Risk Factors, Clinical Features, and Outcomes of Recurrent Fungal Keratitis after Corneal Transplantation

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Purpose: To study the risk factors, clinical features, and treatment of recurrent fungal keratitis after corneal transplantation.

Design: Retrospective, interventional case series.

Participants: Eight hundred ninety-nine patients (eyes) with fungal keratitis who underwent corneal transplantation at the Shandong Eye Institute between January 2000 and October 2008. Six hundred fourteen patients underwent penetrating keratoplasty (PK) and 285 patients underwent lamellar keratoplasty (LK).

Methods: All patients failed to respond to topical and systemic antifungal drugs treatment before corneal transplantation. A trephine that was 0.5 mm larger in diameter than the infection area was used during PK or LK. Medical records of each patient were reviewed retrospectively. The species of pathogenetic fungi causing recurrence were analyzed. The clinical features, including recurrence time, position, symptom, and physical signs, were summarized. Based on clinical features, appropriate topical and systemic antifungal treatment was determined for all patients; some patients also received combined subconjunctival or intracameral injection of fluconazole. If there was treatment failure, a conjunctival flap or keratoplasty was performed.

Main Outcome Measures: Species of pathogenetic fungi, clinical features, and apparent therapeutic effects.

Results: Fifty-seven patients (6.34%) experienced recurrence after corneal transplantation. There was no difference between PK (6.79%) and LK (5.96%) in recurrence rate ($P = 0.883$). A higher rate of recurrences was found in those with preoperative hypopyon (10.90%), corneal perforation (12.00%), corneal infection expanding to limbus (20.69%), or lens infection with extracapsular cataract extraction (50%; $P<0.05$). The 3 main kinds of recurrence were: (1) recurrent infection from recipient bed to graft, and once recurrent infection invaded the graft, the inflammation progressed more rapidly; (2) white mushroom-shaped hypopyon with anterior chamber recurrence; (3) infection in the posterior chamber and vitreous opacity on posterior segment recurrence. Location of recurrence was: recipient bed (70.18%), anterior chamber (7.02%), and posterior segment (22.81%). The overall cure rate was 82.46%, which included drug therapy (28.07%) and surgical treatment (54.39%).

Conclusions: Hypopyon, corneal perforation, corneal infection expanding to limbus and lens infection are major risk factors for recurrence of fungal keratitis after corneal transplantation. Based on the clinical features of recurrence, appropriate treatment options can help to control the recurrent infection.

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Fungal keratitis causes severe ocular morbidity and blindness worldwide, especially in developing countries.[1–5] Because the cure rate with antifungal drugs remains unsatisfactory,[6–8] corneal transplantation by penetrating keratoplasty (PK) or lamellar keratoplasty (LK) is still a necessary treatment.[2,9–11] An important cause of treatment failure is fungal recurrence after surgery, with the rate of recurrence of fungal keratitis reported to range from 5% to 14%.[12–15] Thus, fungal recurrence after keratoplasty is still a significant challenge for ophthalmologists. Several factors can make it difficult to prevent recurrence; these include difficulties in making the correct diagnosis, distinguishing the clinical characteristics of recurrence, and obtaining confirmation from the microbiology laboratory. There are also difficulties in choosing the appropriate method of treatment for patients who experience recurrence after surgery.

To date, there is no report of a study with a large case series to analyze fungal recurrence. Investigating risk factors is helpful for preventing recurrence, and summarizing the clinical features of recurrence is beneficial in determining diagnosis and appropriate treatment. This study retrospectively reviewed the medical records of patients who underwent LK and PK for fungal keratitis at the Shandong Eye Institute from January 2000 through October 2008 and attempted to analyze the risk factors, clinical features, treatment, and outcomes for patients in whom fungal recurrence developed after surgery.

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Patients and Methods

Patients

A total of 899 fungal keratitis patients who did not respond to topical and systemic antifungal drugs underwent corneal transplantation by means of PK and LK at the Shandong Eye Institute from January 2000 through October 2008. The medical records of all patients in whom recurrence developed were reviewed retrospectively.

