

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of corneal endothelial transplantation

Some diseases can affect the clear section at the front of the eye (the cornea), and in particular the layers that help to maintain its clarity (the endothelium). Instead of a whole corneal transplantation, this procedure aims to replace the innermost layers of the cornea with a healthy section from a donor eye, leaving the rest of the cornea in place. Eye medication is given for a short time after surgery.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2008.

Procedure name

- Corneal endothelial transplantation

Specialty societies

- Royal College of Ophthalmologists

Description

Indications and current treatment

The corneal endothelium is a single layer of cells comprising the innermost layer of the cornea, which are responsible for removing excess fluid from the cornea, and so maintaining its transparency. Dysfunction of the endothelium results in progressive clouding and haze of the cornea, with resulting visual

impairment. The most common causes of dysfunction of the corneal endothelium are Fuchs' dystrophy (a genetic disorder) or degenerative changes (bullous keratopathy). Other reasons for endothelial dysfunction may include trauma, infection or iatrogenic damage.

Current surgical treatment includes penetrating keratoplasty (transplantation of the whole cornea). This procedure requires multiple sutures to anchor the donor cornea in the recipient eye.

What the procedure involves

The procedure includes a range of corneal transplantation techniques in which diseased or dysfunctional corneal endothelial cells are replaced and healthy portions of the patient's cornea are retained, maintaining endothelial function. Corneal endothelial transplantation encompasses a range of techniques such as endothelial keratoplasty (EK), deep lamellar endothelial keratoplasty (DLEK), Descemet's stripping endothelial keratoplasty (DSEK) and Descemet's stripping automated endothelial keratoplasty (DSAEK). The elements of the procedure may vary; however, the surgical technique involves the following stages. Usually with the patient under general anaesthesia (or local anaesthesia in suitable patients), a scleral incision of a few millimetres is made and a tunnel to the anterior chamber is created. The inner layers of the diseased endothelium can either be removed with the aid of a microkeratome or simply by manual dissection. A cornea from a cadaveric donor is dissected to create a flap containing the inner layers and a portion of stroma. A laser may be used to assist in this process. The donor portion of cornea is usually folded and inserted into the recipient eye and laid on the prepared corneal surface with viscoelastic material to help secure it in place. A suture is sometimes required to close the incision. Topical and / or systemic antibiotic and steroids, and immunosuppressants are often prescribed for a period following surgery. In more complicated cases heavier immunosuppression may be required.

OPCS code

List of studies included in the overview

This overview is based on approximately 6306 eyes of patients treated by corneal endothelial transplantation from one randomised controlled trial¹, two non-randomised controlled trials^{2,3}, four case series^{4,5,6,7}, and one patient registry⁸.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

Only two of the seven studies included in table 2 of this overview reported on efficacy outcomes.

Visual acuity

A randomised controlled trial of 28 eyes reported a significant improvement in mean uncorrected visual acuity (UCVA) in 13 eyes treated by endothelial keratoplasty (EK) from 0.81 ± 0.19 (standard deviation) at baseline to 0.60 ± 0.20 at 6-month follow-up ($p = 0.01$). In the 15 eyes treated by penetrating keratoplasty (PK), the improvement in UCVA was not significant, from 0.94 ± 0.38 at baseline to 0.87 ± 0.30 at 6-month follow-up (p -value not stated)¹. However, there was a statistically significant difference in mean best spectacle corrected visual acuity (BSCVA) in both the EK and PK groups at 12-month follow-up. There was no significant difference in contrast sensitivity between the two groups at any timepoint.

A non-randomised comparative study of 177 eyes (129 treated by EK techniques) reported that BSCVA ($p = 0.001$) and UCVA ($p = 0.05$) were significantly better following EK procedures than following PK at 15-month follow-up³. Similarly, astigmatism was significantly lower following EK than following PK ($p < 0.0001$).

Graft survival

A patient registry of 4513 patients reported a significant difference in 1-year graft survival in patients with Fuchs' dystrophy treated prior to 2006/07 by PK ($n = 183$) (97%; 95% confidence interval [CI] 93 to 99) compared to EK ($n = 69$) (88%; 95% CI 78 to 94) ($p = 0.0003$). A significant difference was also reported in 1-year graft survival rate between patients with Fuchs' dystrophy treated 2007/08 by PK ($n = 88$) (98%; 95% CI 91 to 99) compared to EK ($n = 75$) (77%; 95% CI 63 to 86) ($p = 0.0002$). The registry reported significant differences in 1-year graft survival in patients with pseudophakic bullous keratopathy (PBK) treated 2006/07 by PK ($n = 182$) (95%; 95% CI 90 to 97) compared to EK ($n = 67$) (84% 95% CI 73 to 91) ($p = 0.007$). This significant difference was maintained 2007/08 between patients with PBK treated by PK ($n = 76$) (88%; 95% CI 75 to 94) and EK ($n = 55$) (79% 95% CI 65 to 88) ($p = 0.04$)⁸.

Safety

Conversion to PK or need for EK revision procedures

Rates of conversion to PK during procedures planned as EK were reported as 2% (2/100)⁷, 9% (11/118)⁶ and 19% (3/16)¹ across the studies. Repeat EK procedure was required in 2% (2/98)⁷, 8% (10/118)⁶ and (1/13)¹ of patients. The reason for repeat procedure varied and was described as surgical error in recipient bed preparation, failures from DSEAK, or inadvertent perforation.

