HHS Public Access

Author manuscript

Curr Opin Ophthalmol. Author manuscript; available in PMC 2022 July 18.

Published in final edited form as:

Curr Opin Ophthalmol. 2021 July 01; 32(4): 331–337. doi:10.1097/ICU.0000000000000767.

Advances in corneal graft rejection

Jia Yin

Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Purpose of review—Immune rejection after corneal transplantation is a major risk for graft failure. We aim to summarize recent advances in the understanding and management of graft rejection.

Recent findings—Immune rejection remains the leading cause of graft failure in penetrating keratoplasty. While ABO blood type and sex match between donor and recipient may reduce rejection, human leucocyte antigens class II matching in a randomized study did not reduce the risk of rejection in high-risk penetrating keratoplasty. Compared with penetrating keratoplasty, deep anterior lamellar keratoplasty, descemet stripping automated endothelial keratoplasty, and descemet membrane endothelial keratoplasty have lower immune rejection rates of 1.7–13%, 5–11.4%, and 1.7–2.8%, respectively, based on long-term (5 years and more) studies. Whether immune rejection is a major risk factor for graft failure in these lamellar keratoplasties is unclear. While there have not been major advances in the systemic management of graft rejection, topical nonsteroid agents such as tacrolimus and anti-vascular endothelial growth factor (VEGF) have shown promise in high-risk cases.

Summary—Immune rejection remains the leading cause of graft failure in penetrating keratoplasty. Lamellar keratoplasties have significantly lower rejection rates compared with penetrating keratoplasty. The significance of rejection in the failure of lamellar grafts warrants further investigation.

Keywords

corneal transplantation; graft rejection; immune rejection; lamellar keratoplasty; penetrating keratoplasty

INTRODUCTION

Corneal transplantation (keratoplasty) is the most common form of solid organ transplantation and enjoys high success rates when performed in non-vascularized and noninflamed (low-risk) host beds. In contrast to other forms of allogeneic organ/tissue transplantation, corneal grafts often do not require systemic immunosuppression, owing

Correspondence to Jia Yin, MD, PhD, MPH, Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, 243 Charles St, Boston, MA 02114, USA. Tel: +1 617 912 0272; jia_yin@meei.harvard.edu.

Conflicts of interest

No relevant conflict of interests to declare.

to the cornea's angiogenic and immune privileges. Despite high long-term success rates of low-risk corneal transplantation, 30–60% high-risk penetrating keratoplasty grafts can have rejection episodes and 70% may fail within 10 years [1■]. Immune rejection after penetrating keratoplasty remains the leading cause of graft failure. Therefore, strategies to prevent and manage rejection are critical to the survival of a corneal allograft. Numerous publications have examined immune rejections in penetrating keratoplasty, and several recent (within the past 5 years) reviews have highlighted the management of penetrating keratoplasty graft rejection [1■,2■,3,4■]. While there have not been significant changes in the systemic management of high-risk corneal transplantation since these publications, several recent studies explored topical agents in treating immune rejection and we will highlight these in this review. Given the rapid progress of lamellar keratoplasty in the past 2 decades, studies reporting their long-term graft rejection and successes are emerging. We will provide an update on the immune reaction of anterior and posterior lamellar grafts as well.

UPDATE ON GRAFT REJECTION OF PENETRATING KERATOPLASTY

Long-term (>10 years) survival rates for penetrating keratoplasty range between 52–80% in several large cohort studies with mixed surgical indications [5■]. Allograft rejection remains the leading cause of graft failure, representing approximately 30% of graft failures [5■]. A recent report on 1206 primary penetrating keratoplasty performed at the Singapore National Eye Centre demonstrates that graft rejection occurred in 178 optical, four tectonic, and 12 therapeutic grafts (total rejection rate of 16.1%) in a 20-year follow-up period and that irreversible allograft rejection and late endothelial failure accounted for more than 60% of graft failures [6]. Similarly, the 2018 Australian Corneal Graft Registry found that 17% of penetrating keratoplasty grafts experienced at least one episode of rejection [7].

