




# Current Perspectives on Corneal Transplantation

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**Abstract:** Disease of the cornea is the third leading cause of blindness worldwide. Corneal graft surgery is one of the most successful forms of solid organ transplantations in humans, with ever-increasing developments in surgical technique. To date, approximately 4504 corneal transplants are performed in the United Kingdom each year. While full thickness transplantation was the most commonly performed keratoplasty over the last few decades, selective lamellar transplantation of the diseased layers of the cornea has been universally adopted. This comprehensive review aims to provide an updated synthesis on different types of corneal transplantations, their treatment outcomes, and the associated complications of each procedure in both adult and paediatric population. In addition, we also present an up-to-date summary of the emerging therapeutic approaches that have the potential to reduce the demand for donor-dependent keratoplasty.

**Keywords:** corneal transplantation, corneal blindness, keratoplasty, graft rejection, graft survival

## Introduction

In health, the cornea is a transparent and avascular connective tissue that provides protective and refractive components that contribute to visual function. Numerous degenerative, dystrophic, infectious, inflammatory or traumatic conditions can compromise corneal clarity, all with the potential to cause visual loss. Corneal disease is the third leading cause of blindness worldwide after cataracts and glaucoma.<sup>1,2</sup> Infectious eye diseases such as trachoma remain the leading cause of corneal blindness in the developing world, whereas degenerative or iatrogenic causes such as Fuchs' endothelial corneal dystrophy (FECD) and pseudophakic bullous keratopathy (PBK) are more common in developed countries. Once corneal clarity is lost, transplantation is the current therapeutic intervention of choice with the goal of improving visual acuity.

Corneas are the most frequently transplanted human tissue worldwide. This success is primarily attributed to corneal "immune privilege", resulting in a reduced inflammatory response following transplantation due to the lack of afferent lymphatic and efferent blood vessels in the recipient cornea, a lack of major histocompatibility antigens class II, and the anterior chamber-associated immune deviation.<sup>3,4</sup> It is estimated that 12.7 million people are waiting for a corneal transplant worldwide, but there is huge variability in the availability of donor tissues across different geographical locations.<sup>1</sup> In the UK, 4504 corneal transplants were performed in 2019;<sup>5</sup> In the USA, there were 85,601 corneas transplanted in the same year.<sup>6</sup> The USA, Sri Lanka, and Italy are some of the few countries with a surplus of donor tissue for exportation, accounting for 85%, 9%, and 3% of the total number of exported tissues, respectively. In addition, other exporting countries were the Philippines, the Netherlands, the Czech Republic, France, Australia, and Colombia (by decreasing number of exported corneas ranging from 588 to 17).<sup>1</sup> In stark and disappointing contrast, at least 55.3% of the world's population have no access to corneal transplant material.<sup>1</sup>

## The Structure and Function of the Cornea

The human cornea consists of six discernible layers. The surface epithelium comprises four to six layers of stratified, non-keratinizing squamous cells.<sup>7</sup> The most superficial two to three layers of epithelial cells have apical microvilli and microplacae, which allow adherence and even spread of the overlying tear film. The tight junctions between neighboring cells prevent external pathogens from passing through the epithelial layers into the deeper layers. The two to three cell

layers underneath, the suprabasal layers, also possess similar tight intercellular junctions. The singular “basal cell layer” secretes the underlying basement membrane and attaches to it by hemidesmosome networks, which prevents the epithelium from shedding from the deeper layers. The epithelial basement membrane is formed by collagen type IV and laminin, which mediates epithelial wound repair.<sup>8</sup> Corneal epithelial cells have an average lifespan of 7 to 10 days. Regeneration is enabled by limbal epithelial stem cells (LESC), a group of slow cycling cells that fulfil the characteristics of stem cells: slow-cycling, lack of differentiation, and high proliferative capacity.<sup>9–11</sup> LESCs reside in the palisades of Vogt, a radially orientated fibrovascular ridges and epithelial crypts located at the limbus.<sup>12,13</sup> When activated, for example, in response to corneal epithelial wounding, LESCs proliferate and differentiate into progeny transient amplifying cells, which migrate centripetally towards the central cornea until the advancing ends meet along ‘Y-shaped contact lines’ to re-establish epithelial cover of the corneal surface.<sup>14–16</sup> During states of increased LESCs replicative turnover, a whorled appearance on the cornea reflecting the path of epithelial cell migration is visible and has been termed “hurricane keratopathy”.<sup>17</sup> Dua and Forrester further demonstrated that in corneal epithelial defects involving the limbus, LESCs preferentially reepithelialised the limbus first prior to covering the central cornea.<sup>18</sup>

Beneath the corneal epithelium, the Bowman’s layer is the acellular, non-regenerative anterior portion of the stroma. Eighty percent of corneal thickness and its structural framework is provided by the stroma, which is composed of type I and type V collagen. They are arranged in parallel fibrils in order to ensure transparency in addition to mechanical strength. The specialized proteoglycans and keratocytes surrounding the collagen regulate hydration and homeostasis. Posterior to the stroma, the Descemet membrane (DM) is secreted by the underlying endothelial cells from 8-weeks gestation and acts as a basement membrane. The innermost endothelial layer consists of a monolayer of hexagonal cells with intercellular tight and gap junctions. The well-documented  $\text{Na}^+/\text{K}^+$  ATPase pump maintains deturgescence and clarity of the cornea. Corneal endothelial cell density (ECD) progressively declines throughout life at an average rate of approximately 0.6%:<sup>19</sup> During the first decade of life, the mean ECD has been reported to be about 4640, then it declines to 2970 by 30 years of age, and it continues to drop to 2400 at 80 years of age.<sup>20</sup>

