Innovation in corneal grafting

Rogers Innovation Adoption Curve

Mark Daniell
Adoption of new technique

Five Stages in the Decision Innovation Process

Knowledge  Persuasion  Decision  Implementation  Confirmation

Reject  Accept
Persuasion

• Patient outcomes improved
• Complication profile improved
• Theoretical benefit to patient
• New technique is simpler/quicker/more efficient
• Perceived marketing advantage
• Fear of appearing out of date

Factors preventing change
• Comfort in established technique
• Learning curve
• Inertia (new instruments, training courses, fear of complications)
• Skepticism to innovation
Rogers Adoption/Innovation curve

Innovators
Innovators are willing to take risks, have closest contact to scientific sources and interaction with other innovators. High risk tolerance

Early adopters
They are more discreet in adoption choices than innovators. They use judicious choice of adoption to help them maintain a central communication position. These individuals have the highest degree of opinion leaders among the adopter categories.

Early Majority
Thoughtful people, careful but accepting change more quickly than average

Late Majority
They adopt an innovation after the average participant. These individuals approach an innovation with a high degree of skepticism and after the majority of society has adopted the innovation.

Laggards
They are the last to adopt an innovation. These individuals typically have an aversion to change-agents. Laggards typically tend to be focused on “traditions” and critical towards new ideas.
Rogers Innovation Adoption Curve

- Innovators: 2.5%
- Early Adopters: 13.5%
- Early Majority: 34%
- Late Majority: 34%
- Laggards: 16%

Market share %

0 25 50 75 100
Pattern of use of corneal tissue is changing

![Graph showing domestic surgery use of U.S. supplied intermediate-term preserved tissue]
ACGR Graft type by year of registration
Corneal endothelial cell loss

Corneal Endothelium

To lens, retina.

Stroma

Air
DSAEK

- Most commonly performed type of EK
- Initial results many patients failed to achieve 20/20 vision
  - Debate around effect of graft thickness
  - Stromal interface
  - Regularity of the cut

- Early DSAEK highly variable thickness in graft

- Double pass microkeratome technique developed to yield ultra thin DSAEK lenticule
Innovators

**Descemet’s Membrane Endothelial Keratoplasty**  
Ophthalmology  Volume 118, Number 12, December 2011  
Prospective Study of 1-Year Visual Outcomes, Graft Survival, and Endothelial Cell Loss

Frederico P. Guerra, MD, Arundhati Anshu, MD, Marianne O. Price, PhD, Arthur W. Giebel, MD, Francis W. Price, MD

**Ultrathin Descemet’s Stripping Automated Endothelial Keratoplasty with the Microkeratome Double-Pass Technique**  
Two-Year Outcomes  Ophthalmology  Volume 120, Number 6, June 2013

Massimo Busin, MD, Silvana Madi, MD, Paolo Santorum, MD, Vincenzo Scorcia, MD, Jacqueline Beltz, FRANZCO

**Three-Year Visual Acuity Outcomes after Descemet’s Stripping Automated Endothelial Keratoplasty**  
Ophthalmology  Volume 119, Number 6, June 2012

Jennifer Y. Li, MD, Mark A. Terry, MD, Jeffrey Goshe, MD, David Davis-Boozer, MPH, Neda Shamie, MD
BSCVA in Eyes with 6/6 Potential

DMEK

UT-

DSAEK

DSAEK

Three Years BSCVA Trend Comparison

logMAR BSCVA

0 0,1 0,2 0,3 0,4

0 6 12 18 24 30 36

UT-DSAEK  DMEK  DSAEK
UT DSAEK 5 year Results

Busin M & Beltz J
Retrospective Case Series
354 eyes in 348 patients
Standardized Double-Pass Technique
UT DSAEK preparation
Surgical technique standard
DSAEK
Long-term Clinical Outcome After Descemet Membrane Endothelial Keratoplasty

ANDREAS SCHLÖGL, THEOFILOS TOURTAS, FRIEDRICH E. KRUSE, AND JULIA M. WELLER

Descemet Stripping Endothelial Keratoplasty for Fuchs’ Endothelial Corneal Dystrophy

Five-Year Results of a Prospective Study

Katrin Wacker, MD, Keith H. Baratz, MD, Leo J. Maguire, MD, Jay W. McLaren, PhD, Sanjay V. Patel, MD, FRCOphth

Ultrathin descemet's stripping automated endothelial keratoplasty with the microkeratome double-pass technique: five-year outcomes.
BSCVA in Eyes with 20/20 Potential Case series comparison

