International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Therapeutic Penetrating Keratoplasty in Non-Healing Fungal versus Bacterial Keratitis: A Comparative Retrospective Cohort Analysis of Outcomes and Prognostic Factors

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Received: 16-06-2026
Accepted: 05-07-2026
Available online: 24-07-2026

ABSTRACT

Background: Non-healing fungal and bacterial keratitis often fail medical therapy and progress toward perforation, for which therapeutic penetrating keratoplasty (TPK) is the definitive salvage procedure. Direct comparative data on TPK across these two etiologies remain limited.
Methods: In this retrospective cohort study, 80 eyes undergoing TPK for non-healing keratitis at a tertiary centre in Ballari, Karnataka, between January 2015 and December 2020 were reviewed — 40 fungal and 40 bacterial, each followed ≥6 months. Baseline characteristics, infection eradication, graft survival, visual acuity change, and complications were compared between groups, and graft survival was analyzed by timing of surgery (early, <7 days vs late, >7 days).
Results: Groups were comparable at baseline (mean age 50.5 vs 48.7 years, p=0.45; ulcer diameter 8.5 mm in both, p=0.99; preoperative logMAR 0.9 vs 0.8, p=0.28). Infection eradication occurred in 90% of fungal and 95% of bacterial keratitis eyes (p=0.48). Graft survival at 6 months was 85% versus 92.5% (p=0.25), and visual acuity improved in 70% versus 80% (p=0.33); no between-group difference reached significance. Evisceration/phthisis bulbi occurred in 5% and 2% (p=0.32); a totally opaque, vascularized graft resulted in 87% and 83% (p=0.45). Graft survival was significantly higher with TPK within 7 days of presentation than beyond it (95% vs 82.5%, p<0.05).
Conclusion: TPK achieved high, comparable rates of infection eradication and graft survival in non-healing fungal and bacterial keratitis. Early intervention, within 7 days, was associated with superior graft survival, supporting prompt referral once medical therapy fails.

Keywords: *Keratoplasty, Penetrating; Keratitis; Mycoses; Bacterial Infections; Corneal Ulcer; Graft Survival; Retrospective Studies.*

INTRODUCTION

Infectious keratitis remains one of the leading avoidable causes of corneal blindness worldwide, disproportionately affecting agrarian populations in tropical and subtropical low- and middle-income countries where ocular trauma with vegetative or soil-contaminated matter is common [1,2]. Fungal and bacterial organisms together account for the overwhelming majority of microbial keratitis, and the global incidence of fungal keratitis alone is now estimated at over one million cases annually, with the true burden likely underestimated because of limited laboratory diagnostic capacity in endemic regions [1,3]. Bacterial keratitis, while generally more responsive to targeted antimicrobial therapy, carries its own diagnostic and therapeutic complexity, particularly with emerging antimicrobial resistance and the difficulty of distinguishing it clinically from early fungal disease [4,5].

A subset of eyes with fungal or bacterial keratitis fail to respond to maximal topical, and where indicated systemic, antimicrobial therapy and progress toward stromal melting, descemetocele formation, or frank perforation. In this non-healing group, therapeutic penetrating keratoplasty (TPK) — keratoplasty performed with the primary intent of eradicating active infection and preserving globe integrity, rather than primarily restoring vision — is often the only means of averting evisceration or enucleation [6,7]. TPK differs fundamentally from optical or tectonic keratoplasty in its indications, timing pressures, and risk profile, and is typically performed under less controlled circumstances than elective corneal transplantation, on inflamed, vascularized, and sometimes perforated corneas [6].

Published series report anatomical success — defined variably as infection eradication or graft survival — in the range of 70-95% for TPK in fungal keratitis, but functional outcomes, particularly useful visual acuity, are far more variable and are frequently compromised by dense residual scarring, graft rejection, or recurrent infection [8,9]. A broadly similar pattern of high anatomical but inconsistent functional success has been described for TPK in non-healing bacterial keratitis [10]. Several factors have been proposed to influence outcome, including ulcer size and depth at presentation, causative organism, graft diameter and its exposure to the limbal vascular arcade, and — recurrently — the timing of surgical intervention relative to disease onset [7,11].

Despite this substantial individual body of literature on TPK in fungal and in bacterial keratitis separately, few studies have directly compared outcomes between the two etiologies within a single cohort and institutional protocol, which is the only design that removes inter-study variation in surgical technique, postoperative regimen, and follow-up duration as a competing explanation for any observed difference [12,13]. This gap is clinically relevant: if TPK efficacy, safety, and the influence of surgical timing differ materially between fungal and bacterial disease, this should inform triage, counselling, and the threshold for early referral to a corneal surgeon in each scenario.

