

Microbial keratitis trends following refractive surgery: Results of the ASCRS infectious keratitis survey and comparisons with prior ASCRS surveys of infectious keratitis following keratorefractive procedures

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In 2008, the American Society of Cataract and Refractive Surgery (ASCRS) surveyed its 9121 United States and international members to evaluate the changing trends and incidence, culture results, treatment, and visual outcomes of infectious keratitis following keratorefractive procedures worldwide. This paper presents and analyzes the results with comparisons to the data in surveys conducted in 2001 and 2004. Nineteen infections were reported by 14 surgeons who had performed an estimated 20 941 keratorefractive procedures, an incidence of 1 infection in every 1102 procedures. Sixteen cases presented in the first postoperative week, 1 case during the second week, 1 case between the second and fourth weeks, and 1 case at 1 month or later. The 16 cases that presented in the first week were diagnosed at initial presentation. The most common organism cultured was methicillin-resistant *Staphylococcus aureus* (MRSA). Microbial keratitis following refractive surgery is an increasingly recognized sight-threatening complication.

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Laser in situ keratomileusis (LASIK) and excimer laser surface ablation are commonly performed surgical procedures to correct refractive errors. Laser in situ keratomileusis offers many benefits over photorefractive keratectomy (PRK), including decreased time to visual rehabilitation, decreased stromal scarring, less postoperative pain, minimal regression, and the ability to treat a greater range of refractive disorders.^{1–6} Compared with other refractive procedures, LASIK preserves the integrity of Bowman membrane and the overlying epithelium, thus decreasing the risk for microbial keratitis.⁷ However, microbial keratitis following LASIK and excimer surface ablation has become an increasingly recognized sight-threatening complication of refractive surgery.^{8–31}

The incidence of infectious keratitis following refractive surgery is unknown and can vary widely depending on the study. One large retrospective study investigating the complications associated with LASIK surgery found an incidence of 2 infections in 1062 eyes,³² and a similar study found an incidence of 1

infection in 1019 eyes.³³ A more recent case series of LASIK-associated infections encountered at a single institution reports an estimated incidence between 1:1000 and 1:5000.³⁴ Based on a comprehensive review and analysis of the literature on infections following LASIK, Chang et al.²⁴ noted that the incidence of infection after LASIK can vary widely (0% to 1.5%).

The American Society of Cataract and Refractive Surgery (ASCRS) Cornea Clinical Committee developed a post-LASIK infectious keratitis survey and conducted a survey of the organization's 8600 members in 2001. The purpose was to investigate the worldwide incidence, culture results, treatment, and visual outcomes of infectious keratitis following LASIK among surgeons who were ASCRS members.³⁵ In that study, 116 post-refractive-surgery infections were reported by 56 ophthalmologists who had performed an estimated 338 550 procedures. This corresponded to an incidence of 1 infection in every 2919 procedures. In 2004, the 9129 ASCRS members were surveyed again. In that survey, 48 post-refractive-surgery infections

were reported by 46 surgeons who had performed an estimated 102 300 procedures, an incidence of 1 infection in every 2131 procedures during 2004.

In most cases described in the literature, it is not possible to determine the origin of the infection. Predisposing factors include a history of corneal surgery,^{26,27} breaks in the epithelial barrier,²⁶ excessive surgical manipulation,²⁸ intraoperative contamination,²¹ and delayed postoperative reepithelialization of the cornea.^{26,29}

With the increased use of fourth-generation fluoroquinolones, the rise of methicillin-resistant *Staphylococcus aureus* (MRSA), and the results of the 2001 and 2004 surveys, we further evaluated changing trends and management of infectious keratitis following refractive surgery, including culture results, treatment, and visual outcomes, among domestic and international ASCRS members in the calendar year 2007. This report presents the results of the new survey, conducted in 2008, and compares them with the data collected in the 2001 and 2004 surveys.

