Corneal Transplants:
All the info fit to print
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Outline
• Today's goals: REDUCE CONFUSION!
• **Improve clinical and conceptual understanding of keratoplasty**
  – Describe important physiologic and mechanical/tectonic effects of transplantation
  – Increase awareness of newer surgical techniques and the strengths and weaknesses of each
  – Develop appropriate expectation for how each graft type behaves clinically

Cornea
• Function: Optical and structural
• Five (or is it six...) layers thick:
  – Epithelium, Bowman’s Membrane, Stroma, (Dua’s Layer), Descemet’s Membrane and endothelium
  – Cellular reservoirs are the epithelium, keratocytes and endothelium
  – Corneal substance is primarily acellular connective tissue
Cornea

- Four keys to understanding grafting
  - The fate of transplanted nucleated cells
  - Endothelial function and decline
  - Corneal Immunology and how graft rejection is impacted by this
  - Impact of sutures on the cornea

Key# 1: Fate of Nucleated Cells

- Human Luekocyte Antigens (HLA) are expressed on the surface of nucleated cells and identify the cell as part of the organism, or foreign
  - HLA markers are the ONLY component of a transplant that can be identified as foreign by host immunity
  - HLA markers only reside on nucleated cells, not connective tissue which means only transplanted cells can generate rejection episodes

Fate of transplanted cells

- Nucleated Cells are the only targets of rejection in grafted tissue.
  - Epithelium – transient, replaced in first month
  - Keratocytes – transient, unclear duration, likely somewhere between 6-60 months with central cells lasting the longest
  - Endothelium – permanent
Key #2: Cornea: endothelial function

- The endothelium’s primary function is to maintain dehydration of cornea relative to aqueous by way of NA/K+ ATPase pump function

Cornea: endothelial function

- Born with an excess of cells, near 4,000 c/mm²
- This number declines throughout life at a rate of 0.6% per year via apoptosis
- Sufficient until level drops to around 700c/mm²
- At this point, corneal edema occurs — called endothelial decompensation
- Endothelial decompensation occurs at an accelerated rate in grafted eyes

Endothelial Function and graft failure

- When transplanted, decompensation occurs more rapidly
  - Leads to finite life span
  - 15-25 years average
- Process occurs regardless of rejection, but can be accelerated by rejection
Key #3: Cornea: Immunology

- Corneal tissue rejects at much lower rates than other tissue
  - Cornea tissue is not routinely HLA matched from donor to host
  - CDS showed PKs have an 85% 5 year success rate
  - Skin transplants that are not HLA matched will reject at near 100%

Cornea: Immunology

- Considered immune privileged
  - Weak expression of Major Histo Compatability (MHC) antigens
  - Lack of both afferent (lymphatic) and efferent (vascular) arms of immune system
  - Lack of substantial load of native immune cells/APC
  - Presence of the Fas Ligand
  - Beneficiary of the Anterior Chamber Associated Immune Deviation (ACAID)

Cornea Immune Privilege

- How much inflammation will immune privilege tolerate?
  - What happens to immune privilege and vascular equilibrium when you put a suture through the cornea?
    - What about when you put a contact lens on it?
      - What about when you have chronic dry eye?
      - What about when you are using glaucoma medications?
    - What about when you have glaucoma surgery?
  - Immune privilege is relative!
Rejection

• Simply: Rejection is the immune system attacking cellular components of the graft
  – Rejection is CD4+ T cell mediated, attack mounted by the host against the foreign graft.
• Rejection may lead to graft failure through collapse of endothelial pump, or occasionally, scarring

Rejection

• Clinical Evidence
  – The term rejection indicates the body has mounted an immune response against the graft. What evidence of this is required clinically?
• **WHITE CELLS WITHIN THE GRAFT**

Types of Rejection

– Because there are three separate cellular lineages in the cornea, rejection can manifest as one of three processes:
  • Epithelial Rejection
  • Stromal Rejection
  • Endothelial Rejection
Types of Rejection

• Epithelial rejection – Body attacking epithelial cells
  • Manifests as a grey slightly elevated epithelial zone
  • Does not cause failure
  — Limbus is the stem cell region for epithelium and is not transplanted (with exception of KLAU) — therefore, host epithelial cells will eventually replace donor regardless of rejection
  • BUT: Indicates the body has developed acquired immunity to the transplant.

