ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 7, Issue – 3, June – 2022 , Page No. : 124 - 132

Short Term Outcomes of Therapeutic Penetrating Keratoplasty (TPK) In Fungal Keratitis

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Citation this Article: Dr. Sadatia Rutviben Ravjibhai, Dr. Abraham Kurian, Dr. Iodine Reghunadhan, Dr. Bhavisha Vegada, "Short Term Outcomes of Therapeutic Penetrating Keratoplasty (TPK) In Fungal Keratitis", IJMSIR- June - 2022, Vol – 7, Issue - 3, P. No. 124 – 132.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Aim: To evaluate the short term outcomes of TPK as the primary surgical intervention in fungal keratitis. The primary outcomes assessed were eradication of fungal infection and retention of anatomical integrity of globe, while secondary outcomes included graft clarity, visual outcome and complications.

Materials and Methods: This is a prospective, observational study of 28 patients with fungal keratitis who underwent TPK as the primary surgical intervention at tertiary eye care centre and the short term outcomes were studied. Fungal keratitis was diagnosed clinically and confirmed by KOH mount and/or fungal culture and underwent TPK were included in the study. These patients were followed up for minimum 6 months for assessment of the primary and secondary outcomes.

Results: Eradication of infection and anatomical integrity was achieved in 23(82.1%) eyes. Corneal graft remained clear only in 3 eyes(10.7%) during follow up. Visual acuity > 6/60 was achieved only in one eye (3.6%).Recurrence of infection occurred in 5 eyes, one of which was treated medically & 4 were eviscerated because of uncontrolled panophthalmitis. One more eye required evisceration in view of panophthalmitis which occurred independent of graft infection. Graft rejection developed in 15 eyes (53.6%), graft failure in 2 eyes (7.1%), secondary glaucoma in 8 eyes (28.6%), cataract in 3 eyes (10.7%) and persistent epithelial defect in 12 eyes(42.9%).

Conclusion: TPK alone as the primary surgical intervention is an effective approach for eradication of infection & maintainance of anatomical integrity. However further and often multiple surgical interventions may be required eventually to ensure an acceptable final outcome.

Keywords: Fungal Keratitis, Potassium Hydroxide, Sabouraud dextrose agar, Therapeutic Penetrating Keratoplasty

Introduction

Fungal keratitis is very challenging among all microbial keratitis in terms of diagnosis and successful treatment for an ophthalmologist. Annual burden of fungal keratitis is ~1 million globally [1] . In comparison of developing countries versus developed countries, fungal keratitis is more prevalent in developing country like India. Out of all culture positive corneal ulcers at least 50% cases are fungal etiology in India. The recent trend shows number of reported cases of fungal keratitis has been increased [2-5]. It may be because of 1.The inadevertent use of broad-spectrum topical antibiotics which promote fungi growth by providing them a noncompetitive environment for the same. 2.Use of topical corticosteroid suppresses host immune response which again promotes the growth of fungi. 3. The increase in number of fungal keratitis related to soft contact lens users [3,6-8].

The management of fungal keratitis can be entirely challenging, usually needs long term and intensive topical and systemic antifungal therapy, sometime along with surgical intervention like therapeutic penetrating keratoplasty, conjunctival flap, Glue and BCL (Bandage contact lens) application, intracameral/intrastromal antifungal injections etc. required when medical treatment fails. So purpose of our study is to evaluate the short term outcomes in patients who underwent TPK as the primary surgical intervention, whenever it was indicated in the management of fungal keratitis.

Materials & Methods

A prospective, observational study was conducted on 28 eyes of 28 patients with fungal keratitis who underwent TPK at tertiary eye care center. The study was conducted from July 2012 to December 2013. Prior written informed consent was taken from all the patients. Permission from institutional ethics committee (IEC/23/2012) was obtained. The study was adhered to the tenets of the Declaration of Helsinki.

Based on pattern of hyphae or yeast on KOH mount and characteristics of colony morphology & color on culture media (sabouraud dextrose agar (SDA), chocolate agar, blood agar), we started patients on different systemic antifungals like ketoconazole, fluconazole, voriconazole, amphotericin B etc. Topical antifungals (Natamycin, Fluconazole, Amphotericin B etc.) ,cycloplegics, lubricants and prophylactic antibacterials were also used. We considered fungal ulcers for TPK, which were not starting to show any signs of resolution after 3 weeks of intensive topical, systemic, intrastromal and intracameral antifungal treatment and extention to pheripheral cornea including sclera. The patients were evaluated and followed up for a period of 6 months following the intervention.

