Does this sound familiar? “Doctor, I don’t understand what’s wrong. I have been wearing my contact lenses overnight for years and this has never happened before.” Upon close examination, you note the presence of small, grayish aggregates in the corneal epithelium. The diagnosis? Corneal infiltrates. But how do you tell if they are sterile or infectious—harmless, or a potential serious problem?

As practitioners, we have seen any number of contact lens-related complications walk through our doors. Corneal infiltrates and ulcers are two such examples that have long been an unfortunate reality of patient care. In the 19th century, treatment of corneal ulcers included chemical cauterization with silver nitrate. While we’ve come a long way since those days in the care we provide, when such adverse events occur, differentiating infectious and sterile infiltrates is still no easy task.

**BREAKING IT DOWN**

Corneal infiltrates result from the penetration of white blood cells into the corneal tissue as part of the body’s inflammatory response to the presence of bacterial toxins, enzymes and byproducts. A corneal ulcer, by comparison, is an epithelial defect with underlying inflammation (which typically leads to necrosis of corneal tissue).

Infiltrates and ulcers are similar in that they both involve disruption of the corneal epithelium; indeed, a staining infiltrate may be the beginning of a corneal ulcer. The difference, however, is that while corneal infiltrates are not sight-threatening, corneal ulcers involve active tissue damage caused either by infectious or non-infectious etiologies. Infectious ulcers are caused by fungus, virus, or parasites like *Acanthamoeba* or, most commonly, bacteria. Alternately, noninfectious ulcers result from autoimmune, neurotrophic keratitis, allergy (e.g., shield ulcers), inflammation from blepharitis or chemical burns, or idiopathic conditions (e.g., Mooren’s ulcer).

In the case of microbial insult, the damage typically results in an excavation of the corneal stroma, which triggers an anterior chamber response of flare with or without cells (Figures 1, 2 and 3). For this reason, the terms *microbial keratitis* and *bacterial ulcer* are sometimes used interchangeably.

Four subtypes of contact lens-related corneal infiltrates exist: *microbial keratitis, contact lens-induced peripheral ulcer (CLPU), contact lens-induced acute red eye (CLARE)* and *infiltrative keratitis*. While the etiology of these subtypes is multifactorial, research shows significant overlap between their clinical presentations, suggesting it is not possible to clinically differentiate between them; rather, they should be considered as stages of a single disease spectrum.

**DIFFERENTIATING BETWEEN THE TWO**

Requires close observation and analysis. Here’s a results-oriented approach.

**By Jeffrey Sonsino, OD, and Shachar Tauber, MD**

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THE “TWO CORNEAS”
When determining whether the corneal infiltrate is infectious or sterile, one helpful method is to divide the cornea into two distinct regions. Consider that the central cornea encompasses the 6mm of the cornea apex whereas the peripheral cornea is a 2mm to 4mm doughnut, with the limbus as its posterior border.

Based upon the close approximation of the peripheral cornea to the limbus (with its preponderance of stem cells and vascularity), investigators believe the immune response to be more active in this region of the cornea. Quantification of the nerve fibers shows a densely innervated cornea and a five to six times lower innervated peripheral cornea. Higher mitotic activity has also been demonstrated in the peripheral cornea.

These observations indicate the two distinct regions of the cornea have key anatomic, physiologic and pathologic differences, allowing for the generalization that infiltrates in the periphery of the cornea are non-infectious while infiltrates in the central 6mm of the cornea may have an infectious etiology.

ALWAYS TAKE NOTES
As with any medical concern that presents to the clinic, careful history taking can lead the eye care practitioner to identify the proper diagnosis and resultant treatment that gives the patient the best possible outcome with the least risk.

• **Contact lenses.** Contact lens use is one identified risk factor for the development of corneal infiltrates, as evidence shows continuous wear of contact lenses increases the risk of ocular complications. However, it is not the primary cause of corneal infiltrates; rather, it is simply one of several contributors. Other risk factors for corneal infiltrate development in continuous wear contact lens patients include age (i.e., between 18 and 29 years) and a history of smoking, corneal scarring, contact lens acute red eye or corneal infiltrates.