## Aim of Paper

We aim to provide a comprehensive literature review of the different types of corneal transplantations, their treatment outcomes, and the associated complications of each procedure within the same article. In addition, we also present an up-to-date summary of the emerging therapeutic approaches that have the potential for reducing the demand for donor-dependent keratoplasty. We follow the same approach for reporting outcomes of each form of corneal transplant to produce a more intuitive article for the reader. We also provide a summary [Table 1](#) that helps to display this information in one place.

## Method

All studies included in this review were collated through online databases PubMed and Scopus using the search terms “corneal transplantation”, “corneal blindness”, “keratoplasty”, “graft rejection”, “graft survival”. Promising studies listed in selected articles were also reviewed for potential inclusion. Inclusion criteria include availability in English full text, relevancy to corneal diseases and keratoplasty, quality of the data and the source published and whether other studies have cited the articles.

## Penetrating Keratoplasty

Zirm performed the first successful penetrating keratoplasty (PK) in 1905. Until recently, PK was the most frequently performed corneal transplantation technique globally. However, both anterior and posterior lamellar keratoplasty techniques have become increasingly popular in the last decade as they are less invasive with reduced risks of complications.<sup>21</sup> As a result of the rapid adoption of these new methods, the proportion of PK grafts has reduced from 45% to 27% over the last 10 years in the UK.<sup>5</sup> The same phenomenon is also observed in other areas of the world.<sup>21–23</sup>

**Table 1** Synthesis of the more commonly (A) and less commonly (B) performed transplant procedures discussed in the review article

<b>A More Commonly Performed Transplant Procedures</b>					
<b>Procedure</b>	<b>No of cases performed in the UK 2019-2020 (% of total number of cases)<sup>1</sup></b>	<b>Indications</b>	<b>Survival rate</b>	<b>Rejection rate</b>	<b>Other common complications</b>
PK	1218 (27.0%)	Keratoconus FECD PBK Ulcerating keratitis Infectious keratitis Re-graft Dystrophies Ectasias Trauma Opacification	Mixed-pathology data: - 98% at 2 years - 90% at 5 years - 60-80% at 10 years - 72% at 15 years Keratoconus-specific data: - 98% at 2 years - 89% at 10 years PBK-specific data: - 87% at 2 years - 40% at 10 years FECD-specific data: - 97% at 2 years - 73% at 10 years	21-31%	Primary graft failure 0.3-12% Late endothelial failure 2.8-9.2% Glaucoma 0.4-21.5% Microbial keratitis 1.76-25%
DALK	420 (9.3%)	Keratoconus Anterior stromal scarring Dystrophies Infectious keratitis	Mixed-pathology data: - 99.3% at 9 years - 93.9% at 10 years Keratoconus-specific data: - 90.0-90.4% at 5 years	0.8-10.9%	Primary graft failure 0.9% Late endothelial failure 0.4-3.8% Glaucoma 0.0-9.0% Microbial keratitis 0.2-27.7%
DSAEK	1487 (33.0%)	FECD PBK PPMD CHED	Mixed-pathology data: - 78.4-94.2% at 5 years - 79% at 10 years FECD-specific data - 97% at 5 years - 92% at 10 years PBK-specific data - 89% at 5 years - 62% at 10 years	2.2-7.9	Primary graft failure 1.4-4.7% Late endothelial failure 2.6-5.3% Raised IOP 11.9% Microbial keratitis 0.5% Graft detachment 0.7-17.8%
DMEK	1042 (23.1%)	Same as DSAEK	Mixed-pathology data: - 90.0-97.4% at 5 years	0.1-5%	Primary graft failure 0.2-4.1% Late endothelial failure 1.3-2.8% Raised IOP 1.6-25% Graft detachment 4.0-34.6%

(Continued)

Table I (Continued).