Types of rejection

• Stromal rejection – Body attacking keratocytes
  • Anterior stromal nummular zones of infiltration
  • Does not cause failure unless significant scarring results, but again, represents acquired immunity to graft antigen

Types of Rejection

• Endothelial rejection – Body attacking endothelial cells
  • Manifests as keratic precipitates. May be paired with stromal edema
  • Represents immune response against endothelium, which persists indefinitely
  • May cause failure via endothelial collapse
  • Shortens the life expectancy of the graft even when effectively treated
Types of Rejection

• Acute “Stromal” Rejection
  – The exception to the rule of needing to see white cells in the graft to classify as rejection
  – A sudden onset edematous corneal graft without evidence of immunologic activity
  – All cases of sudden onset edema should be treated as if the graft is rejecting
  – Has been reported with PK, DALK and PLK

Acute Stromal Rejection: DSAEK

Treatment/prevention of rejection

• Primary treatment of rejection is prevention
  – Options
    • Blanket reduction in immune response
      – Corticosteroids, topical or oral
    • Specific reduction in T cell activity
      – Topical Cyclosporin A 1-2% or tacrolimus
        » Has to be combined with corticosteroid for full effect
      – Oral immune modulators – mycophenolate (Cellcept) tacrolimus (Prograf)
Typical taper strategies in uneventful recoveries

- PK – typically starts with prednisolone acetate dosed qid-q2h. This is then tapered by one drop every 3-6 months, eventually transitioning to lotoprednol with stopping considered in the 18-24 month range
- DALK – PA1% beginning at qid may be tapered over the first 6-12 months postoperatively
- DSAEK – PA1% qid then tapering over 18 months
- DMEK – similar taper to DALK

When rejection attacks

- When a rejection episode occurs, initial treatment is an immediate increase in topical steroid...don’t be shy with the dose
- Taper from here only after rejection episode clears
  - Any rejection episode means the patient must always maintain some dose of steroid in the setting of a DSAEK/DMEK or PK
- Over 50% of acute rejection episodes in a PK can be treated effectively – but any successfully treated episode still reduces grafts expected life span

Quick case: Non-Acute impact of endothelial rejection

Graft is 8 years old with two document cases of rejection within the first two years of transplantation
Key 4: Sutures

- Visual recovery of anterior and full thickness transplants is significantly impacted by corneal irregularity created by sutures

Key #4: Sutures

**Good**
- Holds transplant in place
- ...
- ...
- Well, holding the transplant in place is pretty important

**Bad**
- Leads to high amounts of astigmatism
- Slows visual recovery
- Erodes immune privilege by promoting vascularization and lymphangiogenesis

Suture types

**Interrupted**
- Primary suture type used. All grafts receive some interrupteds
- Involves placement of multiple single sutures, typically 16

**Running**
- Typically a 24 bite single continuous suture running the circumference of the graft
- Quicker to place intra-operatively, though technically less forgiving
Sutures

- Sutures must remain in place until graft-host interface is sufficiently scarred to hold in place:
  - PK: 18-36 months
  - DALK: 9-18 months
- Further, removing sutures will result in change of corneal curvature and refraction, even if delayed for several years
- Antigenic sutures should be removed as soon as possible
- Loose interrupted sutures do nothing to support graft and should be removed when encountered
- Suture infiltrates require increased use of corticosteroids

Sutures

- Securing sutures are not used in:
  - DSAEK
  - DMEK
- And because of this, the visual recovery of these grafts is much more rapid

Summary of the 4 key concepts

- Only endothelium is a permanent graft antigen – grafts without endothelium avoid long term risk of rejection
- Only endothelial rejection commonly leads to failure – grafts without endothelium have little to no risk of rejection induced failure
- Even without rejection, transplanted endothelium will fail resulting in finite life span of grafts which carries endothelium
- Immune privilege of the cornea shields against rejection, but can be lost if there is sufficient increase in inflammatory markers in the cornea. The severity of rejection episodes generally varies by graft type depending on the extent each erode immune privilege
- Sutures are primarily responsible for very slow visual recovery and high amounts of astigmatism.
Keratoplasty types

