# Indications and Outcomes of
# Repeat Penetrating Keratoplasty

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## Abstract

*Purpose*: To evaluate indications, risk factors and outcome of repeat penetrating keratoplasty (PKP) at a tertiary referral eye care center

*Methods*: In this retrospective study, medical chart of patients who underwent repeat PKP at Labbafinejad Medical Center between January 2004 and December 2009 were reviewed.

*Results*: A total of 1,859 corneal transplantations were performed on 1,624 eyes during study period. Of these, 82 cases were repeat PKP which performed on 72 eyes (6.2% of the total number of primary PKP). Seventy-two eyes had two grafts; 10 eyes had three grafts. Among major indications, keratoconus was the least common initial indication for regraft and bullous keratopathies were the most common initial indication. The percentage of graft/regraft ratio ranged from a high of 9.6% for eyes with pseudophakic bullous keratopathy (PBK) / aphakic bullous keratopathy (ABK) to a low of 1.4% for eyes with keratoconus. Eyes with PBK/ABK were significantly overrepresented as a relative contributing factor to repeat PKP compared to initial PKP (29.2% vs. 11.7%, P=0.001), while those with keratoconus were significantly under-represented (13.9% vs. 38.4%, P=0.001).

*Conclusion*: Bullous keratopathies are the leading indication for repeat PKP in our center. It has the highest relative risk for repeat PKP in comparison to other conditions whereas, keratoconus has the least.

*Keywords*: Corneal Transplantation, Penetrating Keratoplasty, Repeat Penetrating Keratoplasty, Regraft

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## Introduction

Corneal blindness is one of the major public-health problems; specially in developing countries.[1] Corneal transplantation surgery is the most successful tissue transplantation procedure in humans. Despite advances in ocular immunosuppressive, antibiotic and antiglaucoma therapy, corneal transplantation techniques, and postoperative care, failed graft remains a common clinical indication for penetrating keratoplasty (PKP). Repeat corneal transplantation continues to be an important and increasingly common indication for PKP.[2] In most large eye care centers, repeat PKP is the second leading indication for corneal transplantation, accounting for a mean of approximately 18% (range, 6% to 41%) of cases performed.[3-23]

There are several studies in the literature which have reported the indications and outcomes of repeat corneal transplantation.[3-23] The aim of this study is to provide insights into the contributions of indications and risk factors for repeat PKP, and provides prognostic information about initial PKP.

## Methods

In this retrospective study, hospital charts of patients who had undergone corneal transplantation at Labbafinejad Medical Center from January 2004 to December 2009 were reviewed. All surgeries were performed by members of the anterior segment division of department of ophthalmology. All possible risks and benefits of surgery were informed to the patients and an informed consent were obtained from all of them. The study protocol was approved by ethic committee of Shahid Beheshti University of Medical Sciences. The follow-up schedule after the surgery was daily from day 1 till epithelial healing, 1 week, 1 month, 3 months, 6 months, 1 year and yearly thereafter.

Data obtained from the records included the age of patients, total number of grafts performed, duration of follow-up, the original diagnosis responsible for the decision to perform the first corneal transplant, allograft reaction, graft clarity, reasons for graft failure, final postoperative best corrected visual acuity (BCVA), and conditions leading to reduction in vision in clear grafts. Any graft that was not entirely clear within about 3 mm central area around the visual axis was classified as opaque, irrespective of the level of visual acuity (VA).

