Delphi-Based Global Consensus on Adopting Endothelial Keratoplasty: An Endothelial Keratoplasty Learners Group Initiative

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Purpose: To identify areas of consensus among experts on the performance of endothelial keratoplasty by using a modified Delphi approach, to help create a framework for novice surgeons to adopt these procedures.

Methods: Thirty-one international experts in endothelial keratoplasty participated. Two rounds of electronic survey were followed by a hybrid, virtual meeting. Consensus was set at 75%, and results with agreement between 70% and 75% were deemed as achieving near consensus.

Results: A consensus was reached for 98 statements covering the preoperative, intraoperative, and postoperative aspects of Descemet membrane endothelial keratoplasty (DMEK) and Descemet stripping endothelial keratoplasty/Descemet stripping automated endothelial keratoplasty. Four statements achieved near consensus, and consensus could not be achieved for 11 statements. For DMEK, the panel supported a peel technique to prepare tissue for endothelium out DMEK, implanted via an injector and supported by a near full air/gas fill as a baseline procedure onto which more advanced techniques can be built. DMEK tissue should be marked to ensure correct orientation. An inferior peripheral iridotomy should be used to prevent pupil block when a near full air/gas fill in used in endothelial keratoplasty (EK). Descemet stripping automated endothelial keratoplasty was considered preferable to Descemet stripping endothelial keratoplasty where access to microkeratome preparation was available.

Conclusions: The Delphi process allowed areas of consensus on the performance of EK to be established by a group of international experts. The statements generated are a helpful framework for novice surgeons learning EK. Further research is needed to help determine what specific tomographic features indicate EK, when guttae are considered visually significant and how to approach combined aphakia and endothelial dysfunction.

Key Words: endothelial keratoplasty, descemets membrane endothelial keratoplasty, Delphi concensus, descemets membrane endothelial keratoplasty, DMEK, DSEK, DSAEK

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Endothelial keratoplasty (EK) is considered the gold standard treatment for isolated endothelial dysfunction. EK offers improved visual function,[1,2] faster visual recovery, lower risk of graft rejection,[3–5] and a more predictable refractive outcome[6] than penetrating keratoplasty (PK).[7,8] Over the last 3 decades, as techniques have evolved, 3 iterations of EK have gained widespread adoption: Descemet stripping endothelial keratoplasty (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), and Descemet membrane endothelial keratoplasty (DMEK).

As these techniques have become more established, global adoption has increased. Advances have been aided by the increasing availability of corneal tissue, eye banking initiatives,[9] and centralization of tissue preparation for EK.[10] However, surgeons wishing to adopt endothelial keratoplasty face a vast array of technique variations in both tissue preparation and surgery. In addition, the unique properties of the donor tissue and the host eye can pose additional challenges that do not apply to PK and can be more problematic for DMEK than for DSEK/DSAEK[11] or vice versa.[10,12]

Access to training in EK is limited in much of the world, resulting in some surgeons learning from nonpeer-reviewed resources.[13] Although attending wet labs may introduce the techniques,[14] this does not necessarily shallow the learning curve nor reduce the risk of postoperative graft failure.[15]

Surgeons performing EK who are earlier in the learning curve have a higher rate of complications and graft failure.[16–18] It is also recognized that surgeons performing lower volumes of surgery have a higher rate of complications.[19] Consequently, training in EK may benefit from standardization and the need for a learning framework for EK exists. The aim of this study is to gain consensus from an international group of experts on how novice surgeons should approach EK. This will ultimately allow us to establish a comprehensive set of guidelines that act as a reference for surgeons who wish to adopt EK.

Several different research methods can be used to compare surgical techniques, including randomized control trials[20,21] and systematic reviews.[22] However, these methods are typically used to compare 2 different treatments: for example, visual outcomes and graft failure rates in ultra-thin DSAEK versus DMEK. Variations in surgical technique for the same procedure are often not as rigorously evaluated and the original descriptions of the techniques do not always represent the current real-world practice of subject matter experts.[23] Where the comparisons of variations in a single technique have been conducted using systematic review, the authors themselves often recognize that the quality of evidence is poor because of considerable heterogeneity among the constituent studies.[24]

The Delphi technique is widely used and accepted as a method for achieving consensus. This research tool provides a customizable process for gathering and analyzing data regarding practice patterns using a panel of experts.[25–27] The Delphi methodology has been extensively employed to establish treatment guidelines for various ophthalmic disorders, particularly in cases with limited or no evidence in the published literature[28–30] and has been used to pinpoint research gaps by identifying areas lacking consensus.[31] To the best of our knowledge, the Delphi method has not been previously employed to formulate surgical recommendations for EK.

To achieve a global consensus, we contacted surgeons via the Endothelial Keratoplasty Learner Group (EKLG). The EKLG is an online global community of cornea surgeons from over 100 countries interested in learning and sharing knowledge related to corneal endothelial disorders and management. The group was established as an online learning community by a team of cornea specialists during the 2020 global pandemic. One of the primary aims of EKLG is to help surgeons transition from PK to EK and ultimately improve patient care.

MATERIALS AND METHODS

Structured communication and data-gathering processes were established using a modified Delphi approach. An executive committee (EC) comprising the scientific advisory panel members for the EKLG (M.B., N.G., V.R., J.M., R.P., T.G., A.K., J.M., P.V.) was formed, with R.P. serving as the facilitator.

The EC selected a panel of experts on endothelial keratoplasty for the Delphi process. The inclusion criteria for experts were scientific contributions in peer-reviewed publications (identified through PubMed searches), other forms of written scientific communication, participation in presentations or panels at international meetings, recognition by local corneal societies, and relevant surgical experience. For consensus statements to be applicable to patients from diverse ethnic and racial backgrounds, an effort to select geographically diverse set of panelists was made. All panelists had to have experience in training corneal fellows new to EK. Additional criteria included proficiency in the English language, availability to respond to electronic questionnaires, and willingness to engage in virtual meetings.