B Less Commonly Performed Transplant Procedures				
Procedure	Indications	Survival rate	Visual outcome	Complications
Paediatric Corneal Transplant	PK: congenital corneal opacities, anterior segment dysgenesis, infectious keratitis, corneal scarring, keratoconus. SALK: superficial corneal opacities, Reis-Buckler corneal dystrophy. DALK: keratoconus, corneal scarring, corneal dystrophies, MPS, SJS, chemical injury. DSAEK: CHED, PPMD, Peter's Anomaly, decompensated cornea, rejected PKP grafts. DMEK: corneal decompensation, endothelial dystrophy	PK: 80-100% at 5 years, 90% at 10 years (12-30% at 5 years for Sclerocornea and Peter's Anomaly) DALK: 90-96% at 42 months DMEK: 66.7% at 12 months	PK: 0.5 LogMAR at 10 years (Poor visual outcome for patients <5 years / Sclerocornea) SALK: 0.45 LogMAR at 12 years DMEK: 0.5 LogMAR at 12 months	PK: infection (52%), vascularisation (41%), rejection (36%), endothelial failure, deprivational amblyopia, glaucoma, retransplantation, lensectomy SALK: micro perforation (6.3%), graft melt (2%), deep vascularisation (23%), corneal opacification (26%), suture granuloma (3.3%) DALK: micro perforation (17.6%), DM detachment (0.05% – 7.6%), stromal rejection (5 – 9.8%), unstable refraction, suture related complications, DSAEK: graft detachment (21%), ECL (19 – 53%), lens opacities (40%), IOP rise, graft rejection, persisting stromal haze.
BKPro	Bilateral severe corneal blindness, previous failed corneal transplants with poor prognosis for PK, ocular surface disease (MMP, SJS), neurotrophic cornea, aniridia, chemical injuries, LSCD.	98.9% at 1 year, 94% at 2 years, 75% at 5 years	0.00 to 1.00 LogMAR at 5 years (68% for non-cicatrizing condition, 43 for circatrical pemphigoid, 64% for chemical burns, 0% for SJS)	postoperative glaucoma, infective keratitis, corneal melt, endophthalmitis, retinal detachment, RPM, persistent inflammation
OOKP	SJS, ocular pemphigoid, Lyell syndrome, TENS, epidermolysis bullosa acquisita, trachoma, chemical injury, lid loss (Crouzon disease), complete LSCD, multiple failed PKs, corneal decompensation following vitrectomy and silicone oil filling that cannot be removed safely.	87.8-100% at 5 years, 81% at 20 years	0.48 LogMAR or better at 20 years (46-72%)	intraoperative VH (0-52%) mucosal overgrowth, mucosal ulceration, glaucoma (7-47%), cataracts, endophthalmitis (2-8%)

**Abbreviations:** PK, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty; DSAEK, descemet stripping automated endothelial keratoplasty; descemet membrane endothelial keratoplasty; FECD, Fuchs' endothelial corneal dystrophy; PBK, pseudophakic bullous keratopathy; PPMD, posterior polymorphous corneal dystrophy; CHED, congenital hereditary endothelial dystrophy; IOP, intraocular pressure.

## Indications

PK can be utilised to replace opacifying diseases of all corneal layers.<sup>24–26</sup> With the introduction of modern lamellar transplantation techniques and their associated quicker visual rehabilitation and reduced risk of rejection, there appears to be a trend towards favouring these techniques if they are technically possible. As a result, the commonest indications for PKs nowadays include advanced keratoconus not amenable to DALK, tectonic grafts for acute ulcerating or infectious keratitis, and previous graft failure.<sup>22</sup> Indications for PK also vary greatly depending on geographic locations, with keratoconus being the main indication in Europe and Australia, active keratitis in Asia, and PBK in North America.<sup>27</sup>

## Graft Survival

As the most well-established procedure for corneal transplant, PK overall is a successful and effective treatment for improving visual function. In a case series of 3992 eyes, the graft survival rate was 90% at 5 years and 82% at 10 years.<sup>28</sup> Other studies have also demonstrated a PK graft survival rate higher than 70% at 10 years follow-up.<sup>29–32</sup> However, the outcome of PK is variable depending on several factors, with the indication for surgery playing a major role in influencing the graft survival rate, with keratoconus patients achieving the best long-term results.<sup>33,34</sup> A multi-national registry study based in the European Union reported 2-year real-world graft survival of 98% for keratoconic patients, 97% for FECD, 87% for PBK, 85% for trauma and 74% for infectious keratitis.<sup>35</sup> Australian-based registry data demonstrated an 89% 10-year graft survival rate for keratoconus, 73% for FECD, 70% for non-herpetic scars, 60% for herpetic scars, 40% for PBK and only 37% for re-grafts.<sup>36</sup> A retrospective study with a mean follow-up of 12.8 years also showed a much higher graft survival rate of 94.7% in keratoconics compared to 11.1% for a re-graft.<sup>37</sup> In developing countries, the graft survival rate was lower than in many western studies. This is hypothesised to be due to the higher percentage of patients with high-risk indications, lower quality of donor corneas and reduced access to medicines and expert care.<sup>38,39</sup> There is also evidence that suggests graft survival rates are higher in those cases performed at specialist centres.<sup>40,41</sup>

## Graft Rejection

Immunological corneal graft rejection is one of the main reasons for graft failure in PK.<sup>42,43</sup> Rahman et al reported 21% of the cases experienced at least one episode of graft rejection after PK,<sup>44</sup> whereas Olson et al reported allograft reaction in 31% of the cases but none progressed to graft failure.<sup>45</sup> Long-term large studies demonstrated that 28–34% of graft failures are caused by irreversible rejection.<sup>28,30–32,36</sup> Even in the absence of rejection, donor corneal endothelial cell loss is progressive for 10 years post-PK, which causes late failure of the graft.<sup>46</sup> The rate of endothelial cell loss was reported to be about 33% to 40% within the first 2 years, 53–70% at the end of the fifth year and stabilising at 12% after 10 years.<sup>47–50</sup> Armitage et al proposed that the surgical trauma leads to chronic pro-inflammatory anterior chamber environment and therefore endothelial decay.<sup>51</sup> Late endothelial failure accounts for 20–45% of post-PK graft failure.<sup>28–31,36,47,48</sup> Primary graft failure, defined as “the failure of an oedematous graft to clear with no identifiable reason within 2 weeks post-transplant”, occurs in 0–12% of cases<sup>29,52,53</sup> and constitutes 1–14% of overall graft failure.

