



Management of Post-refractive Infectious Keratitis

a report by

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Reports of keratitis after laser *in situ* keratomileusis (LASIK), as well as after laser-assisted subepithelial keratectomy (LASEK) or photorefractive keratectomy (PRK), have become increasingly common in recent years, although they are still rare. Keratitis is classified as being of infectious or non-infectious aetiology. Non-infectious keratitis – classified as diffuse lamellar keratitis (DLK) and staphylococcal marginal hypersensitivity¹ – is not covered in this paper. Infectious keratitis after refractive surgery can be caused by bacterial, viral, fungal and amoebic pathogens. In contrast to infectious keratitis of other origins, a different pathogenic spectrum occurs after refractive procedures, including atypical micro-organisms with multiple resistance that frequently challenge treatment.²

There are multiple sources for infection and several pre-disposing factors, including the eyelids of patients, systemic associations such as HIV, pollution from microkeratome blades or other surgical instruments, previous refractive surgery, epithelial defects during surgery, excessive surgical manipulation, intra-operative contamination, interface debris, delayed re-epithelialisation of the cornea, bandage contact lens use, application of topical steroids and post-operative pathogen inoculation by the patient.³ Symptoms and ocular findings for infectious keratitis after refractive procedures, which are also commonly seen in cases of corneal keratitis, may include pain, decreased or blurred vision, photophobia, ciliary hyperaemia, corneal epithelial defects, single to multiple and nummular to crystalline infiltrates, ring-shaped infiltrates, hypopyon, ulcers, keratic precipitates, additional oedematous to necrotic flaps in LASIK or flap separation.

Published rates of infectious keratitis after LASIK range from 0 to 1.5%.^{1,4,5} Infectious keratitis has also been reported after LASEK and PRK (0.02% for both).⁵⁻⁷ In 2004, Chang et al. published a literature review of infections following LASIK procedures. They overviewed a total of 103 infections involving 83 patients described in 43 articles. In cases of early onset of infectious keratitis after LASIK – within seven

days of the last refractive procedure (49.4%) – the majority of pathogens were Gram-positive bacteria (53.7%) followed by *Candida* (12.2%). In contrast, in late-onset cases – after 10 days or longer (50.6%) – the majority of causing pathogens were *Mycobacteria* (57.1%), followed by Gram-positives (21.4%) and fungus (19.0%). Gram-positive infections were significantly more associated with pain and discharge than infections caused by other micro-organisms; patients with Gram-positive infections more frequently presented with epithelial defects, flap separation and anterior chamber reactions. Fungal infections were significantly more likely than others to present with redness and tearing. Mycobacterial infections were not significantly associated with partial symptoms or signs.⁴

Post-refractive Bacterial Keratitis

Refractive corneal surgery is the fourth most common cause of bacterial keratitis, after trauma, foreign body injury and wearing contact lenses.⁸ Pathogens for bacterial keratitis after refractive procedures include *Mycobacteria*, *Streptococcus*, *Staphylococcus aureus* – including methicillin-resistant *S. aureus* (MRSA) – *Pseudomonas aeruginosa*,⁹⁻¹¹ *Diphtheroids*, *Nocardia*¹² and *Bacillus*. In a synopsis by members of the American Society of Cataract and Refractive Surgery (ASCRS) of 116 post-LASIK infections, the main pathogens were atypical *Mycobacteria* in 33 of 69 culture-positive eyes and *Staphylococcus* in 23 eyes.³ Typical *Mycobacteria* are the organisms most commonly isolated in post-LASIK bacterial keratitis.¹³ Bilateral involvement has been described.¹⁴ This species is widely found in soil, water, milk, sputum, the skin of healthy individuals and the environment, and may colonise body surfaces and fluids such as skin, sputum and the gastric content of otherwise healthy individuals. Biofilm of the *Mycobacteria* may play a role in evading the host defence mechanism and promoting resistance to conventional disinfection.^{15,16} The course of this infection is often protracted because of delayed diagnosis due to indolent course, the use of corticosteroids, inadequate drug penetration and slow response to therapy.