Inclusion criteria

- When there was no improvement or worsening of fungal ulcer despite aggressive medical management, then the patients were taken up for TPK as the primary surgical intervention
- The cases with impending/perforated corneal ulcer with known fungal etiology were also taken up for TPK as the primary surgical intervention

Exclusion criteria

- Polymicrobial infections of the cornea

Study results were analysed under two headings like primary & secondary outcomes. The primary outcomes assessed were eradication of fungal infection and retention of anatomical integrity of globe, while the secondary outcomes included graft clarity, visual outcome and complications.

The patients data was collected using case record form - Patient's data, Detail history, Ocular Examination, Investigations, Diagnosis, Treatment and Follow up notes.

Ocular examination included visual acuity which was recorded by using a Snellen's chart, detailed slit lamp examination, IOP (intraocular pressure), fundus examination by indirect ophthalmoscopy or ultrasound B-Scan in cases where fundus view was not clear because of hazy media were also done in all cases.

Routine blood examination, liver function test, lacrimal syringing, B-scan in cases where it was necessary, gram staining, KOH (Potassium Hydroxide) mount for demonstration of fungal filaments, culture on sabouraud dextrose agar (SDA) media, chocolate agar, blood agar, histopathological examination of corneal button and microbiology of corneo-scleral rim of donor were done.

Donor corneas of optical grade, in the form of corneo-scleral buttons, were obtained from local eye banks for the TPK.

TPK in our study was done under peribulbar anaesthesia. Body- weight dependent infusion of IV Mannitol was given preoperatively in all cases to reduce the intraoperative vitreous up-thrust.

Under all aseptic precautions, the eye was confirmed and the area painted and draped. We routinely placed either a Flieringa ring or superior and inferior rectus sutures to provide scleral support. For the host bed preparation a handheld trephine mounted on an obturator was used to make a deep partial thickness trephination. After that the anterior chamber was entered either by using side port blade or 11 no. surgical blade , and later the host button was removed by using corneal scissors. Freehand technique to prepare host bed was used in cases with impending/perforated corneal ulcer. Clear margin of 1 mm around ulcer was maintained during host bed preparation whenever possible. Pseudocornea and exudative membranes were also removed. Peripheral anterior synechia were released using iris spatula. Open sky technique was performed in one case with traumatic intumescent cataract for cataract extraction and the patient was kept aphakic. To reduce the incidence of secondary glaucoma, superior peripheral iridectomy was performed between 10-2 o'clock position according to convenience in the all cases. When vitreous loss was encountered, open sky vitrectomy was done.

The donor button preparation was done by keeping it's endothelial side up on a Teflon block and punched it using a trephine mounted on an Iowa punch. The donor corneal trephine 0.25 or 0.50 mm diameter greater than the recipient corneal trephine was used. Freehand technique to prepare the graft was used to suit the defect in cases where there was no round recipient bed available.

The donor cornea was sutured to the host with 16 interrupted sutures of 10-0 monofilament nylon. There was need of more than 16 interrupted sutures in 18 patients with large grafts.

Pre-operative antifungal drugs were continued for an average period of 6 week postoperatively. After total epithelialization of the graft, all patients were started cautiously on weaker topical steroid like loteperdnol etabonate 0.5% three times a day, later increased frequency and switched to more potent topical steroid like prednisolone acetate 1%. Later tapering dose topical steroid was continued for an average of one year. All patients were given topical and systemic antifungals, topical and systemic antibiotics, topical cycloplegics and lubricants.

The patients were followed up daily from day 1 till epithelial healing, then once a week for 1 month, once a

month there after for a 6 months as per follow up schedule after surgery.

Follow up examination sequences were same as pre-operative examination sequences. Which was followed to note the patient's condition?

Statistical Analysis

The data was entered into Microsoft office excel and analyzed by epiinfo software. Quantitative variables were described using the absolute numbers (n) and frequencies (%). Wilcoxon Signed Ranks Test was used to assess the visual outcome after TPK. $P < 0.05$ was considered as statistically significant

Results

This study included 28 eyes of 28 patients. The mean age of the patients was 51 years (ranging from 30.2 years to 71.8 years).Majority (64.3%) were male. The maximum incidence was noted in agricultural workers (28.6%) followed by house wives (25%).Trauma was identified as the initiating factor in 78.6% cases of which injury with vegetative matter accounted for 63.6%.