Invitations were sent via email to the eligible individuals. The modified Delphi process consisted of 2 rounds of electronic questionnaires, followed by a hybrid face-to-face meeting. The finalized statements were then sent to all participants to ensure they were clear and unambiguous. To minimize the influence of seniority, presumptions of expertise, and dominant characters, the experts were kept anonymous throughout the first 2 rounds. The participants are listed in the Supplemental Digital Content 1 (see Appendix, http://links.lww.com/ICO/B750) and form the Endothelial Keratoplasty Delphi Approach Working Group.

The EC created questions with short open answers, multiple choice, unit-based, or true/false answers for the electronic surveys. The questions were divided into general EK, DMEK, and DSEK/DSAEK specifics. The first round of questions was beta-tested by the EC members. The final, revised first-round questionnaire was circulated electronically to the group using Google Forms (https://drive.google.com) with an email reminder. A free text box was included with all

questions so that respondents could comment on any ambiguity or suggest alternate wording.

Questions with consensus were rewritten as statements that could be confirmed by yes/no in further rounds. Open answer questions and questions without consensus were reformulated, and the resultant new questions were added to each subsequent round and face-to-face meeting. For instance, for the question "Is there a cutoff age below which you would not accept tissue for DMEK?," individual responses had a skewed distribution, with a lower limit of approximately 35 years. A new statement, "Tissue from donors younger than 35 year old should be avoided for DMEK if alternate tissue is available," was created, and consensus was sought. Where appropriate, responses from more than 1 question were amalgamated for clarity and presented in the subsequent rounds. For example, responses on how to size EK transplants and the typical EK size were combined in the statement A typical EK graft would have a diameter of 8.0 to 8.5 mm. Most grafts should be at least 2.5 mm smaller than the vertical white-to-white diameter.

The level of agreement required to meet consensus was defined before data analysis and was set at 75%. Statements with an agreement between 70% and 75% were classified as near consensus. These cutoffs were selected based on similar studies within ophthalmology and accepted standards for the Delphi method.[32,33]

If statements met consensus, they were removed from subsequent rounds, allowing respondents to focus on areas that had not yet reached a consensus. Some statements failed to reach a consensus as the surgical preferences of the respondents were split among several possible options. In certain cases, we wished to establish whether the consensus was that each alternative was acceptable and reworded the statements with this goal. For example, "Performing a descemetorhexis under air may enhance visibility of the descemetorhexis edge but may also be complicated by repeated air escape and collapse of the anterior chamber unless an air pump is used. It is safe to perform descemetorhexis under air, cohesive ophthalmic viscoelastic device (OVD), or balanced salt solution infusion, but not under a dispersive OVD."

To better interpret the responses, all participants answered demographic questions on the availability of technologies and eye banks capable of processing corneal tissue for transplantation. This helped to narrow responses, for example, on the acceptability of manual tissue preparation for DSEK in areas where access to microkeratome tissue preparation is not widely available; "If microkeratome prepared tissue is unavailable, manual tissue preparation is acceptable."

After the completion of the 2 electronic survey rounds, a hybrid, live video conference (http://www.zoom.com) was convened to discuss outstanding areas that had not reached a consensus. To ensure maximal participation of the geographically diverse group of delegates, participating from different time zones, panelists were given the option to submit final responses via online form or attend the live video conference. If submitting responses via online form, delegates were required to evaluate any new statements generated in the video conference and submit their agreement during the final questionnaire round.

R.P. acted as a facilitator in live video conference and did not vote. Each question was presented via a virtual slide show by a technical assistant. Each panelist was required to vote using a live polling system. The responses from those attending live meetings and those who had submitted questionnaire responses before the face-to-face meeting were combined in real time to determine whether consensus had been achieved. If there was no consensus, the questions were discussed by 13 voting participants who attended live.

If the agreement on any vote was less than 50%, we elected to establish the conclusion as "no consensus" and report it as such. The question was discussed only if initial agreement was between 50% and 70%. To avoid the risk of predominance by any 1 panelist, the order of the participants' comments in each round was randomly determined by the nonparticipating support research staff.

Where deemed helpful to gain consensus, question reformulation was done by open group discussion. All participants then revoted confidentially. If consensus or near consensus was not obtained after the second round, we defined the result as no consensus. The final consensus statements, some having arisen from the face-to-face meeting, were circulated to all participants to ensure that they were clear and unambiguous, but no further discussion or questionnaires were followed.

RESULTS

The panelists and their geographic locations are provided in Supplemental Digital Content 1 (see Appendix, http://links.lww.com/ICO/B750). Thirty-one of the 35 surgeons agreed to participate in the study. Experience in EK ranged from 60 to >5000 cases, with 97% of experts having performed EK in over 250 cases. Thirty surgeons responded to the first electronic survey and 26 responded to the second survey.

Twenty-nine voting surgeons and the facilitator participated in the hybrid videoconference to evaluate the remaining 45 reformulated and nonconsensus statements from the previous rounds. Of the final 113 statements, 95 achieved consensus before the final, live discussion. Nine statements did not achieve a 50% cutoff for discussion. Of the 7 questions requiring discussion, consensus was achieved for 3 modified statements and near consensus for 4, giving a total of 98 consensus statements, 4 near consensus statements, and 11 nonconsensus statements (Fig. 1).