Diagnostic Methods

Patient corneas were examined using confocal microscopy or a culture of corneal scrapings, as well as slit-lamp microscopy. A portion of each scraping was incubated with potassium hydroxide and was examined as a wet mount. Another portion of the scraping was subjected to fungal culture and strain identification. Fungal presence in the potassium hydroxide preparations or confocal microscopic images, or positive culture results for fungal filaments, confirmed the diagnosis of fungal keratitis. All patients underwent B-scan ultrasounds before corneal transplantation to exclude endophthalmitis.

Medical Treatment before Surgery

Before surgery, patients at the Shandong Eye Institute received an hourly dose of 0.5% fluconazole combined with 0.25% amphotericin B or an hourly dose of 0.5% fluconazole combined with 5% natamycin, such that 1 drop was received every 30 minutes while the patients were awake. Antifungal ointments of 1% fluconazole and 1% amphotericin B were used at night. The patients also were treated with 200 mg of fluconazole daily. Patients with hypopyon received an intravenous injection of fluconazole (100 mg) twice daily. If the status of corneal ulcers deteriorated or did not improve after 5 to 10 days of antifungal therapy, surgical intervention by means of PK or LK was recommended.

Surgical Procedure

Before surgery, both slit-lamp and confocal microscopy were used to help determine whether the infection had reached the endothelium. The choice of PK or LK was made for each patient depending on the depth of infiltration of the cornea: (1) PK was used when fungal infection had reached the corneal endothelium or when corneal perforation was imminent or had occurred; and (2) LK was used when the fungal lesion had just reached the deep corneal stroma but not the corneal endothelium.

The diameter of the Hessburg-Barron trephine used for cutting out the infection in both PK and LK was, in most cases, 7.5 mm if the infiltrated diameter was 7.0 mm or less. In this study, there was only 1 case (3-mm infiltrate near the limbus) for which a 3.5-mm graft in PK was used. If the infiltrated diameter was more than 7.0 mm, the trephine used was 0.5 mm larger than the area of fungal infection.

For routine PK, after removal of the diseased cornea, the anterior chamber angle and iris surface were irrigated carefully with 0.2% fluconazole. For cases with spontaneous rupture of the lens capsule resulting from fungal infection, extracapsular cataract extraction (ECCE) was performed. Corneal grafts were secured with 16 interrupted 10-0 nylon sutures.

For LK, the depth of the trephine incision, 350 to 400 μm, was deeper than the actual penetration of the fungal ulcer. After the infected lamellae were excised, the recipient bed was washed with 0.2% fluconazole. If there was gray residual infiltration in the lamellar corneal bed, excision was continued until the clear portion was visible. If the surgeon suspected that hyphae had penetrated the corneal endothelium, PK was performed rather than LK to ensure that infected tissues were removed completely. A donor lamellar corneal graft, 0.25 mm larger in diameter than the recipient site, was secured with 16 interrupted 10-0 nylon sutures.

Postoperative Treatment

After surgery, topical 0.5% fluconazole, 0.25% amphotericin B, or 5% natamycin, in addition to antibiotic drops and nonsteroidal anti-inflammatory drops, were administered 4 times daily. Administration of oral fluconazole began on the day before surgery and continued for 21 days. In addition, a fluconazole or amphotericin B ointment was administered before bedtime. Antifungal chemotherapeutic treatment was continued for 2 weeks and was tapered thereafter. Generally, if no typical signs of recurrence were present 2 weeks after surgery, low-concentration topical steroids (0.02% fluorometholone eye drops) were administered twice daily for 2 to 3 days, later increasing the frequency to 4 times daily.

Diagnostic Methods for the Detection of Fungal Recurrence

In the postoperative examination of the patients with suspected recurrence, confocal microscopy was used routinely to examine the area of infection. Corneal scrapings were incubated and examined as wet mounts with potassium hydroxide; they then were subjected to fungal culture and strain identification. The corneal tissue cut from the second transplantation and samples of aqueous humor in anterior chamber recurrence or vitreous humor in posterior segment recurrence were subjected to fungal culture and strain identification. The finding of fungal filaments from any of the above examinations served as confirmation of fungal recurrence.