Graft rejection and failure

A non-randomised comparative study of 907 eyes (199 treated by EK) reported that graft rejection (defined as any anterior chamber inflammatory episode with keratic precipitates on the transplanted endothelium requiring an unscheduled increase in steroid medication) was significantly lower in the EK

group (8% [15/199]) than in the PK group (13% [92/708]) at 2-year follow-up ($p = 0.035$)². Graft failure (not otherwise defined) following rejection was lower in the EK group (7% [1/15]) than in the PK group (28% [26/92]). However, this difference was not statistically significant ($p=0.063$). In this study, 80% of patients treated by EK continued to take topical steroids at 2-year follow-up.

A second non-randomised comparative study of 177 eyes (129 treated by EK) reported no significant difference between the EK and PK groups in terms of rate of graft rejection or primary graft failure ($p = 0.78$ and $p = 0.91$, respectively, at 15-month follow-up)³. However, graft dislocation was significantly more common following EK procedures than PK procedures ($p = 0.0004$). There was no significant difference in percentage endothelial cell loss following EK or PK procedures ($p = 0.70$) at 15-month follow-up.

Endothelial cell loss measurement

In a case series of 263 eyes treated by EK, a subset of 34 eyes with 2-year follow-up demonstrated cumulative endothelial cell loss of 34% at 6 months, 36% at 12 months, and 41% at 24 months⁴.

Retinal detachment

A case series of 118 eyes undergoing EK (41 of which had concomitant phacoemulsification and intraocular lens insertion for cataract) reported retinal detachment in 4% (5/118) of patients (sequelae not described)⁶.

Miscellaneous / combined outcomes

A case series of 200 eyes treated by EK using an automated technique reported no incidents of primary graft failure, endothelial failure or papillary block at a minimum follow-up of 4 months⁵.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to corneal endothelial transplantation. Searches were conducted of the following databases, covering the period from their commencement to 28th October 2008, and updated to 04th March 2009: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with any corneal diseases
Intervention/test	Corneal endothelial transplantation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Patient safety and reduction of risk of transmission of Creutzfeldt-Jakob disease (CJD) via interventional procedures. NICE interventional procedures guidance 196 (2006). Available from www.nice.org.uk/IPG196

Table 2 Summary of key efficacy and safety findings on corneal endothelial transplantation

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.								
Study details		Key efficacy findings				Key safety findings	Comments	
Patel S V (2008) ¹		Visual acuity				Complications	Both types of surgery performed by two surgeons	
Randomised controlled trial		Mean UCVA (decimal) and standard deviation				19% (3/16) of eyes in the DLEK group were converted to PK due to inadvertent perforation. At 12-month follow-up, 1 of these eyes had BSCVA of 20/40 with 8D astigmatism, one had BSCVA of 20/25 with 2D astigmatism, and one eye fell to BSCVA of 5/200 during graft rejection but improved to 20/40 with 1.25D astigmatism.		
USA		Baseline	1 month	3 months	6 months		12 months	Method of patient recruitment not reported.
Study period: Not reported		DLEK	0.81±0.19	0.66±0.24	0.61±0.22	0.60 ± 0.20	0.54 ± 0.21	
Study population: Patients with corneal oedema attributable to endothelial dysfunction. Either pseudophakic (i.e. previous IOL insertion) or with cataract requiring extraction. Age: 74 years (mean).		PK	0.94 ± 0.38	0.88 ± 0.25	0.78 ± 0.34	0.87 ± 0.30	0.80 ± 0.32	Patients underwent concomitant crystalline lens extraction and intraocular lens insertion as necessary. Number treated not stated.
n = 28 eyes (n=13 DLEK)		Mean BSCVA (decimal) and standard deviation				Light scatter	Study was powered to detect difference of 2 lines BSCVA between the groups at 12 months requiring 20 patients in each arm.	
Inclusion criteria: patients were excluded if central corneal scarring, uncontrolled glaucoma or history of herpetic keratitis were present.		DLEK	0.57 ± 0.20	0.50 ± 0.17	0.4 ± 0.17	0.41±0.18		0.34±0.16
Technique: DLEK with either local or general anesthesia with a 9–10 mm scleral tunnel incision. Donor graft created manually or by mechanical microkeratome. Compared with PK sutured with double running technique with viscoelastic filler. Postoperative topical antibiotics and steroids		PK	0.68 ± 0.38	0.55 ± 0.21	0.36 ± 0.26	0.30 ± 0.13	0.25 ± 0.21	Authors state that recruitment to the study was hindered because many patients were not willing to be randomised to a treatment arm, and because of a recent change in surgeon and patient preference for DSEK rather than DLEK.
Follow-up: 12 months (median)		Magnitude of spherical correction was lower after DLEK than after PK at 1-, 3-, 6- and 12-month follow-up.				Contrast sensitivity		
Conflict of interest: none						No significant difference in contrast sensitivity between the eyes in the different treatment groups was reported.		

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.						
Study details	Key efficacy findings		Key safety findings		Comments	
Allan B S D (2007)² Non randomised comparative study USA / UK / Sweden Study period: 1996 to August 2004 Study population: patients with pseudophakic bullous keratopathy or Fuchs' corneal endothelial dystrophy. Age: 74 years (mean); sex: 69% female. n = 907 eyes (n=199 DLEK/DSEK) Inclusion criteria: no recognised pre-existing risk factors for graft rejection. Technique: EK by either DSEK (76%) or DLEK (24%) via a 5–9 mm scleral incision vs PK (techniques not described). Follow-up: 2 years (median) Conflict of interest: not reported	Efficacy outcomes were not reported on.	Complications			Consecutive patients treated at four participating centres. Retrospective case note review in 3 centres.	
		Rejection episodes were defined as any anterior chamber inflammation with keratic precipitates on the transplanted graft requiring an increase in topical steroid medication.				
		Outcome	EK	PK	p	Rejection rate compared with historical controls in similar cases from a registry.
		Rejection	8% (15/199)	13% (92/708)	0.035	
		Failure of graft following rejection	7% (1/15)	28% (26/92)	0.063	
		Mean time to rejection	11 months (range 4–23)		Not reported	Periods of treatment with either EK or PK overlapped.
		Taking topical steroids at 2 years	80%	Not reported (continued use after 1 year 'unusual')	Not reported	
		93% (14/15) of the corneas in the EK group following graft failure remained clear after successful treatment with intensive topical steroids.				Patient demographics between the two groups were similar but measure of significance was not reported.
						Selection bias present with 85% of patients treated with EK had Fuchs' endothelial dystrophy, compared with 53% of the PK group.
						3 eyes in the EK group had documented superficial corneal neovascularisation at baseline.
				Postoperative steroid medication was not standardised across the study and may have influenced rejection rate.		

