitro studies have shown that cultured corneal epithelial cells with prior exposure to a contact lens lose their ability to upregulate antimicrobial pep-
tides on their surface in the face of bacterial threat. In addition, reduced tear exchange underneath a contact lens results in the accumulation of tear film debris and can provide a space for microbes to flourish and replicate. Another important factor is the ability of microbes to adhere to the posterior surface of contact lenses and form exceptionally virulent and antimicrobial resistant biofilms.

The most commonly isolated culprit in contact-lens related keratitis is the gram-negative rod-shaped bacteria Pseudomonas aeruginosa, followed by coagulase-negative Staphylococci. Risk factors for bacterial keratitis include overnight wear, infrequent storage case replacement, improper disinfection of lenses and cases, smoking, and storing or rinsing contact lenses in tap water. Cosmetic contact lenses, which have gained popularity especially among adolescents, are also associated with a higher risk of infection and are likely to result in aggressive disease. A systematic review of ocular complications associated with contact lenses obtained from unregulated sources showed that over-the-counter supply (comprising beauty salons, video stores, flea markets, tat...
the most common causative organism, followed by Fusarium being less than 5% of cases, with Fusarium being the most common causative organism, followed by Aspergillus and Candida. Known risk factors include ocular trauma, especially direct corneal trauma with vegetable matter, predisposing ocular surface or systemic disease, and systemic immunosuppression. Lastly, protozoal infection predominantly by the free-living, cyst-forming ameba Acanthamoeba is highly associated with contact lens wear, with nearly 85% of cases being attributed to contact lens wear.

**Modifiable behaviors to reduce the risk of contact lens-related infections**

Modifiable risk factors for developing contact lens-related infectious keratitis include overnight wear, improper disinfection of lenses and cases, poor hand hygiene, infrequent case replacement, storing or rinsing contact lenses in tap water, swimming or showering in contact lenses, and prolonged use of the same bottle of disinfecting solution. Counselling patients on proper contact lens hygiene is a crucial component of patient care for any eye care professional. These guidelines include, in part, the following: never sleep or nap in contact lenses (regardless of lens type or material); keep water away from lenses and cases; avoid showering, bathing, or swimming in contact lenses or wear swim goggles; adhere to replacement schedules for monthly or weekly contact lenses (relative to the date of opening the box); avoid contacts not prescribed by a licensed eye care professional; replace cases at least once every 3 months; and use fresh lens solution to clean and store lenses (do not top off old solution). Further, it is important to comply with the expiration date of contact lens solutions, wash hands prior to contact lens insertion and removal, and keep the contact lens case away from sources of bacteria and tap water (bathroom sink). It must be stressed that overnight wear, regardless of contact lens type, is the main risk factor for all types of infectious keratitis and thus this practice must be avoided.

Daily disposable contact lenses eliminate the need for two of the most frequently contaminated lens accessory items – lens cases and disinfecting solutions. In situations where there is concern for patient compliance with disinfection regimens or scheduled lens and case replacements, such as in adolescents, daily disposable lenses are a much-preferred option. Daily disposable contact lenses have also been shown to result in infections which are less severe in nature with lower risk of vision loss compared to the aggressive central corneal infections which result from extended wear lenses used for overnight wear.

All patients should be counselled to remove lenses and seek immediate medical advice at the onset of any concerning signs or symptoms. In addition, for patients who are not good candidates for contact lens use, either secondary to contact lens intolerance, a history of vision threatening contact lens related infectious keratitis, or a lack of compliance with proper contact lens hygiene, refractive surgery should be strongly considered.

**Differential diagnosis of contact lens-related infections**

When a contact lens associated infection is suspected, a thorough history to elucidate further risk factors, such as overnight wear, hygiene practices, recent eye trauma, exposure of lenses to non-sterile water, as well as a history of immunosuppressing systemic disease and medications, should be taken.

The classic presentation of bacterial keratitis is similar to that observed without contact lens exposure, namely acute onset of pain and photophobia, diffusely and often intensely hyperemic bulbar conjunctiva, one or more corneal infiltrates with overlying epithelial defect, possible anterior chamber inflammation with a hypopyon, and decreased visual acuity. The most commonly responsible agent is Pseudomonas aeruginosa, which produces enzymes including protease and elastase that digest collagen and can cause corneal melt and perforation followed by an intense immune response. A hallmark feature of this infection is a stromal infiltrate with a “soupy” appearance.