MATERIALS AND METHODS

In January 2008, the ASCRS Cornea Clinical Committee sent an e-mail worldwide to 9121 ASCRS members asking them to respond to a questionnaire titled "Infectious Keratitis Following Keratorefractive Procedures" (Figure 1). The ASCRS members were asked to complete the questionnaire and e-mail their responses. The responses were confidential, and the identity of the respondents was not known by the authors. No financial incentive was provided for returning the questionnaire. Because of the retrospective nature of anonymously reporting unidentified case reports and that the research was neither prospective nor interventional, there

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was no Institutional Review Board involvement. Survey results received by the deadline of February 12, 2008, were tabulated in a Microsoft Excel 2003 database developed for this survey.

To address changing trends, the 3 infectious keratitis surveys have been modified and the particular questions and the years those questions were asked are identified in Figure 1. For example, in 2008, 3 new questions were included; these addressed whether LASIK was performed with a keratome or a femtosecond laser, whether the infection was resistant to the antibiotic agent methicillin, and whether the patient was a healthcare worker. The definition of positive microbial culture used in this report was the clinical appearance of a corneal ulcer combined with a positive culture result.

RESULTS

Nineteen infections were reported by 14 surgeons, who had performed an estimated 20 941 procedures, an incidence of 1 infection in every 1102 procedures during the calendar year 2007. Results are reported for the categories in which respondents answered the questions in the survey. Of the 19 cases, 8 (42%) were LASIK performed with a microkeratome and 2 (10.5%) were LASIK performed with a femtosecond laser; 8 cases (42%) had surface ablation procedures. The time of presentation ranged from 1 week to more than 1 month (Table 1).

The most common organisms cultured were MRSA (28%), followed by non-MRSA staphylococci (18%) (Table 2 and Figure 2, A). Of the 3 MRSA infections, 2 cases occurred in healthcare workers; 1 patient had LASIK with a microkeratome, and 1 had a surface ablation procedure.

In 58% of the infectious keratitis cases, the flaps had been elevated and scraped for cultures (Figure 3). Most cases were diagnosed at the initial presentation (85%) (Figure 4). In 9 cases, the prophylactic antibiotic agent was a fourth-generation fluoroquinolone; in 1 case, it was a prior-generation fluoroquinolone; and in 2 cases, it was tobramycin. The corrected distance visual acuity (CDVA) remained 20/40 or better in 14 eyes, was worse than 20/40 in 3 eyes, and was unknown in 2 eyes. Two cases required penetrating keratoplasty (PKP) for visual rehabilitation.

DISCUSSION

This third follow-up survey of ASCRS members provides useful information about infectious keratitis following keratorefractive procedures. The incidence, culture results, treatment, and visual outcomes in the 2008 ASCRS survey are summarized and compared with the results in the 2004 and 2001 surveys.

We believe that responses by 19 refractive surgeons who had performed an estimated 20 941 procedures from a worldwide geographic distribution provide

Infectious Keratitis Following Keratorefractive Procedures Questionnaire

The ASCRS Cornea Clinical Committee surveyed the membership in 2002 and 2004 to determine how surgeons were managing infectious keratitis following LASIK. With increased bacterial resistance and advancement in refractive surgery, we would once again like to survey the membership. We need your assistance in helping elucidate the magnitude, treatment, and scope of this vision-threatening problem. On behalf of the Cornea Clinical Committee of ASCRS, we thank you in advance, for your efforts in filling out this questionnaire.