Risk Factors and Clinical Features of Recurrence

The recurrent rate of topical steroid (e.g., glucocorticoid) treatment before surgery, hypopyon recurrence, corneal perforation, corneal infection expanding to the limbus, and lens infection with ECCE in cases of fungal keratitis were calculated. The time to recurrence, site, symptoms, and physical signs observed in recurrent cases of fungal keratitis after corneal transplantation were recorded and summarized. The follow-up time was at least 6 months for recurrent patients, and no patients were lost to follow-up.

Treatment for Recurrence

Appropriate treatment methods were chosen according to the different sites of recurrence. All recurrent patients received eye drops of 0.5% fluconazole every 30 minutes combined with eye drops of 0.25% amphotericin B or 5% natamycin every 2 hours and an intravenous injection of fluconazole (200 mg) once daily. For patients with recipient bed recurrence, a subconjunctival injection of fluconazole (2 mg) was administered in the recipient bed once daily. Anterior chamber recurrence was controlled with an intracameral injection of fluconazole (0.1 mg) once daily. Patients with posterior segment recurrence also received an intravitreal injection of fluconazole (0.1 mg) once daily.

Surgical treatment was used when drug therapy was shown to be ineffective after approximately 5 to 7 days. When the area of recurrence (diameter $\leq$2 mm) was in the superficial layer of the recipient bed, the infected corneal tissue was cut off and covered with a conjunctival flap. When the area of recurrence (diameter $>$2 mm) was in the deep layer of the recipient stroma, PK was performed again, removing an area larger than the site of recurrence. When recurrence was observed in the central recipient bed

after LK, PK was performed with a trephine of a similar diameter. When the recurrence occurred in the posterior segment, an intravitreal injection of fluconazole was administered along with a pars plana vitrectomy.

Statistical Analysis

SPSS software version 13.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. The recurrence rate after PK and LK and the presence of different risk factors were compared with chi-square analysis. An initial univariate stratified analysis was performed to identify and select important risk factors for recurrence in the regression model. Multiple logistic regression analysis was used to estimate the relative risk of the main prognostic factors. A *P* value of less than 0.05 was considered statistically significant.

Results

Of the 899 cases, 614 patients underwent PK and 285 received LK. Fungal hyphae were found in 758 cases (84.30%) on examination of corneal scrapings and in 845 cases (94.00%) examined by confocal microscopy. A total of 832 specimens (92.50%) had positive culture results for fungi. Of these, 612 (73.56%) pathogens were identified as *Fusarium* species, 96 (11.54%) were identified as *Aspergillus* species, 32 (3.85%) were identified as *Alternaria* species, 25 (3.00%) were identified as *Candida* species, 23 (2.76%) were identified as *Penicillium* species, and 15 (1.80%) were identified as other species. There were also 29 (3.49%) fungi whose species remained unidentified.

In 57 patients (6.34%), recurrence of fungal keratitis developed after corneal transplantation. Their average age was 45.2 years (range, 12–74 years). Of the patients who experienced recurrence, 29 were men and 28 were women. The interval between the day of onset and the day of surgery ranged from 6 to 60 days (mean, 24.5 days). Among the 57 recurrent patients, 28 had a history of corneal trauma, with plants being the major traumatic agent. A total of 29 patients did not indicate any event that might have induced the infection. None of the cases were related to contact lens use. In 40 patients, recurrence developed after PK, and in 17 patients, recurrence developed after LK. There was no difference between the rates of recurrence after PK (6.79%) and after LK (5.96%; $P = 0.883$).

Among the 57 patients in whom recurrence developed, 55 were found to be infected with the same species of fungi as had been identified before corneal transplantation; the remaining 2 patients were found to have negative results by fungal culture but responded to the administration of antifungal medication in clinic. In eyes affected by *Aspergillus* infection, 11.46% (11/96) experienced recurrence; this rate of recurrence is significantly higher than that observed in eyes with *Fusarium* keratitis (6.21%, 38/612; $P<0.001$). Additionally, 12.50% of patients (4/32) with *Alternaria* species and 8.70% (2/23) of those with *Penicillium* species experienced recurrence.