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.															
Study details		Key efficacy findings					Key safety findings					Comments			
Bahar I (2008) ³		Visual acuity					Complications					All procedures undertaken by one of two surgeons.			
Non randomised comparative study			PK	DLEK	DSEK	DSAEK	p		PK	DLEK	DSEK	DSAEK	p	Endothelial keratoplasty surgery was the first attempted at the study centre.	
		BSCVA	0.42 ± 0.14	0.60 ± 0.33	0.45 ± 0.22	0.34 ± 0.17	0.001	Disc dislocation	0%	9% (6/68)	13% (2/16)	16% (7/45)	0.0004		
Canada		UCVA	0.75 ± 0.35	0.68 ± 0.32	0.65 ± 0.43	0.55 ± 0.21	0.05	Graft leak	6% (3/48)	0%	0%	0%	0.04	Visual and safety outcomes were analysed at 12 months due to significant differences in follow-up period between groups.. However, in the DSAEK group only, follow-up at a minimum of 6 months was available.	
Study period: 2003 onwards		Astigmatism (D)	3.78 ± 1.91	1.61 ± 1.26	1.86 ± 1.1	1.36 ± 0.92	<0.0001	Persistent epithelial defect >1 month	8% (4/48)	0%	0%	0%	0.01		
Study population: patients with corneal oedema secondary to aphakic / pseudophakic bullous keratopathy, Fuchs' corneal endothelial dystrophy, failed graft, or iridocorneal endothelial syndrome. Age: 75 years (mean); sex: 37% male.		p-value represents analysis of variance across all groups					Glaucoma	6% (3/48)	13% (9/68)	13% (2/16)	7% (3/45)	0.52	There were some significant differences between groups in demographic and ophthalmological characteristics at baseline. However, UCVA was similar in all groups.		
n = 177 eyes (n=129 DLEK/DSEK/DSAEK)							Rejection	4% (2/48)	4% (4/68)	0%	2% (1/45)	0.78			
Inclusion criteria: not reported							Primary failure	2% (1/48)	3% (2/68)	0%	2% (1/45)	0.91	Authors state that the nonrandomised nature of the study may have led to selection bias.		
Technique: EK (under neuroleptic anaesthesia) by DSEK (n=16), DLEK (n=68) or DSAEK (n=45) via a 5 mm scleral incision vs PK with 16 interrupted sutures.							Cystoid macular oedema	2% (1/48)	1% (1/68)	6% (1/16)	2% (1/45)	0.71			
Follow-up: 15 months (mean)							% endothelial cell loss	36.9 ± 26.3 %	43.4 ± 22.2 %	38.2 ± 22.0 %	36.4 ± 15.2 %	0.70			
Conflict of interest: none							Rejection and primary failure definitions are not provided.								

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.

Study details	Key efficacy findings	Key safety findings	Comments
Price M O (2008)⁴ Case series USA Study period: Dec 2003 to Aug 2006 Study population: patients with corneal oedema secondary to bullous keratopathy (9%), Fuchs' corneal endothelial dystrophy (91%), or iridocorneal endothelial syndrome (< 1%). Age: 67 years (mean), sex: 66% female. n = 263 eyes Inclusion criteria: not reported Technique: under topical anaesthesia or retrobulbar block and intravenous sedation, EK by DSEK via a 5 mm scleral incision with viscoelastic bedding. Phacoemulsification and IOL insertion where necessary. Follow-up: 6 months (median) Conflict of interest: Supported by manufacturer	Efficacy outcomes were not reported on	Complications <i>6-month follow-up</i> Graft detachment occurred in 6% (17/263) eyes at 6-month follow-up, requiring a reattachment procedure. Mean ECD was 2000 ± 550 cells/mm² (range 410–3400 cells/mm²) at 6-month follow-up. Graft failure occurred in < 1% (1/263) of patients due to endothelial decompensation. Donor age, donor ECD, type of forceps used for insertion, combined surgery with phacoemulsification, and detachment were independent factors associated with endothelial cell loss at 6-month follow-up. Combined, these factors explain 14% of variance in endothelial cell loss. <i>24-month follow-up</i> 34 eyes were available for evaluation at follow-up of up to 2 years. The cumulative cell loss was 34% at 6 months, 36% at 12 months, and 41% at 24 months.	Retrospective study 263 eyes of 500 treated with 6-month follow-up at the same centre are analysed. There were no significant differences in demographic or donor tissue characteristics, or surgical variables in either the reported group or the overall cohort. Multivariate analysis was used to identify which donor or surgical variables has a statistically significant effect on follow up ECD. The graft insertion process changed during the course of this series. Authors state that baseline ECD measurements may have varied between the 29 donor centres.

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.