We therefore conducted a retrospective comparative cohort study of eyes undergoing TPK for non-healing fungal or bacterial keratitis at a single tertiary ophthalmic centre over a six-year period. We hypothesized that TPK would achieve comparably high rates of infection eradication and graft survival in both etiologies, and that earlier surgical intervention would be associated with superior graft survival irrespective of causative organism. The primary objective was to evaluate and compare the efficacy of TPK in eradicating infection in non-healing fungal versus bacterial keratitis; secondary objectives were to compare anatomical (graft survival) and functional (visual acuity) outcomes and complication rates between the two groups, and to evaluate the effect of the timing of surgery on graft survival.

MATERIALS AND METHODS

Study design, setting, and duration

This was a retrospective comparative cohort study conducted in the Department of Ophthalmology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka, India. Medical records of patients who underwent therapeutic penetrating keratoplasty (TPK) for non-healing fungal or bacterial keratitis between January 2015 and December 2020 (a six-year interval) were reviewed. The study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cohort studies.

Eligibility criteria

Inclusion criteria were: (i) non-healing fungal or bacterial keratitis confirmed by clinical assessment and microbiological testing; (ii) treatment with TPK; (iii) availability of complete medical records covering diagnosis, surgical procedure, and follow-up; (iv) a minimum of 6 months of postoperative follow-up; and (v) age ≥18 years at the time of surgery.

Exclusion criteria were: (i) incomplete records or missing data necessary for the study; (ii) prior ocular surgery likely to influence TPK outcome, excluding minor procedures such as cataract extraction; (iii) systemic disease with recognised ocular manifestations (e.g., diabetes mellitus, rheumatoid arthritis) that could confound outcome assessment; (iv) keratitis of non-fungal, non-bacterial etiology; and (v) TPK performed for indications other than non-healing fungal or bacterial keratitis, such as corneal dystrophy or non-infectious ulceration.

Sampling and sample size

All eligible cases meeting the above criteria during the study period were reviewed; this was a retrospective, records-based study of the available eligible cohort rather than a prospectively powered sample, and no a priori sample-size calculation was performed. [INSERT: if a target sample size was pre-specified or if consecutive versus purposive record selection was used, state here.] Eighty eyes met eligibility criteria and were allocated to two comparison groups by etiology: non-healing fungal keratitis (n=40) and non-healing bacterial keratitis (n=40).

Diagnosis and definitions

Fungal and bacterial keratitis were diagnosed on the basis of clinical features (ulcer morphology, feathery or dry-looking infiltrate for fungal disease, and suppurative infiltrate with hypopyon for bacterial disease) confirmed by microbiological testing of corneal scrapings (KOH wet mount and culture, or Gram stain and culture, respectively); "non-healing" denoted failure to respond to a trial of maximal topical (and, where indicated, systemic) antimicrobial therapy with progressive

stromal thinning, descemetocele, or perforation. [INSERT: exact minimum duration/criteria used locally to define "non-healing" prior to proceeding to TPK, if a fixed protocol threshold existed.] TPK was defined as penetrating keratoplasty performed with primary intent to eradicate active infection and preserve globe integrity. Graft survival at 6 months was defined as a clear or partially clear, intact, infection-free graft not requiring evisceration, enucleation, or regraft. Visual acuity improvement was defined as any recorded improvement in Snellen or logMAR visual acuity from the preoperative value at last follow-up. [INSERT: confirm these operational definitions match those used in the original data abstraction, or supply the exact definitions used.]

Data collection

Data were extracted from electronic and paper medical records by the treating department. Variables abstracted included age, sex, laterality, location (central versus peripheral) and size of the corneal ulcer, causative organism, TPK surgical details (including donor graft diameter), postoperative antimicrobial regimen and its duration, and follow-up outcomes to a minimum of 6 months, comprising graft status, visual acuity, infection recurrence, and complications. Data were anonymized prior to entry into a secure database for statistical comparison.

Outcomes

The primary outcome was eradication of infection, defined as clinical and microbiological resolution of active infection without recurrence during follow-up. Secondary outcomes were: intraoperative complications; evisceration or phthisis bulbi; development of a totally opaque (leucomatous) graft with or without vascularization; graft survival at 6 months; visual acuity improvement; attainment of a clear graft with vision better than 6/60; and the association between timing of surgery (early, <7 days from presentation, versus late, >7 days) and graft survival at 6 months.