**DSAEK**

**DMEK**

**UT-DSAEK**
5 Year Outcomes of UT-DSAEK compare favorably with those of conventional DSAEK and do not differ substantially from those of DMEK.
Standard DSAEK technique is “ultrathin”

- Moria microkeratome
- Single pass, linear system, aiming for 100u (UT DSAEK)
- Organ culture storage of cornea
- 24-48 hours in thinning media
- Central corneal thickness measured
- Adjusted nomogram from Moria to select cutting head (350-450u)
DMEK

• Gaining popularity but still challenges with preparing and handling tissue

Advantages
• Retrospective studies show quicker visual recovery and improved visual acuity
• May have less rejection
• Preparation is done manually so no microkeratome required

Disadvantages
• Graft preparation delicate technique (SCUBA)
• Donor selection critical ( >65, no previous surgery, no diabetes, good cell count)
• Surgical technique more difficult
• Re-bubbling rate 20% post operatively
Current DMEK pre stripping technique

- Partial strip in eyebank prior to surgery (SCUBA technique)
- 3mm biopsy punch to stroma allows marking in OTS
- Sent in Viewing Chamber
Pre stripped and marked DMEK
DSAEK versus DMEK

- Learning curve different
- BCVA no difference between groups (3/12 vision 1.5 lines better in DMEK)
- Higher order aberrations better DMEK
  - Differences narrow over time
- Endothelial cell count similar
- Rejection rate DMEK 1-3%, DSAEK 5-6%
- Complication rates
  - Re-bubbling DMEK 24%, DSAEK 1%
  - Primary graft failure DMEK 2%, DSAEK 1%
State of the Art: Cell therapy

- Kinoshita et al 2018
- 11 patients with PBK
- $1 \times 10^6$ CEC with ROCK inhibitor
- 10/11 resolution of corneal oedema, increased cell density
The future

Tissue engineered endothelial transplant
30+ grafts from one donor
Ex vivo expansion of CEC
Biodegradable, biocompatibility scaffold
Corneal stromal disease
Keratoconus

Crosslinking of the cornea

• Dresden protocol highly effective (30 minute soak with 30 minute treatment)
• Reduced rate of progression, good safety
• Reduced need for corneal grafts (approx. 25% reduction already)

Dresden protocol RCT at CERA

No change in:
  – BSCVA
  – Subjective refraction: sphere, cylinder or spherical equivalent
• Endothelial cell density

• Progression >1D
  – Control group: 28 eyes
  – CXL group: 1 eye (1.4D)
Change in keratometry (Ksteep over 4 years)

ΔKsteep (D)

control

CXL

mean ± SD shown
All p <0.001
CXL Conventional versus Accelerated

- Bunsen Roscoe effect 3mW/cm² over 30 minutes equivalent to 9mW/cm² over 10 minutes
- “can’t bake the cake quicker by turning up the heat”

Review of literature

C-CXL was superior regarding
- minimum keratometry (p < 0.00001)
- demarcation line depth (p < 0.00001)

Appears to have similar clinical efficacy.
- No differences in:
  - uncorrected and corrected distance visual acuity,
  - spherical and cylindrical error
  - maximal and average keratometry central corneal thickness
  - corneal biomechanical properties
  - time of reepithelialization
  - subbasal nerve density
  - endothelial cell density and morphology

A CXL slightly reduced penetration of effect but similar clinical efficacy
Australian Corneal Graft Registry
DALK versus PK for keratoconus
DALK versus PK

Despite the popularity of DALK amongst corneal surgeons for keratoconus, there is a paucity of high quality RCTs. Cochrane review 2014

- DALK reduced rejection OR 0.33
- PK better visual outcomes
  - better LogMAR BCVA at ≥6 months and better LogMAR UCVA
- Graft survival and CEC count similar
- Surgical factors
  - Learning curve
  - Additional theatre time
  - Failed big bubble
  - DALK unable to be completed as planned
Mesenchymal stem cells for stromal scar

- Fibroblast-like multipotent mesenchymal stromal cells
- Derived from bone marrow, umbilical cord and adipose tissue
- Mechanism of factors in secretotome, exosomes
- Transdifferentiation ability to assume phenotypes of neural ectodermal cells and epithelial cells including limbal epithelial cells and keratocytes
- Evidence of regenerative ability in corneal abrasion and chemical burn model (more rapid healing, less scar and neovascularisation)
- Injection of isolated human stromal stem cells restored stromal transparency in a lumican-null mouse model with corneal opacity

MSC applied to Stromal opacity
- Induces stromal tissue regeneration
- Allows tissue to regenerate itself
Stem cell treatments in the eye

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Vision Loss after Intravitreal Injection of Autologous “Stem Cells” for AMD