Risk Factors

Thirty-three patients had been treated with glucocorticoids before surgery; recurrence developed in 21.02% of them. This value was significantly higher than that found in patients not treated with glucocorticoids before surgery (3.23%; $P<0.001$). The recurrence rate with preoperative hypopyon was 10.90%, compared with 2.14% in eyes without preoperative hypopyon ($P = 0.036$). With preoperative corneal perforation, the recurrence rate was 12.00%, compared with 5.83% without this risk factor ($P = 0.002$). The recurrence rate for patients with a preoperative corneal infection expanding to the limbus (20.69%) was higher than in patients without this risk factor (4.80%; $P = 0.042$). Significant risk factors also included lens infection with ECCE, which resulted in a recurrence rate of 50%, compared with 5.75% in eyes without ECCE ($P<0.001$). The extent of the infection also was noted. The rate of recurrence with a diameter of fungal infiltration of 10 mm or more was 17.46%. The rate of recurrence with a diameter of infiltration of 10 mm or less was 5.50%. The difference was not significant ($P = 0.523$; Table 1).

Features of Recurrence

Fungal recurrence developed in patients between 1 and 60 days after surgery. In 49 patients (85.96%), recurrence developed within

Table 1. Rates of Fungal Recurrence after Corneal Transplantation with and without Risk Factors

Characteristic	No. of Patients (%)	Risk Ratio	95% Confidence Interval	*P* Value
Glucocorticoids				
Present	33/157 (21.02)	6.51	0.04–0.22	<0.001
Absent	24/742 (3.23)			
Hypopyon				
Present	47/431 (10.90)	5.09	0.18–0.94	0.036
Absent	10/468 (2.14)			
Corneal perforation				
Present	9/75 (12.00)	2.06	1.97–17.84	0.002
Absent	48/824 (5.83)			
Corneal limbus involvement				
Present	18/87 (20.69)	4.31	1.03–7.07	0.042
Absent	39/812 (4.80)			
Lens involvement with ECCE				
Present	6/12 (50.00)	8.7	0.01–0.22	<0.001
Absent	51/887 (5.75)			
Diameter of infiltration ≥10 mm				
Present	11/63 (17.46)	3.2	0.33–1.77	0.523
Absent	46/836 (5.50)			

ECCE = extracapsular cataract extraction.

Figure 1. Images showing fungal keratitis recurring in the recipient bed. **A**, Recipient bed with a gray hyphal infiltration after penetrating keratoplasty. **B**, Recipient bed with a gray hyphal infiltration combined with sterile hypopyon. **C**, Central recipient bed recurrence after lamellar keratoplasty (LK) in the central recipient bed; the hyphal infiltration is under the graft. **D**, Recipient bed under the graft showing an interlayer empyema on recurrence after LK.

7 days; in 3 patients, recurrence developed after 15 to 30 days; and in 3 patients, recurrence developed after 31 to 60 days.

There were 3 main sites of recurrence: the recipient bed (70.18%), the anterior chamber (7.02%), and the posterior segment (22.81%). A total of 40 patients, including 25 PK patients and 15 LK patients, experienced recurrence in the recipient bed. Recurrence in recipients of LK occurred in 2 sites: in the center of the recipient bed (under the graft, 11 cases) and on the edge (around the graft, 4 cases). Four cases (7.02%), including 3 PK patients and 1 LK patient, had anterior chamber recurrence. Posterior segment recurrence was observed in 13 cases (22.81%) after PK.

The main clinical features of recurrence at different sites were as follows: (1) recipient bed recurrence, in which recurrent infiltrate first appeared in the recipient bed (Fig 1A), followed by infection invading the graft; the inflammation expanded more rapidly as soon as the graft became infected and hypopyon and endothelial plaque were observed (Fig 1B); recurrence in the central recipient bed after LK showed infiltration or interlayer empyema (Fig 1C, D); (2) anterior chamber recurrence, in which white, mushroom-shaped hypopyon was observed rooted in the iris surface (Fig 2A) or in the angles of the anterior chamber (Fig 2B, C); and (3) posterior segment recurrence: hypopyon overflowed from the posterior chamber through the pupil and into the anterior chamber, forming a layer of infiltrate membrane covering the pupil (Fig 2D) by the time vitreous opacity would have been detected easily by B-scan.