Of the different corneal infiltrate types, microbial keratitis is the most severe complication of contact lens wear. In the 1980s and 1990s, risk of microbial keratitis was found to be four cases per 10,000 lens wearers per year for daily wear and 20 cases per 10,000 wearers per year for extended wear. Pseudomonas aeruginosa has been identified as the most common bacterial source of microbial keratitis in contact lens wearers.

• **Corneal trauma.** Risk of microbial keratitis also increases any time there is a history of corneal trauma or foreign body presence due to the possibility of incomplete removal. This is especially true when the foreign body is vegetative matter, which is more likely to be contaminated by pathogens. Corneal trauma may also include iatrogenic etiologies, such as retained or broken sutures in penetrating keratoplasty patients.

• **History of surgery.** Because anterior segment surgery compromises epithelial barrier function, any corneal surgery carries a risk of resultant infiltrative keratitis and infectious ulcer. In particular, infiltrative keratitis is associated with astigmatic keratectomy, penetrating keratoplasty, DSAEK, pterygium removal, trabeculectomy, LASIK

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**Fig. 1.** Slit beam evaluation of a corneal ulcer. Deviation of the beam shows corneal excavation.
IS THAT CORNEAL INFILTRATE STERILE OR INFECTIOUS?

Fig. 2. Sodium fluorescein evaluation of a corneal ulcer. The hyperfluorescence is attributed to staining of the mucous plug.

Fig. 3. Contact lens-related microbial keratitis. Ulcer filled with mucous plug.

and cataract surgery.\textsuperscript{14-17} It is not clear if the relative risk is greater with regards to a particular corneal surgery.

• \textit{Ocular surface disease.} Sterile peripheral (i.e., marginal) corneal infiltrates may result from a compromised ocular surface. \textit{Staphylococcus} blooms in the lids spill bacterial byproducts onto the cornea, which triggers a hypersensitivity reaction that is theorized to lead to infiltrates.\textsuperscript{18,19} Often small and multiple in nature, these infiltrates are typically positioned roughly 1 mm from the limbus. Marginal infiltrates may be asymptomatic, or may be accompanied by conjunctival injection. Pathogenesis includes bacterial, allergic or autoimmune etiologies.

In the case of severe blepharitis and meibomian gland dysfunction (MGD), the bacterial blooms within the meibomian glands can produce a hypersensitivity reaction, leading to peripheral, non-staining subepithelial infiltrates (SEIs). The body responds to the to antigen presented by this presence of \textit{Staphylococcus} bacteria in the lids by recruiting white blood cells to the area as part of an antibody response. For this reason, the SEIs associated with \textit{Staphylococcal} marginal keratitis are typically in the 2 o’clock and 10 o’clock regions and the 4 o’clock and 8 o’clock regions, contiguous with the upper and lower lids.

Similarly, ocular rosacea can lead to MGD. However, with severe rosacea, potential outcomes include marginal infiltrates, chronic conjunctivitis, sterile ulceration, corneal neovascularization and corneal scarring (Figures 4 and 5). It is also critical to rule out herpes simplex keratitis (HSK), which may resemble the infiltrates seen in \textit{Staphylococcal} marginal keratitis. HSK lesions, however, are typically harder to treat and appear with deeper stromal inflammation.\textsuperscript{20}

• \textit{Allergic conjunctivitis.} All eye care practitioners are familiar with the signs and symptoms of seasonal allergic conjunctivitis, atopic conjunctivitis and papillary conjunctivitis. Perhaps less commonly encountered, however, is a variant of allergic conjunctivitis found most often in young boys. Vernal conjunctivitis is a severe bilateral condition characterized by photophobia, chemosis, sticky discharge, eosinophils at the limbus (i.e., Horner-Trantas dots) and shield ulcers.\textsuperscript{21} Secondary bacterial keratitis typically results from 10% of shield ulcers.\textsuperscript{22}

• \textit{Medications.} Contamination of ocular medications has been implicated in numerous case studies of corneal ulceration; the pathogen may originate in topical medication dropper tips or within the medications themselves.\textsuperscript{14,24}

LOOK FOR THE SIGNS

The next step after collecting a complete patient history is to conduct an ocular examination, which can help determine whether an infiltrate is sterile or infectious. The following are all key elements of a physical examination that can help with proper diagnosis:

• Does the patient report symptoms of pain, photophobia or loss of vision? What about corneal sensation? Pain out of proportion with the signs points to \textit{Acanthamoeba}, while loss of corneal sensation (i.e., lack of pain upon history or with the corneal wisp test) signals HSK.