## Other Complications

Post-PK glaucoma is caused by corticosteroid-induced IOP elevation and/or surgical alteration of the anterior chamber angle,<sup>54</sup> and its incidence is estimated to be 21.5%.<sup>55</sup> Treatments for post-PK glaucoma are also associated with an increased risk of graft failure, with a 5-year failure rate of 20%, 29% and 58% in eyes treated with anti-glaucomatous drops alone, glaucoma surgery alone or both, respectively.<sup>56</sup> Post-PK re-epithelization is compromised due to corneal denervation and the use of topical corticosteroids. Ocular surface complications form 18% of graft failure. The rate of microbial keratitis post-PK was reported to range from 1.76% to 25%.<sup>57,58</sup> Gram-positive organisms are the predominant causative agents for microbial keratitis following PK.<sup>59–61</sup> Loose sutures may act as a nidus for organisms and compromise the epithelial barrier to infection, and prolonged corticosteroid use may alter host defence mechanisms; therefore, both are iatrogenic risk factors for microbial keratitis.<sup>59,61</sup> More than half of the grafts affected by microbial keratitis are reported to eventually progress to failure.<sup>60</sup>

## Visual Outcome

Various authors reported different visual outcomes of PK. Paglen et al and Pramanik et al reported best-corrected visual acuity (BCVA; expresses in Snellen; refractive errors corrected by either contact lens or spectacles) of more than 6/12 in 73% of the patients at more than 10 years of follow-up,<sup>33,34</sup> whereas only 48% achieved the same level of vision at 5 years in a case-series by Rahman et al.<sup>44</sup> In the developing world, only a minority of patients managed to attain BCVA above 6/18 with spectacle and contact-lens correction.<sup>62,63</sup>

## Deep Anterior Lamellar Keratoplasty

Despite PK being the first form of ocular transplantation, with the progressive developments in lamellar surgical techniques, deep anterior lamellar keratoplasty (DALK) has become a popular surgical technique for treating stromal pathology, theoretically eliminating endothelial graft rejection as the host DM and endothelium remains. Nine percent of the grafts performed in the UK were for DALK cases between 2019 and 2020.<sup>5</sup>

The most technically challenging and critical step in DALK is the separation of corneal stroma from DM. Most contemporary methods involve initial partial trephination of the cornea, followed by various approaches to delaminate stroma from the underlying DM. Sugita and Kondo's method involves injecting fluid into stroma for hydrodelamination<sup>64</sup>; Melle's technique utilises ophthalmic viscosurgical devices to achieve lamellar dissection.<sup>65</sup> The most widely adopted technique is Anwar's "Big Bubble", where air is injected into the deep stroma, with the air cleaving DM (and in some cases posterior stroma) from the remaining host tissue. A donor corneal button, with DM removed, is then sutured to the host cornea.<sup>66</sup>

## Indication

Keratoconus is the leading indication for DALK.<sup>22</sup> Indeed, expert consensus agrees that DALK is the preferred modality of corneal transplant in keratoconus without deep scars and DM breaks from prior hydrops episodes.<sup>67</sup> DALK is also an option for anterior stromal scarring,<sup>22,68</sup> corneal dystrophies,<sup>69</sup> and infectious keratitis.<sup>22,70</sup>

## Graft Survival

As a relatively new surgical technique for corneal transplantation, long-term follow-up data on DALK are not as detailed as that for PK. From the limited studies published, the survival rate of DALK has been reported to be higher than that of PK. In a retrospective comparative study, Arundhati et al reported a significantly higher proportion of graft survival in patients that underwent DALK in comparison to PK at 10 years follow-up (93.9% vs 72.0%).<sup>71</sup> Sarnicola et al showed a mean survival of 99.3% from a cohort of 660 patients with mixed pathologies at 9 years post-DALK.<sup>70</sup> Other studies have also demonstrated the DALK graft survival rate to be higher than 90% in recipients with keratoconus at 5-year follow-up timepoints.<sup>72–74</sup> On the other hand, the Australian Corneal Graft Registry reported a 77.0% survival rate in 1531 patients at 6 years.<sup>75</sup> From the same registry data, age was shown to be an independent factor that influenced graft survival over a 33-years follow-up period; DALK performed in recipients aged under 60 had superior survival to those performed in recipients aged 60 and over.<sup>75</sup>