Treatment Outcome

Forty-seven patients (82.46%) were cured by either drug therapy (28.07%) or surgical treatment (54.39%). Among the 44 cases of anterior segment recurrence (involving the recipient bed and anterior chamber), 16 cases were controlled by drug therapy, 6 were treated by focal excision combined with a conjunctival flap (Fig 3A), and 21 were cured by PK; 1 patient stopped treatment. The cure rate for anterior segment recurrence was 97.73%. Medical treatment alone was successful only in cases of post-PK recipient bed recurrence that did not infect the graft or anterior chamber (Fig 3B) and post-LK recurrence in the bed around the graft. As soon as the graft was infected or the recurring infection went under the graft, drug therapy was ineffective. Of the 13 patients with posterior segment recurrence, 4 were cured, 6 underwent evisceration of the eye, and 3 stopped treatment; the cure rate was 30.77%.

Discussion

Fungal recurrence after corneal transplantation is a serious surgical complication for fungal keratitis patients. In this study, the rate of recurrence of fungal keratitis was as high as 6.34%. More than 85% of the cases of fungal keratitis recurrence occurred within 7 days of surgery. Therefore, it is important to recognize the early features of recurrence and to identify appropriate methods to control the infection.

Patients with certain risk factors are more prone to recurrence after surgery. Patients misdiagnosed by village clinics and given steroids before surgery before being moved to the hospital also demonstrated a greater likelihood of recurrence. In this study, the recurrence rate for these patients was significantly higher than for patients not treated with steroids or immunosuppressants before surgery. Addi-