Fungal keratitis, on the other hand, is characterized by a gradual onset of symptoms and the infiltrate may have feathery edges and satellite infiltrates may be present with hypopyon. Classic signs of Acanthamoeba keratitis include pseudodendrites, epithelial stippling, perineuritis, subepithelial infiltrates, and pain out of proportion to findings. It is important to note that the classic “ring infiltrate” is a very late finding and actually means the diagnosis was missed when the infection was in the epithelial stage.

A common diagnostic dilemma for eye-care providers is being able to differentiate a sterile infiltrate from an infectious ulcer given the management of each is quite different. Sterile infiltrates, which are generally self-limiting, are a very common complication among contact lens wearers, with the incidence ranging from 2.5% to 6% and as high as 20% to 25% when asymptomatic sterile ulcers are included. Some helpful, albeit not full-proof, differentiating signs and symptoms of sterile ulcers include: minimal to mild conjunctival inflammation, small infiltrate size (often <1mm), absence of discharge, minimal pain, small or no epithelial defect, and absent to mild anterior chamber inflammation.

One of the vital components for appropriate diagnosis and treatment are corneal scrapings for smears and cultures. While practice patterns for when to obtain corneal cultures vary greatly, it should be highly considered in high-risk cases, namely if the infiltrate is central and thus vision threatening, if the infiltrate is larger than 1 mm, if there are any signs of corneal thinning/melt, or if there is an atypical appearance (eg, feathery border, ring infiltrate). Symptoms of pain that are out of proportion to the clinical examination should also prompt sample culture. When taking a corneal sample, it is critical to sample robustly at the leading edge.

**CORE CONCEPTS**

- The incidence of contact lens-related microbial infections of bacterial, fungal, and protozoal origin is on the rise.
- Preventative measures can be implemented by contact lens wearers to minimize the risk of infection.
- Differential diagnosis of microbial keratitis and sterile keratitis is critical to ensure immediate and appropriate management.
- Optometrists and ophthalmologists have an important role in educating contact lenses wearers on the risk of contact lens-related infection and to report adverse events to the FDA.

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of the infiltrate where the microbial yield will be highest. For fast detection of potential microorganisms, smears on slides are extremely valuable, as they provide immediate information upon which the treating physician may tailor antimicrobial therapy. In addition to culturing the cornea, the contact lens and lens case should also be cultured if they are available as these often have a very high yield.

Acanthamoeba infection presents several diagnostic challenges, often resulting in misdiagnosis and delay in treatment. Early disease can mimic herpetic keratitis and is often mistreated with topical steroids. Steroids can cause further progression of the infection, making it very difficult to treat, particularly when the active Acanthamoeba trophozoite transitions to a dormant cyst encased in a double-layer cellulose wall. Patients unresponsive to appropriate length of treatment with antimicrobial therapy, patients with presumed herpetic inflammatory keratitis with worsening signs after use of topical steroids, or those with a history of using non-sterile water to rinse or store their lenses should prompt the eye care provider to consider Acanthamoeba as a possible source of infection and obtain appropriate stains and culture. Where available, confocal microscopy is also informative.

Management options for the treatment of infectious keratitis

Patients presenting with microbial keratitis related to contact lens use should be started on broad-spectrum antibiotic therapy to cover both gram-negative and gram-positive organisms. Monotherapy with a topical fluoroquinolone may be adequate for small, peripheral ulcers but broad-spectrum fortified antibiotics are advised for more severe cases. Empiric antibiotic decisions should be based on regional surveillance data and then tailored based on microbiologic results. Frequent antibiotic dosing is highly recommended initially and patients must be educated on the importance of compliance. In situations where there is a high suspicion for methicillin-resistant Staph. aureus (MRSA) infection, such as in patients with a prior history of MRSA infection or active colonization of MRSA anywhere in the body, initiation of empiric MRSA therapy with vancomycin is recommended. If vancomycin is unavailable, gentamicin and a 4th generation fluoroquinolone can be used.

If topical antibiotics are dosed appropriately, resulting in high concentrations of drug being delivered effectively to decrease bacterial loads, the issue of antibiotic resistance with topical antibiotics is minimal. Subtherapeutic dosages run the risk of resistance; therefore, the tapering of antibiotics to subtherapeutic doses is never recommended.

Additionally, the judicial use of adjunctive topical steroids may be considered in select patients to limit sequelae of corneal scarring and neovascularization. We generally use steroids in cases of bacterial keratitis when the patient has shown a nice initial response to antibiotic therapy. Steroids are avoided when the diagnosis is uncertain and the etiology may be fungus or Acanthamoeba. Corticosteroids can have many deleterious effects and can significantly delay healing and even exacerbate infection. If initiated, it is imperative to monitor patients frequently and have a low threshold for stopping steroids if the clinical course worsens.