Indications, Preoperative Assessment, and General Considerations for Endothelial Keratoplasty

The first set of questions focused on the indications for EK, preoperative assessment and planning, and factors complicating EK (Table 1). Consensus was achieved for selecting EK in all cases of isolated endothelial dysfunction and endothelial dysfunction after previous PK (provided that the original transplant was free from scarring and high astigmatism). Where corneal factors that could limit the final visual acuity were present, EK was still considered an option

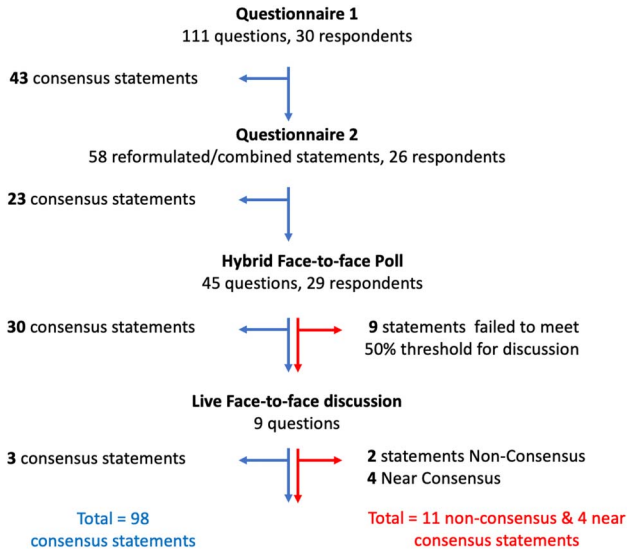

FIGURE 1. Flowchart outlining the number of questions and respondents in each round of the Delphi process, with the number that achieved consensus, near consensus, or failed to achieve consensus. (The full color version of this figure is available at www.corneajrnl.com.)

if there was a high risk of rejection or if the visual potential was limited by factors other than the cornea. In cases of Fuchs endothelial corneal dystrophy (FECD) or uncomplicated pseudophakic corneal edema, where the visual potential is high, the advantage of DMEK over DSAEK/DSEK was considered to be most significant. The expert panel agreed that DMEK was preferable to DSEK/DSAEK, where it was technically possible, and DMEK was preferred to DSEK/DSAEK when treating grafts that had failed because of previous rejection. DSEK/DSAEK may still be a better option in cases in which the surgeon's view of the anterior chamber is compromised; the chamber is difficult to shallow or the prolonged gas tamponade cannot be achieved.

In patients with FECD, diurnal variation in vision and tomographic changes were indications for combined cataract and EK surgery.[34] The specific tomographic features used by the surgeons were not defined. Central corneal thickness should not be used in isolation to determine whether EK is warranted. Similarly, although many experts agree that guttae could degrade vision, no consensus on when guttae are visually significant enough to warrant EK could be reached in the absence of tomographic changes and visual symptoms.

The next set of questions focused on the common principles applicable to DSAEK/DSEK and DMEK. The standard graft size is typically between 8.0 and 8.5 mm, with adjustments made for white-to-white measurements, the disease process, and the size of previously penetrating keratoplasties. Successful surgery depends on the correct orientation of the EK graft, and marking schemes, OCT, or indirect signs can be used to confirm this.

The panelists agreed that descemetorhexis could be performed under air, cohesive viscoelastic, or balanced salt solutions, but no consensus on which of these was best could be achieved in the early rounds of questions. It was agreed that dispersive viscoelastic should be avoided, as it can be retained in the graft–host interface and interfere with adhesion. Consensus was achieved for prestripping and precutting tissues in the eye bank for DMEK and DSAEK, respectively. The use of tissue preloaded into an injection system was not deemed advantageous.

Table 2 summarizes the consensus on combined cataract surgery and EK. The triple procedure (combining cataract surgery and EK) is not associated with a significantly increased risk of graft failure or poor outcome. Hydrophobic intraocular lenses (IOL) should be used to reduce the risk of opacification. When combined with simultaneous EK surgery, routine use of toric or multifocal IOL is not advisable, as lens performance could be compromised by a less predictable refractive outcome. For patients who wish to have correction of astigmatism or presbyopia, DMEK is preferable to DSEK/DSAEK, and performing cataract extraction after DMEK may be appropriate.[35–37] If an eye with an unstable IOL requires EK, it should be managed before or at the same time as EK. Replacing stable anterior chamber IOLs in all eyes that require EK is not recommended. There is no consensus on what additional steps should be taken to avoid opacification of hydrophilic lenses implanted before DMEK; however, removing a clear hydrophilic IOL as a precaution is not recommended.

Postoperative Management and Rebubbling

Postoperative management after EK is summarized in Table 3. All patients need to be reviewed 1 to 2 hours after surgery to ensure that they are not in the pupil block, and gas should be released if a pupil block is observed at the early postoperative review. There was a near consensus (70%) for reviewing patients the day after surgery, and the remaining 30% of surgeons seeing patients at various intervals of up to 7 days after surgery.

Supine posturing was found to be beneficial, but inability to posture was not an absolute contraindication to EK. No consensus on the exact amount of time patients should posture was achieved, with responses ranging from 30 minutes to 4 days.

Experts felt that immunosuppression with topical steroids was sufficient in primary, uncomplicated EK. In the absence of contraindications, continued use of low-dose topical steroids was considered beneficial, and patients on steroid treatment should remain under the care of a corneal specialist. The routine use of postoperative ocular antihypertensives is not warranted unless the patient has glaucoma. There is agreement that strenuous activity should be avoided until gas tamponade has resorbed.

Table 4 summarizes the management of graft detachment and failure. Observation of shallow, small peripheral detachments, with adjusted posturing if residual gas remained, achieved a consensus. A consensus was reached that DMEK grafts with >20% detachment should be rebubbled. It was noted that the presence of a tight scroll in the detached area might prompt earlier rebubbling.