## Graft Rejection

Donor-derived corneal endothelial cells are susceptible to recognition by host immune mechanisms. As the host endothelial cells are preserved in DALK, endothelial immune-mediated graft rejection cannot occur, though stromal and sub-epithelial and epithelial rejections are still possible. Feizi et al report that 10.9% and 3.1% of the cases suffer sub-epithelial and stromal graft rejection episodes following DALK, respectively.<sup>76</sup> The 2014 systemic review by Keane et al and the more recent meta-analysis by Song et al concluded that graft rejection episodes were more likely to occur in PK than in DALK (meta-analysis result: Odds ratio=2.69, 95% confidence interval: 1.62–4.48).<sup>77,78</sup> William et al documented the percentage of graft failure due to irreversible immunological rejection in DALK was 1.7%, compared to 28% in PK.<sup>75</sup> Comparative studies demonstrated lower levels of endothelial cell loss after DALK when comparing DALK versus PK at different time points of post-surgery follow-up: 14.90–15.04% vs 15.44–25.71% at 12 months, 16.32–18.12% vs 26.98–36.24% at 24 months, 19.39 vs 46.05% at 36 months, and 21.02% vs 47.82% at 48 months after

surgery.<sup>50,69</sup> Over a longer follow-up period, endothelial cell density was shown to progressively decrease after PK until it stabilises approximately 10 years post-surgery, by which time 67% endothelial cell loss had occurred,<sup>31</sup> in contrast, endothelial cells appeared to decrease in the immediate post-operative period after DALK but tended to stabilise at around 6-months to 1-year and remain stable for nearly 10 years after DALK.<sup>79</sup> Interestingly, endothelial cell counts have also been reported to be stable or even higher after DALK.<sup>80</sup> Therefore, late corneal failure due to progressive endothelial decay is less likely after DALK.<sup>79</sup>

## Other Complications

The incidence of post-DALK glaucoma was reported to be less than 5%, a figure much lower than that reported in PK.<sup>81</sup> It has been postulated that the potential distortion of the iridocorneal angle is reduced as the anterior chamber is not breached in DALK, therefore the risk of developing glaucoma is lower than in PK.<sup>82</sup> Use of post-DALK topical corticosteroids is often shorter than that required in PK, which lowers the risk of corticosteroid-induced IOP elevation. Studies comparing the incidence of glaucoma after DALK versus PK had found that glaucoma developed in 0.0–9.0% of DALK patients, in contrast to 9.6–15.0% of PK cases.<sup>83–86</sup> Up to two-third of the PK cases with post-operative glaucoma required surgical interventions, while most patients with post-DALK glaucoma needed medical treatment alone.<sup>85,87</sup> A 12-year retrospective analysis in the UK reported that 27.7% of the DALK cases developed microbial keratitis, compared to 6.7% of eyes undergone PK.<sup>58</sup> The incidence of fungal keratitis post-DALK was reported to be 0.052%.<sup>88</sup>

Although there are some advantages to DALK compared to PK, there is a subset of complications unique to DALK. Intraoperative micro-perforations can occur when trying to split DM from the stroma. It is said that those of 1mm or less can be managed intraoperatively and does not prevent transplantation of the onlay anterior stromal graft, but post-operative DM detachment and formation of a double anterior chamber may develop.<sup>89</sup> This may require rebubbling with an air or gas tamponade into the anterior chamber, which can in turn cause endothelial cell loss and pupillary block by the tamponade, and in severe cases, precipitate an attack of aqueous misdirection.<sup>90,91</sup>

In cases of macro-perforations or large lamellar splits of DM, conversion to PK is usually required intraoperatively; one study conducted in 2010 had reported a conversion rate as high as 60%.<sup>92</sup> As DALK gained popularity, the complication rate reported by a recent large series had reduced to 16.2% to 20.7%.<sup>93–95</sup> Interface haze from residual stroma may cause glare or reduced acuity, but is unlikely to occur if DM is completely bared during the procedure.<sup>68</sup> Rarely, interface haemorrhage from stromal neovascularization may occur.<sup>83</sup> Microbial infections are also possible as DALK grafts still succumb to the same issues as PK in terms of having sutures present on the ocular surface for many months post-surgery, in addition to prolonged topical steroid usage.<sup>96,97</sup> As with any intraocular procedure, epithelial downgrowth may also rarely arise after DALK; a cohort study had reported two cases of post-DALK epithelial downgrowth, which led to graft failure in one case.<sup>83</sup>

## Visual Outcome

The currently available literature suggests that both DALK and PK are successful in improving visual outcomes. A review by Reinhart et al concluded that DALK and PK lead to comparable BCVA and refractive outcomes;<sup>68</sup> Shi et al, on the other hand, suggest that PK provides greater BCVA improvement with no differences in refractive outcomes.<sup>98</sup> More recently, a systematic review by Henein and Nanavaty demonstrated strong evidence of superior post-operative refractive astigmatism following DALK, but no difference in post-operative spherical equivalence or keratometric astigmatism between the two procedures.<sup>99</sup> These findings are broadly in concordance with a Cochrane review by Keane et al, which also showed no significant differences in keratometric astigmatism and spherical equivalent comparing DALK to PK.<sup>77</sup> Intriguingly, a recent meta-analysis by Song et al concluded that there was no significant difference in post-operative BCVA and astigmatism in comparison to PK, but spherical equivalents were found to be greater in DALK than in PK.<sup>78</sup> The disparity between these findings is in part attributed to newer studies being included, which reflect the improvement of surgical techniques over time, such as refining donor graft size and achieving a more uniform dissection of the stroma. It is also important to note that most existing comparative studies recruited solely keratoconic patients as subjects. Long-term follow-up data reported a mean BCVA of 6/7.5 at 4 to 6 years follow-up post-DALK,<sup>73,79</sup> and 29% of the patients with BCVA of 6/6 at 5 years.<sup>72</sup>