Initial follow-up is based on the severity of the disease and ranges from 1–4 days. A lack of response to fortified antibiotics in a compliant patient after 48 hours should prompt the provider to consider other diagnoses, such as fungal or protozoal infection, secondary infection, antimicrobial resistance, or topical anaesthetic abuse. Therapy should be guided by clinical response determined by patient's symptoms, infiltrate consolidation, epithelial healing, and decreased anterior chamber inflammation or hypopyon size.

For the management of filamentary fungal keratitis (Fusarium and Aspergillus being the most common agents), the randomized controlled Myotic Ulcer Treatment Trial (MUTT) showed natamycin to be the most effective choice of therapy.

For deep fungal ulcers and scleritis, oral voriconazole can be also prescribed, although patients require baseline and monitored liver function tests and must be made aware of systemic side effects.

Acanthamoeba trophozoites respond well to many chemotherapeutic agents; however, cysts are mostly resistant. Off-label biguanides and diamidines are the most effective cysticidal agents.

Long term consequences of contact lens-related infections: impact on future lens wear

Even with good, early control of infection, prognosis after contact lens related infections can still be poor secondary to the inflammatory response to infection resulting in corneal melting, scarring, and perforation.

The incidence of vision loss from contact lens associated microbial keratitis has been reported to be 0.3 to 3.6 per 10,000 users.

Multidimensional strategies involving microbial keratitis prevention, improved early and accurate diagnostics techniques, and adjuvant therapies that focus on modifying the immune response to the infection are required to improve overall outcomes. Current adjunctive treatments include autologous serum eyedrops, bandage contact lenses, amniotic membrane transplantation, and punctal occlusion. For patients in whom a large central scar remains in association with compromised vision, scleral contact lenses may be indicated to help reduce the scar-related aberrations and astigmatism. If this does not help, lamellar or penetrating keratoplasty (corneal transplant) may be considered.

The role of optometrists and ophthalmologists is critical in educating patients for whom contact lenses have been prescribed. Further, practitioners are encouraged to report with vigilance every case of a contact lens-related adverse event to the Food and Drug Administration (FDA MedWatch site: https://www.fda.gov/safety/medwatch) since daily wear and overnight extended wear contact lenses are, respectively, Class 2 and Class 3 medical devices. Additional resources for current antibiotic susceptibility data, standard antibiotic therapies, and lab diagnostic testing methods can be found at the Charles T. Campbell Eye Microbiology Lab website, ie http://eyemicrobiology.upmc.com.

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adulthood. Factors that influence microbiota makeup include host genetics, geography and culture, exposures in childbirth and infancy, diet, ingestion of prebiotics (microbiota nutrients) and probiotics (exogenous bacteria in capsule form), and selective pressure related to antibiotic and heavy metal exposure.

Ultimately, the gut comes to contain 100 trillion microbes, mostly in the colon, which is on the order of 10 times greater than the number of human cells in the body. Smaller microbial populations inhabit the skin, vaginal mucosa, nasal and oral mucosa, and to a lesser extent, the ocular surface.

The theory of co-evolution of the human holobiont dictates that human cells and the microbiome evolved over the millennia as a unit, taking on complimentary sets of functions and rendering each dependent on the other for health. Roles attributed to the microbiota include those related to host immune system maturation and resistance to colonization by pathogenic microbes. The gut microbiota participates in a range of metabolic pathways related to, among others, nutrient breakdown and absorption (eg, the breakdown of dietary fiber), gut-level metabolic processes (eg, recycling of bile, energy storage via fat), detoxification of ingested toxins, and vitamin biosynthesis. Interestingly, gut microbes also interact bidirectionally with the brain, influencing neurologic and endocrine functions remotely and contributing to brain development, mood, and behavior.

Among the most important roles of the gastrointestinal microbiota as it relates to human disease is assisting in the maintenance of the gut epithelial barrier. Alterations in gut microbiota populations have been observed in patients with inflammatory bowel disease (IBD), obesity, vaginosis, autism, rheumatoid arthritis, diabetes, and other disorders. In theory, dysbioses may increase permeability of the intestinal epithelial barrier, which then interferes with the ability of gut associated lymphoid tissue (GALT) to differentiate between normal and pathogenic organisms, setting the stage for inflammatory or autoimmune reactions in the gut or systemically.