• Do you observe blepharitis, nasolacrimal duct obstruction, poor or incomplete blink or lagophthalmos, entropion/ectropion or conjunctival injection? Is the conjunctival injection localized or diffuse? How about circumlimbal? Be sure to grade the injection (i.e., 1-4+). What about corneal foreign bodies?

• Is there discharge and, if so, what are its characteristics?
• What is the location, depth and size of the infiltrate(s)? Do you observe stromal loss?
• Is there visible loss of corneal endothelium? What about plaque or pigment on the endothelium?
• What is the status of the patient’s corneal graft, if they have one?
• Do you observe any stromal haze and edema?
• Do you observe anterior chamber reaction, cells/flare or hypopyon?
• Are there vitreous cells present? Note, a corneal ulcer will rarely lead to endophthalmitis with vitreous cells present.

THE CULTURAL REVOLUTION
In the last 20 years, a major shift in thought regarding the need to obtain corneal material to identify offending organisms and determine sensitivity to antibiotics has occurred. Today, broad-spectrum fluoroquinolones are readily available as the primary treatment for a corneal infiltrate believed to be infectious. Thus, the majority of community-acquired cases of bacterial keratitis are typically resolved with empiric therapy and managed without smears or cultures.

However, such tests are indicated in certain cases, including those that involve a corneal infiltrate that is central, large and extends to the mid to deep stroma, particularly with significant thinning of the cornea or scleral extension; those chronic in nature or unresponsive to broad-spectrum antibiotics; and those that present with atypical clinical features suggestive of fungal, amoebic or mycobacterial keratitis. Smears and cultures may also be helpful in cases with an unusual history, such as trauma caused by vegetable matter or if the patient wore contact lenses while in a hot tub.

Additional specialized studies can help identify atypical organisms, for example in sight-threatening or severe keratitis of suspected microbial origin. However, the American Academy of Ophthalmology—noting that the hypopyon that occurs in eyes with bacterial keratitis is usually sterile—recommends aqueous or vitreous taps should not be performed unless there is a high suspicion of microbial endophthalmitis, such as following an intraocular surgery, perforating trauma or sepsis.

When obtaining corneal material, proper technique is critical to identify the causative organism and select the proper antibiotic, antiviral, antifungal or antiprotozoal medications. The process of obtaining corneal material should first involve the instillation of a topical anesthetic agent (note that tetracaine should be avoided due to its antimicrobial effect) followed by the use of a heat-sterilized platinum spatula, blade, jeweler’s forceps or other similar sterile instrument to obtain scrapings of material from the advancing borders of the infected area of the cornea. Culture yield may be improved by avoiding anesthetics with preservatives.

A thiol or thioglycollate broth-moistened dacron/calcium alginate or sterile cotton swab can also be used to obtain material. However, solid as well as liquid plating media is always recommended. If treatment is refractory and cultures do not yield results, it is advisable to halt antibiotics in order to isolate the exact pathogen for further treatment. It is also important to consider culturing contact lenses, contact lens cases and contact lens solutions if appropriate and available.

TREATMENT OPTIONS
Topical antibiotics are the first-line therapy for suspected or culture-proven bacterial keratitis; however, the selection depends on severity. A peripheral infiltrate associated with lid margin disease may be appropriately managed with inexpensive early fluoroquinolones such as ofloxacin, ciprofloxacin, azithromycin or a polymixin-bacitracin ointment, while central or more aggressive infiltrates warrant use of fourth-generation fluoroquinolones such as gatifloxacin, moxifloxacin or levofloxacin.

Fig. 4. Severe ocular rosacea. Visible on the lid is tyalosis, scalloped lid margin and telangiectasia, which signals severe inflammation within the meibomian glands.
Fig. 5. Corneal scarring with severe ocular rosacea.

For more serious keratitis, the use of bexifloxacin has recently been advocated. This new fluoroquinolone has high MIC values for many common ophthalmic pathogens and a unique compound containing polycarbophil, edetate disodium dihydrate and sodium chloride, which allows for greater ocular surface contact time. Additionally, its position as the only ophthalmic fluoroquinolone not used systemically makes it unique by reducing the risk of antibiotic resistance.