Study details	Key efficacy findings	Key safety findings	Comments
Terry M A (2008)⁵ Case series USA Study period: Sept 2005 to Mar 2007 Study population: patients with any-eye vision loss owing to endothelial dysfunction otherwise considered for PK. Age: 69 years (mean), sex: 63% female. n = 200 eyes Inclusion criteria: no significant anterior stromal scarring. Technique: Under retrobulbar anaesthesia, EK by DSAEK via a 5 mm scleral incision, with microkeratome for graft construction (71%), or pre-cut at the eye bank (29%). Vasoelastic preparation of recipient bed. Phacoemulsification where necessary (52%). Follow-up: minimum 4 months Conflict of interest: Supported by manufacturer	Efficacy outcomes were not reported on.	Complications Graft detachment occurred in 2% (3/200) eyes at up to 3-day follow-up. All were successfully reattached with a single repeat air bubble. Graft decentration (superiorly) was reported in 1% (2/200) of eyes. 12% (23/200) of eyes demonstrated no decentration but an edge of the graft retained a small cleft of interface fluid. No intervention was required and all grafts resolved spontaneously within 2 weeks. There were no reports of primary graft failure, endothelial failure or pupillary block in this series. No patients complained of pain or discomfort following surgery to examination on the first postoperative day.	Prospective series. All procedures undertaken by four surgeons. These are the first cases treated by DSAEK in the institution. Mean or median follow up period is not described. Authors state that prospective studies of long term donor endothelial survival should be done to obtain more specific data to support EK technique modification.

Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.

