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Approach to Infectious Keratitis: Clinical Pearls While on Call

Introduction

Microbial keratitis is a vision-threatening infection of the cornea and an important cause of ocular morbidity that can result in blindness. It is estimated that over 1.5 million people worldwide will develop blindness from infectious corneal ulceration each year. If left untreated or treated incorrectly, it can result in progressive tissue destruction with corneal perforation or extension of the infection to the adjacent tissue. Outcomes of these patients depend on timely diagnosis and treatment with close follow-up.[1,2]

Epidemiology in Canada

An understanding of the most common pathogens and antibiotic sensitivity in various geographical areas is essential in guiding the clinical diagnosis and empirical treatment.

In a study conducted at our centre from 2006 to 2011, the microbiology of infectious corneal ulcers at tertiary centres in Vancouver, British Columbia was reviewed.[3] In 281 corneal scrapings, the positive culture recovery rate was 75%, with 27% being polymicrobial. Overall, bacterial keratitis accounted for 84.8% of culture-positive ulcers, followed by fungal (10%) and Acanthamoeba (5.2%).

The most frequent cultured organism was coagulase-negative Staphylococcus (CoNS) and thus it was also the most common gram-positive bacterium. The most common gram-negative bacteria were Moraxella species. Over time, an increase in gram-negative bacteria vs gram-positive bacteria was noted. In non-contact lens-related polymicrobial ulcers, 100% of the infections involved gram-positive bacteria, 27.7% gram-negative bacteria, and 4.3% fungi. Contact lens-related polymicrobial ulcers showed 72.7% gram-positive involvement, 9.1% gram-negative, 9.1% fungal and 9.1% Acanthamoeba.

In a 20-year retrospective case series of fungal keratitis in Toronto, Candida species accounted for 60.8% of positive fungal cultures, followed by Filamentous species at 35.3%.[4] Similar

Bacteria	Fungi	Acanthamoeba
• Contact lens use*	• Trauma with vegetative material*	• Contact lens use*
• Trauma	• Contact lens wear	• Exposure to potentially contaminated fresh water
• Contaminated ocular medications	• Corticosteroid use	
• Ocular surface disease	• Ocular surface disease	
• Previous ocular surgery	• Previous ocular surgery	
• Atypical mycobacteria: LASIK	• Systemic immunosuppression	

Table 1. Risk factors for infectious keratitis.
*Most common risk factors

results were observed in Vancouver, where 62.5% of culture-positive fungal keratitis were attributed to Candida.[5]

In other series from our institution, the most commonly isolated microorganisms in pediatric patients were Staphylococcus epidermidis and Acanthamoeba. Acanthamoeba was isolated in 67% of contact lens-related corneal ulcers, while the remaining 33% of contact lens-related corneal ulcers were associated with Pseudomonas aeruginosa.[6]

Bacteria are the most common cause of infectious keratitis in the adult Canadian population, with CoNS as the most common isolate. The prevalence of fungal keratitis and Acanthamoeba is significantly lower, although the incidence of fungal keratitis in Canada has been increasing in the last 20 years.[5]

Risk Factors

The main predisposing risk factor for the development of infectious corneal ulcers in Canada is contact lens use. In our previous study, contact lens-related ulcers were caused primarily by bacteria (67.4%), followed by parasites (20.9%) and fungi (11.6%). Furthermore, more than 80% of Acanthamoeba cases were contact lens-related.[3]

Several clinical studies have evaluated the specific risk factors for each type of infectious keratitis. For example, bacterial keratitis has been frequently associated with contact lens wear. Contact lens use has also been recognized as an emerging risk factor for fungal keratitis. In a 20-year retrospective multicentre study across Canada, patients with yeast keratitis had more ocular surface disease than those with filamentous keratitis (79% vs 28%) and were more likely to manipulate their bandage contact lenses (36% vs 6%), while patients with filamentous keratitis wore more refractive contact lenses (78% vs 19%).[7]

In children, the major predisposing factors are contact lens wear and pre-existing ocular surface conditions including blepharitis and Stevens-Johnson syndrome.[6]

Table 1 summarizes the main risk factors associated with bacterial, fungal and Acanthamoeba keratitis.

Clinical Presentation

The clinical appearance of infectious keratitis is not a reliable indicator of the causative pathogen, but can help differentiate bacterial from fungal or amoebic keratitis.

Bacterial corneal ulcers typically present as a single superficial, suppurative infiltrate associated with an epithelial defect (**Figure 1A**). An endothelial inflammatory plaque, marked anterior chamber reaction and hypopyon can be present in bacterial keratitis and are more common in gram-negative bacteria.