1. Did you have a corneal infection following keratorefractive surgery in 2007?
Yes (if yes, please continue) _____ No _____
 2. In the 2007 calendar year, approximate number of LASIK procedures performed with a keratome _____
 3. In the 2007 calendar year, approximate number of LASIK procedures performed with a femtosecond laser _____
 4. In the 2007 calendar year, approximate number of surface ablation procedures performed _____
 5. Total number of infectious keratitis cases during the 2007 calendar year _____
- Of the cases reported in question #5:
6. Number of cases of infectious keratitis following LASIK with a keratome _____
 7. Number of cases of infectious keratitis following LASIK with a femtosecond laser _____
 8. Number of cases of infectious keratitis following surface ablation _____
- Please complete this portion of the survey for each individual case of infection you have treated following keratorefractive procedures in 2007.
9. Time of presentation of infection following surgery:
1–7 Days _____ 8–14 Days _____ 15–28 Days _____ >1 Month _____
 10. Surgery performed:
LASIK keratome _____ LASIK femtosecond laser _____ Surface ablation (PRK, LASEK, epi-LASIK) _____
 11. Prophylactic antibiotic used following surgery:
4th-generation fluoroquinolone (Zymar, Vigamox) _____
2nd- or 3rd-generation fluoroquinolone (Ocuflox, Ciloxin, Quixin) _____
Tobramycin _____
Other (please specify) _____
 12. Was the diagnosis made on initial presentation? Yes _____ No _____
 13. Treatment: Was the flap elevated and scraped for cultures and sensitivity? Yes _____ No _____
 14. Organism cultured:
Staphylococcus _____ Streptococcus _____ Other gram positive bacteria _____ MRSA _____
Gram-negative bacteria _____ Culture-negative _____ Mycobacteria _____ Fungal _____ Nocardia _____
Other _____
If you selected other, please specify: _____
 15. Visual result: Best-corrected visual acuity (please answer in Snellen acuity; ie, 20/20, etc.) _____
 16. Visual result: Uncorrected visual acuity (please answer in Snellen acuity; ie, 20/20, etc.) _____
 17. Treatment: Was keratoplasty required? Yes _____ No _____
 18. Was the patient a healthcare worker? Yes _____ No _____

Figure 1. The ASCRS Cornea Clinical Committee 2007 Questionnaire: Infectious Keratitis Following Keratorefractive Procedures.

representative information on the changing trends and spectrum of organisms involved in infectious keratitis following keratorefractive procedures. Limitations of the survey are (1) the inability to identify whether the information from survey respondents differed from the experience of nonrespondents; (2) the retrospective noncontrolled nature of the study; (3) the lack of information on the sensitivities of the organisms; also, (4) the responses of non-ASCRS members were not considered; (5) the anonymous nature of the survey did not allow determination of

geographical or climate clustering; (6) only 19 of 8500 ASCRS members responding to the survey stated they had experienced infections after refractive surgery; (7) there might be surgeons who did not experience infections and did not report procedures, which would make the incidence of infections lower than reported; and (8) not all the questions in the infectious keratitis questionnaire were answered for all the cases, so the total for some categories does not equal the overall number of cases. Our incidence of 1 in 1102 considers only responding ophthalmologists who

Table 1. Timing of post-refractive-surgery infectious keratitis cases reported in the 2008, 2004, and 2001 ASCRS surveys.

Time of Presentation	Number of Cases		
	2008 Survey	2004 Survey	2001 Survey
First Week	16	30	76
Second Week	1	8	7
Between second and fourth week	1	7	17
After 1 month	1	3	16

encountered infections following refractive surgery and includes culture-negative and uncultured eyes. No attempt to estimate the actual incidence of infectious keratitis following keratorefractive procedures was made because ophthalmologists who did not experience infectious keratitis were not considered in the questionnaire. The true incidence is likely to be significantly lower.