We used donor corneas which fulfilled all requirements of the Eye Bank of Iran. Transplantations were done within 72 hours of enucleation in most of the cases. Sclerocorneal rims were made at the time of surgery, the donor buttons being punched out of the endothelial side with Hessburg-Barrun Vacuum Trephine having a diameter equal to or 0.2 to 0.5 mm larger than that of the recipient. The grafts were sutured to the recipient corneas with sixteen interrupted 10–0 nylon sutures. Lens extraction, anterior vitrectomy, intraocular lens (IOL) implantation, or IOL removal were done as necessary. The patients received a subconjunctival injection of cefazolin (100 mg) and dexamethasone (2-4 mg) at the end of surgery. Topical betamethasone 0.1%, chloramphenicol 0.5% and ocular lubricants (polyvinyl alcohol)/artificial tears were prescribed as a postoperative treatment. Systemic prednisolone (30–60 mg/day) was administered as necessary. The dosage of steroid was individualized according to each patient's clinical course. Topical treatment was tapered over several months; from 6 times a day postoperatively through once daily at month 3. Patients with healed herpetic keratitis were given oral acyclovir 400 mg twice a day for 1 year after keratoplasty. Patients who developed immunological rejection were treated intensively with topical and systemic steroids. The usual treatment for allograft rejection included the instillation of steroid eyedrops every 1 or 2 hours, steroid ointment at bedtime, subconjunctival injection of 1.2 to 2.0 mg dexamethasone and systemic administration of prednisolone (30–60 mg/day) for 1 to 2 weeks with tapering off. Most patients were evaluated on the first postoperative day, after 2 weeks, after 3, 6, 9, 12, 18, 24 months, and yearly thereafter. The protocol for suture removal varied between ophthalmologists, with some removing all sutures after 12–36 months, and others only selectively removing loosened sutures or tight sutures that induced unacceptable astigmatism.

Reasons for previous graft failure were categorized into the following: allograft rejection (defined as new keratic precipitates

and/or endothelial rejection line), endothelial failure without evidence of allograft rejection, marked astigmatism (greater than 10.0 diopters), recurrence of initial disease process, unknown, and other (corneal ulcer, corneal scarring, wound dehiscence, epithelial downgrowth, membrane formation, and nonhealing epithelial defect). An episode of allograft rejection was diagnosed according to having one or more of the following: graft edema, endothelial rejection line, keratic precipitates, or increased aqueous cells. The time of graft failure was defined as the visit at which irreversible loss of graft clarity was first documented. Intraocular pressure greater than 21 mm Hg on two separate occasions was taken as secondary glaucoma. Aphakic or pseudophakic patients who underwent keratoplasty for corneal decompensation were considered to have aphakic bullous keratopathy (ABK) or pseudophakic bullous keratopathy (PBK), regardless of the underlying mechanism of corneal decompensation (e.g. Fuchs' endothelial dystrophy (FED), toxic anterior segment syndrome, or complicated surgery).

General data were expressed as mean ± standard deviation using SPSS software version 17 (SPSS Inc., Ill., the US). The absolute number and relative frequency of each indication and surgical technique are provided, as well. A $P<0.05$ was considered statistically significant.

## Results

Between January 2004 and December 2009, a total of 1,859 corneal transplantation were performed on 1,624 eyes at Labbafinejad Medical Center. Techniques of corneal transplantations included PKP (n=1,318, 70.9%), deep anterior lamellar keratoplasty (DALK; n=373, 20.1%), conventional lamellar keratoplasty (LKP; n=81, 4.4%), and Descemet's stripping automated endothelial keratoplasty (DSAEK; n=42, 2.3%). The remaining methods included automated lamellar therapeutic keratoplasty (ALTK), endothelial keratoplasty, and sclerokeratoplasty.

Eighty-two repeat PKP were performed on 72 eyes (52 male, 30 female) with a mean age of 50.74±18.24 years (11 to 83 years). The number of eyes in which repeat PKP was done was 6.2% of the total number of primary PKP. A greater number of men (52 of 82, 63.4%) compared to women (30 of 82, 36.6%) underwent repeat graft. Seventy-two eyes had two grafts; 10 eyes had three grafts. Patients with keratoconus were the youngest (mean age, 29.8 years) and those with FED were the oldest (mean age, 65.0 years). The mean follow-up, defined as the time from the last graft until the last clinical attendance, was 45.0±54.4 months (6 to 240 months). Table 1 shows the distribution of the initial indications for repeat PKP. Bullous keratopathy was the most common indication (21 eyes; 29.2%), followed by herpetic keratitis (13 eyes; 18.1%), keratoconus (10 eyes; 13.9%), chemical burn (10 eyes; 13.9%), vascularized corneal scar (9 eyes; 12.5%) and the other smaller groups.

The percentage of graft/regraft ratio ranged from a high of 9.6% for eyes with PBK/ABK to a low of 1.4% for eyes with keratoconus. Eyes with PBK/ABK were significantly overrepresented as a relative contributing factor to repeat PKP compared to initial PKP (29.2% v 11.7%, $P<0.001$), while those with keratoconus were significantly under-represented (13.9% v 38.4%, $P<0.001$) (Table 2). There was no significant difference in the relative contributions of the indications of corneal scars, FED, corneal hereditary endothelial dystrophy (CHED), or stromal dystrophy to initial or repeat PKP. The average number of years between the first and second corneal transplant varied depending on the initial diagnosis and ranged from 23.3 months for eyes with keratoconus to 156.0 months for eyes with CHED (Table 3).

