THE CORNEA DONOR STUDY (CDS) AND IMPLICATIONS FOR CORNEAL TRANSPLANTATION

ALAN SUGAR MD
KELLOGG EYE CENTER
UNIVERSITY OF MICHIGAN
JUNE 23, 2012
NO FINANCIAL INTEREST

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CDS DESIGN

- Determine effect of donor age on corneal transplant success
- Randomize donors <66 or ≥66
- Masked surgeon and recipient to age
- Surgery and treatment per surgeon’s routine
- Originally 5 year follow-up, now ending 10 years

PENETRATING KERATOPLASTY
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

Causes of Corneal Disease

- Fuchs' Dystrophy: 4%
- Pseudophakic/Aphakic Corneal Edema: 34%
- Endothelial cell density: 62%

Key Donor Eligibility Criteria

- Age 10 to 75 years
- Endothelial cell density: 2300-3300
- EBAA criteria met

Donor Age

- Mean = 58 years
- Range 12 to 75 years
- Cornea from donor ≥ 66 yrs: 383 (35%)
- Cornea from donor < 66 yrs: 707 (65%)
**Median Baseline Endothelial Cell Density by Donor Age**

- Baseline Endothelial Cell Density
- Donor Age (Years)

**5-Year 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%

Cornea Donor Study Investigator Group, Ophthalmology 2008;115:620

**Graft Success by Donor Age Group**

- Success Probability
- Years since Surgery

**Causes of Graft Failure**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Donor Age &lt; 66y</th>
<th>Donor Age ≥ 66y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1,090</td>
<td>N=707</td>
<td>N=383</td>
</tr>
<tr>
<td><strong>Total Graft Failures</strong></td>
<td>135 (12%)</td>
<td>90 (13%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td><strong>Primary Donor</strong></td>
<td>3 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Refractive</strong></td>
<td>8 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Graft Rejection</strong></td>
<td>48 (4%)</td>
<td>32 (5%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td><strong>Non-rejection</strong></td>
<td>76 (7%)</td>
<td>50 (7%)</td>
<td>26 (7%)</td>
</tr>
</tbody>
</table>

Majority non-rejection failure
SECONDARY CDS OUTCOMES RELATED TO EYE BANKING AND DONOR CHARACTERISTICS

### DONOR RISK FACTORS FOR GRAFT FAILURE

<table>
<thead>
<tr>
<th>Retrieval / Timing Factor</th>
<th>N</th>
<th>5-yr Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Retrieval</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enucleation</td>
<td>218</td>
<td>13%</td>
</tr>
<tr>
<td>In situ</td>
<td>872</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Death to Preservation Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 hours</td>
<td>206</td>
<td>17%</td>
</tr>
<tr>
<td>&gt;4–8 hours</td>
<td>577</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;8–10 hours</td>
<td>165</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;10 hours</td>
<td>142</td>
<td>18%</td>
</tr>
</tbody>
</table>


### DONOR RISK FACTORS FOR GRAFT FAILURE

<table>
<thead>
<tr>
<th>Retrieval / Timing Factor</th>
<th>N</th>
<th>5-yr Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Refrigerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>255</td>
<td>15%</td>
</tr>
<tr>
<td>Yes</td>
<td>835</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Death to Surgery Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–&lt;3 days</td>
<td>146</td>
<td>16%</td>
</tr>
<tr>
<td>3–&lt;4 days</td>
<td>597</td>
<td>14%</td>
</tr>
<tr>
<td>4–8 days</td>
<td>347</td>
<td>12%</td>
</tr>
</tbody>
</table>

DONOR RISK FACTORS FOR GRAFT FAILURE

- Slit lamp characteristics
- No effect on graft outcomes

CDS: ABO Compatibility (N=1002)

- Effect of ABO matching in CCTS trial
- 64% ABO compatible
- ABO compatibility did not vary by any recipient or donor demographics including self-reported race/ethnicity


CDS: ABO Compatibility and Graft Failure

<table>
<thead>
<tr>
<th>Graft Failure Type</th>
<th>ABO Compatible</th>
<th>ABO Incompatible</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>6%</td>
<td>4%</td>
<td>0.20</td>
</tr>
<tr>
<td>Any Cause</td>
<td>13%</td>
<td>30%</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Probability of Rejection

- No association with donor factors

CDS: **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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CDS DATA QUESTION CURRENT STANDARDS FOR:

- Death to preservation time
- Death to surgery time
- Refrigeration time
- Cadaver storage time
- Slit lamp characteristics

CDS SPECULAR MICROSCOPY ANCILLARY STUDY (SMAS)

- 31 eye banks
- 41 sites
- 596 subjects
- 347 at 5 years
Baseline Endothelial Cell Density
(only includes subjects with graft success through 5 years)

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>N</th>
<th>Baseline ECD* (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>347</td>
<td>2698</td>
</tr>
<tr>
<td>66.0 to &lt;76.0 years</td>
<td>108</td>
<td>2585</td>
</tr>
<tr>
<td>12.0 to &lt;66.0 years</td>
<td>239</td>
<td>2731</td>
</tr>
</tbody>
</table>

*Baseline ECD from SMRC for 229 and from Eye Bank for 118

5-Year Endothelial Cell Density
(only includes subjects with graft success through 5 years)

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>N</th>
<th>5-Year ECD (Median)</th>
<th>% Loss (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>347</td>
<td>778</td>
<td>70%</td>
</tr>
<tr>
<td>66.0 to &lt;76.0 years</td>
<td>108</td>
<td>654</td>
<td>75%</td>
</tr>
<tr>
<td>12.0 to &lt;66.0 years</td>
<td>239</td>
<td>824</td>
<td>69%</td>
</tr>
</tbody>
</table>