Repeat penetrating keratoplasty

Several publications recently reported the allograft rejection and survival of repeat keratoplasty. Barut Selver *et al.* reviewed 149 regrafts of 105 eyes with a mean follow-up time of 8.05 ± 5.03 years and found that 62 eyes (59%) had clear grafts at the end of follow-up. Late endothelial failure (36.9%), glaucoma-related endothelial failure (18.8%), allograft rejection (17.4%), and graft infection (14.1%) were the most common reasons for failed grafts [8]. Lu *et al.* reported outcomes and survival of repeat keratoplasty within the New Zealand National Eye Bank. In 242 cases of repeat penetrating keratoplasty, the median survival was 12.0 years for first, 3.5 for second and 2.3 for third repeat keratoplasty. Graft rejection was identified as one of several factors associated with graft failure [9]. Eghtedari *et al.* [10] reported 76 repeat penetrating keratoplasty followed for 5 years and noted main causes of graft failure were endothelial dysfunction, infection, immunologic rejection (11 rejection, or 14.5%), technical problems, and recurrence of primary disease. These newer studies confirm that repeat penetrating keratoplasty in general has lower survival rate compared with primary penetrating keratoplasty and interestingly point out that immune rejection is still a significant risk factor for but may not be the leading cause of graft failure.

Pediatric penetrating keratoplasty

Young host age, particularly pediatric host, has been shown to be correlated with worse graft survival [3]. Two recent reports confirmed this observation and highlighted that immune rejection is the dominant cause of failure of these grafts. Sun *et al.* examined 165 eyes of primary penetrating keratoplasty in children with Peters anomaly and found that 54 eyes (32.7%) demonstrated graft failure along with various degrees of graft opacity. Approximately half of the grafts failed within 6 months postoperatively and irreversible immune rejection accounted for 61.1% of all graft failures [11]. Xavier Dos Santos Araujo *et al.* examined 56 penetrating keratoplasty in children with congenital and acquired corneal opacity and found graft survival rate of 64.7% within 24-month follow-up period. Immune rejection was the most frequent postoperative complications (34% of all complications), and 63.6% of grafts that experienced rejection progressed to graft failure [12].

Donor tissue match

Several risks factors for corneal allograft rejection have been identified: young recipient age, active host bed inflammation/neovascularization, anterior synechiae, history of herpetic eye diseases, diabetes, glaucoma, repeat graft, and concurrent surgeries [1■]. It is generally accepted that optimizing recipient ocular conditions such as reducing inflammation and neovascularization prior to keratoplasty is critical. The utility of matching of donor tissue with the host to potentially reduce immune reactions, however, remains controversial. There have been conflicting reports regarding the benefits of human leucocyte antigens (HLA) matching and several earlier studies suffer from errors in typing methods or retrospective/nonrandomized nature [1■]. Recently the much-anticipated Corneal Transplant Follow-up Study II randomized 1133 high-risk penetrating keratoplasty to HLA Class II matching against a background of HLA class I matching and followed these grafts for 5 years [13■■]. The authors found that HLA Class II matching did not reduce the risk of allograft rejection and confirmed that younger recipient age, multiple preoperative risk factors, and cataract surgery after penetrating keratoplasty increased rejection risk. Regarding non-HLA matching, the Cornea Donor Study has found ABO blood type compatibility is not directly correlated to graft rejection/failure of low-risk and moderate-risk penetrating keratoplasty, while the Collaborative Corneal Transplantation Studies found blood group ABO incompatibility a risk factor for graft failure in high-risk setting [2]. Given the relative ease of blood type match, it can be considered for keratoplasty at high-risk for rejection. There are increasing reports on the role of minor histocompatibility antigens (such as the sex H-Y antigen) in donor graft survival, therefore sex-matching, particularly avoiding male donors to female recipients, is prudent in high-risk transplantation [1■].

Case reports of graft rejection in altered systemic immune status

Graft rejection can occur when host immune status changes in various systemic conditions. Checkpoint inhibitors including pembrolizumab are a new treatment modality for cancers and a case of bilateral penetrating keratoplasty rejection was recently noted in an 85-year-old woman who started pembrolizumab immunotherapy 3 months earlier. The rejection was managed with topical corticosteroid drops but recurred after cessation of the drops. The pembrolizumab treatment was eventually stopped to prevent recurrent corneal graft rejection

after consulting the treating oncologist [14]. The coronavirus disease 2019 (COVID-19) pandemic swept the world in 2020 and Jin *et al.* reported a case of acute graft rejection of an uncomplicated penetrating keratoplasty 3 months after surgery with concurrent onset of COVID-19 symptoms. The authors argue that given that COVID-19 is known to cause conjunctivitis with possible ocular transmission, it may disrupt immune balance leading to graft rejection [15].

