



## Topical Antibiotic Treatment Combined with Corneal Lavage for Acute Interface Bacterial Infection after SMILE: A Case Series

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### Abstract

**Background:** Various therapeutic approaches have been used to treat bacterial infections following SMILE procedures. While interface irrigation and debridement typically serve as primary treatments, these methods carry a risk of corneal lamellar flap rupture during debridement - a complication that could significantly compromise visual outcomes. This study presents a novel combined treatment strategy for achieving rapid control of post-SMILE bacterial infections.

**Methods:** A retrospective chart review was conducted of interface bacterial infections following SMILE treated in our institution between June 2019 and October 2021. Our treatment protocol mainly included topical administration and corneal lavage of antibiotics, as well as photoactivated chromophore for keratitis-corneal cross-linking (CXL). Key interventions contributing to rapid eradication of infections were analyzed.

**Results:** 7 eyes of four patients with interface bacterial infections following SMILE were treated. All 7 eyes received topical and corneal lavage of vancomycin/tobramycin. Additionally, 6 eyes received CXL and 1 eye interface antibiotic irrigation. Without knowing causal pathogens, continuous lavage accelerated the clearance of the infections. Time taken to control the infections in this case series ranged from 1 to 8 days (median 4 days), and time taken to achieve clinical cure from 5 to 15 days (median 7 days), with the best corrected visual acuity  $\geq 20/25$  at the last follow-up.

**Conclusions:** Combining topical antibiotics with continuous corneal lavage can quickly control interface bacterial infections after SMILE and preserve vision. CXL appears to have limited additional therapeutic effect.

**Keywords:** Corneal refractive surgery; Post-SMILE infection; Corneal lavage; Corneal cross-linking

### Abbreviations

SMILE: Small Incision Lenticular Extraction; LASIK: Laser-assisted in Situ Keratomileusis; PACK-CXL: Photoactivated Chromophore for Keratitis-corneal Cross-linking

### Introduction

The small incision lenticule extraction (SMILE) is the most advanced corneal refractive surgery today [1]. Despite increased safety due to smaller incision and minimal invasiveness [2], interface infections can still occur postoperatively. Several case reports of postoperative infection after SMILE have been published in recent years. Pathogens identified in these infections included bacteria, fungi, and viruses, with bacteria being the most common. In contrast to laser-assisted in situ keratomileusis (LASIK), surgical site infections after SMILE occur within a relatively confined pocket space. Interface irrigation and debridement often are the treatment of first choice, but corneal lamellar flap rupture may occur during debridement<sup>3</sup> which could severely affect patient's

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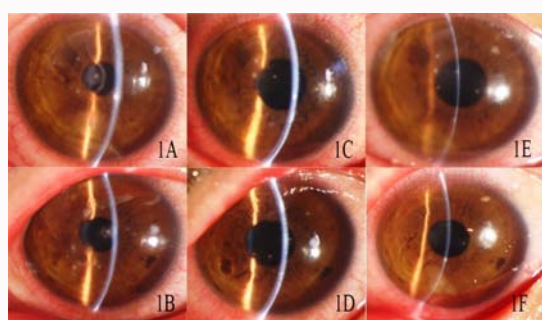
final vision.

To date, there have been a variety of therapeutic interventions employed for managing bacterial infections following SMILE [3-8]. This case series reports a combined treatment approach for rapid control of such infections, which includes topical instillation and continuous corneal lavage using antibiotics, and photoactivated chromophore for keratitis-corneal cross-linking (CXL). This method does not rely on microbiology identification of the causal pathogens, can be implemented promptly, and often without the need for interface irrigation and debridement.

## Case Presentation

### Case 1

An 18-year-old man underwent SMILE on both eyes 4 days prior and complained of redness, pain, and decreased vision in both eyes for 3 days. He had been treated with moxifloxacin, amikacin, and vancomycin eye drops for 3 days elsewhere without improvement. At presentation, his visual acuity was 20/100 in the right eye and 20/600 in the left eye. Slit-lamp examination revealed scattered gray-white nummular infiltrates in corneal stroma, worse in left eye, epithelial defects at the incision, and no hypopyon (Figure 1A and B). Treatment at our institution was continued using 5% vancomycin, 0.5% moxifloxacin, 2% amikacin, and 0.3% tobramycin eye drops to both eyes, alternating every 15 minutes. Since no significant change was noted for two days, he underwent epi-on CXL on both eyes. On the second day post-CXL, the corneal infiltrates were more localized and visual acuity improved to 20/50 in the right eye and 20/40 in the left eye (Figure 1C and D). The medications were then reconciled to include 5% vancomycin and 0.5% moxifloxacin eye drops every hour, tacrolimus eye drop twice a day to suppress the immune response, and deproteinized calf blood extract ophthalmic gel 6 times a day to protect the corneal epithelium. However, corneal infiltrates and vision seized to improve in the next two days. While continuing the same regimen, corneal lavage was initiated through a Morgan lens [9] at 10 ml/hour with 2.5% vancomycin for 1 hour, followed by 1.5% tobramycin for 1 hour, twice a day. After 3 days of lavage, the corneal infiltrates became localized, and the epithelium healed (Figure 1E and F). Corneal scrapings were taken from both eyes at presentation, only Group A Streptococcus grew from the left eye after 5 days of culturing. Since the infection had already improved, this microbiology result did not influence our selection or use of antibiotics. On the 15th day of treatment (7th day after corneal lavage), although there were