Study details	Key efficacy findings	Key safety findings	Comments																								
Suh L H (2008)⁶ Case series USA Study period: May 2005 to Jun 2007 Study population: patients with pseudophakic bullous keratopathy, or requiring replacement graft for previous DSAEK failure. Sex: 47% male. n = 118 eyes Inclusion criteria: not reported Technique: EK by DSEK via a 5 mm scleral or limbal incision, with microkeratome for graft construction. Phacoemulsification and IOL insertion where necessary (41 eyes). Topical antibiotics and steroids. Follow-up: Not reported Conflict of interest: None	Efficacy outcomes were not reported on.	Complications <table><tr><td>Graft detachment</td><td>23% (27/118)</td></tr><tr><td>Successful reattachment</td><td>68% (17/27)</td></tr><tr><td>Graft failure</td><td>18% (21/118)</td></tr><tr><td>Graft rejection</td><td>6% (7/118)</td></tr><tr><td>Retinal detachment</td><td>4% (5/118)</td></tr><tr><td>Cystoid macular oedema</td><td>4% (5/118)</td></tr><tr><td>Posterior graft dislocation</td><td>1% (1/118)</td></tr><tr><td>Retained Descemet's membrane</td><td>2% (2/118)</td></tr><tr><td>Interface blood</td><td>1% (1/118)</td></tr><tr><td>Epithelial ingrowth</td><td>1% (1/118)</td></tr><tr><td>Suprachoroidal haemorrhage</td><td>1% (1/118)</td></tr><tr><td>Pupillary block</td><td>2% (2/118)</td></tr></table> Detachments occurred between 1 and 25 days follow-up. Spontaneous reattachment occurred in 1 eye by 6-month follow-up. Repeat DSAEK was required in 8% (10/118) of eyes, and 9% (11/118) underwent subsequent penetrating keratoplasty.	Graft detachment	23% (27/118)	Successful reattachment	68% (17/27)	Graft failure	18% (21/118)	Graft rejection	6% (7/118)	Retinal detachment	4% (5/118)	Cystoid macular oedema	4% (5/118)	Posterior graft dislocation	1% (1/118)	Retained Descemet's membrane	2% (2/118)	Interface blood	1% (1/118)	Epithelial ingrowth	1% (1/118)	Suprachoroidal haemorrhage	1% (1/118)	Pupillary block	2% (2/118)	Consecutive patients treated by 10 surgeons at 1 centre. First patients treated / initial experience. Retrospective study Not clear whether cases of retinal detachment were related to IOL insertion or DSAEK alone. Some of the participating surgeons used paracentral vents during graft insertion.
Graft detachment	23% (27/118)																										
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Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.																																										
Study details		Key efficacy findings		Key safety findings		Comments																																				
Terry M A (2007) ⁷ Case series USA Study period: Mar 2000 to Mar 2004 Study population: patients with endothelial decompensation in any eye otherwise considered for PK. Age: 70 years (mean), sex: 53% female. Fuchs' dystrophy (89%), bullous keratopathy (11%). n = 100 eyes Inclusion criteria: no significant anterior stromal scarring. Technique: EK by DLEK via a 5 mm or 9 mm scleral incision. Vasoelastic preparation of recipient bed. Donor graft was folded for insertion when the 5mm incision technique used. Follow-up: 24 months (median) Conflict of interest: Supported by manufacturer		Efficacy outcomes were not reported on.		Complications 2% (2/100) patients converted to PK due to surgical error in recipient bed preparation. <table><tr><td></td><td>Baseline</td><td>6 months</td><td>12 months</td><td>24 months</td></tr><tr><td>Mean ECD (cells/mm²)</td><td>2836</td><td>2140</td><td>2090</td><td>1794</td></tr><tr><td>Mean % cell loss</td><td>N/A</td><td>25%</td><td>26%</td><td>37%</td></tr></table> The progressive loss from 12 to 24 months was statistically significant (p < 0.001) Mean % cell loss <table><tr><td></td><td>Baseline</td><td>6 months</td><td>12 months</td><td>24 months</td></tr><tr><td>9mm incision</td><td>N/A</td><td>23%</td><td>22%</td><td>27%</td></tr><tr><td>5mm incision</td><td>N/A</td><td>25%</td><td>28%</td><td>43%</td></tr><tr><td>p=</td><td>0.562</td><td>0.392</td><td>0.013</td><td>0.001</td></tr></table> 5% (5/98) of eyes had an episode of graft rejection at 2-year follow-up. All were treated with topical steroids and the cornea cleared. 2% (2/98) of eyes had late endothelial failure at 16- and 24-month follow-up. One eye was treated with repeat DLEK graft with a good result, and one had not been replaced at the time of reporting. Repositioning of the graft due to decentration was required in 3% (3/98) patients at 1-day follow-up.			Baseline	6 months	12 months	24 months	Mean ECD (cells/mm ²)	2836	2140	2090	1794	Mean % cell loss	N/A	25%	26%	37%		Baseline	6 months	12 months	24 months	9mm incision	N/A	23%	22%	27%	5mm incision	N/A	25%	28%	43%	p=	0.562	0.392	0.013	0.001	First experience with EK surgery. All procedures undertaken by one surgeon. Prospective study of consecutive patients. No clinical or other criteria were used to determine whether a 5 mm or 9 mm incision technique was used. 98 eyes were available for assessment at 6 months, 96 at 12 months (1 patient died and 1 moved), and 85 at 24 months (1 had graft replacement due to endothelial failure, and 10 unavailable for follow-up). Patients in the 9 mm incision group were significantly older (75.0 ± 8.8 years) than those in the 5 mm incision group (67.5 ± 18.3 years) (p < 0.001)	
	Baseline	6 months	12 months	24 months																																						
Mean ECD (cells/mm ²)	2836	2140	2090	1794																																						
Mean % cell loss	N/A	25%	26%	37%																																						
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Abbreviations used: BSCVA, best spectacle corrected visual acuity; DLEK, deep lamellar endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; ECD, endothelial cell density; EK, endothelial keratoplasty; IOL, intraocular lens; PK, penetrating keratoplasty; UCVA, uncorrected visual acuity.																																																						
Study details	Key efficacy findings		Key safety findings																																																			
NHS Blood and Transplant, Ocular Tissue Advisory Group (2009)⁸ Unpublished registry UK Study period: Apr 1999 to Dec 2007 Study population: patients receiving a first PK or EK for Fuchs' dystrophy or pseudophakic bullous keratopathy (PBK). n = 4513 (2136+1937 PK and 211+179 EK) Inclusion criteria: not reported Technique: EK not otherwise described. Follow-up: to 2 years Conflict of interest: Not reported	Visual Acuity In 132 patients with Fuchs' dystrophy treated by EK, mean visual acuity improved from 0.88 ($\pm$ 0.67 standard deviation [SD]) at baseline to 0.35 ($\pm$ 0.36) at 1-year follow-up. In 1676 patients treated by PK in the same registry the mean visual acuity improved from 1.04 ($\pm$ 0.80) at baseline to 0.44 ($\pm$ 0.48) at 1 year follow up. In 95 patients with PBK treated by EK, mean visual acuity improved from 1.74 ($\pm$ 0.92 SD) at baseline to 0.77 ($\pm$ 0.79) at 1-year follow-up. In 1389 patients treated by PK in the same registry the mean visual acuity improved from 1.96 ($\pm$ 0.91) at baseline to 0.84 ($\pm$ 0.82) at 1-year follow-up. Graft Survival Graft survival at 1-year in patients with Fuchs dystrophy <table border="1"> <thead> <tr> <th></th><th></th><th>Graft survival %</th><th>95% CI</th><th>p-value</th></tr> </thead> <tbody> <tr> <td>2006/07</td><td>PK (n=183)</td><td>97</td><td>93 to 99</td><td></td></tr> <tr> <td></td><td>EK (n=69)</td><td>88</td><td>78 to 94</td><td>0.0003</td></tr> <tr> <td>2007/08</td><td>PK (n=88)</td><td>98</td><td>91 to 99</td><td></td></tr> <tr> <td></td><td>EK (n=75)</td><td>77</td><td>63 to 86</td><td>0.0002</td></tr> </tbody> </table> Graft survival at 1-year in patients with PBK <table border="1"> <thead> <tr> <th></th><th></th><th>Graft survival</th><th>95% CI</th><th>p-value</th></tr> </thead> <tbody> <tr> <td>2006/07</td><td>PK (n=182)</td><td>95</td><td>90 to 97</td><td></td></tr> <tr> <td></td><td>EK (n=67)</td><td>84</td><td>73 to 91</td><td>0.007</td></tr> <tr> <td>2007/08</td><td>PK (n=76)</td><td>88</td><td>75 to 94</td><td></td></tr> <tr> <td></td><td>EK (n=55)</td><td>79</td><td>65 to 88</td><td>0.04</td></tr> </tbody> </table>				Graft survival %	95% CI	p-value	2006/07	PK (n=183)	97	93 to 99			EK (n=69)	88	78 to 94	0.0003	2007/08	PK (n=88)	98	91 to 99			EK (n=75)	77	63 to 86	0.0002			Graft survival	95% CI	p-value	2006/07	PK (n=182)	95	90 to 97			EK (n=67)	84	73 to 91	0.007	2007/08	PK (n=76)	88	75 to 94			EK (n=55)	79	65 to 88	0.04	Safety outcomes were not reported on.	
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				Data from 9 names participating and other UK sites (46 centres in total). Experience at some sites was limited; the smallest contributor only provided 1 case. Completeness of follow-up varies between the participating sites; 1-year follow-up varies between 0% and 100%. The average is 79%, which is lower than the national average of 87% for all follow-up forms.																																																		

Validity and generalisability of the studies

- There was variability within and between studies in terms of whether concomitant eye surgery was performed (such as phacoemulsification or intraocular lens insertion).
- There are a range of techniques available to perform corneal endothelial transplantation (DLEK, DSEK, DSAEK). The preparation of the graft can be undertaken manually, with a microkeratome, or with laser assistance.
- The definition for graft rejection varied considerably between studies.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr B Allen (Royal College of Ophthalmologists), Mr F Figueiredo (Royal College of Ophthalmologists).