Ten eyes were undergone 3 corneal transplantations. The initial clinical diagnoses of these 10 multiple regrafts were bullous keratopathy (1, 10%); FED (2, 20%); herpes simplex keratitis (2, 20%); corneal scar (2, 20%) and chemical burn (3, 30%). At the end of the study period, 73.2% ($^{60}/_{82}$) of patients had clear cornea. A final VA of $^{20}/_{80}$ or better was achieved in 42 patients. Twenty-two regrafts was opaque at the last follow-up. Table 4 shows the original diagnoses for the failed regrafts.

Ocular surface disease was the most frequent associated risk factor for graft failure (65% in regraft vs. 17% in clear graft; $P<0.001$). Other risk factors included as follow: endothelial graft rejection (60% in

regraft vs. 26% in clear graft; P<0.001), microbial keratitis (60% in regraft vs. 28% in clear graft; P<0.001), glaucoma (55% in regraft vs. 22% in clear graft; P=0.015) and neovascularization (51% in regraft vs. 28% in clear graft; P=0.027). Simultaneous cataract surgery was not a significant risk factor.

**Table 1**. Distribution of the initial indications for repeat penetrating keratoplasty

| Initial indication | Frequency | Percent |
|---|---|---|
| Bullous keratopathy | 21 | 29.2 |
| Herpes simplex keratitis | 13 | 18.1 |
| Keratoconus | 10 | 13.9 |
| Chemical burn | 10 | 13.9 |
| Corneal scar | 9 | 12.5 |
| Fuches endothelial dystrophy | 5 | 6.9 |
| Adherent leucoma | 2 | 2.8 |
| Corneal hereditary endothelial dystrophy | 2 | 2.8 |
| Total | 72 | 100.0 |

**Table 2**. Distribution of the initial indications for primary and repeat penetrating keratoplasties

| Initial indication | Number of primary grafts (Percent) | Number of regrafts (Percent) |
|---|---|---|
| Keratoconus | 714 (38.4%) | 10 (13.9%) |
| Bullous keratopathy | 218 (11.72%) | 21 (29.2%) |
| Infectious ulcers | 188 (10.11%) | 13 (18.1%) |
| Non-herpetic corneal scar | 142 (7.63%) | 9 (12.5%) |
| Endothelial Dystrophies | 77 (4.14%) | 7 (9.7%) |

**Table 3.** Time between transplants for various kinds of indications

| Initial indication | Months (Mean) | Std. Deviation | Minimum | Maximum |
|---|---|---|---|---|
| Bullous keratopathy | 28.57 | 21.95 | 12.00 | 96.00 |
| Keratoconus | 23.30 | 26.92 | 8.00 | 96.00 |
| Herpes simplex keratitis | 46.15 | 56.25 | 12.00 | 192.00 |
| Fuches endothelial dystrophy | 40.60 | 51.47 | 11.00 | 132.00 |
| Corneal scar | 62.55 | 73.02 | 11.00 | 240.00 |
| Chemical burn | 65.10 | 77.50 | 7.00 | 228.00 |
| Adherent leucoma | 108.00 | 50.91 | 72.00 | 144.00 |
| Corneal hereditary endothelial dystrophy | 156.00 | 118.79 | 72.00 | 240.00 |

**Table 4.** Initial Indication of corneal transplantation for failed regrafts at the last follow-up

| Initial indication | Frequency | Percent |
| --- | --- | --- |
| Bullous keratopathy | 7 | 33.3 |
| Herpes simplex keratitis | 3 | 23.1 |
| Fuches endothelial dystrophy | 1 | 20.0 |
| Corneal scar | 3 | 33.3 |
| Chemical burn | 3 | 30.0 |
| Adherent leucoma | 1 | 50.0 |