Three patients in whom severe bilateral visual loss developed after they received intravitreal injections of autologous adipose tissue–derived “stem cells”

Need rigorous clinical trials and appropriate regulation
Epithelial disease
**Limbal stem cell transplantation**

Cultivation of confluent layer of corneal epithelial cells ex vivo

Autologous source of cells and serum

Cell transfer technologies
  - HAM
  - Other substrates

Potential advantages of ex vivo amplification
  - Less donor tissue required
  - More rapid recovery
  - More stem cells transplanted
Surgical options for bilateral disease

- Keratolimbal allograft (KLAL) with systemic immunosuppression combined with PK/ DALK
  - 6/8 studies
  - Improved vision 30-67% (not given in 4/8)
  - Reduced vision 0-18%
  - Normalised corneal epithelium (clinically) 7/8 studies
  - Follow-up 18-38 months
  - Glaucoma 26-32%
  - Microbial keratitis 8-14%

- Cultivated autologous oral mucosal epithelial transplantation (COMET)
  - Improved BCVA 67%
  - Long term failure common

- Eccentric PK with transplantation of section of limbus
  - Graft failure 72%

Cauchi et al AJO 2008;146:251-259
Kerato limbal allograft (bilateral disease)

- 43 cases
- Cornea-scleral rim for donor
- Up to 360° graft
- Incorporating AMT
- 51% stable epithelium
- 60% improved BCVA
- Follow-up 38 months

Tsubota et al NEJM 1999
Cultivated limbal epithelial transplant (CLET)

- Cultivated limbal epithelial transplant
- Requires systemic immunosuppression for 12 months
- Overall success rate of CLET 72% (1029 autografts, 135 allografts), 2 year follow up
- Two-line visual improvement 55% of patients

Holland EJ. Management of limbal stem cell deficiency: a historical perspective, past, present, and future. Cornea. 2015
Cultivated oral mucosa epithelial transplant (COMET) for bilateral disease

- Autologous source, biopsy 2 weeks prior
- Ex vivo expansion on AMT
- No immunosuppression required

Useful for Aniridia with epithelial breakdown or dense subepithelial scar
- Improved BCVA 67%
- Early decline in transplanted oral mucosal epithelial stability over the first 6 months, remaining comparatively stable thereafter (1 year, 64.8%; 2 years, 59.0%; and 3 years, 53.1%).
- Postoperative persistent epithelial failure developed within the first 3 months in 25%
- Long term failure with gradual fibrovascular tissue invasion of the corneal surface

Satake et al Long-term Outcome of Ocular Surface Reconstruction
Ophthalmology 2011;118:1524–1530
Simple limbal epithelial transplant (unilateral disease)

- Single stage procedure, 2x2mm limbal biopsy, 8-10 pieces
- 8-10 pieces scattered over AMT, fibrin glue
- 125 cases, 76% success, 67% 6/18 or better

Ophthalmology 2016
Induced pluripotent stem cells for cornea

Co-ordinated ocular development from human iPS cells and recovery of corneal function


- generation from human induced pluripotent stem cells of a self-formed ectodermal autonomous multi-zone (SEAM) of ocular cells.
- cells isolated from the ocular surface ectodermal zone of the SEAM can be sorted and expanded *ex vivo* to form a corneal epithelium that recovers function in *vivo*. 
a, A typical SEAM of differentiated human iPS cells after 40 days of culture. c–f,
g, The SEAM of human iPS cells induced different kinds of cells of ectodermal lineage, mimicking anterior and posterior eye development in vivo.

CNS, central nervous system; NE, neuroectoderm; OC, optic cup; NR, neuroretina; NC, neural crest; LE; lens; OSE, ocular surface ectoderm; SE, surface ectoderm; CE, corneal epithelium; EK, epidermal keratinocyte.
Indications for penetrating corneal graft

2011-2016 Trends in Common PK Surgical Indications - U.S. Eye Banks

- Post-Cataract Surgery Edema
- Ectasias/Thinnings
- Endothelial Dystrophies
- Repeat Corneal Transplant
- Other Degenerations or Dystrophies
- Other Causes of Corneal Opacification or Distortion

The Royal Victorian Eye & Ear Hospital
The University of Melbourne
Centre for Eye Research Australia
Highly innovative period in corneal surgery

Lamellar surgery, targeting the layer effected by disease, is here to stay
Each innovation requires careful assessment before adopting new technique

Recommend process of
• Knowledge – follow developments in the field
• Persuasion- rigorous analysis of results
• Decision – weigh the advantages/disadvantages of technique; yes or no
• Implementation – training, planning, case selection
• Confirmation- audit results

Are you an early adopter or a laggard ??
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