Infective Complications Following LASIK

11

Adam Watson, Sheraz Daya

Core Messages

- Infective complications following LASIK are a rare, potentially sight-devastating complication but often have good outcomes
- Early diagnosis helps prevent rapid steroid-related progression of infection
- Atypical organisms are common, especially non-tuberculous mycobacteria
- Early presenting cases (7–10 days) and late presenting cases (>10 days) have a different microbiological profile
- Intact epithelium inhibits antibiotic penetration. Flap lift, antibiotic soak and epithelial defect creation are useful strategies
- Reculture, biopsy and flap amputation may be necessary for worsening keratitis despite treatment
- Informed consent and attention to risk factors are crucial

11.1 Introduction

Since its development in 1989 by Pallikaris followed later by FDA approval in the United States in 1999, LASIK (laser-assisted in situ keratomileusis) has become an extremely commonly performed surgical procedure. Infective complications are rare [4] but present special challenges. Infective keratitis following LASIK often involves organisms unusual in other forms of infective keratitis. It usually occurs in the flap interface and may be relatively inaccessible to topical antibiotics. Bilateral infection, although not common, occurs at least partly due to the common practice of performing bilateral simultaneous LASIK procedures. Clusters of infection have also been reported [3, 7, 11]. Finally it should be noted that it is a vision-threatening complication occurring in people with generally high visual expectations, adding to its gravitas.

11.2 Frequency and Presentation

The reported frequency of infection following LASIK ranges from 0% to 1.5%, with the frequency in most large case series being less than 0.2% [4]. Gram-positive and non-tuberculous mycobacterial infections are commonest, with these organisms accounting for 26% and 47% of culture-positive infections respectively in a review of published cases [4]. Mycobacterial infections are probably overrepresented due to reporting bias but do represent a strikingly high proportion of cases of post-LASIK infection. Gram-negative organisms, by contrast, account for very few cases. Fungal and *Acanthamoeba* infections have also been described (Table 11.1).

There are almost certainly predisposing factors for post-LASIK infection. Uncontrolled meibomian gland dysfunction and blepharitis probably contribute to staphylococcal infection [12]. Performing LASIK on eyes that have previously undergone photorefractive keratectomy (PRK) seems to be a risk factor [4]. Post-LASIK trauma is undoubtedly associated with infection. However, the commonest association with reported infections is a breakdown in sterility during the procedure, with systematic contami-

Table 11.1. Organisms reported to have caused post-LASIK keratitis

Bacteria
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus viridans
Coagulase-negative staphylococci
Pseudomonas aeruginosa
Nocardia asteroides
Mycobacteria
Mycobacterium chelonae
Mycobacterium mucogenicum
Mycobacterium abscessus
Mycobacterium szulgai
Fungi
Candida albicans
Curvularia lunata
Scedosporium apiospermum
Fusarium solan
Fusarium oxysporum
Colleotrichum (*Fusarium*-like)
Other
Acanthamoeba

nation of the surgical field probably being responsible for three reported clusters of mycobacterial infection [3, 7, 11].

11.3 Characteristics

Patients with post-LASIK infective keratitis tend to present with varying combinations of pain, photophobia, discomfort, redness and discharge. Deterioration in postoperative visual acuity is commonly noted and may be the sole presenting symptom. Patients may also be asymptomatic with the infection identified at a routine postoperative examination.

The timing of the onset of symptoms varies – between zero days and several months [4, 12]. Post-LASIK infections may usefully be divided into early and late groups depending on the length of time from surgery to the onset of symptoms. Those presenting early occur in the first 7–10 days and are more likely to be caused by "typical" Gram-positive bacteria. Late infections, presenting beyond 10 days, are more likely to be atypical infections, especially non-tuberculous mycobacteria but also including fungal infection.