(Table 1), (Figure 1)

Twenty four (24) patients out of 28 were positive on 10% KOH mount preparation. On sabouraud dextrose agar, five (5) patients out of 28 were positive for fungal growth. Isolated fungi from these five (5) culture positive result were fusarium (2), aspergillus (2) and candida (1).

(Table 2)

The study intervention was primarily aimed at eradication of infection which was achieved in 22 eyes (78.6%) eyes and anatomical integrity of globe was maintained in 23(82.1%) eyes.

(Table 3)

The secondary outcomes assessed were graft clarity and final visual outcome. The complications encountered which affected the outcomes were also analysed.

Graft size was <8 mm in 10 patients (Small graft). It was ≥8 mm in 18 patients. (Large graft). Graft clarity was considered as grade 1 when there was no visualization of the iris details with graft haze, grade 2 when there was poor visualization of the iris details with graft haze and grade 3 when there was good visualization of the iris details with clear graft.

(Figure 2)

Visual acuity was considered as Grade 1 when it was PRI (projection of rays inaccurate), Grade 2 when it was PRA (projection of rays accurate), Grade 3 when it was between 6/60 – CFCF (counting fingers close to face) and Grade 4 when it was >6/60

At 6 month of follow up, the grafts were clear in only 3(10.7%) cases in our study. All 3 of which were clear grafts were small grafts. Causative factors for loss of clarity of the graft amounted to graft rejection in 15 eyes (53.6%), graft failure in 2 eyes(7.1%), graft infection in 5 eyes (17.9%) and secondary glaucoma in 8 cases(28.6%).

In our study visual acuity of >6/60 could be attained in only 3.6% eyes. The causes of reduced visual acuity in our study were graft rejection (53.6%), graft failure (7.1%), and secondary glaucoma (28.6%), graft infection(17.9%). Among the 5 cases of graft infection, only one responded to medical treatment but had residual scarring which adversely affected final visual outcome. The remaining cases of graft infection required evisceration. We had 6 cases of panophthalmitis (including the 5 cases of graft infection) out of which 5 required evisceration. In 3 cases despite a clear graft, visual acuity was low due to other causes- cataract in one patient and thick fibrous pupillary membrane in two patients. However most of our cases (64.3%)were larger grafts and some were (46.4%) sclerocorneal grafts as they were done in advanced cases with limbal

involvement with scleral extension as well in 2 cases which may have contributed to our relatively poor outcome in terms of both graft clarity and visual outcome.

The significant postoperative complications encountered on follow-up which had a bearing on the outcomes were graft infection, graft rejection, cataract, secondary glaucoma and persistent epithelial defect in the graft.

Discussion

This study included 28 eyes of 28 patients. The mean age of the patients was 51 years (ranging from 30.2 years to 71.8 years) in our study. Lixin Xie et al's study showed patients age ranging from 21 to 60 years in 88% of cases [9]. Majority (64.3%) were male which is comparable with Lixin Xie et al study (64.8%) [9]. This trend is because males are more prone to develop corneal trauma and easy accessibility for them to health care facility in developing country as compare to females. The maximum incidence was noted in agricultural workers (28.6%) in this series. Lixin Xie et al study showed 85.1% were farmers [9]. This is because fungal keratitis is most common after vegetative injury. Injury with vegetative matter was noted in 63.6% cases in our study where as it was 49.1% in Lixin Xie's study [9].

The study intervention primarily aimed at eradication of infection & retention of globe integrity of which eradication of infection was achieved in 22 eyes (78.6%) eyes. Study by Y-F Yao et al in 45 patients who underwent TPK for severe fungal keratitis showed successful eradication of infection without recurrence in 86.7% [10]. However this series is not directly comparable with our study since they used cryopreserved donor corneas.

Anatomical integrity of globe was maintained in 23(82.1%) eyes in our series. Comparision with similar studies Y-F Yao et al, **S.** Gupta and Gurbax Singh et al showed comparable rates of anatomical success (85-95%) [10-12]. The secondary outcomes assessed were graft clarity and final visual outcome. The complications encountered which affected the outcomes were also analysed.

At 6 month of follow up, the grafts were clear in 3 (10.7%) cases in our study. The remaining cases with hazy grafts, were of Grade 1 clarity in 9 (39.1%) cases and Grade 2 clarity in 11 (47.8%) eyes. Causative factors for loss of clarity of the graft amounted to graft rejection in 15 eyes (53.6%), graft failure in 2 eyes (7.1%), graft infection in 5 eyes (17.9%) and secondary glaucoma in 8 cases (28.6%). Study by Lixin Xie et al had clear corneas in 79.6% during the 6–24 month follow up period, where as in S. Gupta's study grafts remained clear in 40.9% eyes at 1 year follow up and they had explained that graft size significantly correlated with graft clarity with smaller grafts remaining clear compared to the larger grafts [9,11]. Considering this aspect in our study, all the 3 of our clear grafts were small grafts. Lixin Xie et al,however had a longer follow up period during which the eyes were subjected to repeated keratoplasties. Better final outcomes in their series may probably be attributed to this fact [9].