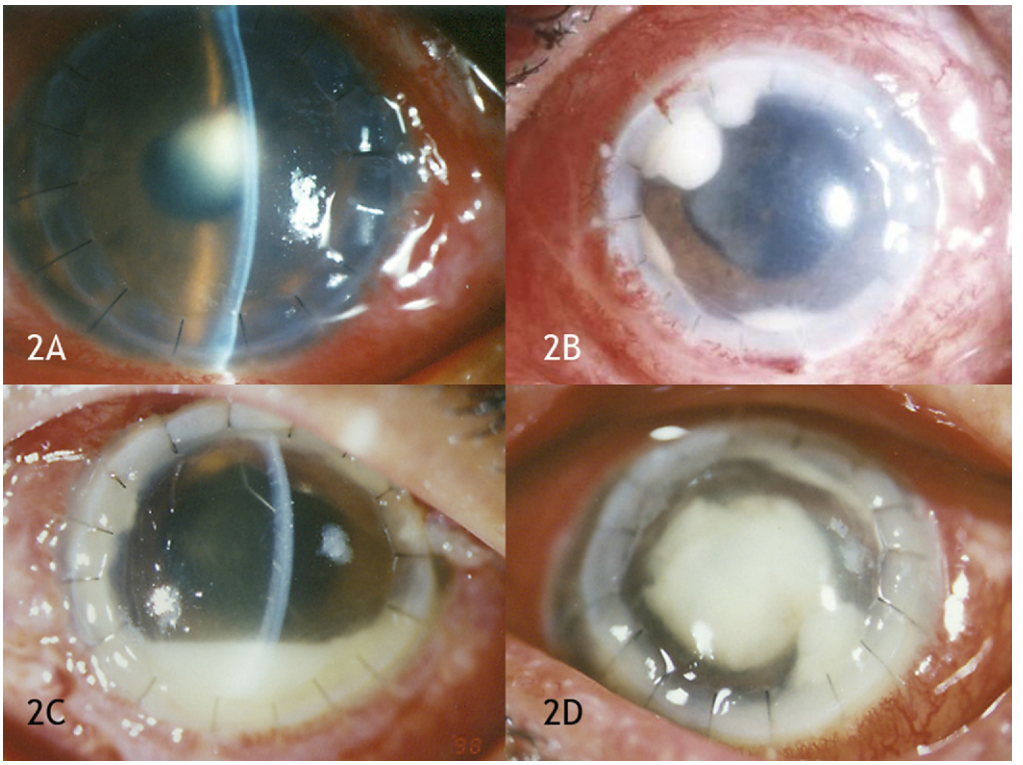

Figure 2. Images showing fungal recurrence in intraocular tissue. **A**, White, mushroom-shaped hypopyon located on the iris. **B**, White, mushroom-shaped hypopyon located in the chamber angle. **C**, **D**, Hypopyon overflowed from the posterior chamber into the anterior chamber and significant vitreous opacity noted on posterior segment recurrence.

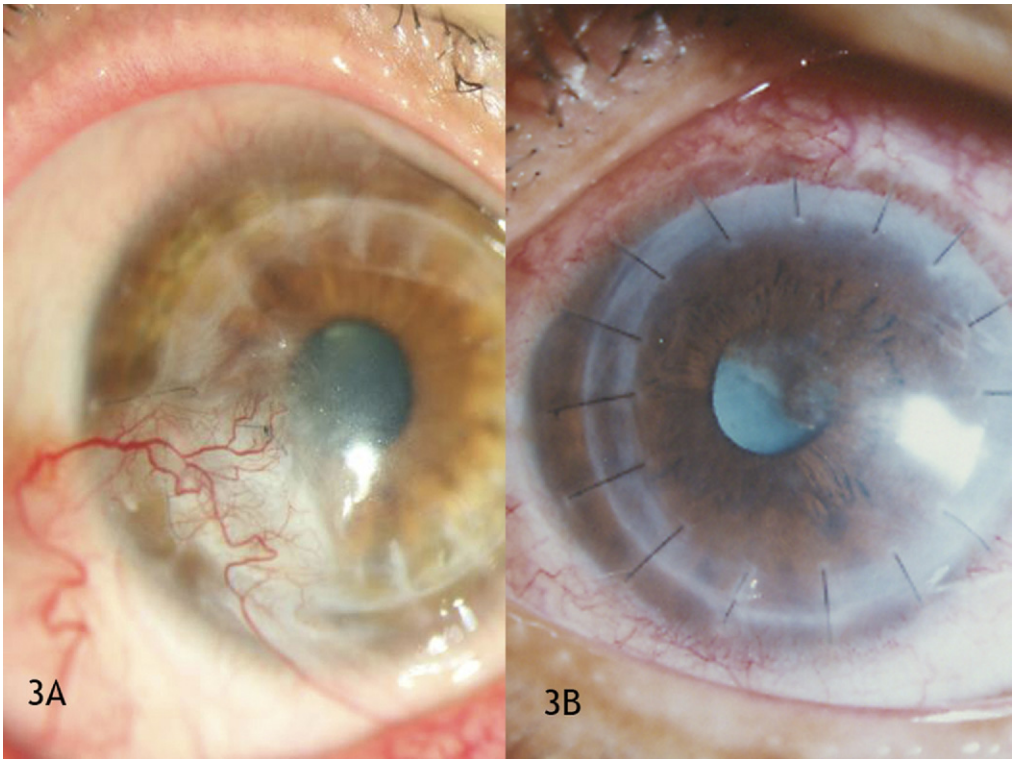

Figure 3. Treatment outcomes. **A**, Recurrence in the recipient bed cured by focal excision combined with a conjunctival flap. **B**, Recurrence in the anterior chamber (Fig 2A) cured with an intracameral injection of fluconazole.

tionally, it has been reported that steroid use may increase the severity of disease and the rate of recurrence in eyes treated with preoperative corticosteroid treatment.[16–18]

The recurrence rate for patients with preoperative hypopyon was 5 times higher than for patients without hypopyon. Preoperative corneal perforation also was a risk factor for recurrence. Fungi easily can implant in the intraocular tissue, causing corneal perforation, and the recurrence rate in such tissue was higher than that in tissue without perforation. It is suggested that careful use of irrigation with fluconazole on the iris surface and in chamber angles is effective in reducing recurrence.