**Gut Microbiota and Ocular Autoimmunity**

Recent studies using mouse models of autoimmune uveitis suggest a potential pathogenic link between gut microbiota and autoimmune uveitis. In an animal study, shifts in intestinal microbiota, increased gut permeability, and increased effector T cells in mesenteric lymph nodes were observed during the course of experimental autoimmune uveitis. Similarly, Caspi and colleagues have demonstrated activation of gut lymphoid and retinal T cells by gut commensal microbiota. They also observed that oral inflammation was reversed with the depletion of gut microbiota following administration of an oral broad-spectrum antibiotic cocktail. In a separate study using a different murine uveitis model, ocular anti-inflammatory effects of oral antibiotics were mediated by increased T regulatory cells and decreased effector T cells and cytokines.

Roles for non-ocular microbiomes in retinal diseases are currently under investigation. A study showed that glaucoma patients had more bacteria in their oral microbiota compared with healthy control subjects. It may be that chronic, low-level exposure to nonocular anti-genic stimuli (eg, antigens among gut or skin microbiota) could be misperceived by the immune system as foreign, resulting in peripheral inflammation and autoimmune phenomena at remote anatomical sites. In support of this theory, studies have shown that DBA/2J and C57BL/6 mice (established animal models for glaucoma) developed retinal and optic nerve microglial activation and glaucomatous progression two months following peripheral (footpad) injection of bacterial lipopolysaccharide. And there is growing evidence that glaucomatous neurodegeneration is partially mediated by T cells present in human tissue exposed to commensal microbial flora.

**Ocular Surface Microbiota**

The ocular surface microbiota functions to defend against invading pathogens while simultaneously providing a reservoir of potential pathogens when defenses are breached. Tolerance of commensal microbes on the ocular surface is likely mediated by secretory IgA.

It is generally accepted that organisms commonly cultured from ocular infections, mainly Staphylococcus aureus; coagulase-negative staphylococci (CoNS), including Staphylococcus epidermidis; Streptococcus pneumoniae; Pseudomonas aeruginosa; and Haemophilus influenzae, are members of the ocular surface microbiota. Studies characterizing the microbiota in healthy individuals have revealed a relatively consistent paucibacterial (roughly 150-fold lower than oral mucosa or skin microbiomes) ocular surface microbiome, in which a limited number of species predominate. However, the species comprising the ocular microbiota differ between individuals and in the same individual over time.

The most consistently isolated organisms are coagulase negative staphylococcus (CoNS), including Staphylococcus epidermidis, isolated from 20% to 80% of conjunctival swabs and from 30% to 100% of lid margin swabs; followed by Propionibacteria and diphtheroids such as Corynebacterium. Less common species include Streptococcus viridans, S. aureus, Micrococcus, Bacillus, Lactococcus, Neisseria, Sphingomonas, and Streptophyta. Gram negatives, including P. aeruginosa, Klebsiella, Acinetobacter, Proteus, and Escherichia coli, are uncommon.

**Contact Lens Wear**

Although evidence from gene sequencing studies, including those cited above, point to at least a semi-stable “core” ocular microbiota, many factors have been shown to influence it, including contact lens wear, keratoprosthesis, dry eye disease (DED), antibiotic exposure, and infection.

Contact lens wear increases risk for infectious and inflammatory adverse events at the ocular surface. Further, in separate studies, contact lens bacterial bioburden and elevations in tear film IL-6 have been associated with increased risk for corneal infiltrative events (CIE) among contact lens wearers. These findings raise the question, do conjunctival microbiome changes caused by contact lens wear affect infection risk? The answer may vary according to age group, contact lens type, and duration of wear.

Shin and colleagues recently studied conjunctival and skin microbiota structure among contact lens wearers (n = 9) compared with non-contact lens wearers (n = 11) using 16S rRNA gene sequencing technology. Compared with conjunctival microbiota among non-contact lens wearers, conjunctival microbiota structure among contact lens wearers was more variable between individuals and more skin-like (in distribution of species) (P < 0.001). Further, relative to non-contact lens wearers, conjunctival microbiota of contact lens wearers had higher concentrations of Methyllobacterium, Lactobacillus, Acinetobacter, and Pseudomonas, which are ocular opportunistic pathogens.
The authors postulated that contact lenses provide a surface for and/or exert a selective pressure for microbes predominant on skin to flourish on the eye. Interestingly, species identified on the conjunctiva did not correlate with species on the skin of subjects’ hands, which were also tested, suggesting that lens-hand contact during insertion could not explain these shifts.