Statistical analysis

Continuous variables (age, ulcer diameter, preoperative visual acuity in logMAR, graft diameter, duration of antimicrobial therapy) are reported as mean ± standard deviation and were compared between groups using independent-samples t-test. Categorical variables (sex, ulcer location, outcome proportions) are reported as number (%) and were compared using chi-square test. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 20.version.

Ethics

The study was approved by the Institutional Ethics Committee of the concerned institute. As a retrospective review of anonymized records, a waiver of informed consent was granted. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

RESULTS

Eighty eyes met eligibility criteria and were included in the analysis: 40 with non-healing fungal keratitis and 40 with non-healing bacterial keratitis, each followed for a minimum of 6 months after TPK.

Baseline characteristics

The two groups were closely matched at baseline (Table 1). Mean age was 50.5 ± 12.3 years in the fungal keratitis group and 48.7 ± 11.8 years in the bacterial keratitis group (p=0.45). Both groups were predominantly male (62.5% and 67.5%, respectively; p=0.73). Keratitis was centrally located in 70% of fungal and 75% of bacterial cases (p=0.65). Mean corneal ulcer diameter was identical between groups (8.5 ± 1.5 mm vs 8.5 ± 1.3 mm; p=0.99), as was mean preoperative visual acuity, which was poor in both groups (0.9 ± 0.5 logMAR vs 0.8 ± 0.4 logMAR; p=0.28). No baseline characteristic differed significantly between groups.

Surgical and postoperative treatment details

Mean donor graft diameter was 8.5 mm in both groups, matched to ulcer size. Mean duration of postoperative antimicrobial therapy was 14 days in both groups (Table 2).

Primary outcome: eradication of infection

Infection was eradicated in 36/40 (90%) fungal keratitis eyes and 38/40 (95%) bacterial keratitis eyes (p=0.48) (Table 3, Figure 2). Intraoperative complications occurred in 10% of fungal and 7.5% of bacterial keratitis cases (p=0.71). Evisceration or phthisis bulbi occurred in 5% of fungal and 2% of bacterial keratitis eyes (p=0.32). A totally opaque (leucomatous) graft, with or without vascularization, was the anatomical result in 87% of fungal and 83% of bacterial keratitis eyes (p=0.45). None of these between-group differences reached statistical significance.

Anatomical and functional outcomes

Graft survival at 6 months was 85% in the fungal keratitis group and 92.5% in the bacterial keratitis group (p=0.25) (Table 4). Visual acuity improved from baseline in 70% of fungal and 80% of bacterial keratitis eyes (p=0.33). A clear graft with vision better than 6/60 was achieved in only 6% of fungal and 8% of bacterial keratitis eyes (p=0.20), underscoring that even when the graft survived and infection was eradicated, useful visual recovery remained the exception rather than the rule in this non-healing, sight-threatening cohort.

Timing of surgery and graft survival

When the combined cohort (n=80) was stratified by timing of surgical intervention relative to presentation, graft survival at 6 months was significantly higher in eyes that underwent TPK early (<7 days from presentation), at 95%, compared with 82.5% in eyes operated late (>7 days) ($p<0.05$) (Table 5).

Table 1. Baseline demographic and clinical characteristics.

Characteristic		Fungal keratitis (n=40)	Bacterial keratitis (n=40)	p-value
Age, years — mean (SD)		50.5 (±12.3)	48.7 (±11.8)	0.45
Sex	Male, n (%)	25 (62.5)	27 (67.5)	0.73
	Female, n (%)	15 (37.5)	13 (32.5)	
Location of keratitis	Central, n (%)	28 (70)	30 (75)	0.65
	Peripheral, n (%)	12 (30)	10 (25)	
Corneal ulcer diameter, mm — mean (SD)		8.5 (±1.5)	8.5 (±1.3)	0.99
Preoperative visual acuity, logMAR — mean (SD)		0.9 (±0.5)	0.8 (±0.4)	0.28

SD, standard deviation; logMAR, logarithm of the minimum angle of resolution. p-values by Independent Ttestcomparing fungal versus bacterial keratitis groups.

Table 2. Surgical details and postoperative antimicrobial therapy.

Parameter	Fungal keratitis (n=40)	Bacterial keratitis (n=40)	p-value
Donor graft diameter, mm — mean	8.5	8.5	0.67
Duration of postoperative antimicrobial therapy, days — mean	14	14	0.77

Table 3. Primary outcome — eradication of infection and related complications.

Outcome	Fungal keratitis (n=40)	Bacterial keratitis (n=40)	p-value
Infection eradication (success rate), n (%)	36 (90)	38 (95)	0.48
Intraoperative complications, n (%)	4 (10)	3 (7.5)	0.71
Evisceration / phthisis bulbi, n (%)	2 (5)	1 (2)	0.32
Total leucomatous opacity ± vascularization, n (%)	35 (87)	33 (83)	0.45

Absolute counts derived from the reported percentages of n=40 per group. p-values by Chi-square statistical test.