Endothelial Cell Density over 5 Years by Donor Age Group

Spearman Correlation Coefficient (95% CI) = 0.27 (0.17, 0.36, \( r^2 = 0.07 \))
Effect of Donor and Recipient Factors on Endothelial Cell Loss

- Younger Donor Age (P<0.001)
  - 12-<40: 62%
  - 70-76: 75%
- Larger Graft Size (P<0.001)
  - >8.0 mm: 68%
  - <8.0 mm: 75%
- Female Donor (P=0.004): 67% vs. Male 72%

Analysis of ECD Predictive of Graft Failure


Cumulative Incidence of Graft Failure

6 month ECD Predictive of Graft Failure
CDS: Endothelial Cell Density Predictive of Endothelial Graft Failure

- Pre-op ECD unrelated to graft failure due to endothelial decompensation
- Strong correlation of ECD at 6 months with failure due to endothelial decompensation
- 62 grafts clear at 5 years with ECD < 500 cells/mm² (178-497)

BIEXPONENTIAL MODEL OF POST KERATOPLASTY CELL LOSS

- Predicted cell loss by initial density
- Theoretical support for 2000 ECD limit

Armitage, Dick, Bourne. IOVS 2003;44:3326

BIEXPONENTIAL MODEL OF POST KERATOPLASTY CELL LOSS

- If ECD at 5 years is only minimally related to pre-op ECD,
- Then donor cell count may not be as important as we now assume
- If initial severe cell loss correlates with graft failure,
- Then we need to develop better understanding of the causes for initial/early cell loss
- Also, these models assume all recipients act alike

CELL LOSS POST KERATOCONUS PKP

- Representative case
- Less than PKP for endothelial disease
- Predicted 27 years to ECD < 500

**PREDICTED GRAFT SURVIVAL BY HOST ENDOTHELIAL STATUS**

- Keratoconus
- Bullous Keratopathy

**BÖHRINGER ET AL HYPOTHESIS**

- Half-lives of donor and recipient endothelium differ
- Recipient half-life longer than donor in keratoconus
- Donor half-life longer than recipient in bullous keratopathy
- Healthier endothelium moves toward the unhealthy endothelial gradient, or
- Autologous endothelium moves along gradient

**DONOR ENDOTHELIAL DENSITY: TENTATIVE CONCLUSIONS**

- The 2300 cells/mm² ECD used in the CDS should not be the standard lower limit for PKP donors
- The Böhringer hypothesis suggests using older donors for conditions with good endothelium (KC) and younger donors for endothelial disease
- There is little evidence for current limits on ECD

**IMPACT OF DONOR CRITERIA ON TISSUE AVAILABILITY AND COST**

<table>
<thead>
<tr>
<th>Effect of Limiting Cell Density</th>
<th>Minimum Age</th>
<th>Minimum Cell Density</th>
<th>Percent of Suitable Tissue</th>
<th>Median Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>2000</td>
<td>800</td>
<td>100.0%</td>
<td>2,400</td>
</tr>
<tr>
<td>70</td>
<td>2500</td>
<td>71.1%</td>
<td>2,813</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>2800</td>
<td>56.4%</td>
<td>5,427</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Percent of Suitable Tissue</th>
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<tbody>
<tr>
<td>75</td>
<td>2000</td>
<td>90.0%</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>2500</td>
<td>80.4%</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>2800</td>
<td>56.4%</td>
<td></td>
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</table>

**Effect of Combined Restrictions**

<table>
<thead>
<tr>
<th>Minimum Age</th>
<th>Minimum Cell Density</th>
<th>Percent of Suitable Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>2000</td>
<td>50.0%</td>
</tr>
<tr>
<td>70</td>
<td>2500</td>
<td>40.4%</td>
</tr>
<tr>
<td>65</td>
<td>2800</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

Woodward MA, Ross K, Requard JJ, Sugar A, Shtein RM
Impact of the CDS on Eye Bank Practice? Donors Used for Transplant in the US

Complete Data for 7 Eye Banks

<table>
<thead>
<tr>
<th></th>
<th>≥60 years</th>
<th>Median Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before CDS (1998-1999)</td>
<td>19%</td>
<td>53 (39-63)</td>
</tr>
<tr>
<td>During CDS (2000-2007)</td>
<td>21%</td>
<td>54 (41-64)</td>
</tr>
</tbody>
</table>

all p <0.001


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**ENDOTHELIAL KERATOPLASTY**

- 2005 1,398
- 2006 6,027
- 2007 14,159
- 2008 17,468
- 2009 18,221
- 2010 19,159
- 2011 21,555

46% of 46,196

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**PKP VS. DSEK**

Van Dooren BTH, et al. IOVS Sept 12, 2011

Price MD et al. Ophthalmology 2013;118:725
Cornea Preservation Time Study (CPTS)

CPTS STUDY CHAIR
Jonathan H. Lass, M.D.
Charles I Thomas Professor and Chairman
CWRU Department of Ophthalmology and Visual Sciences
Director, University Hospitals Eye Institute
Medical Director, Cleveland Eye Bank

CPTS Clinical Sites

CPTS Eye Bank Sites

Cornea Preservation Time Study (CPTS) Objectives

- To determine if the 3-year graft failure rate following EK (DSEK) 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 EK (DSEK) is related to preservation time.

- To evaluate donor, operative, and postoperative factors on graft failure and endothelial cell density three years following EK (DSEK).

- 1,330 eyes
CDS and Eye Banking

- Much of what we assume regarding donor cornea suitability is not validated
- Eye banking practice and policy are largely driven by regulation rather than science
- More scientific evaluation of eye banking practices is necessary
- The CPTS will examine some donor corneal variables related to endothelial keratoplasty in a large trial