A consensus was reached that rebubbling should be repeated until the graft is attached, with no recommended

TABLE 1. Indications for Endothelial Keratoplasty, Preoperative Assessment, and General Considerations for Performing Endothelial Keratoplasty

	% Consensus	Round	Level of Consensus Achieved
Endothelial keratoplasty is always preferable to penetrating keratoplasty when treating isolated endothelial dysfunction	100	1	C
Delaying treatment of endothelial dysfunction to the point of epithelial oedema can sometimes result in irreversible stromal scarring and remodelling, which can compromise the long-term visual prognosis	87	1	C
Endothelial keratoplasty is the preferred treatment for endothelial decompensation after penetrating keratoplasty, where there is minimal stromal scarring and where the shape profile and astigmatism in the original penetrating keratoplasty were acceptable	93	3	C
Penetrating keratoplasty may still be the preferred treatment in eyes that have endothelial failure in combination with significant scars, high degrees of irregular astigmatism, or severe anterior segment disorganization. However, the increased risk of rejection for penetrating keratoplasty should be balanced against the visual prognosis	93	3	C
DMEK is the treatment of choice for eyes with Fuchs dystrophy and normal anterior chamber anatomy	100	1	C
In eyes that have had previous graft rejection, DMEK is preferable over DSAEK/DSEK, even if there are complicating factors	77	1	C
Less complicated eyes (Fuchs dystrophy and pseudophakic corneal oedema) are likely to benefit the most from the visual enhancements offered by DMEK over DSAEK/DSEK	93	3	C
As an experienced surgeon, I would perform DMEK over DSEK/DSAEK if technically possible	87	1	C
As surgeons become more experienced, it is appropriate to use DMEK in more complicated situations, and most experienced surgeons would perform DMEK for endothelial dysfunction if it is technically possible to do so	80	2	C
For experienced surgeons, DSEK/DSAEK may still be preferable if:			C
The view is very poor	97	3	
The anterior chamber is difficult to control	90	3	
Adequate gas tamponade cannot be maintained	86	3	
Diurnal fluctuation in vision is a strong indicator for corneal decompensation in patients with Fuchs dystrophy	81	2	C
Isolated central corneal thickness measurements should not be used to determine if patients with Fuchs dystrophy should undergo simultaneous EK during cataract surgery. Tomographic features and patient symptoms are more sensitive metrics	97	3	C
Preoperative corneal tomography, AS-OCT imaging, and OCT imaging of the macular and disc are useful preoperative tests that help plan surgery and give an idea of the visual prognosis	77	1	C
AS-OCT can help in assessing the posterior corneal profile, determine the size of the transplant needed, and assess the degree of peripheral anterior synechiae	80	1	C
A typical EK graft would have a diameter of 8.0–8.5 mm. Most grafts should be at least 2.5 mm smaller than the vertical white-to-white diameter	80	2	C
EK diameter may need to be adjusted depending on the white-to-white, the size of a previous penetrating keratoplasty, or the underlying disease process	80	2	C
Situations where it is hard to control anterior chamber depth are associated with increased complexity in endothelial keratoplasty. These include:			C
Vitrectomized eyes for DMEK	97	1	
Eyes with previous surgery for glaucoma	87	1	
Hypotony	85	1	
Eyes with large iris defects	90	2	
Functionally unicameral eyes (aphakia, anterior chamber lenses and scleral fixated lenses)	97	1	
Previous penetrating keratoplasty can make descemetorhexis and graft attachment harder, especially if the posterior profile is irregular	94	1	C
It is advisable to undersize an endothelial transplant by 0.5 mm compared with the previous penetrating keratoplasty	86	3	C
Where available, prestripped/precut tissue for EK is advantageous, helping to avoid cancellations and increasing operating theater efficiency	83	1	C
It is preferable to perform EK under general anaesthetic or local anaesthetic (peribulbar, subtenons) with or without sedation. Surgery under topical anaesthetic with or without sedation is not advisable for novice surgeons	83	3	C
Descemetorhexis is always necessary in eyes with FECD	100	1	C
Descemetorhexis can be avoided in eyes with graft failure after penetrating keratoplasty	77	1	C

(*Continued*)

TABLE 1. (*Continued*) Indications for Endothelial Keratoplasty, Preoperative Assessment, and General Considerations for Performing Endothelial Keratoplasty

	% Consensus	Round	Level of Consensus Achieved
Performing a descemetorhexis under air may enhance visibility of the descemetorhexis edge but may also be complicated by repeated air escape and collapse of the anterior chamber unless an air pump is used. It is safe to perform the descemetorhexis under air, cohesive OVD, or BSS infusion but not under a dispersive OVD	86	2	C
It is essential to ensure the graft is the correct the side up at the end of surgery using indirect signs, marking schemes or intraoperative OCT	100	3	C
Oedema and scars affect the view during surgery, making surgery more challenging. The following may be useful where the view is poor:			C
Removing the epithelium	96	2	
Using an external light pipe	90	3	
Use of intraoperative OCT	90	3	
It is advisable to avoid scoring the graft host interface when performing descemetorhexis in eyes that have had previous penetrating keratoplasties	86	2	C
Preloaded tissue offers a significant advantage in EK			No C
Visually significant guttae in the absence of corneal oedema are an indication for EK			No C

AS-OCT, anterior segment optical coherence tomography; BSS, balanced salt solution.

maximum number of rebubbling attempts. There is no consensus on whether to rebubble with air or sulfur hexafluoride (SF_6). If an attached EK graft fails to clear 6 weeks after surgery, primary graft failure has occurred,[38] and regrafting at this stage should be warranted.

