Considerations in Corneal Transplantation and Impact on Contact Lens Fitting

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Cornea Preservation Time Study

Australian Graft Registry
trends in keratoplasty techniques

Advantages of DALK over PK
- Safer procedure: no open sky
- Retained Recipient Endothelium: no late endothelial cell loss
- No significant rejection issues
- Patient off steroids in matter of weeks, not years
- Sutures can be removed in only weeks after surgery
- Less risk of rupture in future
- Especially great procedure for Atopic pts, Downs syndrome pts, vascularized recipient rim eyes

Disadvantages of DALK to PK
- Less percentage of eyes attain BCVA of 20/20 with DALK than PK eyes, but an equal percentage of 20/25
- DALK is much more technically demanding than PK and takes more O.R. time
- Graft failure rates the same between DALK and PK
In our practice, DALK is rare

- In specialty contact lens practices, KC patients are retained in contact lenses until very advanced disease
  - Cornea is thinned, scarred prior to transplant
  - Hydrops with residual scarring which dictates PK
- Usually prevents successful DALK, therefore PK is still often procedure performed

Australian Graft Registry
DALK vs PK graft survival

Endothelial Keratoplasty:
Multiple names and acronyms

- PLK: Posterior Lamellar Keratoplasty (Melles)
- DLEK: Deep Lamellar Endothelial Keratoplasty (Terry)
- DSEK: Descemets Stripping Endothelial Keratoplasty (Price)
- DSAEK: Descemets Stripping with Automated Endothelial Keratoplasty (Gorovoy)
- DMEK: Descemets Membrane Endothelial Keratoplasty (Melles)
- DMAEK: Descemets Membrane Automated Endothelial Keratoplasty (Price)

DLEK/DSEK/DSAEK
-variations on a theme:

DLEK: Pocket dissected in corneal stroma – Bed stromal fibers exposed
DSEK/DSAEK: No pocket or dissection Smooth recipient bed

Interface fluid resolves without intervention

1 day post-DSAEK
UCVA=20/200

1 week post-DSAEK
UCVA=20/200

3 weeks post-DSAEK
UCVA=20/100

2 months post-DSAEK
+1.25 + 1.00 x 25 = 20/40
UCVA=20/60
Australian Graft Registry

- 2012: Australian Graft registry data published their annual report
  - 8 year follow-up data on PK and EK for pseudophakic bullous keratopathy or FECD.
- Graft survival for PK:
  - 94% at one year, 88% at two years, 74% at four years, and 51% at six years.
- Graft survival EK:
  - 76% at one year and 70% at two years.
- Mean and median survival:
  - PK
    - Mean 63.51 months, median 84 months (seven years).
  - EK
    - Mean 27.60 months, median 38 months (3.2 years).

Better one, or better two?

- Australian Graft Registry
  - EK vs PK graft survival

- Australian Graft Registry
  - EK vs PK graft survival

**EK vs PK**

- Cochrane review Dec 2014:
  - No difference in best corrected visual acuity (BCVA)
- Irregular astigmatism was worse in PK
- Endothelial cell loss greater following EK
  - EK had 50% of ECD compared to PK at 12 months
- DMEK VA potentially best (80% better than 20/25 at 1 year, Price group,
- Adverse Events:
  - graft dislocation, acute IOP elevation, primary donor failure more common in EK
  - wound and suture-related problems more common in PK
  - no important difference in rate of endothelial rejection episodes between groups

Corneal Endothelial Rejection

- (A) K hundreds line
- Donor class I and II MHC Ag ++ minor
- Contact with T-cell
- Macrophages (eg Langhans cells) present Ag
- Inflammatory cells attack the tissue
- HRP on the donor, not the recipient
**NIH Funded Large Scale Studies on Corneal Transplantation**

- Collaborative Corneal Transplant Studies (CCTS)
- Cornea Donor Study (CDS)
- Corneal Preservation Time Study (CPTS)
  - Collectively explored in association with graft success:
    - Tissue/histocompatibility matching (CCTS)
    - ABO blood type matching (CDS)
    - Donor age (CDS)
    - Donor Preservation Time (CPTS)