- One Specialist Adviser considered the procedure to be established and no longer new, while a second classified it as novel and of uncertain safety and efficacy.
- Theoretical and anecdotal adverse events include graft dislocation, graft failure and rejection, interface opacification, and loss of BSCVA
- The key efficacy outcomes for this procedure include rejection rates, UCVA, speed of visual rehabilitation, and quality of life measures such as the VF14 score.
- The main comparator to this procedure is full thickness corneal transplantation (penetrating keratoplasty [PK]).
- It was estimated that 10–50% of corneal specialists are now using this technique.
- The procedure is technically more difficult than PK, and usually requires mechanical graft preparation.
- Training is currently being limited by lack of donor material, with competing pressures for PK grafts. Wetlab training is advised and the first few procedures should be undertaken with a mentor.
- Outcomes are likely to be worse when the recipient does not have an intact lens–iris diaphragm.
- The procedure is more easily performed than PK under local anaesthetic.
- If the procedure was found to be safe and efficacious it was thought likely that it would be offered at a minority of District General Hospitals but at least 10.

Patient Commentators' opinions

Opinion was sought from patients who have undergone the procedure. NICE's Patient and Public Involvement Programme sent 50 questionnaires to one trust

for distribution to patients who had the procedure (or their carers), however we did not receive any responses in sufficient time to incorporate into this overview.

Issues for consideration by IPAC

- Long-term follow-up may be required to capture graft rejection.
- Does endothelial keratoplasty make subsequent penetrating keratoplasty more difficult or less efficacious?
- Many very recent publications are available.

References

- 1 Patel SV, McLaren JW, Hodge DO et al. (2008) Scattered light and visual function in a randomized trial of deep lamellar endothelial keratoplasty and penetrating keratoplasty. *American Journal of Ophthalmology* 145:97-105.
- 2 Allan BD, Terry MA, Price FW, Jr. et al. (2007) Corneal transplant rejection rate and severity after endothelial keratoplasty. *Cornea* 26:1039-1042.
- 3 Bahar I, Kaiserman I, McAllum P et al. (2008) Comparison of posterior lamellar keratoplasty techniques to penetrating keratoplasty. *Ophthalmology* 115:1525-1533.
- 4 Price MO and Price FW, Jr. (2008) Endothelial cell loss after descemet stripping with endothelial keratoplasty influencing factors and 2-year trend. *Ophthalmology* 115:857-865.
- 5 Terry MA, Shamie N, Chen ES et al. (2008) Endothelial keratoplasty a simplified technique to minimize graft dislocation, iatrogenic graft failure, and pupillary block. *Ophthalmology* 115:1179-1186.
- 6 Suh LH, Yoo SH, Deobhakta A et al. (2008) Complications of Descemet's stripping with automated endothelial keratoplasty: survey of 118 eyes at one institute. *Ophthalmology* 115:1517-1524.
- 7 Terry MA, Wall JM, Hoar KL et al. (2007) A prospective study of endothelial cell loss during the 2 years after deep lamellar endothelial keratoplasty. *Ophthalmology* 114:631-639.
- 8 NHS Blood and Transplant, Ocular Tissue Advisory Group (2009) Update of Outcomes following endothelial keratoplasty OTAG (09) January: 1-4.

Appendix A: Additional papers on corneal endothelial transplantation

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of eyes/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bahar, Irit, Kaiserman, et al. (2009) Busin guide vs forceps for the insertion of the donor lenticule in Descemet stripping automated endothelial Keratoplasty. American Journal of Ophthalmology 147 (2) 220-226.	NRCT n=63 FU=6 months	Visual outcomes were not different between the groups, although there was less endothelial cell loss in the Busin guide group.	Comparison of techniques.
Basak SK. (2008) Descemet stripping and endothelial keratoplasty in endothelial dysfunctions: three-month results in 75 eyes. Indian Journal of Ophthalmology 56 (4) 291-296.	Case series n=75 FU=3 months	Descemet stripping and endothelial keratoplasty is a safe and effective procedure in patients with endothelial dysfunction with encouraging surgical and visual outcomes.	Larger studies and studies with longer follow-up included in table 2.
Chen ES, Terry MA, Shamie N, Hoar KL, Friend DJ. (2008) Descemet-stripping automated endothelial keratoplasty: six-month results in a prospective study of 100 eyes. Cornea 27(5) 514-520.	Case series n=100 FU=6 months	DSAEK provides a significant improvement in vision, corneal thickness, and surface regularity. It does not change refractive astigmatism or topographic keratometry.	Larger studies included in table 2.
Cheng YYY, Hendrikse F, Pels E et al. (2008) Preliminary results of femtosecond laser-assisted descemet stripping endothelial keratoplasty. Archives of Ophthalmology 126 (10) 1351-1356.	Case series n=11 FU=6 months	Endothelial cell count and dislocation rate were significant which may relate to the surgical technique.	Larger studies are included in table 2.
Faia LJ, Baratz KH, Bourne WM. (2006) Corneal graft folds: a complication of deep lamellar endothelial keratoplasty. Archives of Ophthalmology 124 (4) 593-595.	Case report n=2 FU=6 months	Two reports of corneal graft folds following DLEK.	Same safety outcome reported in studies included in table 2.
Heidemann DG, Dunn SP, Chow CY. (2008) Comparison of deep lamellar endothelial keratoplasty and penetrating keratoplasty in patients with Fuchs' endothelial dystrophy. Cornea 27 (2) 161-167.	NRCT n=43 (20 DLEK) FU=12 months	DLEK resulted in more rapid vision recovery, less astigmatism than PK surgery.	Larger studies and studies with longer follow-up included in table 2.