DMEK

The subsequent series of questions focused specifically on DMEK (Table 5). Consensus was achieved for using a lower age limit of 35 years for DMEK tissue in settings where the supply of tissue allowed this. No consensus on an upper age limit for DMEK tissue was achieved, but there is acknowledgement that tissue from donors older than 80 behaves differently, which can affect unfolding strategies. Where possible, diabetic tissue should be prepared in the eye bank as there is an increased incidence of graft preparation failure that could lead to patient cancellation if it were to occur in the operating theater. If tearing occurs during graft preparation, implanting a smaller, torn, or noncircular DMEK graft is acceptable. All DMEK grafts should be stained and have orientation marks, but we did not achieve a consensus on how long to stain the grafts. Although it is usual to perform descemetorhexis, it is not mandatory in the absence

TABLE 2. Consensus Statements on Combined Cataract Surgery and EK

	% Consensus	Round	Level of Consensus Achieved
For patients with combined cataract and endothelial dysfunction, combining cataract surgery and endothelial transplantation is preferable. Combined surgery is not associated with significantly worse outcomes or worse long-term graft survival than sequential surgery	90	2	C
Novice surgeons may perform combined cataract surgery and endothelial keratoplasty, but performing these as separate procedures may be easier in the first 5 cases	90	3	C
A postoperative refraction of −0.5 to −1.0 diopter should be targeted to compensate for the hyperopic shift after EK. The hyperopic shift is typically larger after DSEK/DSAEK than DMEK	90	1	C
For patients undergoing simultaneous cataract extraction and EK surgery, a hydrophobic acrylic intraocular lens is preferred to reduce the risk of IOL opacification. In combined surgery, multifocal and toric lenses are usually not advisable	90	1	C
In patients who might benefit from toric or multifocal lenses, staged surgery, with EK performed first, may be an option	85	2	C
In patients who might benefit from toric or multifocal lenses, DMEK is preferable to DSAEK	81	2	C
In combined surgery, a capsulorhexis smaller than the IOL optic (typically 4.5–5 mm diameter) should be targeted to try and help prevent IOL prolapse	85	2	C
An unstable IOL (anterior chamber or posterior chamber) should be stabilized, removed, or replaced in patients undergoing endothelial keratoplasty	93	3	C
Dispersive OVD should be avoided during all EK surgeries, including combined surgery, as coating of the posterior cornea with dispersive OVD may interfere with graft adhesion	85	2	C
Specific precautions should be taken to prevent opacification of hydrophilic IOLs			No C
All anterior chamber IOLs should be replaced prior EK			No C

TABLE 3. Postoperative Management After EK

	% Consensus	Round	Level of Consensus Achieved
Topical immunosuppression should be started either immediately after surgery or from postoperative day 1. A typical steroid regime for uncomplicated patients would be dexamethasone 0.1% drops every 2 h for 1 wk, x 4/d for 1 mo x 3/d for 1 mo, x 2/d for 1 mo, x 1 d ongoing	93	1	C
Routine postoperative topical or oral ocular antihypertensives are not required for patients without a history of glaucoma	80	1	C
After EK, patients should have their first review 1–2 h after surgery to ensure they are not in pupil block and the IOP is acceptable	79	3	C
If patients are in pupil block after surgery, air/gas should be vented through a paracentesis until the gas bubble is past the iridotomy or the pupil edge	90	1	C
Supine posturing after EK surgery may help promote graft adhesion	87	1	C
Patients should avoid face down posturing and strenuous activity until the gas bubble has fully dissolved	81	2	C
Unless there are contraindications, patients may benefit by staying on indefinite, low-dose topical steroid treatment. Patients should remain under the care of a corneal specialist lifelong	90	1	C
Patients should be reviewed the day after EK	70	3D	Near C
A specific amount of postoperative posturing is optimal			No C

of guttae or scarring in the host Descemet membrane and can be avoided if doing so increases the risk of complications, such as after PK. It is essential to try and avoid Descemet membrane tags at the graft–host interface, and this can be achieved by oversizing the descemetorhexis. An inferior peripheral iridotomy should be performed in DMEK to prevent pupil block from the gas bubble in the presence of a constricted pupil.

The consensus for DMEK insertion is to inject the scrolled transplant using a glass or plastic injector connected to a syringe. Longer unfolding times and direct manipulation/trauma to endothelial cells from instruments, incisions, or fibrin were thought to be associated with increased endothelial cell loss. Respondents agreed that double scrolls are easier to unfold and tight scrolls from younger donors and origami/napkin scrolls are typically harder to unfold. Attempts to alter the scroll configuration before injection to one deemed easier to unfold achieved near consensus. No consensus has been reached regarding whether SF_6 is superior to air as a tamponade agent in straightforward cases. Our panel of experts felt that either was acceptable for straightforward cases, but consensus was achieved regarding the use of SF_6 in more complicated cases. No consensus was reached on whether it was necessary to suture incisions.

TABLE 4. Management of Graft Detachment and Risks for Graft Failure

	% Consensus	Round	Level of Consensus Achieved
DMEK detachments involving the central cornea that are progressing or that are >20% of the graft area should be rebubbled. Shallow, small detachments can be observed, and if a residual air/gas bubble is present, patients should be asked to posture such that this supports the area of detachment. The presence of tight scrolling in the detached area may prompt earlier rebubbling	82	3	C
Simple rebubbling can be performed in the office at the slit lamp, in a minor procedures room or in the theater. For complex cases, complete detachments or cases where the graft cannot be visualized clearly, rebubbling in the operating theater may be advantageous	85	2	C
There is no maximum number of recommended rebubbles. If detachment persists despite rebubble, factors affecting adhesion should be considered and treated if possible	90	3	C
If a cornea has failed to clear by 6 wk, primary graft failure is highly likely and donor exchange should be considered	97	3	C
Primary graft failure may prevent graft adhesion. However, it is difficult to evaluate endothelial function in the presence of graft detachment	97	3	C
The following are associated with premature graft failure			
Viral endotheliitis	97	3	C
Glaucoma with previous filtration surgery	93	3	C
An unstable IOL (AC or PC)		3	C
Previous use of silicone oil for retinal detachment surgery	86	3	C
Excessive graft manipulation during initial surgery	97	3	C
Previous rejection	72	3D	Near C
Previous uveitis	72	3D	Near C
Rebubbling should be performed with SF_6			No C

TABLE 5. Specific Statements Concerning Descemet Membrane Endothelial Keratoplasty