**Cornea Preservation Time Study (CPTS):**

- Methods and Analyses of a Multi-Center Prospective Clinical Trial following DSAEK
- NEI grant support: U10EY012358 and U10EY020798

**CPTS Organizaton**

- CWRU
  - Jonathan Lass MD (Study Chair)
  - Loretta Szczotka OD, PhD (Director, Coordinating Center)
  - Beth Ann Benetz, MA (Director, Cornea Image Analysis Reading Center)
- Jaeb Center for Health Research
  - Allison Ayala MS, Director Data Management and Analysis Center
  - Roy Beck MD, PhD
  - Robin Gal MSPH
- National Eye Institute
  - Maryann Redford DDS, MPH

**Cornea Preservation Time Study Clinical Sites**

**CPTS Main Question**

- US surgeons reluctant to use donor tissue beyond 7-8 days from death to surgery
- Limited clinical studies in the United States using donor corneas for PK or EK with extended time out to FDA-approved time in storage of 14 days for Optisol GS at 4°C and none for recently released Life 4°C
- Excellent, but uncontrolled, experience with exported tissue internationally with use of tissue beyond 7 days
**Preservation Time**

**Domestic vs International**

![Graph showing preservation time](image)

**Objectives**

- To determine if the 3-year graft failure rate following DSAEK performed with donor corneas with a preservation time of 8 to 14 days is non-inferior to the failure rate when donor corneas with a preservation time of 7 or fewer days are used.
- To determine if the central corneal endothelial cell density 3 years after DSAEK is related to preservation time.
- To evaluate donor, recipient, operative and postoperative factors on graft failure and endothelial cell density three years following DSAEK.

**Advantages of extending beyond 7-8 days**

- Improve efficiency of tissue evaluation and distribution and reduce need for export
- Change attitudes about longer preservation time among surgeons and patients
- Meet anticipated greater demand for tissue with an aging population
- Respond to future threats to the donor pool related to increase domestic demand and emerging infections

**CPTS Corneal Recipient Stroma Clarity and Graft Failures: Primary Endpoint Measure at 3 years**

- **Clear**
- **Equivocal**
- **Cloudy**

**Grading Scale for Endothelial Keratoplasty**

Images kindly provided by George Rosenwasser MD

**CPTS Graft Rejection Classification**

- **Definite**
  - Mild: presence of one or more of the following signs:
    - one to five KP
    - increase in aqueous cells with less than a 10% increase in total corneal thickness ultrasonically from the previous visit
  - Severe: presence of one or more of the following signs:
    - more than five KP
    - cells in the stroma,
    - a 10% or greater increase in total corneal thickness ultrasonically from the previous visit,
    - a clinically apparent decrease in stromal clarity,
    - endothelial rejection line,
    - or both increased corneal thickness by 10% or greater from the previous visit and increased aqueous cells

**Steroid usage tracked**

Images courtesy of George Rosenwasser MD

**CPTS Classification for Graft Failure**

- Primary donor failure
- Graft rejection failure
- Refractive/visual failure
- Early Failure
- Non-rejection failure

Images courtesy of George Rosenwasser and Mark Terry

**Images courtesy of Lass, Szczotka-Flynn, et al Cornea 2015**
CPTS Graft Rejection Classification Possible/Probable
- Clinically apparent stromal edema impacting stromal clarity with inflammation (keratic precipitates, aqueous cells, ciliary injection) without an endothelial rejection line in a previously clear graft
- OR any of the following:
  - Possible presence of a new KP with difficulty distinguishing between KP vs. pigment

CPTS Secondary Measure Central ECD at 3 years
- Obtaining screening image and ECD from eye bank but not CIARC analyzed
- Postcut image or image obtained prior to shipping for surgeon cut sent to CIARC
- Clinical sites sending images at 6 months, 1, 2, and 3 years for analysis by CIARC
- Dual grading and adjudication process by variable frame analysis to determine ECD