Fungal keratitis has a chronic or indolent clinical course, and tends to present with less dramatic signs and symptoms of an inflammatory

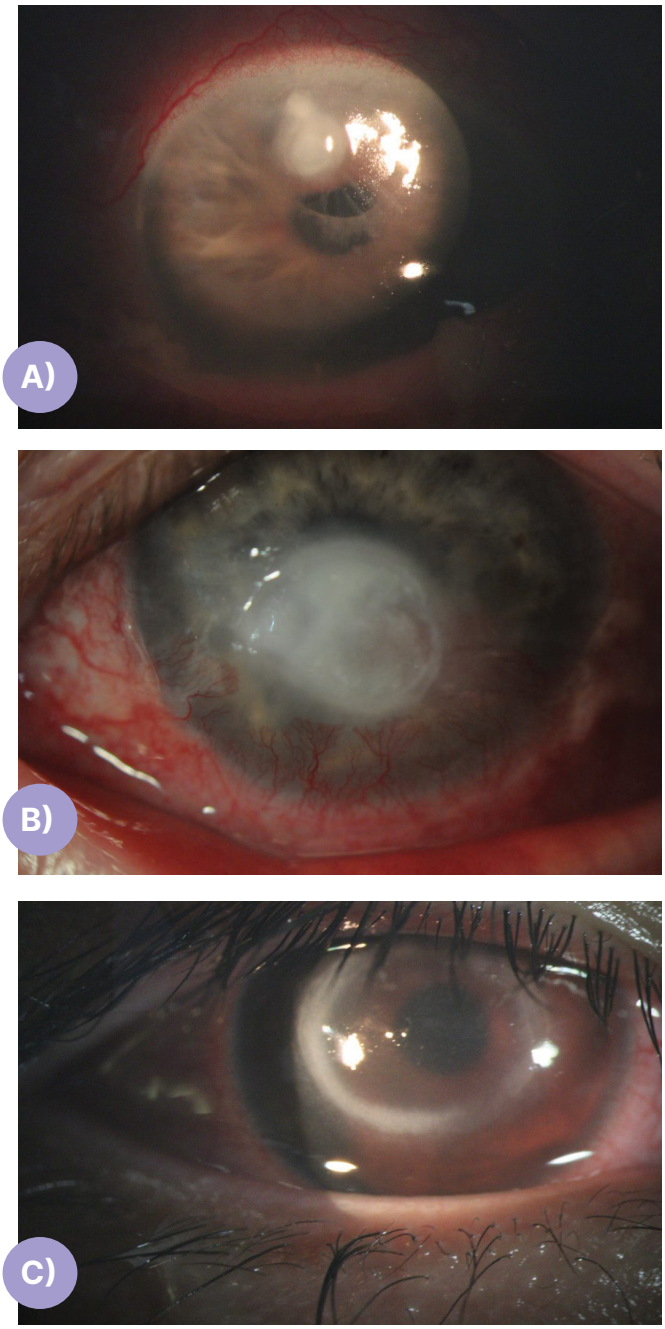

Figure 1. A) Single suppurative infiltrate with epithelial defect and mild anterior chamber reaction, suggestive of a bacterial ulcer.
B) Fungal gray-white infiltrate with irregular feathery margin in a patient with a trauma to the cornea with vegetative material. **C)** Acanthamoeba keratitis presenting with severe ocular pain, no response to topical antibiotics and a central ring infiltrate; *image courtesy of Sonia N. Yeung, MD, Alfonso Iovieno, MD, Barbara Burgos-Blasco, MD.*

response compared to infections of bacterial origin. It classically manifests as gray-white, non-suppurative multifocal or satellite infiltrates with irregular feathery or filamentous margins and a dry texture (**Figure 1B**). In the course of the disease, stromal infiltration without epithelial defect may present, as well as an endothelial plaque or hypopyon, particularly if the fungal infiltrate is deep-seated or large.[2]

Acanthamoeba keratitis typically presents with severe ocular pain that is greater than expected from clinical findings, as well as photophobia, a progressive course and no response to standard topical antimicrobial agents. Slit-lamp examination shows a spectrum of findings ranging from mild epitheliopathy to subepithelial opacities, pseudo-dendritic lesions and radial perineuritis (considered a quasi-pathognomonic sign) to a partial or complete central ring infiltrate (**Figure 1C**).[8,9]

Culture of Corneal Scrapes

Microbial culture of corneal scrapings remains the standard of care for the diagnosis of infectious keratitis. Culture positivity is significantly higher before antibiotic treatment is initiated; therefore, it should be considered the first diagnostic step. It may also be helpful to culture the contact lenses, contact lens cases and solutions if available.