UPDATE ON GRAFT REJECTION OF LAMELLAR KERATOPLASTY

Perhaps the most exciting recent development in our collective understanding of corneal graft rejection lies in the reports of lamellar keratoplasty. Anterior lamellar keratoplasty, most commonly deep anterior lamellar keratoplasty (DALK), replaces the diseased corneal stroma while preserving host endothelium and Descemet's membrane. In posterior or endothelial keratoplasty, the diseased endothelium and Descemet's membrane are removed. In the case of Descemet stripping automated endothelial keratoplasty (DSAEK), donor endothelium, Descemet's membrane, and a thin layer of posterior stroma are transplanted, whereas in the case of Descemet membrane endothelial keratoplasty (DMEK), only the donor endothelium and Descemet's membrane are transplanted.

These lamellar surgical techniques gained increasing popularity in the last decade or so, and mid-term (approximately 5 years of follow-up) outcome data are now available. DALK, predominantly indicated for keratoconus, enjoys a survival rate of 77–99.3% [5■]. Between DSAEK and DMEK, DSAEK is an older procedure that was initially done for Fuchs endothelial cell dystrophy (FECD) and pseudophakic bullous keratopathy but is now more reserved for eyes with endothelial disease and other comorbidities (such as glaucoma, iris defect, or a history of vitrectomy), while DMEK becomes the standard of care for eyes with uncomplicated endothelial diseases. The survival rates of DSAEK grafts are reported to between 89–94.1% in single centers and 56–93.4% in national registries. DMEK data are largely reported by single centers and have survival rates above 90% [5■].

It is theorized that lamellar keratoplasty has inherent lower risk for immune rejections for the following reasons: reduced antigen load as less overall tissue is transplanted; avoidance of endothelial rejection in the case of DALK; and effect of anterior chamber-associated immune deviation and absence of stromal sutures in the case of endothelial keratoplasty [16■■]. Indeed, Woo *et al.* [17] reported long-term outcome of various keratoplasties performed for FECD and bullous keratopathy from the Singapore Corneal Transplant Registry and found that that eyes that underwent DMEK had the lowest rate of graft rejection (1.7% vs. DSAEK 5.0% vs. penetrating keratoplasty 14.1%, $P < 0.001$).

For both DMEK and DSAEK, the clinical presentation of immune rejection differs from that of penetrating keratoplasty. A significant portion of rejection is subclinical and only diagnosed during a routine check. In addition, classical Khodadoust lines are not as common. Current rejection prophylaxis for endothelial keratoplasty is daily use of corticosteroid, and when rejection occurs, intensified steroid treatment is indicated [16■■].

Update on graft rejection of descemet stripping automated endothelial keratoplasty

Long-term (follow-up period of 5 years or longer) rates of endothelial immune rejection after DSAEK including ultrathin DSAEK (central graft thickness <100 μm) are reported to be between 5 and 11.4% [7,17–20]. It is worth noting that the rejection rate is much higher in DSAEK grafts done in eyes with glaucoma (19.5%) [21] and in failed penetrating keratoplasty (29%) [22] and that late endothelial failure (without apparent rejection) often occurs more frequently than rejection in DSAEK [5■].

Whether immune rejection is a significant risk factor for DSAEK graft failure is unclear. Wakimasu *et al.* [23] examined 130 cases of DSAEK and found history of glaucoma surgery and allograft rejection as the only two factors associated with graft failure. The 2018 Australian Corneal Graft Registry also reported that graft rejection is an independent factor significantly affecting graft survival in DSAEK [7]. On the other hand, the Cornea Preservation Time Study found that graft rejection is uncommon after DSAEK, while it increases endothelial cell loss, it is not a leading cause of DSAEK failure [24]. Similarly Price *et al.* [20] found that rejection episodes rarely resulted in graft failure within 5 years with either DMEK or DSAEK. Gomez-Benlloch *et al.* [25] examined 509 failed keratoplasties in a multicenter study and found that while immune rejection remains the leading cause of graft failure in penetrating keratoplasty (primary and regraft), the main reason for failure was endothelial decompensation without rejection in DSAEK, and primary graft failure in the DMEK group. The discrepancies likely lie in the difference in the nature of these studies, surgical indications, and other ocular comorbidities.