## Descemet Stripping Automated Endothelial Keratoplasty

The first attempt at posterior lamellar keratoplasty was reported by Tillett in 1956, a technique that required a large incision and partial trephination of posterior donor cornea, removal of the posterior half of the recipient cornea, and securing of the donor graft via placement of seven double-arm sutures.<sup>100</sup> Since then, more innovative approaches have been described by various authors.<sup>101,102</sup> Terry et al proposed a technique that involved dissecting a posterior lamellar disc from the recipient cornea through a 9mm sclerocorneal incision, followed by the introduction of trephined donor graft tissue of equal size into the anterior chamber.<sup>103</sup> The graft was then tamponaded against the recipient posterior cornea by air while the patient remained in a supine position. This technique was termed deep lamellar endothelial keratoplasty (DLEK), but the procedure was challenging and has not been widely adopted.<sup>104,105</sup> Melles et al refined the technique by utilising a smaller, self-sealing 5-mm tunnel to perform a novel step called descemetorhexis, which involved removal of pathological DM and endothelium from the recipient cornea; this was followed by insertion of “taco-folded” donor tissue, including endothelium, DM and a layer of stroma, into the anterior chamber, which was then adhered to recipient cornea by air injection.<sup>106</sup> This technique was termed Descemet stripping endothelial keratoplasty but soon evolved into Descemet Stripping Automated Endothelial Keratoplasty (DSAEK) when Gorovoy et al integrated the use of an automated microkeratome for donor tissue dissection.<sup>107</sup> Some authors observed that thinner grafts led to better BCVA due to less change in the relationship between the anterior and posterior corneal curvatures of the recipient cornea,<sup>108,109</sup> although this theory is controversial as some studies found no significant correlation between graft thickness and visual acuity.<sup>109,110</sup> Nevertheless, based on this principle, Ultrathin-DSAEK (UT-DSAEK) was developed, which used ultrathin grafts of 100µm, half of the conventional graft thickness.<sup>111</sup>

### Indication

DSAEK (and other endothelial keratoplasty techniques) has been universally adopted as the preferred technique for treating corneal endothelial disease, as it provided predictability and rapid visual rehabilitation. In 2005, endothelial keratoplasty represented only 4.5% of corneal grafts in the United States.<sup>112</sup> As per the NHS Blood Transfusion and Transplant Service,<sup>5</sup> in 2020, a third of the grafts performed in the UK were DSAEKs. The commonest indications were FECD, PBK and previous endothelial graft failure.<sup>105</sup> Posterior polymorphous corneal dystrophy, congenital hereditary endothelial dystrophy, iridocorneal endothelial syndrome and trauma are less common indications.<sup>113</sup>

### Graft Survival

As the surgical learning curve began with various DSAEK techniques, graft survival rates were shown to be variable among different studies.<sup>112</sup> These tended to have smaller sample sizes and the operating surgeons were still refining this relatively new technique. Long-term follow-up data demonstrated overall survival rates for DSAEK to be comparable or better than that for PK. Most single centre studies showed a graft survival rate of 93% or above at 5 years after DSAEK;<sup>114–116</sup> National registry data with large sample sizes report DSAEK graft survival rates of 93.4%, 74.8% and 56% in Netherland, Singapore, and Australia, respectively.<sup>75,117,118</sup> Although lower than the post-DSAEK graft survival rate reported by other single-centre studies (Price et al: 93% at 5-years; Ang et al: 79.4% at 5-year),<sup>116,119</sup> the DSAEK survival in Singapore was still superior to PK in the same dataset at 5-year follow-up (DSAEK 78.4% vs PK 54.6%),<sup>117</sup> while the authors of the Australian registry data concluded that PK exhibited significantly better survival than DSAEK performed for PBK and FECD (at 6-year follow-up, PBK: DSAEK 45.0% vs PK 52.0%; FECD: DSAEK 69.0% vs PK 90.0%).<sup>75</sup> The variable conclusions drawn by different studies may be due to discrepancies in tissue quality and storage techniques, different clinical indications, baseline donor factors such as age or pre-graft endothelial cell density, and recipient factors, eg, preoperative glaucoma. The latest modification of the procedure, UT-DSAEK, demonstrated a survival rate of 94.2% at 5 years, which was comparable to conventional DSAEK.<sup>111</sup>