Visual outcome was poor in our study compared to other similar studies. In our study visual acuity of >6/60 could be attained in only 3.6% eyes. Study by S. Gupta achieved a vision $\geq$6/60 in 20.4% eyes at 1 year of follow up [11]. Gurbax Singh et al in their study achieved the same result in 30 % eyes [12]. The causes of reduced visual acuity in our study were graft rejection (53.6%), graft failure (7.1%), and secondary glaucoma (28.6%), graft infection(17.9 %). Among the 5 cases of graft infection, only one responded to medical treatment but had residual scarring which adversely affected final visual outcome. The remaining cases of graft infection

required evisceration. We had 6 cases of panophthalmitis (including the 5 cases of graft infection) out of which 5 required evisceration. In 3 cases despite a clear graft, visual acuity was low due to other causes- cataract in one patient and thick fibrous pupillary membrane in two patients. However most of our cases (64.3 %)were larger grafts and some were (46.4%) sclerocorneal grafts as they were done in advanced cases with limbal involvement with scleral extension as well in 2 cases which may have contributed to our relatively poor outcome in terms of both graft clarity and visual outcome. In addition a secondary optical kertoplasty is being planned in most cases with opaque grafts and this too has confounded the final visual outcome which was assessed at 6 months.

The significant postoperative complications encountered on follow-up which had a bearing on the outcomes were graft infection, graft rejection, cataract, secondary glaucoma and persistent epithelial defect in the graft. Graft infection and graft rejection were seen in 17.9% and 53.6% cases respectively in our study. Out of the 15 cases of graft rejection only 1 case responded to medical management. Among the five cases of graft infection only 1 case responded to medical treatment. In Lixin Xie et al incidence of graft infection was 7.4% and in S. Gupta study incidence of graft infection and graft rejection were 11.3% and 6.8% respectively [9,11]. This again may be explained by the need to use larger grafts and sclerocorneal grafts, as being a tertiary referral centre, most were advanced cases in our series.

In our study, out of 22 phakic eyes postoperative incidence of cataract was 10.7% (3 eyes). This was comparable with the study by Lixin Xie et al (4.6%) [9]. In one of the cases with clear graft this contributed to the poor visual outcome.

Secondary glaucoma was seen in 28.6% of our cases. All these occurred in the large grafts and could be managed medically. This was relatively high compared to the other studies. While Lixin Xie et al reported an incidence of 1.9% with all the eyes requiring surgical intervention [9], the incidence of secondary glaucoma were 8.9% and 9% respectively in Y-F Yao et al and S.Gupta's study[10,11]. This also may be ascribed to the fact that larger grafts were needed in our series.

Table 1: Characteristics of the patients

Patient Characteristics	No of patients (%)
Age	
11 - 20	2 (7.1)
21 - 30	3 (10.7)
31 - 40	5 (17.9)
41 - 50	4 (14.3)
51 - 60	1 (3.6)
61 - 70	8 (28.6)
71 - 80	5 (17.9)
Gender	
Male	18 (64.3)
Female	10 (35.7)
Occupation	
Agriculture	8 (28.6)
Businessman	4 (14.3)
Office worker	4 (14.3)
Housewife	7 (25.0)
Student	5 (17.9)
Mode of injury	
Ant bite	1 (3.6)
Fish hook	2 (7.1)
Finger nail	5 (17.9)
Insignificant	6 (21.4)
Vegetative matter	14 (50.0)

Table 2: Results of corneal scrapping on staining and culture

Corneal Scrapping	Result	No of patients (%)
Staining		
Gram Staining	Positive	13 (46.4)
	Negative	15 (53.6)
10% Potassium Hydroxide mount	Positive	24 (85.7)
	Negative	4 (14.3)
Culture		
Blood agar	Positive	0 (0)
	Negative	28 (100)
Chocolate agar	Positive	0 (0)
	Negative	28 (100)
Sebouraud dextrose agar	Positive	5 (17.9)
	Negative	23 (82.1)