Update on graft rejection of descemet membrane endothelial keratoplasty

Graft rejection after DMEK is reported to be very low, ranging 1.7–2.8%, based on several recent reports with 5-year follow-up duration [17,20,26]. Gerrit Melles, inventor of modern endothelial keratoplasty, reported the longest-to-date follow-up of his group's initial DMEK cases and noted 4% of eyes developed allograft rejection, the majority of which resolved with intense steroid therapy, within 10 years [27]. DMEK graft rejection in eyes with a history of glaucoma surgery (trabeculectomy or glaucoma drainage device), however, is much higher, ranging from 17.2 to 20.8% in several studies with follow-up up to 4 years [21,28,29]. Similarly, for DMEK performed for failed penetrating keratoplasty (PKP), 21% developed graft rejection, which was the cause of failure in 67% of these cases [22].

DMEK is increasingly performed in eyes that are considered 'high-risk' in the traditional risk stratification for penetrating keratoplasty. For instance, Hayashi *et al.* [30] reported 24 consecutive cases of DMEK in vascularized eyes (involving ≥2 quadrants) and noted rejection in one eye (4.2%) and no primary graft failure. Two case series also reported successful DMEK in the case of corneal endothelial decompensation due to herpes simplex viruses (HSV)-1 infection. Both groups of authors suggested that DMEK is an effective treatment option for corneal edema secondary to HSV-1-related endotheliitis and that intensive long course of antiviral prophylaxis is indicated [31,32].

Update on graft rejection of deep anterior lamellar keratoplasty

Rejection rate of DALK in long-term (5 years) studies (including single-center and registry studies) range between 1.7 and 13% [7,33–35]. This is lower than the rejection rate of penetrating keratoplasty. A recent Systematic Review and Meta-Analysis of penetrating keratoplasty vs. DALK examined 13 studies. The authors found that the rejection rate is 21.3% for penetrating keratoplasty and 8.95% for DALK, and that the risk of graft rejection episodes was more prominent in penetrating keratoplasty than in DALK (odds ratio = 2.69; $P = 0.001$) [36]. While some studies report these (epithelial and stromal) rejection episodes in DALK are often reversed by intense steroid treatment and rarely lead to graft failure [33,37], the report based on the United Kingdom Transplant Database noted that rejection remains a risk factor for graft failure [35]. Significantly ocular surface diseases are found to be a major risk factor for DALK graft failure [25,35].

UPDATE ON NOVEL DIAGNOSIS OF GRAFT REJECTION

Diagnosis of immune rejection after allograft remains a clinical one and slit lamp examination and serial monitoring of central corneal thickness are routinely employed. Various imaging modalities have been explored to objectively identify rejection. Chirapapaisan *et al.* examined the use of in-vivo confocal microscopy in a prospective case–control study where patients with penetrating keratoplasty (with and without rejection) were compared with age-matched controls. The authors found that patients with corneal graft rejection have a significant increase in corneal immune cells, particularly in the sub-basal and endothelial layers, compared with patients with nonrejected grafts and controls [38]. High-definition anterior segment optical coherence tomography has been used to measure the thickness of endothelial/Descemet's membrane complex in patients with healthy or rejecting penetrating keratoplasty grafts. The authors noted that this measurement is a useful parameter for the diagnosis of corneal graft rejection and its diagnostic performance is better than that of the traditional parameters including endothelial cell density and central corneal thickness [39]. Immune rejection after DMEK can often be subtle and asymptomatic. In attempt to capture these 'preclinical' episodes, Baydoun *et al.* retrospectively analyzed the specular microscopy and Scheimpflug images of 22 eyes with clinical rejection after DMEK and noted changes in endothelial cell morphology, cell density, pachymetry, and/or the presence of subclinical keratic precipitates before rejection becomes clinically manifest. The authors propose that recognition of these changes in pattern may allow for early detection and targeted treatment to prevent rejection and endothelial cell loss after DMEK [40].

UPDATE ON TREATMENT FOR GRAFT REJECTION

There are several recent reviews summarizing current practice of managing high-risk corneal transplantation [2,3,4■]. In brief, topical corticosteroid remains the mainstay after transplantation including full-thickness and partial-thickness keratoplasties. Given the lower rejection rates of DALK and endothelial keratoplasty, there have been reports of cessation of long-term steroid use in these cases, but in general corticosteroid use leads to reduced rejection and most authors advocate prolonged and possibly indefinite use of low potency corticosteroid eye drops, if there are no contraindications.