### Graft Rejection

With endothelial keratoplasty, the most immunogenic layer of the cornea is being transplanted. Remarkably, immunological graft rejection rates in DSAEK are much lower than PK. DSAEK is also much less invasive to the recipient eye with less post-operative inflammatory drive and less neurotrophic effect.<sup>115</sup> Price et al published a 5-year graft rejection



rate of 7.9% after DSAEK,<sup>116</sup> the Singapore Corneal Transplant Registry documented a 5.0% rejection rate at 5-year follow-up (14.1% for PK in the same dataset),<sup>117</sup> while Madi et al reported on 3.9% of rejection episode after UT-DSAEK.<sup>111</sup> Australian registry data found 13% of graft failure in DSAEK was due to irreversible rejection.<sup>75</sup> The reported long-term loss of endothelial cell density was 48–67% at 5-year follow-up post-DSAEK.<sup>116,119,120</sup> Initial endothelial cell loss in DSAEK was reported to be higher than in PK, followed by constant low-grade cell loss at a rate of 11.7% per year over 5 years.<sup>115</sup> The immediate post-operative cell loss was attributed to donor trauma during surgery. Late endothelial failure accounts for 32–100% of post-DSAEK graft failure.<sup>121</sup> Primary graft failure rate for DSAEK ranges from 0% to 29%,<sup>122</sup> in contrast to 0–12% after PK.<sup>29,52,53</sup>

## Other Complications

Graft detachment is the most common post-DSAEK complication and is unique to endothelial keratoplasty. Risk factors for graft detachment include the inadequate size of the recipient stromal bed, eye rubbing, traumatic descemetorhexis, excessive surgical trauma or poorly orientated grafts. While most graft detachments can be recognised by corneal oedema or direct visualization of a double anterior chamber on slit-lamp biomicroscopy, anterior segment-optical coherence tomography (OCT) is a highly effective way of confirming detachments. Recent literature reports that the graft detachment rate is 0.7–14.8% of the cases after DSAEK.<sup>111,117</sup> Like most other forms of keratoplasty, raised IOP and glaucoma are well-recognised post-operative complications of DSAEK. In addition to the common corticosteroid-induced IOP elevation, a mechanical pupillary block by residual air left in the anterior chamber can lead to early post-operative acute glaucoma and if prolonged, aqueous misdirection.<sup>123,124</sup> An air bubble extending beyond the inferior pupillary border with the patient upright could hamper aqueous flow into the anterior chamber and trabecular meshwork, and the effect of air misdirection can be exaggerated in eyes with floppy iris and peripheral anterior synechiae formation.<sup>125</sup> Maier et al reported an incidence of post-DSAEK glaucoma in 11.9% of the cases.<sup>126</sup>

## Visual Outcome

DSAEK provides predictable and superior visual outcomes with faster visual recovery in comparison to PK.<sup>117</sup> Woo et al reported 23.6% of the patients had BCVA 6/7.5 or better 3 years after DSAEK<sup>117</sup>; van Rooij et al also found that BCVA of patients who had DSAEK was significantly better than those who had PK at 2-year follow-up (6/12 vs 6/15).<sup>127</sup> Spherical equivalent was not significantly different between DSAEK and PK, but significantly less post-operative astigmatism developed in DSAEK.<sup>127</sup> UT-DSAEK was also shown to deliver superior visual outcomes to PK (6/9.5 vs 6/15),<sup>128</sup> and 50% of the eyes had BCVA of 6/6 or above 5-years post procedure.<sup>111</sup> In comparison to DSAEK, UT-DSAEK was found to provide significantly better post-operative BCVA at 12-months follow-up (6/7.5 vs 6/9.5) in a clinical trial, but no difference in spherical equivalent was demonstrated.<sup>129</sup>

## Descemet Membrane Endothelial Keratoplasty

After introducing DSAEK, Melles et al continued the advancement of lamellar surgery and described a new endothelial keratoplasty, termed Descemet membrane endothelial keratoplasty (DMEK).<sup>130</sup> With DMEK, a 10–15 µm thick graft tissue consisting of only DM and endothelium without any stroma is carefully prepared from donor corneas by a descemetorhexis. Owing to the ultrathin property of its graft tissue, DMEK provides faster visual rehabilitation, better visual outcomes, and lower immune rejection rates than DSAEK.<sup>122,131</sup> This ultrathin graft technique can be technically challenging, and time-consuming donor preparation and graft attachment have been reported as reasons that may have prevented the wider adoption of DMEK.<sup>132,133</sup> One of the most challenging aspects of this procedure is orientating the graft so that the endothelium is facing down into the AC. Several techniques have been developed to aid graft orientation, eg, intraoperative OCT,<sup>134</sup> ultrasound biomicroscopy,<sup>135</sup> and stamping, staining or tearing one side of the graft before insertion.<sup>136</sup> The indications for DMEK are similar, but not identical, to those of DSAEK.

## Graft Survival

Single-centre, retrospective analysis has shown 5-year graft survival rates to be 90–95% in eyes that underwent DMEK.<sup>116,117,137,138</sup> The graft survival rate was said to be 62.5% in eyes with known confounding factors,<sup>139</sup> with

prior trauma, glaucoma drainage device implant, previous failed keratoplasty shown to impact negatively on graft survival outcomes.<sup>140,141</sup> National registry data in Singapore demonstrated a superior graft survival of 97.4%, compared to the 78.4% and 54.6% in DSAEK and PK at 5-year, respectively.<sup>117</sup> Even in patients with PBK, an indication known to produce poorer graft survival outcomes, those who underwent DMEK still had better graft-survival outcomes of 94.7% at 5-years than DSAEK (61.7%).