DMEK	% Consensus	Round	Level of Consensus Achieved
Graft preparation			
Tissue from donors younger than 35 years old should be avoided in DMEK if alternate tissue is available	93	2	C
Although older tissue (80–90 years old) is acceptable for use in DMEK, surgeons should be aware that it may have an increased tendency to form unfavorable configurations, and the tissues tendency to remain flat may make it harder to rotate in the anterior chamber	86	1	C
Tissue from diabetic donors is more likely to be associated with preparation failure. It can still be used for DMEK, but it may be preferable to pre-prepare tissue from diabetic donors to avoid cancellation of surgery	90	1	C
If DMEK preparation failure occurs, it would not be advisable to use the fellow eye from the same donor for DMEK, although it can be used for PK or DSEK/DSAEK	92	2	C
For surgeons without access to pre-prepared tissue, a peel technique (Melles or submerged cornea using backgrounds away)[25,26] is a reliable method to learn for graft preparation	80	1	C
It is preferable to mark all DMEK grafts with a stamp or by excision a peripheral triangle[39]	80	1	C
DMEK grafts should be stained with trypan blue. Brilliant blue can be added if surgeons prefer a darker stain	86	1	C
If a tear occurs during DMEK preparation, it is still possible to complete successful surgery by eccentrically trephining the tissue or by using a smaller, noncircular or torn graft	80	3	C
Preoperative treatment			
For combined cataract extraction and DMEK, fewer and easier to reverse dilating drops (such as phenylephrine with tropicamide) should be used. This will facilitate pharmacological pupil constriction before DMEK insertion	77	1	C
In DMEK surgery, where we wish to achieve a small pupil, adrenaline should be omitted from the irrigating fluid	77	1	C
Host preparation			
A descemetorhexis is routinely performed as part of DMEK. It may be avoided if there are no guttae/scarring in Descemet membrane and if performing a descemetorhexis increases the risk of complications	80	1	C
Descemetorhexis may complicate DMEK surgery after PK failure and may be omitted	87	1	C
The descemetorhexis should be the same size or larger than the DMEK graft, and residual Descemet membrane tags should be removed to promote graft adhesion	90	1	C
In routine DMEK surgery, an inferior peripheral iridotomy/iridectomy should be created	87	1	C
The iridotomy/iridectomy can be performed preoperatively with a YAG laser or intraoperatively with a Sinsky hook, scissors, or a vitrectomy probe. It should be sufficiently large to avoid postoperative blockage with fibrin or iris debris	86	1	C
Standard phacoemulsification incisions, with enlargement of the main incision to accept the DMEK injector, if necessary, are appropriate for combined cataract and DMEK surgery	87	1	C
Graft insertion and unfolding			
DMEK grafts should be injected using a closed glass or plastic injector connected to a syringe	90	1	C
Long unfolding times, direct manipulation of the central endothelial surface of the DMEK, graft inversion, incarceration of the graft within the incisions, and ejection of the graft from the eye are factors associated with significant endothelial loss	93	2	C
Fibrin attaching the DMEK graft to itself or the iris/angle results in more difficult and longer unfolding, potentially increasing endothelial cell loss	90	2	C
Avoidance of irregularities in the posterior host bed, such as stromal and Descemet tags and steps in the previous PK interface, is necessary to prevent graft detachment	79	1	C
Although air may be sufficient for attachment in most routine cases of DMEK, the use of 20% SF_6 is not harmful to the endothelium and is an accepted alternative	81	2	C
SF_6 20% may be especially beneficial in cases at higher risk of graft detachment, such as in vitrectomized eyes, eyes with deep anterior chambers, eyes that have had previous glaucoma drainage surgery or after PK	77	2	C
The "double scroll" DMEK configuration is associated with shorter/easier unfolding	96	2	C
Tight scrolls, tissue from younger donors and napkin/origami scrolls, are associated with longer/more complicated unfolding	79	3D	C
You should try and adjust the DMEK configuration to one that is easier to unfold before graft injection			Near C
Incisions should always be sutured			No C
An upper age limit for DMEK tissue should be applied, irrespective of endothelial cell density			No C

TABLE 6. Specific Statements Concerning Descemet Stripping Automated Endothelial Keratoplasty and Descemet Stripping Endothelial Keratoplasty

DSEK/DSAEK	% Consensus	Round	Level of Consensus Achieved
Graft inversion is less common in DSEK than in DMEK, and marking DSEK grafts is optional depending on the insertion method and complexity of the case	85	2	C
Descemetorhexis size is less important in DSAEK than in DMEK. The central cornea should be cleared of guttae, but a descemetorhexis larger than the graft is unnecessary	80	1	C
Microkeratome prepared tissue is preferred (DSAEK) to manually prepared tissue (DSEK)	87	1	C
If microkeratome prepared tissue is unavailable, manual tissue preparation is acceptable	77	3D	C
DSEK/DSAEK tissue preloaded in the eye bank does **not** offer an useful advantage over precut tissue load in theater	80	1	C
Tissue from diabetic donors and donors of all ages can be used for DSEK/DSAEK	83	1	C
DSEK/DSAEK grafts should be inserted through an appropriately sized limbal or scleral tunnel, 5–6 mm for a sheets glide or folding forceps. Insertion systems may facilitate the safe use of smaller, less astigmatism-inducing incisions	90	3	C
Use of an inappropriate small wound for graft insertion during DSEK/DSAEK causes excessive endothelial cell loss	92.	2	C
Achieving a high intraocular pressure during the intraoperative gas fill is an important step in preventing graft detachment in DSEK/DSAEK	77	1	C
Preventing postoperative chamber collapse by suturing the main incision any other that leak is an important step in preventing graft detachment in DSEK/DSAEK	95	2	C
Removal of interface fluid is important after placement of DSEK/DSAEK grafts, and this can be accomplished using compressive sweeping of the surface of the cornea to "milk out" the interface fluid or by the placement of venting incisions	90	3	C
Venting incisions are usually unnecessary in routine cases but may be beneficial in complex cases, especially when there is a curvature mismatch between the donor and host or when sufficient gas tamponade cannot be maintained	90	3	C
Use of air as a tamponade is usually sufficient in DSEK/DSAEK; however, SF_6 may be beneficial in eyes that have had previous glaucoma filtration surgery or are hypotonus	93	1	C
The use of a suture to fix the DSEK/DSAEK graft to the host may be beneficial in cases at high risk of graft detachment, especially in unicameral eyes, where there is a risk of graft migration into the posterior segment	77	2	C
A specific insertion method is preferable for DSEK/DSAEK insertion			No C
Manually prepared DSAEK grafts have comparable or only marginally worse visual outcomes to those prepared by microkeratome			No C
Stromal roughening is a useful adjunct to DSEK/DSAEK adhesion			No C
Damaged tissue should be modified and implanted			No C