CPTS evaluation of donor, recipient, operative and postoperative factors on graft failure and ECD three years following DSAEK
- Late Complications
  - Rejection
  - Failure/Regraft
  - Epithelial ingrowth
  - Interface opacity
  - Trauma

CPTS status
- Recruitment began in April 2012 and concluded in April 2014
- 1604 eyes consented from 1174 participants
- 1330 surgeries in 1090 patients completed including 240 bilateral cases
- Recipients
  - Median age of 70
  - 90% white, 60% women
  - 94% FECD, 6% PBK
  - 52% phakic preop
  - 18% hx of diabetes

Collaborative Corneal Transplantation Studies
- Between 1986 and 1989, CCTS Group conducted two controlled, double-masked studies addressing donor-recipient histocompatibility matching.
- After 3 years of patient follow-up, participants that received corneal transplants with well-matched antigens did not fare significantly better than those with a poor match.
  - Each patient group had similar rates of initial immune reactions, graft rejection, and graft failure due to rejection or other causes.
  - However, the researchers did note that CCTS patients who were compatible with the donor’s blood type had a better outcome than unmatched patients.
- In short, data from the CCTS indicated that matching patient and donor blood types (combined with treating patients with high-dose topical steroids after surgery) may be potentially effective in improving high-risk corneal transplantation.
Purpose of the Cornea Donor Study

Objective: to determine whether donor age is associated with corneal transplant success in corneal diseases associated with endothelial dysfunction (moderate risk for failure)

Cornea Assignment:
- Corneas assigned from donor ≥66 and from donor <66 using a random approach without respect to recipient factors

Masking:
- Investigator and patient masked to age of donor tissue

Treatment:
- Surgery and postoperative care by surgeons’ usual routine

Study Outcome:
- Graft failure based on clinical exam during 5 year follow up

Enrollment and Participation
- 1,101 subjects enrolled January, 2000 to August, 2002
  - 11 subjects with ineligible diagnoses
  - 1,090 eligible subjects
- 43 eye banks provided corneas to CDS subjects
- 105 surgeons at 80 sites enrolled subjects

5-Year Graft Success Rates

Similar graft success rates
- Donor Age ≥ 66 years 86%
- Donor Age < 66 years 86%

Difference = 0%
- Limit of one-sided 95% CI = 4%
- Less than pre-specified non-inferiority limit of 8%

Graft Success by Donor Age Group

5-Year Graft Success by Donor Age
**Donor Factors Associated with Graft Failure**

- Graft failure rates were not significantly impacted by:
  - any donor characteristics
  - any factors related to the type of tissue retrieval, processing, timing of use of the cornea
  - any characteristics of the donor cornea
- Adjusting for donor age did not affect the results

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**Percent Endothelial Cell Loss from Baseline to 5 Years**

Spearman Correlation Coefficient (95% CI) = −0.20 (−0.30, −0.09)

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**Conclusions**

- 5-yr graft success rate similar with corneas from donors ≥66 yrs and <66 yrs old
- Suggestion of a slightly higher success rate with very young donors
- Endothelial cell loss is substantial over 5 yrs even with successful transplant
- Slightly greater cell loss in corneas from donors ≥66 yrs than <66 yrs old

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**10-Year Graft Success by Donor Age Group**

- *P = 0.11*

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**Median Endothelial Cell Density by Donor Age Group**

(only includes subjects with graft success through 10 years)
Corneal Endothelium 10 Years After Keratoplasty

- Bourne et al, 1997, Ophthalmology
  - Endothelial cell loss was 67%
  - Endothelial cell density was 958 cells/mm²
  - Coefficient of variation was 0.32
  - 5% of grafted cells were 56
  - Corneal thickness was 540 microns
  - Aphakic eyes had the lowest endothelial cell loss
  - Eyes with posterior chamber lens had the greatest endothelial cell loss anterior chamber lenses
  - The central endothelial cells of successful corneal transplants five years after keratoplasty form an unstable monolayer with continued accelerated loss of cells and abnormal cellular morphologic features.
  - This process results in fewer endothelial cells remaining on the central graft with an associated increase in stromal swelling and graft failure.