Mycobacterial-caused keratitis requires aggressive and long-term therapy. With the combined amikacin and clarithromycin topical therapy recommended a few years ago,^{17,18} flap amputation was necessary in up to 80% of patients to allow resolution of the infection; this reflects the limited penetration of these drugs.¹⁹ Today, the fourth-generation fluoroquinolones moxifloxacin and gatifloxacin can be effectively used for treatment of mycobacterial post-refractive keratitis¹⁹⁻²¹ due to their superior penetration with higher corneal concentrations after topical application compared with older generations of drugs. Clinically significant concentrations of moxifloxacin can be achieved in aqueous humour and serum after



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systemic administration.²² In a rabbit model, fourth-generation fluoroquinolones were found to be synergistic to amikacin and clarithromycin against *Mycobacterium chelonae*. This triple combination resulted in a more favourable result than monotherapy with gatifloxacin in terms of reduction of bacterial colonies, but there was no statistical significance.¹⁵ Comparing available data, moxifloxacin was found to be more potent than gatifloxacin against *M. chelonae*; both had equal potency against *M. fortium*.²⁰ Although fluoroquinolones show significant antimycobacterial activity by reducing colony-forming unit counts in monotherapy as well as in combination therapy, cultures remained positive for *M. chelonae* in rabbit corneas after administration of antibiotic therapy. This advocates a more prolonged course of medical therapy and consideration of surgical debridement in the treatment of *M. chelonae* keratitis.¹⁵

As a nosocomial infection, community-acquired MRSA infection is increasingly common. Patients with exposure to a healthcare environment should be considered at additional risk for developing MRSA keratitis after LASIK. Solomon et al. reported on 13 eyes of 12 patients suffering from post-refractive MRSA keratitis. Nine of them were either healthcare workers or had been exposed to a hospital surgical setting. MRSA-related post-LASIK keratitis tends to be more aggressive with worse visual outcome compared with methicillin-sensitive *S. aureus* (MSSA)-associated infectious keratitis. MRSA carriers are at an increased risk of re-infection.¹³ Fourth-generation fluoroquinolones inhibit both DNA gyrase and topoisomerase intravenously (IV), and therefore require two genetic mutations in order for the bacteria to become resistant to the drug.²³ They are more potent against MRSA than prior generations of fluoroquinolones.²⁴

For patients exposed to healthcare facilities, Solomon et al. recommend prophylactically treating blepharitis with lid hygiene and hot compresses pre-operatively and considering a nasal swab for MRSA carriage and bacitracin or a fourth-generation fluoroquinolone for pre-operative prophylaxis, as well as monocular treatment. For the initial treatment of possible MRSA keratitis, they suggest irrigation under the flap with fortified vancomycin (50mg/ml) and recommend switching antibiotics to include better coverage for MRSA-fortified vancomycin every 30 minutes, alternating with topical fourth-generation fluoroquinolone every 30 minutes, applying bacitracin ointment to the eyelids four times daily and stopping steroids.¹³ *Nocardia asteroides* infection reported after LASIK requires treatment with topical trimethoprim-sulfamethoxazole, sulfonamides, amikacin, fourth-generation fluoroquinolones or imipenem.¹² *P. aeruginosa* is known as a highly virulent organism and is resistant to most commonly administered drugs. A topical therapy with local antibiotics according to the results of sensitivity testing in combination with steroids to minimise the inflammatory process is advised.^{9,10}

Post-refractive Viral Keratitis

Viral infectious keratitis after LASIK – which occurs in 0.21% of cases – has been reported as herpetic keratitis presenting with unilateral or even bilateral²⁵ dendritic ulcer and adenoviral keratitis, all with bilateral subepithelial infiltrates.¹ Visual outcome is better after successful treatment for viral keratitis in contrast to non-viral infectious keratitis.¹

Post-LASIK herpes simplex virus (HSV)-associated keratitis has been reported with or without previous history of herpetic disease. Most

people without clinical herpes simplex infection have latent virus. Worldwide, 60–90% of the adult population is positive for the HSV-1 antibody, but only 1–6% of primary infections are clinically recognised.²⁵ The mechanisms by which refractive corneal surgery may trigger reactivation could be damage to or irritation of the corneal nerves, post-operative pain, exposure to ultraviolet light with post-operative corneal inflammation and the use of steroids in post-operative management.²⁶ Given the elevated risk for scarring and subsequent visual loss due to recurrence of ocular herpes, LASIK should not be recommended for patients with a history of HSV infection. In cases in which LASIK is used despite these risks, antiviral agents should be administered prophylactically.²⁷ Dhaliwal et al. demonstrated that antiviral prophylaxis with systemic valaciclovir inhibited the recovery of ocular HSV-1 after LASIK or PRK in a New Zealand white rabbit latency model. A peri- and

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post-operative regimen consisting of systemic aciclovir or valaciclovir 500mg twice daily for one week pre-operatively and two weeks post-operatively and topical aciclovir ointment at bedtime for at least two weeks post-operatively in addition to the topical standard post-operative antibiotic treatment is recommended.^{28,29}

In the treatment of keratitis dendritica, topically applied aciclovir is regarded as the 'gold standard'. Aciclovir has superior corneal penetration to trifluorothymidine (TFT) and is therefore also advised for stromal disciform herpetic involvement. In contrast to keratitis dendritica, stromal herpetic keratitis requires additional low-dose steroid application with delayed onset. In cases of deep stromal involvement or reduced compliance of the patient, an additional treatment with systemic aciclovir (up to 800mg five times daily), valaciclovir or famciclovir may be helpful.^{30,31} In spite of early treatment, almost all eyes lose some degree of best spectacle-corrected visual acuity (BSCVA). After adenoviral post-LASIK keratitis, visual acuity usually returns to baseline BSCVA. Treatment for acute adenoviral keratitis consists of artificial tears and cool compresses with or without topical steroids.