Topical treatment for graft rejection

Prednisolone 1% and dexamethasone 0.1% are routinely used after keratoplasty [4■]. Two recent studies report the use of topical difluprednate, a very high potency corticosteroid, in effectively preventing and treating rejection after penetrating keratoplasty, though toxicity and intraocular pressure need to be monitored closely [41,42].

Nonsteroid topical immunosuppressive agents including cyclosporine A (CsA) and tacrolimus have been used in managing graft rejection, particularly in high-risk cases [2]. Topical CsA, at concentrations of 0.05–2%, can be used in postoperative period in cases of steroid-induced glaucoma, allowing a reduction of topical corticosteroids, but its efficacy to reduce the risk of graft rejection in high-risk corneal transplantation is still questionable [3,4■]. Topical tacrolimus (commonly 0.03%) has shown promises in managing high-risk corneal transplantation [2,3,4■]. In a recent randomized study, patients with high-risk penetrating keratoplasty received either topical tacrolimus 0.1% or CsA 1%. Tacrolimus group had significantly decreased corneal graft rejection rate compared with CsA group ($P = 0.02$) [43]. In another study published in 2021, topical 0.03% tacrolimus was found to be as effective as systemic mycophenolate mofetil as adjuncts to topical and systemic corticosteroids in reducing endothelial graft rejection with 12 months follow-up after repeat keratoplasty [44]. Lastly, in a cohort of 20 very high-risk therapeutic penetrating keratoplasty for severe infectious keratitis, 0.1% tacrolimus eye drops were found to facilitate the reduction of intraocular inflammation in early postoperative period and may extend long-term survival of grafts in cases of severe infectious keratitis [45].

As corneal neovascularization is a major risk factor for graft rejection/failure, at least in the case of penetrating keratoplasty, attempts to reduce vascularization of the recipient beds have the potential to promote graft survival, most notably with the off-label use of anti-VEGF agents. Three recent case series reported the use of topical bevacizumab, intrastromal bevacizumab, and the combination of fine-needle thermal cauterization and subconjunctival injection of bevacizumab, in regressing corneal neovascularization perioperatively of high-risk penetrating keratoplasty and found favorable results in graft rejection and failure [46–48]. A multicenter randomized clinical trial of bevacizumab in high-risk corneal transplantation (ClinicalTrials.gov Identifier: NCT01996826) has completed and is expected to report its findings in 2021. In this study, the treatment arm received one-time subconjunctival injection of 0.1 ml (2.5 mg) bevacizumab at time of penetrating keratoplasty and followed by topical treatment with 1% bevacizumab four times a day for 4 weeks. The study followed a total of 86 patients and preliminary study indicates the cumulative endothelial rejection rates to be 90% in control and 81% in bevacizumab treatment group (P=0.2), respectively, in the 1-year follow-up period (personal communication with study PI Dr Reza Dana). Corneal crosslinking (CXL), a recently Food and Drug Administration-approved procedure to halt progression of keratoconus, has been explored to reduce progressive corneal neovascularization before or concurrent with high-risk penetrating keratoplasty in five patients [49]. The authors found that peripheral CXL resulted in a reduction of corneal neovascularization without revascularization and that all transplants remained clear and without immune reactions through the 16-week follow-up period.

Systemic treatment for graft rejection

There lacks general consensus on the management of high-risk corneal transplantation using systemic medications [50]. Corticosteroids remain the most common agents, while other immunosuppressants such as CsA, mycophenolate mofetil, tacrolimus, and sirolimus have all been examined. It is worth noting that these regimens have variable success rates and comparison among them is difficult due to small number of studies available. In addition, systemic immunosuppression carries significant systemic side effects and requires individualized planning and close monitoring. These systemic agents have been summarized at length in several recent reviews [1■,2,3,4■], and we have not found major new evidence in this area.

CONCLUSION

Immune rejection remains a leading cause of graft failure in penetrating keratoplasty. Repeat penetrating keratoplasty and pediatric penetrating keratoplasty are at higher risk of graft rejection. ABO blood type and sex match between donor and host may reduce graft rejection and should be considered in high-risk cases, given the relative ease and low cost of performing such match. HLA typing, however, has been shown in a large, randomized study not to reduce rejection or promote survival of high-risk penetrating keratoplasty. Lamellar keratoplasties including DALK, DSAEK, and DMEK have significantly lower risk of graft rejection, compared with penetrating keratoplasty. There is conflicting evidence on whether immune rejection is the major cause of graft failure in these cases. The importance and underlying mechanisms of nonrejection loss of corneal endothelial cells in the case of DSAEK and DMEK requires further clinical and basic scientific investigation. In terms of graft rejection management, there still lacks high-quality evidence on the efficacy of systemic immunosuppressive agents, and well planned randomized studies may continue to prove challenging given the limited study population and severe side effects of these agents. Nonsteroid topical regimens, particularly tacrolimus and anti-VEGF agents, may be considered in high-risk cases; and their use in lamellar keratoplasty warrant exploration.