SMAS Images for a Single Subject over 10 Years

- At 15 years:
  - Endothelial cell loss from preoperative donor levels = 71%
  - Endothelial cell density ~872 cells/mm²
  - Corneal thickness ~590 microns
  - Endothelial cell density appears to be unchanged between 10 and 15 years
  - However, corneal thickness increases
  - Mean annual rate of endothelial cell loss from 10 to 15 years after surgery is 0.2% which is similar to unoperated eyes
  - The cumulative probability of developing glaucoma, graft rejection, or graft failure was 20%, 23%, and 28%, respectively

DSEK vs. SMAS PKP Endothelial Cell Loss

- Price et al, 2013, Ophthalmology
- EK vs PK for endothelial cell density

10-15 years after PK

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Lass et al, Cornea Donor Study
Endothelial Cell Density to Predict Endothelial Graft Failure After Penetrating Keratoplasty

- "The histopathologic findings in grafts with low ECD suggest that the remaining endothelial cells are unstable, stressed, and vulnerable."

Oxygen-deficient metabolism and corneal edema
B.K. Leung, J.A. Bonanno, and C.J. Radke

- "……the processes by which hypoxia controls corneal thickness reside primarily at the endothelium”

How can a cornea remain clear with 40% of its ECD?

- Requirements:
  - maintain barrier integrity at low density
  - fluid pump activity
  - Is likely gradually reduced as ECD declines
- Take ECD as an example. The two main functions of the endothelium, barrier and water pump, follow different courses of decline. The barrier function depends on the ability of endothelial cells to fully cover the stromal surface and to maintain cell to cell tight junctions, and both appear to be intact until end-stage disease in FECD. A study suggests that FECD endothelial cells are capable of migration and division to fully populate a stromal surface despite a reduced ability to control stromal water content.

Scleral Lens Considerations after transplant

- Monitor for excessive corneal swelling as a sign of endothelial cell stress
- Examples in Keratoconus:
  - CLAE, 2015 In Press, Soeters, Visser et al
  - Scleral lenses flatter corneal curvature
  - 2.5 % corneal swelling

Scleral lens Dk/t

Hypoxia, transplants, and scleral lenses

\[
Dk = \frac{1}{\frac{(t_1/Dk_1)}{r} + (t_2/Dk_2)}
\]

Holden/Mertz criteria for daily wear for central cornea: 24 × 10^{-9}
Harvitt–Bonanno criteria for the limbal area: 35 × 10^{-9}
Scleral Lens Considerations to Avoid Hypoxia

- Jaynes, Edrington, Weissman, CLAE 2014

18.2 Scleral Lens

- 6.75 mm/3D reverse - 18.2mm OAD -14.00 Optimum Extra

18.2 mm scleral

- 6.75 mm/3D reverse - 18.2mm OAD -14.00 Optimum Extra

18.2 Scleral Lens
Corneal-Scleral Lens

6.5 mm  15.0mm OAD  16.00  Menicon Z  Std. edge

Landing Zone inside limbus
Light touch over apex

Traditional edge lift

Corneal-Scleral Lens

Scleral vs Corneal-Scleral

Dk/t=2.16
For Dk=100

Dk/t=25.5
For Dk=165

Dk/t at limbus
scleral vs corneo-scleral

Dk/t=22.5
For Dk=100

Dk/t=49.6
For Dk=165

For PKs, I always first consider corneal lens Fitting

“Fit” the corneal contour
Graft shape dictates RGP design
Contact Lens Management of Post-Keratoplasty Refractive Error

- 50% of KC pts return to CLs after surgery
  - Geerards, Vreugdenhil, Khazen. Eye Contact Lens 2006
- 84% CL success rates reported after PK
- Little to no graft compromise from long term CL use:
  - normal endothelial density
  - stable & consistent topography