DSEK/DSAEK

Table 6 outlines the statements on DSAEK and DSEK. Descemet membrane tags are less problematic in DSEK/DSAEK, and oversizing the rhexis does not offer a significant advantage in DSEK. Final vision following EK was considered better when microkeratome-prepared tissue was used. Only 35% of the surgeons felt that vision was comparable between DSEK with manual preparation and DSAEK after microkeratome preparation. However, in settings where microkeratome-prepared tissue was unavailable, manual DSEK was deemed an acceptable option.

Neither the age of the donor nor the presence of diabetes was a reason to reject tissue for DSEK/DSAEK, although approximately 25% of respondents said they would not use tissue from very young donors (specified age ranged from to 3–10 year old).

No consensus on the method of insertion was achieved, with 50% using a glide and forceps pull-through, 30% using a sheet glide, and 17% using taco-fold forceps insertion. Most surgeons do not feel that any specific method is associated with an increased risk of endothelial cell loss if performed correctly.

Using an incision too small for the insertion method was believed to introduce the greatest risk of iatrogenic endothelial trauma, and the use of smaller incisions may be facilitated using an appropriate insertion device. Air is an appropriate tamponade for DSEK/DSAEK, and 90% of surgeons use this tamponade. There is a consensus that a longer-acting gas may be beneficial in eyes with glaucoma drainage surgery or hypotony. In DSEK/DSAEK, venting incisions and transcorneal graft fixation sutures are considered useful adjuncts to promote graft adhesion in complex cases, whereas the use of stromal roughening did not achieve consensus.

DISCUSSION

The Delphi method helped us produce 98 guidance statements for novice EK surgeons. Our panel of 31 international experts provides a geographical representation of practicing preferences from all parts of the globe, showcasing a broad spectrum of clinical opinions. Although the exact number of panelists needed to perform a reliable Delphi process is yet to be established, this figure is in

keeping with previous consensus groups used within and outside ophthalmology. It is believed that reliability increases with the number of panelists and rounds of questions.[26]

We set 75% as the level of agreement required to achieve consensus on the questionnaire and face-to-face discussions. Again, there is no clear definition for this percentage of agreement required to meet a consensus opinion, with this varying from 50% to 85% depending on the subject being examined,[28–31] with most Delphi studies in examining corneal conditions using 2 thirds as a cutoff for consensus.[28,29] To increase robustness, we set a higher threshold to meet for consensus (75%) and 87 of the 98 final statements reached a consensus of >80%. We believe that our process of asking open questions in the initial stages, moving to more binary agreement statements, allowed us to limit bias, leading questions, and undue influence from the executive committee.

There is strong agreement that EK is the preferred treatment for endothelial dysfunction and DMEK is the preferred modality if the eye is uncomplicated.[40] As there is always a possibility of the DMEK scrolling into its natural endothelium-out configuration during graft unfolding, the panelists felt that all novice surgeons should learn to perform endothelium-out DMEK first. For many surgical procedures, variations in practice are likely to have comparable safety and clinical outcomes. An example in EK is the step taken to avoid a pupil block from a gas tamponade. This can be achieved either by performing a peripheral iridotomy or by widely dilating the pupil such that the lower meniscus of the gas bubble is higher than the lower pupillary border.[41] Where reasonable variations in surgical techniques exist, the Delphi process was able to come to a consensus on which option is preferable to learn first. Some recommendations and alternative options are presented in Table 7.

The Delphi process allowed us to gather preferred practice patterns, which may differ from recommendations in the published literature. Our experts recommend considering a rebubble if the area or detachment exceeds 20% or if it affects the visual axis. This value was derived first from an open question asking surgeons when they would consider rebubbling before formulating the agreement statement.

TABLE 7. Alternative Approaches to EK and Recommendations Derived From the Delphi Process

Recommended Approach	Alternative Approach
DMEK	
Submerged cornea using backgrounds away or Melles graft preparation	Fluid bubble preparation
Using marked grafts	Using unmarked grafts
Endothelium-out tissue loading	Endothelium-in tissue loading
Implantation via injector	Pull through technique
Inferior iridotomy with gas fill just above peripheral iridotomy	Pupil dilation with gas fill just above the dilated pupil
Supine posturing	No posturing
DSAEK/DSEK	
Microkeratome DSAEK preparation	Manual DSEK preparation

This differs from the initial criteria set out by Dirisamer et al,[42] where detachments smaller than 1/3 of the graft were observed for spontaneous clearance. These differences in practice may reflect increased data supporting the safety of rebubbling and the minimal effect of a single rebubble on endothelial cell density,[43–45] although this is not conclusive.[46] Another reason may be related to the different sizes of DMEK transplants. Compared to 9.5 mm grafts used in the cohort reported by Dirisamer et al, 73% of surgeons we surveyed said the largest DMEK grafts they inserted were between 8.5 and 9.0 mm, with average graft size being 8.0 to 8.5 mm. As the overall number of implanted endothelial cells is lower with a smaller graft,[47] perhaps the tolerance of peripheral detachments, which can fibrose and contract, is lower in our pool of respondents.