Hirano K, Kojima T, Nakamura M, Hotta Y. (2001) Triple anterior chamber after full-thickness lamellar keratoplasty for lattice corneal dystrophy. Cornea 20 (5) 530-533	Case report n=1 FU=6 months	Report of a separation of graft and the host cornea and between the hosts Descemet's membrane and cornea led to the development of a triple anterior chamber. This resolved without surgical treatment.	Same safety outcome reported in studies included in table 2. Larger studies included in table 2.
Jeng BH, Marcotty A, and Traboulsi EI (2008) Descemet stripping automated endothelial keratoplasty in a 2-year-old child. Journal of AAPOS: American Association for Pediatric Ophthalmology & Strabismus 12 (3) 317-318.	Case report n=1 FU=N/R	Rapid recovery and lack of induced astigmatism allowed prompt institution of amblyopia therapy.	Larger studies are included in table 2.
Jun, Bokkwan, Kuo et al. (2009) Refractive change after Descemet stripping automated endothelial keratoplasty surgery and its correlation with graft thickness and diameter. Cornea 28 (1) 19-23.	Case series n=44 FU=4 months	A hyperopic refractive shift occurred after DSAEK surgery.	Larger studies are included in table 2.
Kawashima M, Kawakita T, Den S, Shimmura S, Tsubota K, Shimazaki J. (2006) Comparison of deep lamellar keratoplasty and penetrating keratoplasty for lattice and macular corneal dystrophies. American Journal of Ophthalmology 142 (2) 304-309	NRCT n=84 (41 DLKP) FU=3 years	DLKP is a safe alternative to PK, although patients with macular corneal dystrophy may be less good candidates.	Larger studies included in table 2.
Kymionis GD, Suh LH, Dubovy SR, Yoo SH. (2007) Diagnosis of residual Descemet's membrane after Descemet's stripping endothelial keratoplasty with anterior segment optical coherence tomography. Journal of Cataract and Refractive Surgery 33 (7) 1322-1324.	Case report n=1 FU=4 months	Inadequate Descemet's stripping in the recipient could be a potential cause of DSEK failure.	Same safety outcome reported in studies included in table 2. Larger studies included in table 2.

Lee JK, Eghrari AO, Desai NR, et al. (2009) Presoaking donor corneas reduces graft detachment rates in Descemet stripping endothelial keratoplasty. American Journal of Ophthalmology 147 (3) 439-441.	NRCT n=103 eyes FU=N/R	Pre-soaking the donor tissue in balanced salt solution Plus lowers the detachment rate of DSEK grafts.	Comparison of techniques.
Noble BA, Agrawal A, Collins C, Saldana M, Brogden PR, Zuberbuhler B. (2007) Deep anterior lamellar keratoplasty (DALK): visual outcome and complications for a heterogeneous group of corneal pathologies. Cornea 26 (1) 59-64.	Case series n=80 FU=21 months	The procedure is safe and useful in patients without endothelial involvement. Graft rejection is a significant complication but is associated with good recovery as the endothelium is spared.	Larger studies included in table 2.
O'Brien PD, Lake DB, Saw VP et al (2008). Endothelial keratoplasty: case selection in the learning curve. Cornea 27(10):1114-1118.	NRCT n=85 FU=7 months	Initial cases should be selected with an intact lens/iris diaphragm	Larger studies are included in table 2
Prasher P, Muftuoglu O. (2009) Herpetic keratitis after descemet stripping automated endothelial keratoplasty for failed graft. Eye & Contact Lens: Science & Clinical Practice 35(1) 41-42.	Case report n=1 FU=1 week	Herpes simplex virus epithelial keratitis can occur after DSAEK for failed grafts.	Larger studies with this safety outcomes are included in table 2.
Price MO, Price FW, Jr. (2007) Descemet stripping with endothelial keratoplasty for treatment of iridocorneal endothelial syndrome. Cornea 26 (4) 493-497.	Case series n=50 FU=6 months	Compared to PK, DSEK causes minimal refractive change and provides rapid visual recovery for patients with epithelial dysfunction.	Larger studies and studies with longer follow up included in table 2.
Tay E, Rajan MS, Saw VP, Dart JK. (2008) Dislocated intraocular lens into the vitreous cavity after DSAEK. Journal of Cataract & Refractive Surgery; 34(3):525-526	Case report n=1 FU=2 hours	Case described of intraocular lens dislocation into the vitreous cavity during a combined DSAEK and cataract procedure.	Not clear whether outcome relates to the DSAEK element of the procedure.
Terry MA, Shamie N, Chen ES et al. (2008) Endothelial keratoplasty: the influence of preoperative donor endothelial cell densities on dislocation, primary graft failure, and 1-year cell counts. Cornea 27 (10) 1131-1137.	Case series n=629 eyes FU=12 months	Preoperative endothelial cell density was not associated with donor dislocation. Higher cell density at baseline was not associated with cell density at 1-year follow-up.	Terry (2007) included in table 2 of the overview reports outcomes to 2 years for Endothelial cell loss in 100 eyes.