According to the American Academy of Ophthalmology guidelines, specimens for culture should be obtained in the following cases: central infiltrate; large infiltrate; significant stromal involvement; corneal melting; previous corneal surgery; multiple sites of corneal infiltration; perforation; unresponsive to broad-spectrum antibiotic therapy; or atypical clinical features suggestive of fungal, amoebic or mycobacterial keratitis.[10]

Multiple corneal samples for culture on various growth media are typically used. However, this may not always be accessible to all eye care specialists, as most culture media require refrigeration and have a short shelf life. An alternative to common culture media is the ESwab (Copan Diagnostics, Inc, Murrieta, California), a nylon-tipped swab placed in 1 mL of modified Amies medium. It maintains bacterial sample viability for 48 hours. The shelf life of this swab at room temperature is 18 months. The ESwab has been validated for microbiological use, culture results being comparable to the multi-sample method.[11]

Initial Treatment

Initial treatment consists of empiric, broad-spectrum topical antibiotics that should cover the most frequent and serious pathogens in a specific geographical area and should be initiated immediately, while awaiting a definite microbiological diagnosis.

In routine corneal ulcers, topical fluoroquinolone monotherapy has excellent penetration at commercially available concentrations and provides outcomes equivalent to those of combination therapy.[8] Second generation fluoroquinolones (ciprofloxacin, ofloxacin) have excellent Pseudomonas coverage but lack useful gram-positive activity. Third- and fourth-generation fluoroquinolones (e.g., moxifloxacin, gatifloxacin, levofloxacin, and besifloxacin) have improved gram- positive and atypical mycobacterial coverage, but have limited activity against methicillin-resistant Staphylococcus aureus (MRSA). While considered generally effective against Pseudomonas in North America,[12] recent evidence may suggest an increasing rate of moxifloxacin resistance in ocular Pseudomonas isolates in British Columbia, in particular from corneal samples. Conversely, susceptibility of Pseudomonas to tobramycin has significantly increased over time and it may represent a good treatment option.[13]

A possible protocol for initial empirical treatment is the use of topical fluoroquinolone monotherapy hourly for five days while the patient is awake, followed by a taper to qid for 7–10 days if the infection is responding.[8]

Fortified antibiotics are compounded at higher concentrations than those commercially available and can be difficult to obtain. They are sometimes required in severe ulcers, particularly in large gram-positive or vision-threatening ulcers, when MRSA is suspected, or after failure of the initial therapy.

In fungal keratitis, natamycin 5% is generally recommended for filamentous fungal keratitis, particularly Fusarium. Topical amphotericin B 0.15% should be used in cases of yeast keratitis such as Candida or filamentous keratitis caused by the Aspergillus species.[14] However, recent evidence by our group shows that over 90% of Candida isolates in Canada are sensitive to fluconazole.[13]

Systemic antibiotics or antifungals are not usually necessary, but should be added to topical treatment if scleral or intraocular extension of the infection is suspected. If this is the case, fluoroquinolones are the treatment of choice in bacterial cases given their excellent ocular penetration (ciprofloxacin 250 mg bid or moxifloxacin 400 mg daily). In fungal keratitis, oral fluconazole (100 mg bid), voriconazole (200–400 mg/day), and posaconazole (800 mg/day) are good options due to their excellent intraocular penetration and broad coverage.[10,15]

The role of corticosteroid therapy for infectious keratitis remains controversial and it should be considered with caution. Corticosteroids are effective at managing the inflammation and reducing tissue destruction, but can also inhibit the host's response resulting in worse outcomes or complications. In bacterial keratitis, the use of topical corticosteroids in large central ulcers and 48 hours after initiating topical antibiotics may improve clinical outcomes.[16,17] However, this is not the case for fungal or Acanthamoeba keratitis. Therefore, when in doubt, topical corticosteroids are not initially recommended.

In addition, topical cycloplegic agents to reduce pain and the formation of synechiae and pressure-lowering medications can be used if needed. Oral doxycycline and vitamin C supplementation can be considered in severe cases to prevent keratolysis.[18]

Follow-up

Once treatment is initiated, patients should be monitored closely every 24–48 hours. The clinical response should guide patient management and if clinical improvement is noted, therapy should be continued. The first indication of a positive clinical response to antimicrobial treatment is an improvement in pain. Other signs of possible improvement are re-epithelialization; blunting of the perimeter of the stromal infiltrate; decreased density of the stromal infiltrate; improvement of corneal thinning; reduction in stromal edema; decrease of endothelial inflammatory plaque; and reduction in anterior chamber inflammation.[18,19]

If the patient appears to be worsening on treatment despite good compliance, one can consider switching to fortified broad-spectrum antibiotics if the initial therapy was fluoroquinolone monotherapy. However, if there is worsening of the clinical signs, the infection is severe or sight threatening, there is risk of perforation, or an atypical pathogen such as fungal or Acanthamoeba is suspected, the patient may need to be referred to a Corneal Unit.

Conclusion

Microbial keratitis is an ophthalmic emergency that needs to be treated imminently in order to avoid extensive visual impact. A delay in initiating appropriate therapy is the most important factor associated with a worse prognosis in corneal ulcers. Certain risk factors and clinical features may be helpful in identifying the infectious agent, but ultimately an etiological diagnosis with standard microbiology techniques is generally mandated. If deterioration is observed on close follow-up, referral to a cornea specialist or a tertiary centre should be considered.

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