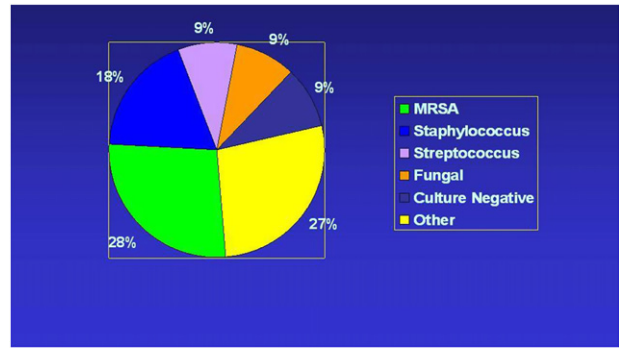
Compared with the 2001 and 2004 survey results, the number of post-refractive-surgery keratitis cases has decreased, from 116 cases in 2001 to 48 cases in 2004 to 19 cases in 2008. Treatment is no longer delayed by lack of suspicion of infectious keratitis. In 2001, the majority of cases were diagnosed at initial presentation (58.6%). In contrast, in 2004, the majority of cases were not diagnosed at initial presentation (64.6%). This improved in 2008 as the majority of cases (84%) were again diagnosed at initial presentation.

In 2001, 76 cases presented in the first week following surgery, 7 during the second week, 17 between the

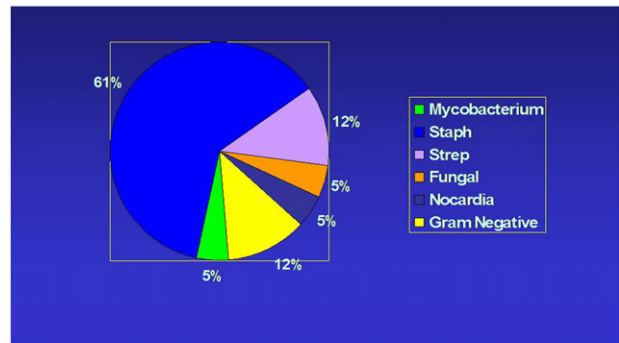
Table 2. Post-refractive-surgery infectious keratitis cases reported in the 2008, 2004, and 2001 ASCRS surveys.

Infectious Agent	Number of Cases		
	2008 Survey	2004 Survey	2001 Survey
Bacterial			
Staphylococci	1	26	23
MRSA	4	NA	NA
Streptococci	1	5	2
Gram-negative	—	5	2
Opportunistic			
Atypical mycobacteria	—	2	33
<i>Nocardia</i>	—	2	2
Fungal	1	2	7
Culture-negative	1	5	26
Other	3	—	—
Not cultured	8	0	21
Total	19	48	116

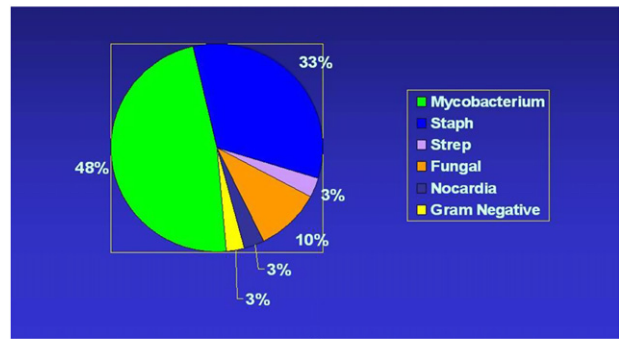
MRSA = Methicillin-resistant *Staphylococcus aureus*; NA = not available



A



B



C

Figure 2. A: The ASCRS 2008 culture results of post-LASIK infectious keratitis. B: The ASCRS 2004 culture results of post-LASIK infectious keratitis. C: The ASCRS 2001 culture results of post-LASIK infectious keratitis.

second and fourth weeks, and 16 after 1 month. Most infections also presented in the first week after surgery in the 2004 and 2008 surveys. In the 2004 survey, 30 cases presented in the first week, 8 during the second week, 7 between the second and fourth weeks, and 3 at 1 month. Sixteen cases presented in the first week in the 2008 survey, with only 3 cases presenting afterward. It is advantageous that a greater number of cases of infectious keratitis following keratorefractive procedures are being diagnosed at initial presentation, as misdiagnosis at initial presentation may result in delayed diagnosis and significant vision loss.