Flap interface infiltrate is the commonest sign evident on examination although infiltrate may be confined to the lamellar flap or the underlying corneal stroma [4]. Other features of infection that may be present are those found in other forms of infective keratitis, including anterior chamber reaction, keratic precipitates, corneal abscess and epithelial defects. Epithelial defects are found far less frequently in post-LASIK keratitis and tend to be associated with Gram-positive infection. The lack of an epithelial defect has important implications for treatment, as topical antimicrobial penetration is poorer in the absence of a defect. An intact epithelium presents a relatively impermeable barrier to topical antibiotic penetration.

Crystalline keratopathy has also been reported in several cases associated with *Mycobacterium chelonae* infection [2, 22]. This appearance is highly suggestive of *M. chelonae* infection.

11.4 Differential Diagnosis

11.4.1 Diffuse Lamellar Keratitis (DLK, "Sands of the Sahara")

DLK, a non-infectious inflammation occurring after LASIK in approximately 2–4% of cases [13], may present with mild pain, redness and photophobia in the 1st week after surgery. In the milder stage 1 and stage 2 forms of DLK the infiltrates are light and diffuse and unlikely to be confused with infection. More severe stages of DLK involve clumping of cellular infiltrates and, in stage 4 cases, stromal melting. The possibility of infection should always be considered in these cases and, since treatment of more severe DLK involves flap lift and irrigation, it is prudent to take a scrape sample for microbiology when lifting the flap [16]. Use of topical steroids for presumed DLK may lead to initial apparent improvement in infective keratitis with subsequent rapid progression of infection and destructive stromal necrosis.

11.4.2 Steroid-Induced Intraocular Pressure Elevation with Flap Oedema (Pseudo-DLK)

This uncommon phenomenon generally presents with decreased visual acuity, flap oedema and variable inflammation and may be mistaken for DLK. Increased frequency of steroid use then leads to worsening of the condition. The centrally measured intraocular pressure (IOP) is often normal and careful examination may reveal a fluid cleft in the flap interface. Peripheral IOP measured with a Tono-Pen (Medtronic-Solan) reveals an elevated IOP and the condition will resolve with control of IOP, usually with topical agents, and tapering or cessation of steroids [10, 15].

11.5 Management

The principles of management are similar to those in regular infective keratitis, namely:

- Suspect infection
- Obtain a microbiological sample prior to starting treatment
- Give broad spectrum empirical therapy initially
- Tailor therapy depending on clinical response and microbiological results (Gram and other stains, culture, sensitivities)
- If there is a worsening clinical situation and no microbiological information to guide, consider temporary withdrawal of treatment for rescrape or corneal biopsy

Post-LASIK infective keratitis differs from regular infective keratitis in that:

- Atypical infections (non-tuberculous mycobacteria) are relatively common
- Antibiotic penetration may be poor due to an intact epithelium
- Flap complications such as striae, epithelial ingrowth, flap melt and dehiscence may be problematic, related to infection or flap lift

We propose a management algorithm that takes some of these factors into account (Fig. 11.1).

11.5.1 Flap Lift

This should be carried out in most circumstances. An exception is if the focus of infection is very peripheral and associated with overlying flap necrosis allowing an adequate microbiological sample and debridement of infectious material (Fig. 11.2).

The flap may be lifted completely or partially, depending on the extent and location of infiltrate. Flap lift should be carried out beneath an operating microscope under sterile conditions with or without patient sedation. Some prefer to initiate the flap lift at the slit lamp where the flap border may be more easily identified. Initiation of flap lift is generally with a blunt spatula or Sinskey hook to break the epithelium and open the interface for one or two clock hours, then completed with non-toothed LASIK flap forceps.

11.5.2 Specimen Taking

Gentle scraping of material for microbiological examination and culture and to debride infective debris follows this. A hypodermic needle, number 15 Bard-Parker blade or Kimura spatula may be used. The authors prefer to plate the specimens themselves on culture media immediately. We suggest as a minimum, if the amount of material allows, an air-dried slide for immediate Gram stain, blood, chocolate and Sabouraud's agar plates and brain-heart infusion broth. If *Mycobacterium* is suspected, then culture on Lowenstein-Jensen medium should be considered. Useful additional stains for late-presenting cases include auramine-rhodamine for acid-fast bacilli [22] and periodic acid–Schiff (PAS) for fungi [21].