Table 3: Distribution of patients according to primary outcomes

Primary outcomes	No of patients (%)
Eradication of infection	
yes	22 (78.6)
No	6 (21.4)
Anatomical integrity	
achieved	23 (82.1)
Not achieved	5 (17.9)

Table 4: Distribution of patients according to postoperative complications

Postoperative complications	No of patients (%)
Wound leakage	6 (21.4)
Iris incarceration	2 (7.1)
Persistent epithelial defect	12 (42.9)
Graft failure	2 (7.1)
Graft rejection	15 (53.6)
Graft infilteration	5 (17.9)
Secondary glaucoma	8 (28.6)
Cataract	3 (10.7)
Endophthalmitis	4 (14.3)
Loose suture	4 (14.30

Table 5: Comparison of vision before and after intervention

Vision	Before	After	$Z^{\#}$	p
	No of patients (%)	No of patients (%)		
Lost eye	-	5 (17.9)	1.412	0.158
Grade1	2 (7.1)	1 (3.6)		
Grade 2	12 (42.9)	8 (28.6)		
Grade 3	13 (46.4)	13 (46.4)		
Grade 4	1 (3.6)	1 (3.6)		

- Wilcoxon Signed Ranks Test,

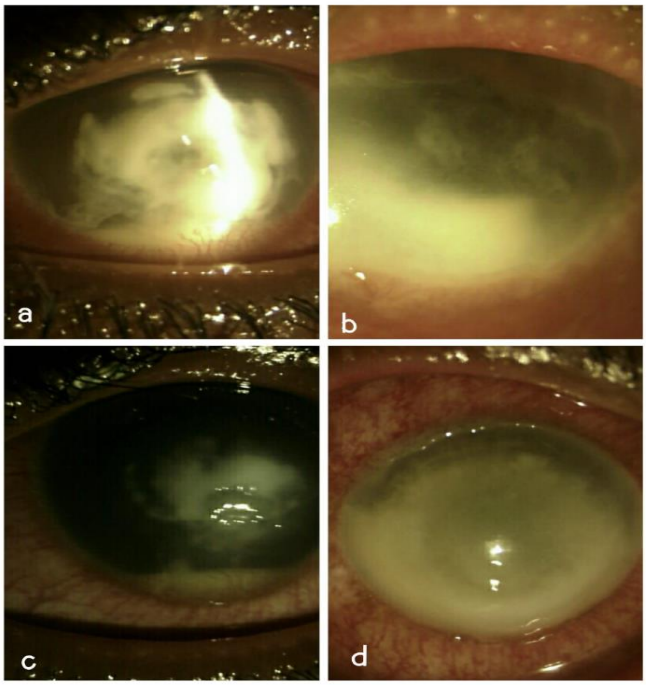

Figure 1: Various presentations of fungal keratitis a. Impending corneal perforation b. Fungal keratitis encroaching to sclera c. Hypopyon fungal keratitis d. Fungal keratitis encroaching to limbus