Our panel did not recommend exchanging stable anterior chamber intraocular lens (ACIOL's) in all eyes that underwent EK. Woo et al[48] found that 5-year graft survival was significantly higher in eyes with posterior chamber lens-fixated IOL's than in those in which an ACIOL was retained or placed at the time of surgery. They did not comment on the stability of ACIOL at the time of surgery. Approximately 80% of the patients had ACIOL's removed during surgery, with 20% being aphakic. The study was a nonrandomized comparison of cohorts, and iris-fixated and scleral-fixated posterior chamber lenses were performed more recently, perhaps pointing to improved outcomes as part of a learning curve.

Tannan et al[49] only exchanged unstable anterior chamber lenses or those shallowing the anterior chamber too much for safe DSAEK implantation. They found no increase in primary graft failure, secondary graft failure, or rejection in eyes that underwent DSAEK with retained ACIOL's and those that underwent IOL exchange. They found an increased complication rate in eyes that underwent ACIOL exchange.

As our guidance is primarily aimed at novice surgeons adopting EK, combining IOL exchange and EK may not be advisable because of its technical difficulty and complication rate. If the patient is aphakic and has corneal decompensation, it would seem sensible to perform posterior chamber fixation of the IOL, although this question was not specifically presented to the consensus panel. Further research on the impact of combined scleral fixated lens implantation and EK is needed.

Although there was a clear consensus on avoiding DMEK tissue from young donors (under 35 years old) if alternate tissue was available, no upper age limit for DMEK was suggested if the tissue met the appropriate endothelial cell quality standards. However, most (60%) surgeons seldom received tissue from donors aged over 75 years. For those surgeons who received tissue from donors above 75 years of age, 80% felt tissue from donors aged 80 to 90 behaved less predictably. The group felt that this should be acknowledged but that further research into the intraoperative behavior and postoperative outcomes of tissue from donors from this age range was warranted.[50]

Surgical practice patterns may also be significantly influenced by tissue availability and eye bank expertise. In

our cohort, surgeons who had access to eye bank prepared DSAEK tissue preferentially used this over manual DSEK tissue. However, there was consensus that DSEK was still preferable to PK even if microkeratome prepares tissue was unavailable. Although prestripped DMEK tissue was favored where available, the routine use of preloaded tissued did not meet consensus. There is some evidence that preloaded tissue can be associated increased complication rates,[51,52] but this is not a universal finding[53] and may be related to graft storage time and media.

Preloaded tissue may improve adoption of endothelium-in DMEK, a technique that is gaining popularity, although data supporting improved outcomes over conventional endothelium-out DMEK are not yet available,[24,54,55] and additional eye bank training and quality control processes will be needed before this is widely available.

Areas of near consensus or no consensus were categorized into 2 groups. For some questions, responses were divided among different options such that no single answer achieved a clear consensus. An example of this was the timing of the postoperative review. Although all respondents agreed that the patients should be seen within 7 days, only 70% saw patients on the day after surgery. This may be related to individual surgeon specifics such as the type of tamponade used. Given that the risk of gas concentration error is eliminated if air is used, surgeons using air tended to review their patients later, and those using SF_6 sooner. The Delphi survey was not constructed in a manner that allowed us to assess the responses in such granular detail. The authors would advise surgeons using SF_6 to have a low threshold to see patients the day after surgery, especially in the early stages of adoption when theater staff may be unfamiliar with gas dilution and more prone to making errors.

The second group of nonconsensus questions occurred when specific statements about aspects of management could not be agreed upon. Although changes in tomography findings are an indication for DMEK in patients with FECD, there is no consensus on the specific tomographic parameters that should be applied. Similarly, there is no consensus on how to manage hydrophilic intraocular lenses at the time of EK to prevent opacification. A third area of nonconsensus was how to define visually significant guttae. Some surgeons believe that confluent central guttae degrade vision, but the point at which this should warrant endothelial keratoplasty when an isolated finding could not be agreed upon. Although there is some evidence that guttae without subclinical edema do not affect vision,[34] other studies support visual dysfunction from guttae in the absence of corneal edema.[56] Further investigation is warranted to help determine what the ideal practice in these situations should be.

Our study has some limitations. Although an effort to have a geographically diverse group of panelists was made, most panelists were from the Europe and North America. Although bias may be introduced, as biometric differences between different races may affect surgical practice, given that 20% of panelists were from Asia and many others work in cosmopolitan cities with ethnically diverse populations, we believe our study is applicable to patients of all ethnic backgrounds.

The EC was self-selected, and the initial surveys were produced by the EC. However, by starting with open questions and using the Delphi process, we believe that the undue influence of any individual was avoided.

Consensus for most statement was achieved early in the Delphi process, with only 9 questions needing to be addressed and modified during the hybrid live discussion. Thirteen panelists attended the live video conference. The question of whether in-person guideline generation is superior to mail-only panels was examined by Washington et al.[27] They found no difference between the 2 methods.[25] We chose to accept online submissions for the third round rather than exclude the valuable opinions of experts who could not attend the live video conference. The final consensus statements were sent to all delegates, and no statements that had reached a consensus during the first 3 rounds needed to be substantially altered.

This study did not explore pre-Descemet endothelial keratoplasty[57] or Descemet stripping only[58] as they were not widely used by the expert panel. Future work to determine a consensus on the exact parameters that should prompt Descemet stripping only over EK is warranted.

Although these statements represent recommendations for novice surgeons, they do not comprise new clinical data from a large patient cohort. The recommendations do not apply to all situations or to all patients. However, we believe that they will form a suitable basis to inspire confidence in the decision making of novice corneal surgeons embarking upon EK and help them adopt best practices for the treatment of endothelial dysfunction. As surgical practice is constantly evolving, the Delphi consensus should be repeated in several years to ensure best practice guidelines remain up-to-date and relevant.

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