In 2004, the epidemic of atypical mycobacteria that was seen in 2001 ended (Table 1 and Figure 2, B and C). Cases of atypical mycobacteria decreased from 48% to

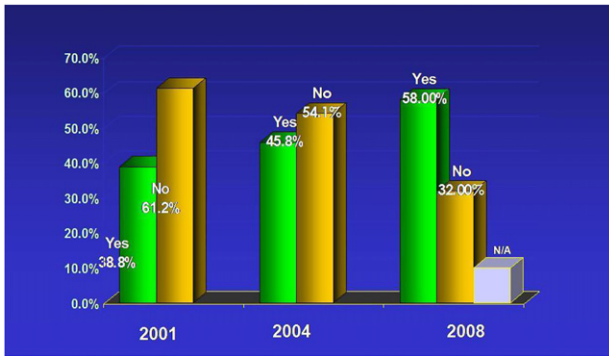


Figure 3. Percentage of LASIK corneal flaps elevated and scraped versus flaps not cultured—2008 survey results compared with 2001 and 2004 results (N/A = not available).

5% to zero in the 2001, 2004, and 2008 surveys, respectively. Furthermore, no patient who received prophylaxis with a fourth-generation fluoroquinolone experienced an infection with atypical mycobacteria in 2004 or 2008.

This decrease may be due to the use of fourth-generation fluoroquinolones, which have improved in vitro activity against atypical mycobacteria compared with prior-generation fluoroquinolones, as well as increased awareness and improved sterile techniques.^{34–36} In addition, the overall number of infectious keratitis cases decreased from 2001 to 2004 to 2008.

In the 2001 survey, the infectious keratitis incidence was 1 infection in 2919 procedures performed by physicians returning the questionnaire (116 infections following refractive surgery were reported by 56 refractive surgeons, who had performed an estimated 338 550 procedures). This result contrasts with 1 in 2131 procedures in 2004 and 1 in 1102 procedures in 2008 (19 infections were reported by 14 surgeons who had performed an estimated 20 941 keratorefractive procedures). The decrease in the number of infections is presumably due to increased awareness, increased caution, and prophylactic measures.

Methicillin-resistant *Staphylococcus aureus* is now the most common cause of infectious keratitis following keratorefractive procedures (Table 2, Figure 2, A).³⁷ Culture results had revealed opportunistic infections and gram-positive bacteria as the most common organisms in 2001 (Table 2, Figure 2, B). In contrast, gram-positive bacteria increased in incidence in 2004, while the incidence of opportunistic infections markedly decreased (Table 2, Figure 2, C). In 2008, MRSA was the most frequently cultured organism (28%).

Other results of the 2001 survey, which revealed 10 cases that required PKP and 1 case that required enucleation, improved in the 2004 survey, with 3 cases requiring transplantation and no cases requiring

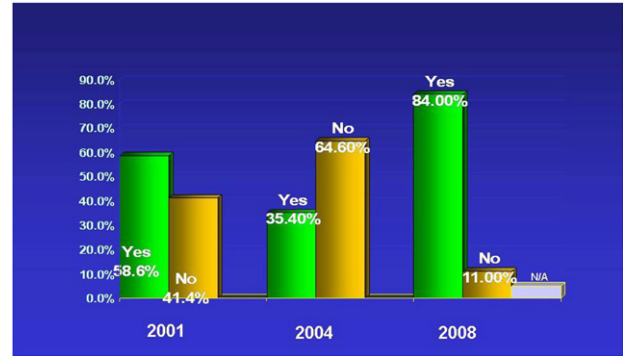


Figure 4. Percentage of infectious keratitis cases diagnosed at initial presentation—2008 survey results compared with 2001 and 2004 results (N/A = not available).

enucleation, and in 2008, in which only 2 cases required PKP and, again, no cases required enucleation. Ophthalmologists are increasingly elevating and scraping the beds of infections following refractive surgery, from 38.8% in 2001 to 58.0% in 2008 (Figure 4).