Summary for the Clinician

- **A microbiological specimen prior to treatment is essential**
- **Flap lift is usually necessary**

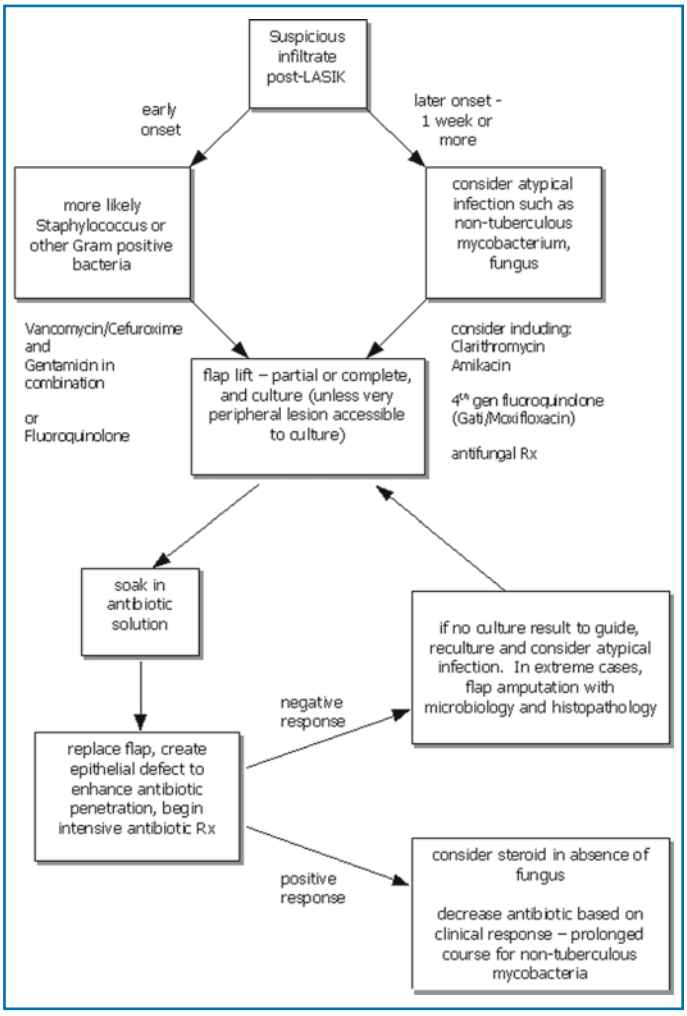

Fig. 11.1. Algorithm outlining an approach to post-LASIK infective keratitis

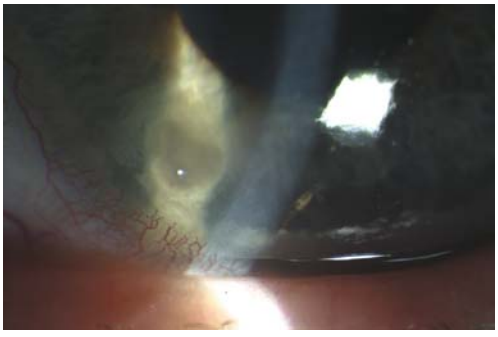

Fig. 11.2. Peripheral infiltrate 3 weeks after LASIK with focal flap melt

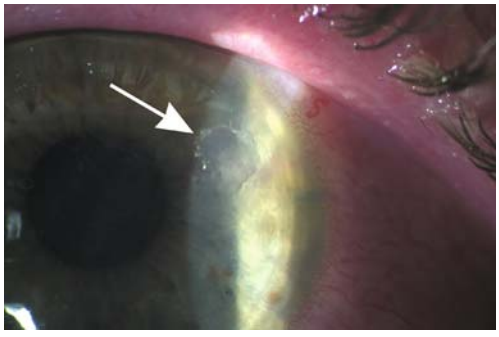

Fig. 11.3. *Arrow* indicates an epithelial defect created over a peripheral interface infiltrate after raising part of the flap for an interface scrape. The defect aids antibiotic penetration

11.5.3 Treatment

A moistened lint-free sponge may be used to remove residual debris, followed by "soaking" of the flap and stromal bed in antibiotic solution. The choice of antibiotics may depend on whether the keratitis falls into the early or late group (Fig. 11.1). Soaking should be for 2 min or more with each antibiotic solution in turn, followed by careful relaying of the flap. If there is little or no epithelial defect overlying the suspected infection, an epithelial defect should be created to aid antibiotic penetration (Fig. 11.3).