The recurrence rate for patients with corneal limbus involvement was 4.3 times higher than for patients without limbus involvement. This high rate was related to the difficulty of identifying the scleral lesion under the microscope. Therefore, to avoid recurrence, the surgeon should cut off the area as long as infection is suspected.

Another risk factor was lens involvement with ECCE, which resulted in a recurrence rate of 50%. All patients with lens involvement experienced posterior segment recurrence. The lens is the barrier between the anterior and posterior segments of the eye. If the barrier is broken, mycotic endophthalmitis can occur easily. Maintaining the integrity of the lens is very important for reducing recurrence. If a patient demonstrates only a cataract without capsule rupture, a secondary operation of the cataract is a good choice.

After surgery, systemic and topical antifungal treatments may be used for 2 weeks routinely.[19,20] For patients with these risk factors, however, prolonged topical and systemic antifungal therapy (possibly for 6 to 8 weeks) should be initiated. Additionally, patients should be followed up carefully for recurrence.

The extent (or size) and depth of infection were not major relevant risk factors for recurrence. Instead, the clearness of the infected lesion's edge was important; this is not surprising, because this parameter reflects a surgeon's ability correctly to judge and remove the infected corneal tissue thoroughly during the keratoplasty. If the infected area was near the limbus, even though the infected area was of relatively small size, it was considered to have a high risk of recurrence. Thus, regardless of the lesion's size, as long as the infiltrate area can be judged clearly by microscopy and the surgeon can remove the infected tissue cleanly, recurrence is unlikely to occur. If the infected area is near the limbus, it is difficult to judge the infiltrate edge by microscopy; consequently, the infected tissue cannot be removed easily in its entirety. This leads to a high risk of recurrence. Although both slit-lamp and confocal microscopy were used in helping to determine whether the infection had reached the endothelium before surgery, they could not reveal clearly the severity of infection in all patients. The severity of infection in some patients (approximately 20%) can be determined only during the operation.[11]

Most cases of recurrence after LK occurred in the bed under the graft. Because it is very difficult for antifungal medications to reach the recurrence area, antifungal therapy is very ineffective and surgical treatment is necessary. This type of recurrence occurred because of the incomplete removal of the infected central corneal stroma resulting from surgical inexperience. Additionally, it is possible that some fungal hyphae were oriented vertically and penetrated through the cornea.

The morphologic features of fungal growth in the corneal stroma were investigated, and different patterns in different fungal species were observed.[20,21] In this study, the higher rate of recurrence in eyes infected with *Aspergillus* species may be related to the perpendicular growth of fungal filaments, which allows the infection to penetrate deep into the corneal layers or the anterior chamber in a short time. This type of penetration prevents thorough tissue excision with PK or LK.

Appropriate treatment methods can be chosen based on the appearance of different clinical features. Timely and reasonable treatment can control most recurrence cases. Antifungal drugs should be used and administered approximately 5 to 7 days after the procedure. If antifungal therapy is ineffective, then surgical treatment should be performed without delay. The key to successful treatment is the total eradication of the recurrent infection. Geria et al[22] reported that the partial conjunctival flap is an effective surgical procedure for the treatment of abscesses in PK procedures when medical treatment has failed. In this study, if the recurrent infection was in the recipient bed of a postoperative PK patient (in a shallow layer and with a diameter smaller than 2 mm), focal excision combined with a conjunctival flap was effective. For infiltrations larger than 2 mm in diameter or in a deep layer, PK with a larger trephine diameter should be performed. Post-LK recurrence in the central recipient bed under the graft could not be controlled by drug therapy because of problems with drug penetration into the bed. Intracameral antifungal medication has been identified as an effective adjunctive treatment for fungal keratitis in previous reports.[23,24] In this study, intracameral injections of fluconazole were effective for some patients with anterior chamber recurrence. For recurrence in the posterior segment, intravitreal injection of fluconazole combined with vitreous removal should be performed as soon as possible. However, the cure rate for this type of recurrence is low.

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