The results of this survey and an analysis of the trends seen in the data can guide the prophylaxis and treatment of infections keratitis following refractive surgery. Infectious keratitis is a potentially devastating complication of refractive surgery. A high degree of suspicion, coupled with rapid diagnosis and appropriate therapy, can result in good visual recovery.

For prophylaxis against infectious keratitis following refractive surgery, several steps should be considered. Preoperatively, the eyelids and lacrimal apparatus of all patients considering refractive surgery should be thoroughly examined. To decrease the bacterial load on the ocular surface, which theoretically could reduce the risk for bacterial keratitis, infectious lid disease should be treated prior to refractive surgery with warm compresses and a topical antibiotic ointment applied 3 times daily to the lid margin. A minority of surgeons recommend performing monocular surgery or using a separate set of instruments when performing bilateral surgery.³⁸ Some recommend the use of sterile drapes, gowns, gloves, and masks by the treating surgeon and assisting technician. A 5% or 10% povidone-iodine solution (Betadine) lid prep prior to cataract surgery has been shown to decrease the incidence of endophthalmitis following cataract surgery and is recommended by many surgeons when performing refractive surgery.³⁹ Proper sterilization techniques can prevent the use of contaminated instruments. As several epidemics of atypical mycobacteria have been associated with the use of nonsterile water to clean instruments or the use of ice during keratorefractive surgery,^{21,30,31} all fluids applied to the eye before, during, and after refractive surgery should be sterile.³⁶ Postoperatively, avoiding

exposure to contaminated water, close contact with pets, and contaminated work environments until the epithelium heals may reduce the risk for developing post-LASIK infections.⁴⁰

We divide infectious keratitis following refractive surgery into 2 categories: early-onset (within the first 2 weeks of surgery) and late-onset (which can occur from 2 weeks to 3 months following surgery).³⁶ The organisms seen in early-onset infectious keratitis are common bacterial pathogens, such as staphylococcal and streptococcal species. Gram-negative organisms are rare. The organisms seen in late-onset infectious keratitis are usually opportunistic, such as fungi, *Nocardia*, and atypical mycobacteria. The literature review of infections associated with refractive surgery by Chang et al.²⁴ supports this classification of infection. In their study, gram-positive organisms were more likely to present within 7 days of surgery ($P = .001$), whereas mycobacterial infections were more likely to present 10 or more days after surgery ($P < .001$).²⁴

Since the organisms responsible for infectious keratitis following LASIK may not respond to empiric antibiotic therapy, we recommend, as in the previous survey, lifting the flap, scraping, and culturing all suspicious cases, and selecting appropriate culture media including blood agar, chocolate agar, Sabouraud agar, and thioglycolate broth.³⁵ For infectious keratitis occurring after 2 weeks, we recommend, in addition to the other culture media, special growth media for atypical mycobacteria, such as Lowenstein-Jensen or Middlebrook 7H-9 agar, as these cultures are better at identifying atypical organisms. If these special media are unavailable, we recommend using blood or chocolate agar, as atypical mycobacteria grow quite well on these plates. At the time of culture, we also recommend scraping the infiltrate and performing a Gram stain and Ziehl-Neelsen stain to rule out unusual pathogens such as *Nocardia*, atypical mycobacteria, and, if the infection is long-standing, Gomori-methenamine silver stain to rule out fungi, which tend to have a later onset. For cases in which cultures are negative and the infection continues to progress, other measures (ie, corneal biopsy, polymerase chain reaction) should be considered.⁴¹

For the treatment of both early-onset and late-onset infectious keratitis, we recommend elevating the flap and irrigating the interface with antibiotic solution. Irrigation of the flap interface with an appropriate antibiotic solution (fortified vancomycin 50 mg/mL for early-onset keratitis and fortified amikacin 50 mg/mL or clarithromycin 10 mg/mL or azithromycin 2 mg/mL for late-onset keratitis) may be helpful.³⁶

For early-onset keratitis, we recommend giving a fourth-generation topical fluoroquinolone such as gatifloxacin 0.5% or moxifloxacin 0.5% in a loading

dose every 5 minutes for 3 doses and then every 30 minutes, alternating with an antimicrobial agent that is rapidly bactericidal and has increased activity against gram-positive organisms, such as vancomycin 50 mg/mL every 30 minutes.