Post-refractive Fungal Keratitis

The main pathogens that cause fungal keratitis after refractive surgery are species of *Aspergillus*, *Candida*, *Fusarium* and *Curvularia*.^{32–34} Most cases of corneal mycotic infections occur after trauma, especially when vegetative material is involved. Symptoms are usually non-specific, although possibly more prolonged (lasting for five to 10 days) than in bacterial ulcers.³⁵ However, pyramidal-shaped hypopyon has been described as being characteristic of fungal origin in contrast to bacterial organisms with horizontal hypopyon, as the fungus forms a scaffold for leukocytes.³⁶ Fungal infection may develop secondary to DLK, possibly due to the associated intense antibiotic and steroid application.³³

Although keratomycosis is rare after refractive procedures, once an organism is established the infection is extremely difficult to eradicate because the corneal epithelium serves as a barrier. Corneal penetration of antifungal agents is poor in comparison with antibacterial therapy. Fungal infections infiltrate the deeper stroma and may penetrate the Descemet's membrane, and are therefore sequestered from the ocular surface defence mechanisms. Beside aggressive topical, systemic and intravitreal antifungal therapy, foudroyant courses with a need for enucleation were reported.³²

Positive cultures for *Candida albicans* require topical application of fluconazole and amphotericin B as first-line drugs. Topical application of fluconazole leads to effective eradication of intrastromal *Candida* species even without the removal of the corneal epithelium, in contrast to amphotericin B.^{37,38} In cases of late onset, an additional low-dose steroid application to reduce the inflammatory response is considered.³⁹ Schreiber et al. demonstrated in a rabbit model that the combination of steroids and antifungal therapy is not contraindicated and that clinical success depends on timing and dose. Immediate onset of antimycotic therapy with delayed corticosteroid application may be beneficial in the treatment of fungal keratitis in humans.⁴⁰

Selection of antifungal therapy depends on direct microscopic examination of corneal scrapes or corneal biopsies. If hyphae are definitively seen by microscopy, topical natamycin 5% is the drug of choice.³⁵ Amphotericin B 0.15% is another therapeutic option, especially if natamycin is available only in lower concentrations of 1 or 2%.⁴¹ If yeasts or pseudohyphae are seen on microscopy, topical amphotericin B 0.15%, fluconazole 2%, natamycin 5%, other azoles or 1% flucytosin eye drops can be used. Topical therapy is usually applied hourly around the clock for several days, and the frequency of application is then gradually reduced. The presence of deep lesions necessitates the addition of systemic therapy, such as voriconazole, the current drug of choice, or the more recent posaconazole. Negative scrapings during therapy do not always indicate that fungal infection has been eradicated, since there may be active fungi in the deeper stroma. Hence, therapy should be continued for several weeks.

Post-refractive Amoebic Keratitis

Acanthamoeba keratitis is rare after LASIK.⁴²⁻⁴⁴ *Acanthamoeba* is a free-living, non-parasitic protozoan found in soil, fresh water, salt water, distilled water, saliva and nasal mucous membranes. The mechanism of corneal infection by this organism seems to involve many factors, including epithelial trauma, a large inoculation of organism and compromised host defence mechanisms. Kaur et al. reported a case of amoebic keratitis developing after sustaining an ice-chip injury one year after LASIK.⁴² This case suggests that amoebic keratitis can divide and spread rapidly in the LASIK flap and in deeper layers of the corneal stroma – probably along the pre-formed interface – even a long time after the LASIK procedure. Due to rapid progression of the keratitis, excision of the LASIK flap was necessary. Amoebic cysts were plentiful at 30 cysts per high-power field, and were widely distributed in the excised LASIK flap 15 days after presumed inoculation.