## Discussion

Despite advances in ocular immunosuppressive, antibiotic and antiglaucoma therapy, corneal transplantation techniques, and postoperative care, repeat corneal grafts remain a drain on existing resources for corneal transplantation. Moreover, the rise in the number of regrafts parallels the rise in number of primary keratoplasties. Incidence of regrafts was 6.2% in our study which is in line with the nationwide report while, it is in contrast with studies from the USA, Britain, and Canada.[9,24-26] The lower incidence of regrafts in our study can be explained by good-quality grafts harvested from young donors. In our study, bullous keratopathy was the most common indication for corneal regraft, followed by herpetic keratitis, keratoconus, chemical burn, vascularized corneal scar and the other smaller groups. Aphakic and PBK were the common primary indications for regrafts in developed countries.[4-7,15,23] A report by Kanavi et al[25] on the indications for PKP in Iran between 1997 and 2003 showed that the most common indication was keratoconus followed by corneal opacities and scars, PBK, corneal dystrophies, ABK, and regrafts in descending order.

Bullous keratopathy has become more prevalent probably due to the shift in the technique of cataract surgery from extracapsular extraction to phacoemulsification with more damage to endothelial cells. It can be also due to increase in the number of IOLs implanted during or after cataract surgery, particularly with anterior chamber closed loop implants and iris clip lenses.[3,20,27] It has been reported, the presence of an anterior chamber IOL after transplantation among eyes with ABK/PBK increased the graft failure risk 2-fold compared with the presence of a posterior chamber IOL.[28] If the presence of an IOL can cause ongoing insult to the endothelium, then this process can continue after corneal transplantation. Consistent with this theory, Langenbucher et al[29] found the rate of endothelial cell loss after keratoplasty to be higher in eyes with ABK/PBK than in those with Fuchs' dystrophy. It should be borne in mind that in contrast to some endothelial diseases such as Fuchs' dystrophy, the presence of the IOL, or the process of cataract extraction and IOL insertion in patients with ABK/PBK, is largely independent of preoperative endothelial abnormality.[30] One other possibility is the extended life expectancy of patients. There may be an increase in ABK/PBK in individuals as they age. Also, previous grafts are more prone to fail the longer the recipient is alive. In patients with ABK/PBK, a history of glaucoma or ocular hypertension substantially increased the failure rate, particularly if the subject had undergone surgery for glaucoma and was being treated with medication to lower intraocular pressure at the time of transplantation.

The percentage of graft/regraft ratio ranged from a high of 9.6% for eyes with PBK/ABK to a low of 1.4% for eyes with keratoconus in the current study. PBK/ABK was also significantly overrepresented as a relative contributing factor to repeat PKP compared to initial PKP. In contrast, keratoconus is the most common indication for primary corneal transplantation.

However, lower chance of graft/regraft can be explained by a good quality donor corneas procured from the Eye Bank of Iran. Keratoconus was also significantly under-represented relative contributing factor for repeat corneal transplantation which is in accordance with study by Al-Mezaine et al.[2]

Different success rates and visual outcome in corneal regrafts have been reported from 51% to 74% in the earlier studies.[2-3,7,15,17] The clarity rate was achieved in 73.2% ($^{60}/_{82}$) of our patients. A final VA of $^{20}/_{80}$ or better was achieved in 42 eyes of our patients. Recent studies report a VA of $^{20}/_{40}$ or better in only 15% to 41% of clear regrafts.[2-3,7,15,17]

Ocular surface problem was the leading cause of failure of primary graft in this study. These eyes were intensively treated with preservative-free lubricants to improve the ocular surface before performing regraft. Patients who undergo repeat corneal grafts carry the risk of developing variable amount of corneal neovascularization as was seen in our cases. Corneal neovascularization is an independent risk factor that can jeopardize the outcome of a successfully performed keratoplasty by causing episodes of graft rejection. However, in contrast to the studies from the developed countries which report graft rejection and recurrence of dystrophies as the main causes for failure of regrafts,[2-3,7,15,17] our study highlights that ocular surface disease and endothelial graft rejection are the leading causes of failure of repeat grafts.

## Conclusion

The current study was performed in a university hospital (tertiary eye care center) which deals with patients referred throughout the country. Therefore, it is possible this report consists of more challenging and complicated patients that are not usually managed in private and less qualified centers. In conclusion, PBK/ABK is the leading indication for repeat keratoplasty in our study. It has highest relative risk for repeat PKP in comparison to other conditions whereas, keratoconus has the least.

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