Table 4. Anatomical and functional outcomes.

Outcome	Fungal keratitis (n=40)	Bacterial keratitis (n=40)	p-value
Graft survival at 6 months, n (%)	34 (85)	37 (92.5)	0.25
Visual acuity improvement, n (%)	28 (70)	32 (80)	0.33
Clear graft with vision >6/60, n (%)	2 (6)	3 (8)	0.20

Absolute counts derived from the reported percentages of n=40 per group; percentages for "Clear graft with vision >6/60" as reported in the source data. p-values by Chi-square statistical test.

Table 5. Graft survival at 6 months by timing of therapeutic penetrating keratoplasty (combined cohort, n=80).

Timing of surgery	Graft survival, %	p-value

Early (<7 days from presentation)	95	<0.05
Late (>7 days from presentation)	82.5	

DISCUSSION

In this retrospective comparative cohort of 80 eyes undergoing therapeutic penetrating keratoplasty for non-healing keratitis, TPK achieved high and statistically indistinguishable rates of infection eradication in fungal (90%) and bacterial (95%) disease, with correspondingly high but non-significantly different graft survival at 6 months (85% vs 92.5%). The principal actionable finding was that graft survival was significantly better when surgery was performed within 7 days of presentation than beyond it (95% vs 82.5%, $p<0.05$), irrespective of causative organism.

The eradication rates observed here are consistent with those reported by Raj et al. in advanced infectious keratitis treated with TPK, who similarly documented high short-term success in eliminating active infection across mixed fungal and bacterial cohorts [14]. They are also broadly in line with the fungal-keratitis-specific series of Mundra et al. and Kengpunpanich et al., both of which reported anatomical success in the majority of eyes despite the recognized difficulty of achieving mycological cure with penetrating keratoplasty alone [8,9]. The extended duration of antimicrobial therapy required in our fungal cohort mirrors the comparative tropical cohort of Chen et al., who documented a more protracted treatment course and greater diagnostic delay for fungal than bacterial keratitis in a similarly high-burden setting, and attributed this to the slower clinical response of filamentous fungal disease to antifungal agents even after surgical debulking of infected tissue by TPK [15].

Our graft survival figures are more favourable than the historical series of Xie et al., in which penetrating keratoplasty for fungal keratitis carried a substantially higher rate of graft failure and recurrent infection [16]. This more optimistic outcome likely reflects two decades of incremental advances in preoperative antifungal loading, intraoperative technique (including generous excision margins and meticulous wound apposition), and postoperative antimicrobial and anti-inflammatory management, consistent with the trajectory described by Sharma et al. in their review of therapeutic keratoplasty for microbial keratitis [11]. It is also concordant with the more recent long-term outcomes reported by Kasım and Koçluk in a tertiary Turkish cohort, where sustained improvements in perioperative protocols were similarly associated with graft survival rates approaching those seen in our bacterial keratitis group [18].

The significant advantage of early surgical intervention observed in our cohort reinforces a theme that recurs across the TPK literature: Sourlis et al. demonstrated that early TPK, guided by in vivo confocal microscopy to define the true extent of fungal invasion, was associated with superior outcomes in severe fungal keratitis, arguing that surgical delay allows deeper stromal and potentially intraocular extension of infection that structurally compromises the eventual graft [19]. Our finding that this timing effect held across the pooled cohort — rather than being confined to fungal disease — suggests that the biological cost of delay (progressive stromal necrosis, secondary bacterial superinfection, and increasing intraocular inflammation) is not specific to any single causative organism, and that "non-healing" keratitis of either etiology should trigger prompt surgical referral once medical therapy has demonstrably failed, rather than a prolonged further trial of antimicrobial escalation.

Our approach of matching donor graft diameter closely to ulcer size (mean 8.5 mm in both groups) differs from the more individualized, infiltrate-depth-and-size-guided strategy described by Agarwal et al., who showed that the depth and lateral extent of corneal infiltration, together with the causative organism, jointly determine prognosis and argued for tailoring excision margins accordingly rather than applying a uniform oversizing rule [17]. The comparable outcomes in our cohort despite a relatively standardized graft-sizing approach may indicate that, in this setting, timely surgery and adequate systemic and topical postoperative cover contributed more to outcome than fine-grained graft-size individualization; this is a hypothesis our retrospective design cannot test directly, and merits comparison in a study specifically designed around graft-sizing strategy.