Watson SL, Ramsay A, Dart JK, Bunce C, Craig E. (2004) Comparison of deep lamellar keratoplasty and penetrating keratoplasty in patients with keratoconus. Ophthalmology 111(9) 1676-1682.	NRCT n=51 (26 DLK) FU=28 months and 55 months	BSCVA, refractive results and complication rates are similar after DLK and PK.	Larger studies included in table 2.
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Appendix B: Related NICE guidance for corneal endothelial transplantation

Guidance	Recommendations
Interventional procedures	Patient safety and reduction of risk of transmission of Creutzfeldt-Jakob disease (CJD) NICE interventional procedures guidance 196 (2006) 1.1 For high-risk surgical procedures (intradural operations on the brain and operations on the retina or optic nerve – ‘high-risk tissues’): Steps should be taken urgently to ensure that instruments that come into contact with high-risk tissues do not move from one set to another. Practice should be audited and systems should be put in place to allow surgical instruments to be tracked, as required by Health Service Circular 2000/032: ‘Decontamination of medical devices’ and described in the NHS Decontamination Strategy¹. • Supplementary instruments that come into contact with high-risk tissues should either be single use or should remain with the set to which they have been introduced. Hospitals should ensure without delay that an adequate supply of instruments is available to meet both regular and unexpected needs 1.2 For neuroendoscopy: • Rigid neuroendoscopes should be used whenever possible. They should be of a kind that can be autoclaved and they should be thoroughly cleaned and autoclaved after each use. • All accessories used through neuroendoscopes should be single use. 1.3 A separate pool of new neuroendoscopes and reusable surgical instruments for high-risk procedures should be used for children born since 1 January 1997 (who are unlikely to have been exposed to BSE in the food chain or CJD through a blood transfusion) and who have not previously undergone high-risk procedures. These instruments and neuroendoscopes should not be used for patients born before 1 January 1997 or those who underwent high-risk procedures before the implementation of this guidance. 1.4 For all procedures considered in this guidance, with the exception of those involving neuroendoscopy accessories, the evidence on cost effectiveness related to the risk of

	possible transmission of CJD does not support a change to single-use instruments, based on current costs. This includes all other neurosurgery, eye surgery, tonsillectomy, laryngoscopy and endoscopy procedures 1.5 Single-use instruments should be manufactured and procured to specifications equivalent to those used for reusable instruments and should be subject to high standards and consistent quality control. Single-use instruments which are not similar in quality to the reusable instruments which they replace have the potential to harm patients and should not be purchased or used. 1.6 This guidance has been developed on the assumption that new and more effective decontamination methods are likely to become available for routine use in the NHS within the next 5 years. Rigorous evaluation of the safety of these methods and of their efficacy against human prions is urgently required. Until then, the current Advisory Committee on Dangerous Pathogens Transmissible Spongiform Encephalopathies (ACDP TSE) guidelines on decontamination should be followed.
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Appendix C: Literature search for corneal endothelial transplantation

Database	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	28/10/2008	Issue 4, 2008	0
Database of Abstracts of Reviews of Effects – DARE (CRD website)	28/10/2008	N/A	1
HTA database (CRD website)	28/10/2008	N/A	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	28/10/2008	Issue 4, 2008	10
MEDLINE (Ovid)	28/10/2008	1950 to October Week 3 2008	167
MEDLINE In-Process (Ovid)	28/10/2008	October 27, 2008	38
EMBASE (Ovid)	28/10/2008	1980 to 2008 Week 43	269
CINAHL (NLH Search 2.0)	28/10/2008	N/A	30
BLIC (Dialog DataStar)	28/10/2008	N/A	0
National Research Register (NRR) Archive	28/10/2008	N/A	Small incision deep lamellar endothelial keratoplasty study
UK Clinical Research Network (UKCRN) Portfolio Database	29/10/2008	N/A	0
Current Controlled Trials <i>meta</i> Register of Controlled Trials - <i>m</i> RCT	29/10/2008	N/A	0
Clinicaltrials.gov	29/10/2008	N/A	Study of Eye Bank Pre-Cut Donor Grafts for Endothelial Keratoplasty A Comparison Between Full Thickness and Partial Thickness Corneal Transplantation for Corneal Edema Deep Lamellar Endothelial Keratoplasty: Small Incision Technique Descemet Membrane Endothelial Keratoplasty (DMEK) Descemet Stripping (Automated) Endothelial Keratoplasty (DSEK or DSAEK) Early Experience With Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) Comparison of Penetrating Keratoplasty and Deep Lamellar Keratoplasty With the

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

- 1 (descemet* adj3 membran* adj3 (dysfunction* or fail* or disease*)).tw.
- 2 (endothel* adj3 dysfunction*).tw.
- 3 (endothel* adj3 fail*).tw.
- 4 (endothel* adj3 diseas*).tw.
- 5 Fuchs' Endothelial Dystrophy/
- 6 (endothel* adj3 dystroph*).tw.
- 7 or/1-6
- 8 (lamellar* adj3 keratoplast*).tw.
- 9 PLK.tw.
- 10 DLK.tw.
- 11 (deep* adj3 lamellar* adj3 endothel* adj3 keratoplast*).tw.
- 12 DLEK.tw.
- 13 (Descemet* adj3 strip* adj3 automat* adj3 endothel* adj3 keratoplast*).tw.
- 14 DSAEK.tw.
- 15 (Descemet* adj3 strip* adj3 endothel* adj3 keratoplast*).tw.
- 16 DSEK.tw.
- 17 (descemet* adj3 membran* adj3 endothel* adj3 keratoplast*).tw.
- 18 DMEK.tw.
- 19 Descemet Membrane/tr, su [Transplantation, Surgery]
- 20 Endothelium, Corneal/su, tr [Surgery, Transplantation]
- 21 (descemet* adj3 membran* adj3 transplant*).tw.
- 22 (endothel* adj3 transplant*).tw.
- 23 or/8-22
- 24 23 and 7
- 25 animals/
- 26 humans/
- 27 25 not (25 and 26)

28 24 not 27