Time Course of CL Fitting

- as early as 3 months post-op for visual rehabilitation
- Assess sutures for potential impact on graft shape

Post-Irregular Astigmatism Topography

Two Basic Fitting Philosophies

- Fit the corneal contour
- Mask the corneal contour

Corneal Lens Fitting

- “Fit” the corneal contour
- Graft shape dictates RGP design

Waring’s 5 Post-PK shapes:

- Originally Classified on Axial Data
  - Prolate 31%
  - Oblate 31%
  - Mixed (Prolate & Oblate) 17.8%
  - Asymmetric 8.7%
  - Steep to Flat 13.5%
Lens Selection Based on Graft Contour

- **Prolate Cornea**
  - Can simulate normal aspheric topography
  - Central cornea has a steeper radius surrounded by concentric flattening
  - Traditional fitting techniques may be used
  - Exception and not the rule in the CL practice

**PRACTICE PEARL #1:**
Try KC designs

- **Oblate Cornea**
  - Flat Central Topography With Steep Periphery
  - Very Common, at least in one meridian
  - May have heavy central clearance to align with peripheral cornea
  - Here is where the specialty stuff comes in handy

**PRACTICE PEARL #2:**
Start with AXIAL maps to design a reverse geometry lens

- **Mixed Astigmatism**
  - By definition, relatively regular astigmatism encompasses entire graft

**PRACTICE PEARL #3:**
Bitoric lens needed, almost always

### Late Stage Astigmatism after PK for KC


<table>
<thead>
<tr>
<th>Patient</th>
<th>Center</th>
<th>Date of PK</th>
<th>Size of donor button (mm)</th>
<th>Baseline Keratometric astigmatism</th>
<th>Late stage astigmatism</th>
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### PATIENT 1 Initial PK: 11-1985

All sutures removed 04-1986

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<th>Corneal astig.</th>
<th>Manifest refraction</th>
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<td>09-1996</td>
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Patient 2
Initial PK: 03-1989
All sutures removed 12-1989
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<th>Date</th>
<th>Keratometric astigmatism</th>
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<td>05-1997</td>
<td>-0.75 -5.50 X 036 (180°)</td>
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Lens Selection Based on Graft Contour

- **Graft Tilt**
  - Account for approx. 22% of post graft topography
  - One portion of graft steepens, topography 180 degrees away flattens

**PRACTICE PEARL #4:**
GP lens will center over the steepest portion of the graft

That was theory, this is reality.....

**INTRALIMBAL LENSES**

- Dyna Z Intralimal
- GBL Lens
- Rose K2 IC

**PRACTICE PEARL #5:**
Utilize "Asymmetric Corneal Technology" aka steep/flat option

**EXAMPLE: POST PK FOR KC**

Steepest SynergEyes PS available
Intralimbal Lens with ACT

Blanchard
ACT grade 1 (0.7mm)
ACT grade 2 (1.0mm)
ACT grade 3 (1.3mm)

Lens Dynamics
Steepen/flatten
15 steps in either direction
1 step steep 30 μ
1 step flat 50 μ

PK eyes fit with piggybacks

Predicted Tear Oxygen Tensions

PRACTICE PEARL
Watch oxygen delivery in some combinations


Piggyback Lens Systems

- Advantages
  - Comfort
  - Freedom from mechanical trauma

- Disadvantages
  - Two lens per eye daily management
  - Optics?
  - Coatings

Tear Oxygen Tension beneath piggyback lens systems

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<th>RGP Dk/t</th>
<th>SCL Dk/t</th>
<th>Open eye pO₂</th>
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Piggyback lenses

PRACTICE PEARL #5:
- Steep BC needed for some oblate grafts
PRACTICE PEARL #7
Use soft lens to reshape the corneal contour

Topo over +7.00
Days

PRACTICE PEARL #8
Piggyback soft lens can act as a prosthetic device

THANK YOU