Financial support and sponsorship

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1■. Armitage WJ, Goodchild C, Griffin MD, et al. . High-risk corneal transplantation: recent developments and future possibilities. Transplantation 2019; 103:2468–2478. [PubMed: 31765363] The review article highlights critical research areas in the understanding and promotion of high-risk corneal transplants.

2. Jabbehdari S, Rafii AB, Yazdanpanah G, et al. Update on the management of high-risk penetrating keratoplasty. Curr Ophthalmol Rep 2017; 5:38–48. [PubMed: 28959505]

3. Di Zazzo A, Kheirkhah A, Abud TB, et al. Management of high-risk corneal transplantation. Surv Ophthalmol 2017; 62:816–827. [PubMed: 28012874]

4■. Azevedo Magalhaes O, Shalaby Bardan A, Zarei-Ghanavati M, Liu C. Literature review and suggested protocol for prevention and treatment of corneal graft rejection. Eye (Lond) 2020; 34:442–450. [PubMed: 31332293] The article provides a management protocol (algorithm) for various types of corneal transplantation.

5■. Alio JL, Montesel A, El Sayyad F, et al. Corneal graft failure: an update. Br J Ophthalmol 2020.The article provides a comprehensive summary in table format of long-term and mid-term outcomes of penetrating keratoplasty, deep anterior lamellar keratoplasty, and DSAEK.

6. Anshu A, Li L, Htoon HM, et al. Long-term review of penetrating keratoplasty: a 20-year review in Asian eyes. Am J Ophthalmol 2020; 224:254–266. [PubMed: 33129808]

7. Williams KA, Keane MC, Galettis RA, et al. The Australian Corneal Graft Registry 2018 report: South Australian Health and Medical Research Institute. 20l8.

8. Barut Selver O, Karaca I, Palamar M, et al. Graft failure and repeat penetrating keratoplasty. Exp Clin Transplant 2021; 19:72–76. [PubMed: 29697353]

9. Lu LM, Boyle AB, Niederer RL, et al. Repeat corneal transplantation in Auckland, New Zealand: indications, visual outcomes and risk factors for repeat keratoplasty failure. Clin Exp Ophthalmol 2019; 47:987–994. [PubMed: 31268240]

10. Eghtedari M, Kamalzadeh M, Yasemi M, et al. Five years pathological evaluation of corneal regrafts: a study from southern Iran. J Ophthalmol 2020; 2020:2546923. [PubMed: 33489323]

11. Sun Y, Lin Q, Miao S, et al. Analysis of graft failure after primary penetrating keratoplasty in children with Peters anomaly. Cornea 2020; 39:961–967. [PubMed: 32251169]

12. Xavier Dos Santos Araujo ME, Santos NC, Souza LB, et al. Primary pediatric keratoplasty: etiology, graft survival, and visual outcome. Am J Ophthalmol 2020; 212:162–168. [PubMed: 31883464]

13■■. Armitage WJ, Winton HL, Jones MNA, et al. Corneal transplant follow-up study II: a randomised trial to determine whether HLA class II matching reduces the risk of allograft rejection in penetrating keratoplasty. Br J Ophthalmol 2020.The randomized clinical trial demonstrates that human leucocyte antigens (HLA) class II matching, against a background of HLA class I matching, did not reduce the risk of allograft rejection.

14. Vanhonsebrouck E, Van De Walle M, Lybaert W, et al. Bilateral corneal graft rejection associated with pembrolizumab treatment. Cornea 2020; 39:1436–1438. [PubMed: 32452986]

15. Jin SX, Juthani VV. Acute corneal endothelial graft rejection with coinciding COVID-19 infection. Cornea 2021; 40:123–124. [PubMed: 32889957]

16■■. Hos D, Matthaei M, Bock F, et al. Immune reactions after modern lamellar (DALK, DSAEK, DMEK) versus conventional penetrating corneal transplantation. Prog Retin Eye Res 2019; 73:100768. [PubMed: 31279005] The review article provides special focus on the pathogenesis, management, and prevention of endothelial graft rejection.