Intensive topical antibiotics should then be started (hourly alternating around the clock). The choice of antibiotics will be partly determined by the resistance characteristics of bacteria in the local region. Specialist microbiologist advice should be sought if there is doubt. Suggestions for treatment choice are given in Fig. 11.1.

Topical steroids should be avoided in the early stages of treatment and only instituted, if at all, when there is clear clinical evidence of improvement (e.g. less pain, diminishing and coalescing infiltrate, fewer keratic precipitates, healing epithelial defect), suggesting sterilisation of the offending organism. Introduction of any steroid should generally be in low dose (e.g. twice daily prednisolone sodium phosphate 0.5%) and the response closely monitored for signs of worsening infection, e.g. satellite infiltrates. Steroid use without concomitant antibiotic has been implicated in the recrudescence of infection after apparent sterilisation of *Pseudomonas* keratitis [8]. Steroid use should be avoided in cases of fungal keratitis.

Topical antibiotic choice may be altered when microbial sensitivities are available. If the infection is clinically improving, there may be no need to change the antibiotics other than tapering the frequency of use after 2–3 days. If the infection is improving and sensitivity data are available, it may be reasonable to discontinue one of the antibiotics (e.g. gentamicin in a vancomycin/gentamicin combination when treating a staphylococcal infection) to minimise epithelial toxicity and promote healing.

The use of preservative free lubricants to preserve epithelial health should be considered. A cycloplegic (preservative free cyclopentolate or homatropine) should be added if there is significant anterior chamber inflammation.

Summary for the Clinician

- **Choose antibiotics to cover atypical organisms in late-presenting cases**
- **Antibiotic penetration is aided by an epithelial defect**
- **Avoid steroid use unless there is unequivocal improvement suggesting sterilisation of infection**
- **Avoid steroids in fungal infection and without concomitant antibiotic use**

11.5.4 No Improvement

Failure of the infection to show signs of improvement after several days of treatment should prompt a re-evaluation. An attempt at reculturing the infective agent is mandatory, by further corneal scrape or corneal biopsy. If the infection is severe and judged to be threatening the eye, flap amputation may be necessary, with half the flap being sent for histological examination and staining for organisms, the other half being sent for microbial culture. A high suspicion for atypical infection exists at this point and mycobacteria, fungi and *Acanthamoeba* should be specifically looked for.

Failure to control the infection despite treatment, as with regular infective keratitis, may require further surgical intervention including therapeutic penetrating keratoplasty, and intraocular instillation of antimicrobial drugs in the case of perforation with suspected endophthalmitis, with or without lensectomy and vitrectomy depending on the involvement of intraocular structures.

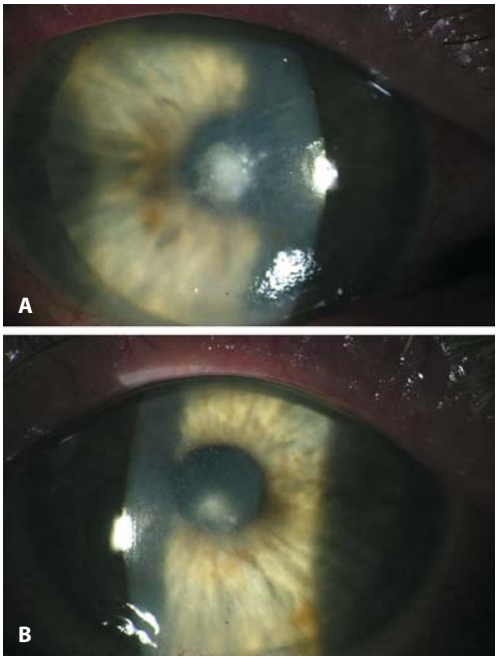

Fig. 11.4 A, B. Bilateral central *Mycobacterium chelonae* post-LASIK keratitis (right eye **A**, left eye **B**). Note central interface infiltrates