## Graft Rejection

Various studies have demonstrated noticeably lower rejection rates after DMEK (0.7–5%) than DSAEK (5–12%)<sup>117,131,132,142</sup> and PK (18–31%).<sup>44,45,117,131</sup> DMEK grafts are said to have 15 times lower risk of rejection than DSAEK 2 years after surgery, and this is thought to be due to the lack of stromal tissue being transplanted in DMEK cases. The Australian Corneal Graft Registry reports that graft failure rates caused by irreversible rejection were 9% for DMEK, compared to 13% and 28% for DSAEK and PK, respectively.<sup>75</sup> It is also worth noting that rejection episodes after DMEK may be under-recognised as some patients may be asymptomatic.<sup>143,144</sup> Regarding endothelial cell loss, most studies found no statistically significant difference between DMEK and DSAEK at 6 months (31% vs 30%),<sup>145</sup> 1 year (44% vs 41%)<sup>146</sup> and 5 years.<sup>116</sup> Primary graft failure for DMEK ranges from 0% to 12.5%<sup>122</sup> while late endothelial failure accounts for 20% of graft failure within 5 years of post-operative follow-up.<sup>116</sup>

## Other Complications

As is the case for DSAEK, graft detachment was the most common complication of DMEK. Early publications on DMEK report a graft detachment rate of 30%<sup>130</sup> and partial detachment rates of 62–63%.<sup>132,133,147</sup> As the surgical learning curve of DMEK increases, graft detachments can be reduced to around 4–34.6%.<sup>144</sup> Although some authors have suggested that the tighter DMEK scroll from younger donors is more challenging to unfold<sup>148,149</sup> and therefore postulate that younger donor age may be associated with a higher risk of graft detachment,<sup>150</sup> others have demonstrated that there is no correlation between donor age and increased re-bubbling rates.<sup>151,152</sup> While most partial graft detachments may not necessitate intervention,<sup>153</sup> 0.2–75% of the cases were reported to require post-operative re-bubbling.<sup>122</sup> Some authors suggest that re-bubbling and hyperinflation significantly impact on endothelial cell survival.<sup>154</sup> In contrast, others argue that earlier re-bubbling provides a better visual outcome and reduces the risk of corneal scarring without affecting endothelial cell density.<sup>144,155</sup> The literature would suggest that the graft detachment rate of DMEK tends to be higher than that of DSAEK, likely due to the tendency of the graft edge to scroll up inherently and peel itself away from the recipient cornea. Moreover, the graft detachment rate in DMEK is probably underestimated as subtle peripheral detachments may not be reported as they are unlikely to require further intervention.

Post-operative IOP elevation is the second most common complication after DMEK. The mechanisms of raised IOP after DMEK are largely the same as those described in DSAEK. The reported incidence of steroid-induced raised IOP ranged from 1.6% to 25%,<sup>156–160</sup> whereas the rates of pupillary block were 2.7–15.4%.<sup>159,160</sup> Judicious tapering of the post-operative steroid regimen, concurrent use of anti-glaucomatous treatments and inferior iridotomy to prevent pupillary block are effective methods for managing IOP elevation after endothelial keratoplasty.<sup>161</sup> The incidence of post-operative glaucoma was reported to be lower after endothelial keratoplasty than PK,<sup>162</sup> and IOP-lowering treatment was less likely to be required after endothelial keratoplasty.<sup>163</sup> Such discrepancies may be due to the variation in surgical indications, ie, endothelial keratoplasties are performed in eyes with endothelial decompensation alone, whereas PK is usually reserved for eyes with more severely disorganised anterior segments.<sup>164,165</sup> Graft failure rate after DMEK is higher in eyes with prior glaucoma surgical interventions than eyes treated with IOP-lowering drops alone,<sup>166</sup> similar to the observation reported after PK and DSAEK.<sup>167,168</sup> The intermittent corneal touch of glaucoma drainage shunts and the chronic endothelial toxicity and proinflammatory state of aqueous after breaching the blood–aqueous barrier are some of the factors that may contribute to chronic endothelial damage.<sup>169–171</sup> Compared to DSAEK, DMEK has been shown to achieve a superior visual outcome (DMEK 40% vs DSAEK 15%, 1-year post-op BCVA 6/12 or higher) and lower rates of graft failure (DMEK 2% vs DSAEK 20%) in eyes with prior glaucoma surgical interventions.<sup>172</sup>

## Visual Outcome

One of the main advantages of DMEK is the enhanced visual outcome compared to DSAEK due to a reduced interface effect. Previous studies have reported 32–85% of the patients achieving BCVA of 6/7.5 or better at 6 months after DMEK.<sup>122</sup> Registry data showed 42.9% and 31.3% of the patients attaining 6/7.5 BCVA at 1 and 3 years after DMEK.<sup>75</sup> Most comparative studies reported significantly better BCVA in patients with DMEK compared to PK, DSAEK, and even UT-DSAEK at 1 year (Woo et al: DMEK 6/9.5 vs DSAEK 6/19 vs UT-DSAEK 6/9.5 vs PK 6/38).<sup>117,122,173</sup>

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## Disclosure

The authors report no conflicts of interest in this work.

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