Knowing that contact lens wear induces chronic change in ocular microbiota and milieu makes contact lens hygiene all the more critical toward preventing infectious and inflammatory events.

DED and the Microbiota

DED is associated with inflammation and aberrations in tear film biochemistry, the etiologic mechanisms for which have yet to be fully elucidated. A prospective, open-label pilot study showed greater bacterial colonization of conjunctival and lid margin surfaces among subjects with DED (both non-autoimmune and Sjogren’s variants) compared with non-DED subjects.21

A separate study by Graham and colleagues comparing the ocular surface microbiota of subjects with and without DED (as demonstrated by culture and 16S rRNA DNA sequencing) revealed increased total bacterial count (mostly coagulase-negative staphylococci) as well as the presence of several rare bacteria, including Klebsiella oxytoca and Propionibacterium acnes, among subjects with DED.15 Also, researchers found a correlation between increased bacterial burden and decreased goblet cell density, suggesting a connection between ocular surface colonization patterns and DED pathophysiology.

Modulating the Microbiota

Success with fecal microbiota transplantation (FMT) for the treatment of Clostridium difficile infection (CDI) is encouraging to researchers eager to apply a growing body of microbiota knowledge clinically. C. difficile infection affects about 500,000 patients each year and typically occurs on the heels of systemic antibiotic exposure that reduces the population of protective bacteria in the gut.2 Treatment of recurrent CDI with FMT reestablishes a healthy gut microbiota and is associated with a 90% cure rate.4

Looking Ahead

Considering the speed with which microbiologic identification technology is advancing—becoming faster and more specific through culture-independent technologies such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, 16S ribosomal RNA sequencing, whole genome sequencing, and next generation sequencing—our current state of understanding of the microbiota is likely a fraction of what is to come in the years ahead. If research continues to implicate the gut microbiome in autoimmune pathogenicity and protection, FMT (or other treatments that correct gut dysbiosis) could conceivably become a viable treatment option for uveitis or other ocular or nonocular indications.22 It is also conceivable that, as the importance of a healthy microbiome becomes more evident and accepted, minimizing impact on the microbiome might become a goal of pharmaceutical development and therapeutic intervention.

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1. Which of the following influence the makeup of the human microbiota?
   A. Route of delivery at birth
   B. Genetic factors
   C. Antibiotics, prebiotics, and probiotics
   D. All of the above

2. In the experimental models of uveitis discussed in this article, ocular inflammation decreased in response to:
   A. Oral antibiotics
   B. Fecal transplantation
   C. Intraocular antibiotics
   D. High-fiber diet

3. Which of the following are possible long-term consequences of contact lens-related microbial infections?
   A. Scar-related astigmatism
   B. Impaired vision
   C. The need for a corneal transplant
   D. All of the above

4. Which of the below is the most common source of contact lens-related infection?
   A. Candida sp
   B. Acanthamoeba
   C. Pseudomonas aeruginosa
   D. Fusarium sp.

5. Bacterial contact lens-related corneal ulcers secondary to Pseudomonas species present with which clinical feature?
   A. Single or multiple white spots in the periphery or mid-periphery of the cornea
   B. Corneal edema and a dense white infiltrate and discharge
   C. Feathery borders
   D. Pain that is out of proportion to the clinical examination

6. The microbe type or genus most consistently found in the ocular microbiota is
   A. Coagulase-negative Staphylococcus
   B. Moraxella
   C. Pseudomonas
   D. Streptococcus viridans

7. The highest incidence of contact lens-related microbial infection is associated with which type of lens?
   A. Rigid gas permeable contact lens
   B. Daily wear soft (hydrogel) contact lens
   C. Extended wear soft (hydrogel) contact lenses
   D. Toric soft contact lenses

8. According to the study by Shin and colleagues, ocular microbiota among contact lens wearers (relative to non-wearers):
   A. Lacked bacterial density
   B. Had greater inter-individual variability
   C. Had fewer pathogenic species
   D. Resembled nasal microbiota

9. A host organism and its microbiota are called the:
   A. Microbiome
   B. Holobiome
   C. Holobiont
   D. Macrobiota

10. Initial management of microbial keratitis (depending on origins) should never include which of the following?
    A. Fluoroquinolone
    B. “Shotgun therapy” using fortified antibiotics
    C. Corticosteroids
    D. Off-label biguanides and diamidines

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