17. Woo JH, Ang M, Htoon HM, Tan D. Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty and penetrating keratoplasty. Am J Ophthalmol 2019; 207:288–303. [PubMed: 31228467]

18. Madi S, Leon P, Nahum Y, et al. Five-year outcomes of ultrathin descemet stripping automated endothelial keratoplasty. Cornea 2019; 38:1192–1197. [PubMed: 31246680]

19. Fajgenbaum MA, Hollick EJ. Modeling endothelial cell loss after descemet stripping endothelial keratoplasty: data from 5 years of follow-up. Cornea 2017; 36:553–560. [PubMed: 28306600]

20. Price DA, Kelley M, Price FW Jr, Price MO. Five-year graft survival of descemet membrane endothelial keratoplasty (EK) versus descemet stripping EK and the effect of donor sex matching. Ophthalmology 2018; 125:1508–1514. [PubMed: 29731147]

21. Alshaker S, Mimouni M, Batawi H, et al. Four-year survival comparison of endothelial keratoplasty techniques in patients with previous glaucoma surgery. Cornea 2020. [Epub ahead of print]

22. Einan-Lifshitz A, Mednick Z, Belkin A, et al. Comparison of descemet stripping automated endothelial keratoplasty and descemet membrane endothelial keratoplasty in the treatment of failed penetrating keratoplasty. Cornea 2019; 38:1077–1082. [PubMed: 31394551]

23. Wakimasu K, Kitazawa K, Kayukawa K, et al. Five-year follow-up outcomes after Descemet's stripping automated endothelial keratoplasty: a retrospective study. BMJ Open Ophthalmol 2020; 5:e000354.
24. Stulting RD, Lass JH, Terry MA, et al. Factors associated with graft rejection in the cornea preservation time study. Am J Ophthalmol 2018; 196:197–207. [PubMed: 30308200]
25. Gomez-Benlloch A, Montesel A, Pareja-Arico L, et al. Causes of corneal transplant failure: a multicentric study. Acta Ophthalmol 2021.
26. Birbal RS, Ni Dhubhghaill S, Bourgonje VJA, et al. Five-year graft survival and clinical outcomes of 500 consecutive cases after descemet membrane endothelial keratoplasty. Cornea 2020; 39:290–297. [PubMed: 31478948]
27. Vasiliauskaite I, Oellerich S, Ham L, et al. Descemet membrane endothelial keratoplasty: ten-year graft survival and clinical outcomes. Am J Ophthalmol 2020; 217:114–120. [PubMed: 32283096]
28. Boutin T, Sorkin N, Einan-Lifshitz A, et al. Descemet membrane endothelial keratoplasty in patients with prior glaucoma surgery. Eur J Ophthalmol 2020.
29. Sorkin N, Mimouni M, Kisilevsky E, et al. Four-year survival of descemet membrane endothelial keratoplasty in patients with previous glaucoma surgery. Am J Ophthalmol 2020; 218:7–16. [PubMed: 32446739]
30. Hayashi T, Zhang W, Hos D, et al. Descemet membrane endothelial keratoplasty in vascularized eyes: outcome and effect on corneal neovascularization. Cornea 2020.
31. Friehmann A, Myerscough J, Giannaccare G, et al. Successful descemet membrane endothelial keratoplasty in proven herpetic endothelial decompensation requires intensive antiviral therapy. Cornea 2020; 39:196–199. [PubMed: 31738241]
32. Basak SK, Basak S. Descemet membrane endothelial keratoplasty in irreversible corneal edema due to herpes simplex virus endotheliitis. Cornea 2020; 39:8–12. [PubMed: 31490277]
33. Arundhati A, Chew MCY, Li L, et al. Comparative study of long-term graft survival between penetrating keratoplasty and deep anterior lamellar keratoplasty. Am J Ophthalmol 2020; 224:207–216. [PubMed: 33253665]
34. Romano V, Iovieno A, Parente G, et al. Long-term clinical outcomes of deep anterior lamellar keratoplasty in patients with keratoconus. Am J Ophthalmol 2015; 159:505–511. [PubMed: 25486540]
35. Kasbekar SA, Jones MN, Ahmad S, et al. Corneal transplant surgery for keratoconus and the effect of surgeon experience on deep anterior lamellar keratoplasty outcomes. Am J Ophthalmol 2014; 158:1239–1246. [PubMed: 25174894]
36. Song Y, Zhang J, Pan Z. Systematic review and meta-analysis of clinical outcomes of penetrating keratoplasty versus deep anterior lamellar keratoplasty for keratoconus. Exp Clin Transplant 2020; 18:417–428. [PubMed: 31724924]
37. Sarnicola V,Toro P, Sarnicola C, et al. Long-term graft survival in deep anterior lamellar keratoplasty. Cornea 2012; 31:621–626. [PubMed: 22406938]
38. Chirapapaisan C, Abbouda A, Jamali A, et al. In vivo confocal microscopy demonstrates increased immune cell densities in corneal graft rejection correlating with signs and symptoms. Am J Ophthalmol 2019; 203:26–36. [PubMed: 30790547]
39. Smith C, Kaitis D, Winegar J, et al. Comparison of endothelial/Descemet's membrane complex thickness with endothelial cell density for the diagnosis of corneal transplant rejection. Ther Adv Ophthalmol 2018; 10:2515841418814187.
40. Baydoun L, Bruinsma M, Santander-Garcia D, et al. Combined specular microscopy and Scheimpflug imaging to improve detection of an upcoming allograft rejection after DMEK. Acta Ophthalmol 2020; 98:261–266. [PubMed: 31486268]
41. Said OM, Saleh MGA, Omar AF, et al. Topical difluprednate for early corneal graft rejection after penetrating keratoplasty. Clin Ophthalmol 2020; 14:3495–3498. [PubMed: 33149542]
42. Sorkin N, Yang Y, Mednick Z, et al. Outcomes of difluprednate treatment for corneal graft rejection. Can J Ophthalmol 2020; 55:82–86. [PubMed: 31712024]
43. Zhai LY, Zhang XR, Liu H, et al. Observation of topical tacrolimus on high-risk penetrating keratoplasty patients: a randomized clinical trial study. Eye (Lond) 2020; 34:1600–1607. [PubMed: 31784702]