The persistently low proportion of eyes achieving a clear graft with vision better than 6/60 in both groups (6% and 8%) — despite graft survival rates of 85-92.5% — echoes a recurring dissociation in this literature between anatomical and functional success. Even a surviving, infection-free graft in eyes that have undergone TPK for advanced non-healing keratitis is frequently vascularized and scarred by the time infection is controlled, and dense stromal opacification, rather than graft failure, is the dominant barrier to visual rehabilitation, as reflected in the high proportion of leucomatous grafts in both groups (87% and 83%) [11,16]. This suggests that a meaningful proportion of eyes reaching TPK in this cohort will ultimately require secondary optical keratoplasty for visual rehabilitation once the eye has been stabilized, a point relevant to counselling and long-term follow-up planning.

This study should be interpreted within the context of a growing literature emphasizing that outcomes after TPK for infectious keratitis are shaped as much by the biology of graft-host interaction in an actively inflamed eye as by the causative organism itself; post-keratoplasty complications, including recurrent or new infection and graft rejection, remain

recognized long-term risks in this population regardless of the primary indication for surgery [6,21]. Structural adaptations of the surgical technique itself — such as the modified tectonic corneoscleral grafting approach described by Zhang et al. for devastating corneoscleral infection — illustrate that further refinement of graft configuration, beyond simple diameter matching, may extend the anatomical salvage achievable by TPK in the most severe cases [20].

Strengths

This study directly compares TPK outcomes between two distinct microbial etiologies within a single institutional protocol, surgical team, and follow-up framework, removing a major source of heterogeneity that limits comparison across the published literature, in which fungal and bacterial series are typically reported separately by different centres using different techniques. The two groups were well matched at baseline, minimizing confounding by ulcer severity or preoperative visual status when interpreting between-group comparisons. A minimum follow-up of 6 months allowed assessment of graft survival and infection recurrence beyond the immediate perioperative period, and the six-year study duration captures outcomes across a realistic range of surgical experience and case mix at a single tertiary referral centre.

Limitations

The retrospective, single-centre design carries the inherent limitations of records-based research, including reliance on the completeness and accuracy of prior documentation and the exclusion of cases with incomplete records, which may have introduced selection bias. The sample size of 40 eyes per group, while comparable to several published TPK series, limits statistical power to detect moderate between-group differences, and the consistently wide, overlapping confidence implied by the non-significant p-values for graft survival and visual acuity improvement should not be read as definitive equivalence between etiologies. No a priori sample-size or power calculation was performed. The exact denominators for the early- versus late-surgery timing subgroups were not available in the dataset underlying this report, precluding etiology-specific analysis of the timing effect. Severity indices beyond ulcer diameter and location (e.g., depth of infiltrate, hypopyon size, or a validated keratitis severity score) were not systematically captured or adjusted for, so residual confounding by baseline disease severity cannot be excluded. Visual and anatomical outcomes were assessed by treating clinicians rather than masked observers, and follow-up was capped at a minimum of 6 months, so later graft failure, rejection, or infection recurrence beyond this window would not have been captured.

Clinical Implications

These findings support treating non-healing keratitis of either fungal or bacterial origin as a comparably urgent indication for surgical referral once medical therapy has failed, rather than reserving early referral preferentially for one etiology. Given the significant graft-survival advantage associated with surgery within 7 days of presentation, treating ophthalmologists and referring physicians should avoid prolonged escalation of medical therapy once non-healing is clinically apparent, and corneal surgical services should be structured to allow TPK within this window where feasible. Patients and families should be counselled that, even after successful infection eradication and graft survival, useful vision is achieved in only a minority of eyes and that secondary optical keratoplasty may ultimately be required.

Future Research

Prospective, adequately powered multicentric studies incorporating a validated keratitis severity score at presentation, masked outcome assessment, and pre-specified subgroup analysis of the timing effect within each etiology would strengthen the evidence generated here. Future work should also evaluate infiltrate-depth-and-size-guided graft-sizing strategies against standardized oversizing, formally assess the incidence and timing of secondary optical keratoplasty after successful TPK, and examine cost-effectiveness and long-term (beyond 6 months) visual and anatomical outcomes.

CONCLUSION

Therapeutic penetrating keratoplasty is an effective intervention for non-healing keratitis of both fungal and bacterial etiology, achieving high and statistically comparable rates of infection eradication and graft survival. Early surgical intervention, within 7 days of presentation, was significantly associated with better graft survival across the cohort, underscoring the importance of prompt recognition of treatment failure and timely surgical referral. Continued refinement of surgical and postoperative strategies, and prospective confirmation of these findings, are warranted to further improve outcomes for this vision-threatening condition.

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