In the past, we recommended topical cefazolin (50 mg/mL) for gram-positive coverage and vancomycin (50 mg/mL) for patients who work in a hospital environment or have been exposed to a hospital surgical setting or healthcare environment because of the added risk for MRSA or methicillin-resistant *Staphylococcus epidermidis* (MRSE). Today, because of the increased incidence of MRSA in the general population, the treating physician may consider vancomycin for better MRSA/MRSE coverage. In addition, we advocate the use of oral doxycycline 100 mg twice daily (to inhibit collagenase production) and also recommend discontinuing corticosteroids with a rapid taper.³⁶

For late-onset keratitis, which is commonly due to atypical mycobacteria, *Nocardia*, and fungi, we recommend beginning therapy with a fourth-generation topical fluoroquinolone such as gatifloxacin 0.5% or moxifloxacin 0.5% in a loading dose every 5 minutes for 3 doses and then every 30 minutes, alternating with amikacin 50 mg/mL every 30 minutes; starting oral doxycycline 100 mg twice a day; and discontinuing corticosteroids. Alternative therapy for late-onset keratitis, which would cover atypical mycobacteria, includes clarithromycin and azithromycin. This treatment will not cover fungal, viral, or amebic infections, and therefore treatment for all cases of infectious keratitis should be modified based on culture and scraping results and response to therapy.³⁶

Infectious keratitis after refractive surgery frequently presents with inflammation in the corneal interface, which can mimic diffuse lamellar keratitis (DLK). Diffuse lamellar keratitis usually occurs within the first few days after refractive surgery, unless there is postoperative ocular trauma.^{42,43} The appearance of an interface inflammation greater than that expected 1 week after refractive surgery should be presumed to be infectious unless proven otherwise. Since DLK usually presents with a diffuse appearance whereas infectious keratitis has a more focal area of infiltration, any focal infiltrate surrounded by inflammation following LASIK should be considered infectious until proven otherwise.

It is interesting to note that in the literature, although 20% of the excimer laser ablations are performed with PRK, 28% of excimer laser ablations are performed with the femtosecond laser, and 50% of excimer laser ablations are performed with a keratome, infections are 2.5 times more common with PRK than with a keratome, 6 times more common with PRK than with the femtosecond laser, and 2.4 times more

common with a keratome than with the femtosecond laser.⁴⁴ Surgeons may want to consider the increased risk for infectious keratitis following PRK and monitor patients carefully for signs of infection.

In conclusion, infectious keratitis is a potentially devastating complication following refractive surgery. Culture results reveal gram-positive bacteria as the most common organisms. Infectious keratitis may present as late as months after refractive surgery, and its frequent misdiagnosis at initial presentation may result in significant vision loss. Antibiotic prophylaxis for LASIK should emphasize the need to provide broad-spectrum coverage with gram-positive emphasis.

Despite the use of prophylactic antibiotic agents, patients with early-onset infectious keratitis most likely are infected with *Staphylococcus species*, including MRSA. A high degree of suspicion should be considered, and elevating the flap and culturing should be performed in all eyes suspected of infectious keratitis following refractive surgery.

We hope the information contained in this report will help refractive surgeons assess their respective approaches to management of infectious keratitis following refractive surgery. This report provides information from which new trends can be compared in future surveys and also increases the information about this infection for all eye-care providers who manage or follow patients after keratorefractive surgery. The goal is to standardize treatment, minimize visual loss, and improve visual outcomes.

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