44. Faramarzi A, Abbasi H, Feizi S, et al. Topical 0.03% tacrolimus versus systemic mycophenolate mofetil as adjuncts to systemic corticosteroids for preventing graft rejection after repeat keratoplasty: one-year results of a randomized clinical trial. Eye (Lond) 2021.

45. Zang Y, Li S, Ruan F, et al. Tacrolimus dye drop treatment for the management of early postoperative intraocular inflammation after therapeutic keratoplasty for severe infectious keratitis. Exp Ther Med 2020; 20:3260–3268. [PubMed: 32855696]

46. Kuo HH, Shen EP. Long-term topical bevacizumab for prevention of corneal graft rejections. Eur J Ophthalmol 2020; 1120672120939504.

47. Gupta AA, Mammo DA, Page MA. Intrastromal bevacizumab in the management of corneal neovascularization: a retrospective review. Graefes Arch Clin Exp Ophthalmol 2020; 258:167–173. [PubMed: 31713747]

48. Hos D, Le VNH, Hellmich M, et al. Risk of corneal graft rejection after high-risk keratoplasty following fine-needle vessel coagulation of corneal neovascularization combined with bevacizumab: a pilot study. Transplant Direct 2019; 5:e452. [PubMed: 31165087]

49. Schaub F, Hou Y, Zhang W, et al. Corneal crosslinking to regress pathologic corneal neovascularization before high-risk keratoplasty. Cornea 2021; 40:147–155. [PubMed: 33395116]

50. Abud TB, Di Zazzo A, Kheirkhah A, Dana R. Systemic immunomodulatory strategies in high-risk corneal transplantation. J Ophthalmic Vis Res 2017; 12:81–92. [PubMed: 28299010]

KEY POINTS

- Immune rejection remains the leading cause of graft failure in penetrating keratoplasty.
- While ABO blood type and sex match between donor and recipient may reduce rejection, human leucocyte antigens class II matching in a randomized study did not reduce the risk of rejection in high-risk penetrating keratoplasty.
- Compared with penetrating keratoplasty, deep anterior lamellar keratoplasty, descemet stripping automated endothelial keratoplasty, and descemet membrane endothelial keratoplasty have significantly lower immune rejection rates.
- Whether immune rejection is a major risk factor for graft failure in lamellar keratoplasties is unclear.
- Topical nonsteroid agents such as tacrolimus and anti-VEGF have shown promise in the management of high-risk penetrating keratoplasty.