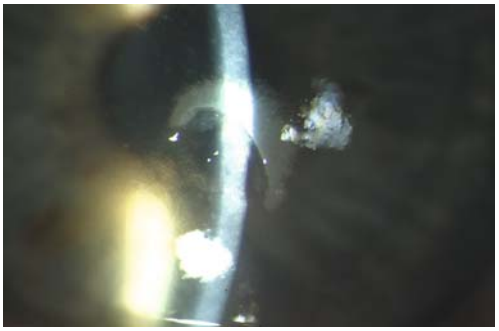

Fig. 11.5. Subsequent right central flap melt in the case of *M. chelonae* keratitis shown in Fig. 11.4

11.6 Special Considerations

11.6.1 Mycobacteria

Topical clarithromycin and amikacin have generally been the agents of choice for treatment of *M. chelonae* keratitis. Tobramycin and the fluoroquinolones are also often effective. There has been recent interest in the fourth generation fluoroquinolones, including moxifloxacin [1] and gatifloxacin, as having greater activity against non-tuberculous mycobacteria. The authors have experience of treating a case (unpublished) of bilateral moxifloxacin-resistant *M. chelonae* post-LASIK keratitis (Figs. 11.4, 11.5). This highlights the benefit of using multiple agents to treat infection empirically until the organism's sensitivities are known, with continued use of multiple antibiotics to which the organism is sensitive to prevent recrudescence. Treatment may need to be continued for 6 months or more with a gradual taper, monitoring closely for signs of recurrence. Viable mycobacteria have been cultured from an amputated LASIK flap despite 9 weeks of appropriate treatment for *M. chelonae* keratitis [19].

11.6.2 Fungal Keratitis

Fungal infections comprise about 14% of reported cases of post-LASIK keratitis [4]. Identification of hyphae, pseudohyphae or yeasts may be possible from direct microscopic examination of appropriately stained slide preparations of a scrape; or culture may yield fungal growth. An additional approach, maybe more applicable in the future, is PCR testing of specimens for fungal DNA, providing a quicker result than fungal culture. This method, while sensitive, does suffer from poor specificity [21].

Treatment of fungal infections should be determined in collaboration with a microbiologist and based on the organism's sensitivities when available. Common topical agents are natamycin 5% and amphotericin B 0.15%, both polyenes with a broad spectrum of activity against filamentous fungi and yeasts although natamycin may be slightly more effective and the preferred choice where available [21]. Topical econazole 1% is also being used where appropriate. Topical treatment should generally be combined with a systemic agent, e.g. one of the azoles such as ketoconazole or itraconazole. Voriconazole, a relatively new triazole agent, has

been reported to have superior activity against *Scedosporium* infections [18].

The use of topical steroids may cause fungal keratitis to progress rapidly to widespread corneal involvement and perforation. Steroids should be avoided when treating fungal infections, at least until effective antifungal treatment has been continued for several weeks. Antifungal therapy needs to be prolonged for at least 6 weeks – agents are generally fungistatic rather than fungicidal at the concentration achieved in the corneal stroma, and elimination of fungus depends ultimately on the host immune response.

11.6.3 Viral Keratitis

Case reports of apparent reactivation of *Herpes simplex* keratitis following LASIK have been published [5, 17]. It is not clear whether the LASIK procedure and/or the postoperative use of topical steroids were causative. However, ultraviolet radiation exposure has been associated with reactivation of latent *Herpes simplex* [20, 6]. In addition to a short-term topical antiviral, consideration should be given to longer-term systemic antiviral prophylaxis (e.g. oral acyclovir 400 mg twice daily).