In severe situations with risk for perforation, failure to respond to monotherapy or central aggressive ulcers with the potential for vision loss, the use of combination fortified-antibiotic therapy should be considered. This should be formulated by a compounding pharmacy that is a member of the Pharmacy Compounding Accreditation Board. Note that methicillin-resistant Staphylococcus aureus (MRSA) has been isolated with increasing frequency from patients with bacterial keratitis. Fluoroquinolones are generally poorly effective against MRSA ocular isolates; however, vancomycin has demonstrated some success. In cases of severe ulcer, consider more complete coverage with combination therapy.

Systemic antibiotics are rarely needed, but may be considered in severe cases where the infectious process has moved to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. Research shows oral tetracycline controls the anti-collagenase activity commonly seen in necrotizing infections such as Pseudomonas. Systemic therapy is necessary in gonococcal keratitis because of the extremely aggressive nature of this organism (corneal penetration in 24 hours with inadequate treatment). For this reason, the CDC recommends immediate hospitalization with IV antibiotics for adult gonococcal infection.

Treating viral, fungal and amoebic keratitis may be challenging and is beyond the scope of this article. Regardless, the eye care provider who has clinical suspicion or laboratory data supporting any of these infectious processes should be fluent in their current treatment options or have available the appropriate consultants to offer prompt referral.

Determining whether an infiltrate is sterile or infectious is not an easy task for even the best clinicians. However, with careful history taking, physical examination, differential diagnosis and proper treatment, patients have the best chance of making the best of a bad situation.


1. All of the following are likely symptoms or signs of corneal infection EXCEPT:
   a. Pain and photophobia.
   b. Discharge and foreign body sensation.
   c. Anterior chamber reaction that includes cell and flare.
   d. Lack of debris at the tear meniscus.

2. There are many reasons to culture corneal ulcers. Which of the following is NOT one of them?
   a. Culturing would be a helpful medico-legal component of your record in case the ulcer doesn’t respond to empiric treatment.
   b. Culturing reveals sensitivities of the organism(s).
   c. Because no single agent is generally effective for all infections.
   d. Because ineffective treatment and organisms are difficult to isolate.

3. Currently, the most effective/complete treatment plan for resistant bacterial infection is:
   a. Vancomycin and cefazidime.
   b. Tobramycin.
   c. Gentamycin and Ocuflox.
   d. Ocuflox and erythromycin.

4. Which of the following statements is true regarding corneal infiltrates?
   a. Sterile infiltrates are often single in number and are found closer to the visual axis.
   b. Corneal infiltrates at least histologically present in all infections.
   c. Large, central infiltrates with overlying stans are probably sterile.
   d. Corneal infiltrates associated with microbial keratitis generally produce little to no pain and photophobia.

5. The most common cause of perennial allergic conjunctivitis is:
   a. Ragweed or tree pollen.
   b. Summer grasses.
   c. Home allergens, such as dust mites and animal dander.
   d. Multipurpose disinfecting solutions used in contact lens care.

6. Which of the following is not true regarding the use of systemic antibiotics?
   a. They often provide a more effective dose to the cornea than topicals alone.
   b. They have a lower chance of producing an allergic response.
   c. They are often ineffective when the infection has scleral extension.
   d. Tetracyclines may aid in patients with an impending corneal melt.

7. Risk for infiltrative keratitis is increased with all of the following EXCEPT:
   a. Poor compliance/hygiene.
   b. Smoking.
   c. History of corneal scarring and CLARE.
   d. Age 39 to 40.

8. The incidence rate for microbial keratitis has been estimated to range from
   a. 18 to 20.
   b. 34 to 38.
   c. 1 to 2.
   d. Because ineffectively treated organisms are difficult to isolate.

9. Which of the following is NOT a risk for microbial keratitis?
   a. Wearing contact lenses overnight.
   b. History of corneal trauma or foreign body.
   c. Prior corneal surgery.
   d. Daily use of aspirin.

10. Which of the following is true regarding monotherapy use in presumed microbial keratitis?
    a. A fourth-generation fluoroquinolone is probably the best overall option and can be used alone for deep central ulcers.
    b. Besiavinc is likely the best option for MRSA infections.
    c. Monotherapy should be reserved for use in central infiltrates only.
    d. Erythromycin is generally the best treatment option pending culture results.