For the management of acanthamoebic keratitis, early therapeutic onset is essential. Effective cysticidal antiamoebic medications are available, including the diamidin derivatives polyhexamethylene

biguanide (PHMB) and chlorhexidine. Combination with aminoglycosids as antibiotic drugs for elimination of the nutrition source for *Acanthamoeba* is recommended. Diamidin derivatives (Brolene®) are primarily effective against trophozoites. PHMB belongs to the class of disinfectious substances. In a 0.02% concentration, it is effective against trophozoites and cysts. Another disinfectious agent is chlorhexidine in a concentration of 0.02 or 0.006%. However, PHMB is more effective and better tolerated. After a few days of antiamoebic local therapy, addition of local steroids is useful to restrict the immunological reaction and therefore the extension of the destruction of the cornea. Monotherapy with local steroids is contraindicated because it weakens the host resistance against the protozoa.^{45,46} During the first 72 hours, alternating drop application every 15 minutes is recommended, even at night-time. After this, application may be restricted during the day, with the addition of application of local steroids two or three times daily. Therapy should last for six or, preferably, 12 months, with very slow offset of therapy under close supervision.⁴⁵ In operative management, the excision of the LASIK flap may be necessary to reduce the amount of pathogens. This will also improve the penetration of the local medication. A penetrating keratoplasty may be indicated in complicated, therapy-resistant situations after delayed diagnosis.⁴⁵

General Therapeutic Recommendations

Infectious keratitis is one of the most vision-threatening complications after refractive surgery and therefore warrants vigilance, fast diagnosis and aggressive treatment. Every focal corneal infiltration should be suspected as infectious until proved otherwise. An empirical broad-spectrum antimicrobial treatment without culturing is not advised. Early lifting of the flap, especially when the infiltrates involve the interface, scrapings for microbiological investigation – including polymerase chain reaction (PCR) – and irrigation may lead to a better outcome.

For the treatment of rapid-onset and delayed-onset infectious keratitis, Donnenfeld et al. (ASCRS guidelines) recommend elevation of the flap, culture and irrigation of the stromal bed with appropriate antibiotic solution (fortified vancomycin 50mg/ml for rapid-onset keratitis and fortified amikacin 35mg/ml for delayed-onset keratitis). For rapid-onset keratitis, after flap lifting and irrigation they recommend a fourth-generation topical fluoroquinolone in a loading dose every five minutes for three doses and then every 30 minutes, alternating with an antimicrobial that is rapidly bacteriocidal and has increased activity against Gram-positive organisms, such as fortified cefazolin 50mg/ml every 30 minutes, oral doxycycline 100mg twice a day to inhibit collagenase production and discontinuation of corticosteroids. For delayed-onset infectious keratitis they recommend beginning therapy with amikacin 35mg/ml every 30 minutes alternating with a fourth-generation fluoroquinolone every 30 minutes, oral doxycycline 100mg twice daily and discontinuation of corticosteroids. Treatment should be modified based on culture and scraping results.⁴⁷

Daily examinations with evaluation of severity of pain, size and depth of the infiltrates, size of the epithelial defects and the anterior chamber reaction are necessary. If the process worsens, the antibiotic regimen should be changed according to the microbiological culture and sensitivity results. If the cultures are negative and the clinical

course is without improvement; the obtaining of specimens should be repeated or a corneal biopsy should be performed.⁴⁸ Sometimes, flap amputation or even penetrating keratoplasty is unavoidable. The extent of injury to the cornea due to the infectious process may be limited by flap amputation and there may be a greater penetration of antimicrobials. In addition, the lamellar flap may help clarify the cause of infection by sending for culture. For adjunctive therapy, cycloplegic drugs for the prevention of synechias and release of the ciliary spasm are considered.

The use of steroids has been controversial. Corticosteroids are administered in addition to antimicrobials to reduce non-specific inflammatory processes, including corneal oedema and intraocular irritation with fibrin and synechiae formation. Additionally, steroids reduce the neovascularisation that occurs due to persistent corneal inflammation. If steroids are given before or immediately after inoculation of pathogens, a worsening of the infection can

be observed. Therefore, in order to reduce the damaging immuno-associated process, low-dose steroids should be given additionally only with late onset.⁴⁹ Indeed, if no organisms are found on initial culture, steroids must be used with caution: many of the cases treated with steroids were later found to be due to *Mycobacteria* or fungus, which resulted in poor outcome due to exacerbated infections.

To avoid infectious keratitis after LASIK, prophylactic use of fourth-generation fluoroquinolones is common. Recent reports suggest the effectiveness of gatifloxacin and moxifloxacin against Gram-positive cocci and mycobacteria, including *M. chelonae*, the most commonly isolated species in mycobacterial keratitis.^{19,50,51} A combination of early diagnosis and proper treatment is demanded in order to achieve better visual outcome for the patient. Rapid recognition of the causative organism and aggressive medical and surgical treatment of the infection may improve the outcome. ■

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