11.7 Visual Outcome

The visual outcome following post-LASIK keratitis is highly variable. Approximately 50 % of reported cases have no clinically significant worsening of best-corrected Snellen visual acuity. Twenty-five per cent suffer a severe reduction [4]. Gram-positive infections are associated with better visual outcomes while fungal infections (excluding *Candida albicans*) are more likely to be associated with severe visual reduction. Reported cases of *C. albicans*, on the other hand, had a good visual outcome – with a best corrected visual acuity average of 20/25 [16]. Reported mycobacterial cases tend to be intermediate between Gram-positive and fungal infection in terms of visual outcome.

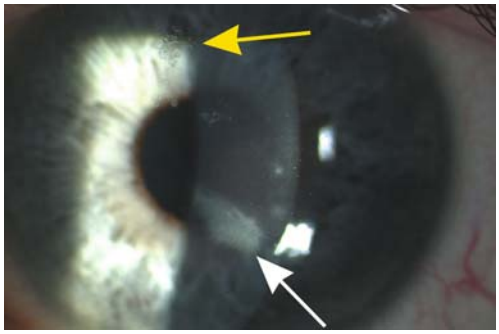

Fig. 11.6. Eye 9 months following treatment for *M. chelonae* post-LASIK keratitis. *Arrows* point to stromal scarring (*white*) and stable interface epithelial inclusions (*yellow*). The uncorrected visual acuity is 6/7.5

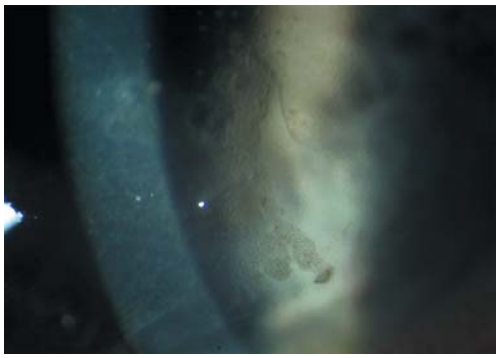

Fig. 11.7. Interface epithelial ingrowth arising from a flap defect in a case of *M. chelonae* post-LASIK keratitis. Tongues of epithelium are progressing peripherally

11.8 Management of Sequelae

Common sequelae of post-LASIK infection include scarring (Fig. 11.6), irregular astigmatism and varying degrees of epithelial ingrowth arising from flap lift or flap melt (Fig. 11.7).

Once the infection has settled, the goal of treatment is to optimise visual acuity in the affected eye. How this is achieved will vary markedly from case to case. Correction of refractive error should initially be explored using glasses, soft contact lens and rigid gas permeable lenses. Significant epithelial ingrowth in-

ducing astigmatism needs to be cleared from the flap interface prior to any further attempts at surgical correction. Irregular astigmatism resulting from scarring may be amenable to contact lens correction.

Consideration of further excimer laser refractive surgery should be approached with caution. In addition to likely patient concern about a repeat procedure, further LASIK will require recutting of a deeper flap to avoid the scarred and irregular interface inevitably present, and PRK or laser epithelial keratomileusis (LASEK) is associated with a high risk of development of haze in an environment with activated keratocytes.

Significant opacity affecting the visual axis, on the other hand, may need to be cleared. Options for this include homoplastic automated lamellar therapeutic keratoplasty (HALTK, a useful technique for opacities limited to the anterior one-third of the corneal stroma) [9], deep anterior lamellar keratoplasty [14] and penetrating keratoplasty.

11.9 Prevention

Rare cases of post-LASIK infective keratitis are inevitable. Attention to patient eyelid hygiene with control of blepharitis, careful patient instruction regarding pre- and postoperative care and avoidance of trauma, and meticulous attention to equipment sterility and operating environment hygiene are likely to lead to fewer cases. The authors strongly advise that separate blades and microkeratome heads be used if carrying out simultaneous bilateral LASIK to diminish the linked risk of bilateral infection. Above all, careful informed consent of the patient prior to surgery is mandatory.