**Figure 1:** Slit-lamp photographs of bacterial infection before and after combined treatment following SMILE.

Interface corneal infiltrates in both eyes in case 1 (1A, B); on the 2nd day after CXL, the corneal infiltrates were more localized (1C, D), and after 3 days of corneal lavage, the infiltrates further diminished, the corneal epithelium healed (1E, F).

still focal opacities in the corneal stroma, his vision in both eyes had recovered to 20/20. Follow-up in 1 year showed no changes.

### Case 2

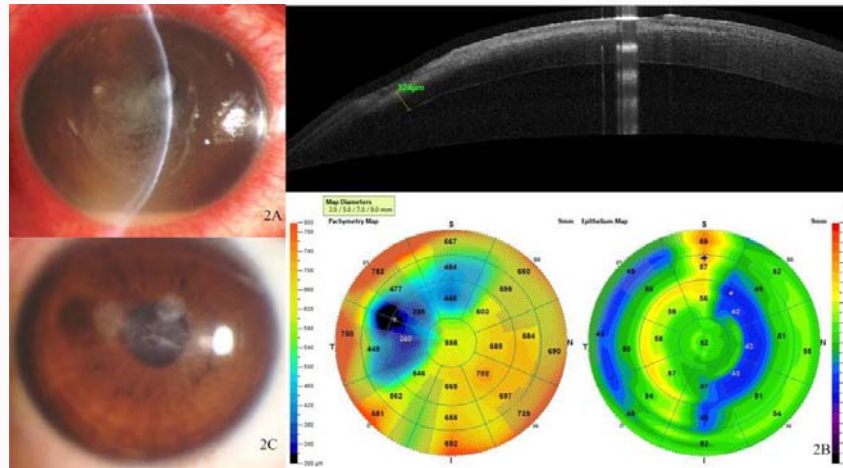
Two days after SMILE, an 18-year-old man complained of increasing redness and tearing in both eyes for 1 day. Visual acuity was 20/20 in both eyes. Slit-lamp examination revealed scattered gray-white dot infiltrates under the central corneal flap without hypopyon in anterior chamber. As the corneal epithelium was intact and the infiltrates were deep, no corneal scraping was performed. The patient was treated with 0.3% tobramycin and 0.5% moxifloxacin eye drops, alternating every 5 minutes, and 5% vancomycin eye drop every 2 hours. In addition, same concentrations of vancomycin and tobramycin were also used for corneal lavage for 1 hour each, but lavage was done only once due to patient's intolerance to the procedure. CXL was then performed on both eyes on the second day. In 2 days after CXL, the infiltrates in the left eye had become lighter and more confined, but vision in the right eye had decreased to 20/50, with worsened corneal edema and infiltrates. 2.5% levofloxacin was then used for lavage of the right eye for 1 hour, twice a day, for 2 days, which essentially eradicated the infection. On the seventh day of admission, although there remained a few punctate hazes in the stroma, visual acuity in both eyes recovered to 20/20.