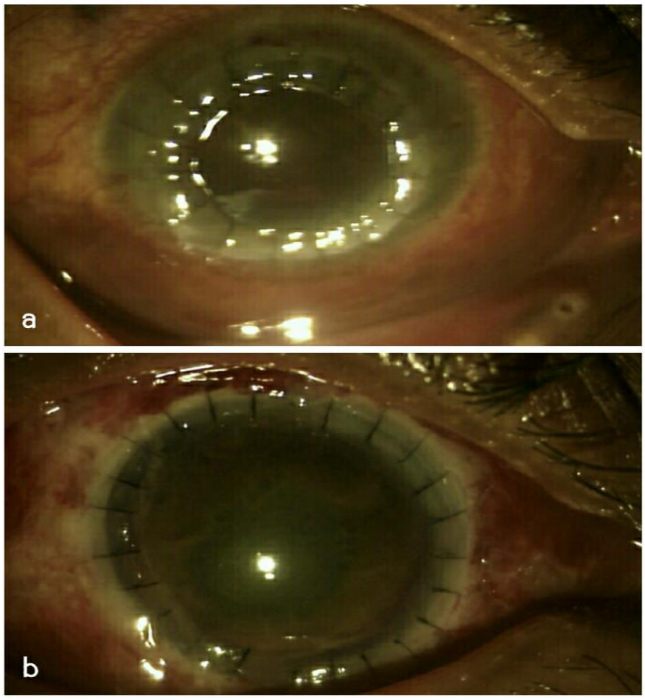

Figure 2: Post Therapeutic Penetrating Keratoplasty

a. Small graft

b. Large graft

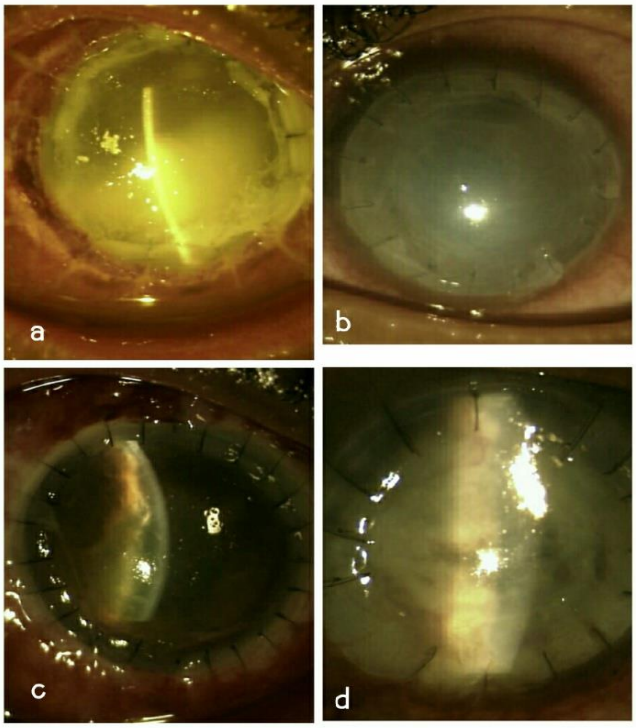

Figure 3: Few Complications Post Therapeutic Penetrating Keratoplasty **a.** Graft reinfection **b.** Graft rejection & loose suture **c.** Severe fibrinous reaction in anterior chamber **d.** Thick pupillary membrane

Conclusion

Therapeutic keratoplasty for microbial keratitis has been in vogue since more than a century. Although associated with high incidence of complications, expected of the procedure, our study revalidates the role of Therapeutic keratoplasty as an important intervention in fungal keratitis to attain its primary goals of eradicating the primary infection and in maintaining the anatomical integrity of the eye. However further and often multiple surgical interventions in the form of repeated therapeutic keratoplasties, optical keratoplasties and other surgeries to tackle related complications may be required eventually to ensure an acceptable final outcome with respect to clarity of the graft and subsequent useful vision.

References

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multinational Prevalence of Fungal Diseases- Estimate Precision. J Fungi (Basel).2017;3(4):57.
2. Alfonso E, Mandelbaum S, Fox MJ, Forster RK. Ulcerative keratitis associated with contact lens wear. Am J Ophthalmol.1986; 101(4):429-433.
3. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of Fusarium keratitis associated with use of a contact lens solution. JAMA.2006; 296(8):953-963.
4. Koidou-Tsiligianni A, Alfonso E, Forster RK. Ulcerative keratitis associated with contact lens wear. Am J Ophthalmol.1989; 108(1):64-67.
5. Liesegang TJ, Forster RK.Spectrum of microbial keratitis in south Florida. Am J Ophthalmol.1980; 90(1):38-47.
6. Alfonso EC, Cantu-Dibildox J, Munir WM, et al. Insurgence of Fusarium keratitis associated with

contact lens wear. Arch Ophthalmol.2006; 124(7):941-947.

7. Gaujoux T, Chatel MA, Chaumeil C, et al. Outbreak of contact lens-related Fusarium keratitis in France. Cornea.2008; 27(9):1018-1021.
8. Ma SK, So K, Chung PH, et al. A multi-country outbreak of fungal keratitis associated with a brand of contact lens solution,the Hong Kong experience. Int J Infect Dis.2008
9. .Lixin Xie, Xiaoguang Dong,Weiyun Shi. Treatment of fungal keratitis by penetrating keratoplasty. Br J Ophthalmol.2001;85:1070–1074.
10. Y-F Yao, Y-M Zhang, P Zhou, B Zhang, W-Y Qiu, S C G Tseng.Therapeutic penetrating keratoplasty in severe fungal keratitis using cryopreserved donor corneas .Br J Ophthalmol.2003;87(5):543–547.
11. Gupta S. Therapeutic penetrating keratoplasty in fungal keratitis: a prospective study.Eur J Ophthalmol.2011;00(00):0 DOI:10.5301/EJO.2011.7671.
12. Gurbax Singh and S. R. K. Malik.Therapeutic keratoplasty in fungal corneal ulcers. Br J Ophthalmol.1972; 56(1), 41-5.