References

1. Abshire R, Cockrum P, Crider J et al. (2004) Topical antibacterial therapy for mycobacterial keratitis: potential for surgical prophylaxis and treatment. Clin Ther 26:191–196
2. Alvarenga L, Freitas D, Hofling-Lima AL et al. (2002) Infectious post-LASIK crystalline keratopathy caused by nontuberculous mycobacteria. Cornea 21:426–429
3. Chandra NS, Torres MF, Winthrop KL et al. (2001) Cluster of *Mycobacterium chelonae* keratitis cases following laser in-situ keratomileusis. Am J Ophthalmol 132:819–830
4. Chang MA, Jain S, Azar DT (2004) Infections following laser in situ keratomileusis: an integration of the published literature. Surv Ophthalmol 49:269–280
5. Davidorf JM (1998) Herpes simplex keratitis after LASIK. J Refract Surg 14:667
6. Dhaliwal DK, Romanowski EG, Yates KA et al. (2001) Experimental laser-assisted in situ keratomileusis induces the reactivation of latent herpes simplex virus. Am J Ophthalmol 131:506–507
7. Freitas D, Alvarenga L, Sampaio J et al. (2003) An outbreak of *Mycobacterium chelonae* infection after LASIK. Ophthalmology 110:276–285
8. Gritz DC, Kwitko S, Trousdale MD et al. (1992) Recurrence of microbial keratitis concomitant with antiinflammatory treatment in an animal model. Cornea 11:404–408
9. Hafezi F, Mrochen M, Fankhauser F 2nd et al. (2003) Anterior lamellar keratoplasty with a microkeratome: a method for managing complications after refractive surgery. J Refract Surg 19:52–57
10. Hamilton DR, Manche EE, Rich LF et al. (2002) Steroid-induced glaucoma after laser in situ keratomileusis associated with interface fluid. Ophthalmology 109:659–665
11. Holmes GP, Bond GB, Fader RC et al. (2002) A cluster of cases of *Mycobacterium szulgai* keratitis that occurred after laser-assisted in situ keratomileusis. Clin Infect Dis 34:1039–1046
12. Karp CL, Tuli SS, Yoo SH et al. (2003) Infectious keratitis after LASIK. Ophthalmology 110:503–510
13. McGhee CNJ, Brahma A (2001) Uncommon complications of LASIK: diffuse lamellar keratitis and epithelial ingrowth. CME J Ophthalmol 5:52–54
14. Melles GRJ, Lander F, Rietveld FJR et al. (1999) A new surgical technique for deep stromal, anterior lamellar keratoplasty. Br J Ophthalmol 83:327–333
15. Nordlund ML, Grimm S, Lane S et al. (2004) Pressure-induced interface keratitis: a late complication following LASIK. Cornea 23:225–234
16. Peng Q, Holzer MP, Kaufer PH et al. (2002) Interface fungal infection after laser in situ keratomileusis presenting as diffuse lamellar keratitis. J Cataract Refract Surg 28:1400–1408

17. Perry HD, Doshi SJ, Donnenfeld ED et al. (2002) Herpes simplex reactivation following laser in situ keratomileusis and subsequent perforation. CLAO J 28:69–71
18. Shah KB, Wu TG, Wilhelmus KR et al. (2003) Activity of voriconazole against isolates of *Scedosporium apiospermum*. Cornea 22:33–36
19. Solomon A, Karp CL, Miller D et al. (2001) *Mycobacterium* interface keratitis after laser in situ keratomileusis. Ophthalmology 108:2201–2208
20. Spruance SL (1985) Pathogenesis of herpes simplex labialis: experimental induction of lesions with UV light. J Clin Microbiol 22:366–368
21. Thomas PA (2003) Fungal infections of the cornea. Eye 17:852–862
22. Verma S, Watson SL, Dart JKG et al. (2003) Bilateral *Mycobacterium chelonae* keratitis following LASIK (letter). J Refract Surg 19:379–380