### Case 3

A 22-year-old man developed infection in the right eye 1 day after bilateral SMILE. He had been treated with 3% levofloxacin, 5% vancomycin, 0.3% tobramycin eye drops, and 0.3% gatifloxacin ophthalmic gel for 2 days with no significant improvement. Vision was counting fingers at 10 cm in the right eye when seen at our institution. Slit-lamp examination revealed a 5 mm patch of gray-white infiltrate in the interface, two white dot infiltrates in the upper flap, as well as a 1 mm hypopyon (Figure 2A). Anterior segment OCT showed melting and thinning of the corneal flap, with the thinnest area being 324  $\mu\text{m}$  (Figure 2B). Confocal microscopy showed abundant inflammatory cells within the infiltrates. While increasing vancomycin, tobramycin drops and gatifloxacin ophthalmic gel to every 5 minutes, vancomycin and tobramycin lavages were also done once for 1 hour each. Given thin cornea, the patient was not offered CXL. Instead, interface irrigation with tobramycin and vancomycin was performed. Interface sampling prior to irrigation identified *Staphylococcus aureus* on culture. One day following irrigation, the infiltrate had become localized and hypopyon decreased. Topical treatment was continued and adjusted accordingly with vancomycin, tobramycin eye drops, and gatifloxacin ophthalmic gel. On the seventh day of admission, the epithelium of the right eye had healed. After 2 weeks of treatment, only a patch of light opacity was visible in the superior paracentral stroma of the right eye. Four months later, the corneal opacity faded in the right eye, and the visual acuity recovered to 20/20 (Figure 2C).

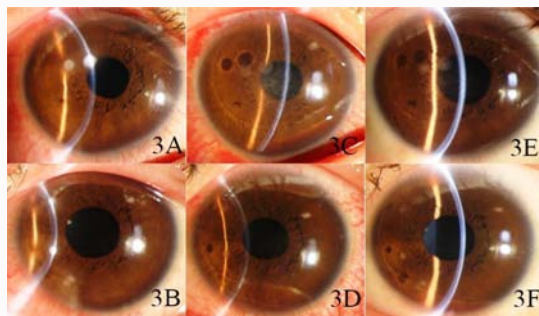
### Case 4

A 20-year-old man presented with redness and foreign body sensation, worse in the left eye, for about 1 day. Bilateral SMILE had been performed 2 days prior. He was treated locally with vancomycin, tobramycin, and levofloxacin eye drops for 1 day with no significant improvement. Upon examination, his visual acuity was 20/40 in the right eye and 20/160 in the left eye. Diffuse punctate infiltrates and edema were observed in SMILE interface in both eyes. Within the superior flaps, two flaky dot infiltrates were visible in the right eye and three larger infiltrates in the left (Figure 3A and B). No scraping



**Figure 2:** Slit-lamp photographs and anterior segment OCT of case 3.

Case 3. A. Before treatment, 2 deep white circular infiltrates in the upper flap were seen with the presence of 1 mm hypopyon; B. Anterior segment OCT shows melting of the corneal flap in the right eye, with the thinnest cornea measuring 324μm; enhanced corneal reflection was seen in the infection site beneath the corneal flap; C. Follow-up visit in 4 months, the corneal opacity in the right eye had faded.



**Figure 3:** Case 4, interface round flaky infiltrates in both eyes (3A,3B). On the 4th day of combined treatment, the infiltrates became lighter, and the corneal epithelium healed (3C, D). On the tenth day, there were only small patches of corneal stromal opacities remaining in both eyes (3E, F).

for culture was performed. He was treated with 2% amikacin, 0.3% tobramycin, and 5% vancomycin eye drops, alternating every 5 minutes for both eyes, combined with same vancomycin and tobramycin lavages for 1 hour each, twice on the first day. On the second day, after 1 hour of vancomycin and tobramycin lavages in the morning, bilateral CXL was performed. No further lavage treatment was continued after CXL. On the fourth day, the corneal infiltrates in both eyes were localized, their density reduced, and corneal edema resolved (Figure 3C and D). On the tenth day, the corneal epithelium in both eyes was intact with small hazes remaining in the stroma, and visual acuity returned to 20/25 in each eye (Figure 3E and F).

## Discussion

Infection that originates deep in the interface after SMILE can lead to rapid deterioration of vision if not treated promptly and effectively, as it can easily alter corneal transparency and refractive property [3,10,11]. Therefore, early diagnosis and treatment are crucial. Unlike infectious corneal ulcers, culture from superficial scraping, even if positive, does not necessarily represent the causal pathogen(s). Interface sampling through needle biopsy is too destructive, whereas opening the SMILE pocket for sampling must disrupt the healing incision site, potentially even causing corneal flap rupture [3] and increasing the risk of epithelial ingrowth. Moreover,

culture and susceptibility can take days to yield any results. Therefore, it is important to develop a less invasive and effective empirical antimicrobial treatment protocol that can be applied timely and universally.

Currently, there is no consensus on the choice of antibiotic drugs for bacterial keratitis after SMILE. Hence, treatment strategy for early-onset bacterial keratitis after LASIK is often referenced. The American Society of Cataract and Refractive Surgery recommends administering fourth-generation fluoroquinolones (0.5% gatifloxacin or 0.5% moxifloxacin) every 5 minutes, alternating with antibiotics such as 5% vancomycin that have enhanced activity against Gram-positive organisms every 30 minutes [12]. However, frequent topical instillation of antibiotics cannot in all cases rapidly control the infections as seen in this case series, possibly largely due to hinderance of penetration of antibiotics by the corneal flaps to deep-seeded infections within the interface.

Previous treatments reported in a few bacterial infection cases following SMILE mainly involved frequent topical medications combined with interface pocket irrigation [3-8]. However, corneal flap rupture occurred during irrigation in one report [3]. Although the infection was controlled in this patient, a large opacity resulted in the central cornea ultimately affected the patient's best corrected vision. Continuous corneal lavage has been shown to be able to increase drug concentrations in the cornea, about 10 folds more efficiently in comparison to topical instillation, in time and drug concentration [13]. Clinically, this method has not only been proven effective for bacterial keratitis [9], but also for fungal keratitis in our previous studies [14]. Hence, such treatment should be effective for bacterial keratitis within the SMILE pockets, even without microbiology identifications of causal pathogens from smears or cultures.

In this case series, all infected eyes received corneal lavage treatment. The basic treatment protocol involved the use of 2.5% or 5% vancomycin and 0.3% or 1.5% tobramycin for lavage, 1 hour each twice a day, with the rest of the time supplemented by frequent topical instillations. In case 2, **2.5% levofloxacin was continued instead and was equally effective**. The choice of vancomycin and tobramycin was based on previous experience in treating acute corneal ulcers

[9]. All 4 patients promptly received frequent yet ineffective topical antibiotics for 1-2 days before seen at our institution. With our treatment protocol, we believe continuous lavage played a crucial role in rapidly controlling the interface bacterial infection after SMILE. Infections in all cases were timely controlled, and vision preserved to the greatest extent possible. In case 3, our most severe case, the infection progressed rapidly with early corneal flap melting. Since CXL could not be performed due to thin cornea, only lavage and interface irrigation were done. Interface irrigation certainly contributed to reducing pathogen numbers and mitigating further tissue damage from local inflammation; however, eradication of infections was achieved without interface irrigation in all other cases in this series.

Prior studies have also reported CXL as a therapy for bacterial keratitis after SMILE. With CXL, Tommy et al. successfully treated a patient with bacterial keratitis after SMILE who had a poor response to frequent topical antibiotics and was unwilling to undergo interface irrigation [4]. Subsequently, Ganesh reported a case in which topical antibiotics combined with interface irrigation and CXL rapidly controlled the infection, improving visual acuity from 20/80 to 20/20 [8]. It is believed that an intact corneal flap after SMILE is beneficial for maintaining the stability of corneal biomechanics [7]. CXL indeed offers an alternative adjunct therapy without the need of lifting the flap. Ultraviolet-A and riboflavin not only have antimicrobial properties but may also provide resistance to proteolytic enzymes and protect corneal integrity [15]. We performed CXL on 6 eyes with corneal thickness greater than 400µm, and no adverse effects were seen in any cases. However, in cases 1 and 2, addition of CXL alone failed to halt the progression of infections, suggesting limited role of CXL in aggressive infections. Whether the addition of CXL to lavage would yield additional benefits requires further investigation.

In previous reports, the duration taken to control bacterial infections following SMILE ranged from 10 days to 3 months [3-8]. Our combined treatment protocol in this series effectively controlled the infections within 1 to 8 days, with the longest lavage treatment being 3 days, significantly shortened the treatment course, and restored vision in all patients.

Patients undergoing refractive surgeries have high expectations for uncorrected postoperative vision. In the event of a postoperative infection, timely and effective treatment is critical to minimize vision loss. The treatment strategy we adopted in this case series can be implemented timely, even in rural settings, in the absence of pathogen identification and antimicrobial susceptibility. Although the number of cases in this series is still small, it is evident that continuous antibiotic lavage had played a significant role. In the future, we plan to further refine the combined protocol of continuous corneal lavage with topical antibiotics and explore the additional benefits of CXL, in hope to minimize treatment time and costs while ensuring therapeutic efficacy.

## Declarations

### Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Beijing Aier Intech Eye Hospital (BJAIER2020IRB10). The authors declare that they adhered to the CARE guidelines/methodology.

### Consent for publication

Written consents were obtained from all involved patients before submission of manuscript.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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## Author Contributions

Shaowei Li contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lin Zhao, Ling Li, Jie Bai and Zexia Dou. The first draft of the manuscript was written by Lin Zhao and Chang Liu. Mingwu Wang drafted the work and revised it critically for important intellectual content. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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