Background: 3 primary graft types

- **Full Thickness**: Penetrating Keratoplasty (PK) – full thickness transplant containing all layers of the cornea
- **Anterior Lamellar**: Deep Anterior Lamellar Keratoplasty (DALK) – all tissue anterior to Descemet’s membrane transplanted – useful for scars and ectasia
- **Endothelial keratoplasties**: family of posterior lamellar grafts useful for endothelial decompensation (DSEK and DMEK)

Penetrating Keratoplasty (PK)

"THE REPORTS OF MY DEATH HAVE BEEN GREATLY EXAGGERATED"

MAK TIVIN

© Lifehack photos
PK

**Strengths**
- One surgery can be applied to all layers
- Relative ease of procedure
- No interface through its thickness
- Historic record
- Best overall survival rate!

**Weaknesses**
- Open Sky procedure means susceptible to expulsive hemorrhage
- Susceptible to all rejection types
- Dependence of chronic steroid use
- Acceleration of endothelial decompensation relative to physiologic levels
- Potential for wound rupture
- Astigmatism/rgp dependence
- Prolonged visual recovery

PK Recovery

**PK recovery is the most difficult of transplants:**
- Slow recovery because of sutures – 18-48 months
- Frequent need for rgp – (50% of eyes nationally)
- Relatively high risk of rejection – Long term corticosteroids
- High risk of glaucoma
PK: life expectancy of graft

- Life expectancy is roughly 15-25 years as, on average, ECD is reduced by about 30% by the surgery itself and decompensation proceeds at a more rapid pace than normal corneas\textsuperscript{2,10}
- After 15 years average ECD is 800 c/mm\textsuperscript{2} of graft

Failed PK

Failed PK
Failed PK

Posterior Lamellar Keratoplasties

- Procedures that target diseased endothium
- Development:
  - PLK -> DLEK -> DSEK -> DSAEK -> DMEK

DSAEK and DMEK

- DSAEK – most common endo transplant. Includes posterior stroma, DM and endo. Supported by air bubble for ~3-4 days
- DMEK – newer. Includes DM and endo only. Supported by gas bubble for ~5-7 days
DSAEK and DMEK OCT

DSAEK over view
- Involves transplantation of donor DM+endo+posterior stroma
- Posterior stroma facilitates handling and insulates endo from surgical trauma

Graft Review:
DSAEK
**Benefit of DSAEK over PK**

- Refractivity close to neutral 1-2 D hyperopic shift. Minimal effect on astigmatism – no dependence on rgps
- **Best corrected acuity as good or better than PK for similar indications (average acuity 20/30-40)**
- Very rapid recovery relative to PK (~6-9 months)
- Quick recovery and strong visual outcome allows for earlier intervention
- Rejection episodes less severe and less likely to lead to failure
- More stable globe than with PK

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**PBK → DSAEK**

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**DSAEK**

- **Weaknesses compared to PK**
- Relative complexity
  - Steep learning curve
  - Prone to early dislocation and failure
Quick Case

• 1 day post DSAEK. HM vision
• Refloated that day with a large air bubble
• Next day VA 20/200 (due to air bubble interference, 1 week later VA 20/30)

Average Course of DSAEK

• Day 1-Day 4 – positioning restrictions in place to tamponade graft with air bubble
  – Chances of graft dislocation ~5-10%
  – When the graft won’t attach after rebubbling, this is known as early graft failure
• Steroid often maintained for ~18 mos (tapered by 1 gt q3mos)
• Visual recovery can be frustrating to patient and clinician
  – Expect Hyperopic shift of 1-2 D
  – Graft may look perfect, but BSVA may be 20/50-60 for first 6-12 mos. Be patient

DMEK

• Involves transplantation of DM and endothelium only
• Surgery is more difficult due to elastic nature of DM
DMEK unrolling

Benefits of DMEK over DSAEK

- Refractivity close to neutral: minimal to no hyperopic shift. Minimal effect on astigmatism – no dependence on rGPS.
- Best corrected acuity as good or better than DSAEK (20/25-20/30, 20/20 outcomes relatively common).
- Very rapid recovery relative to DSAEK (~3-6 months).
- Quick recovery and strong visual outcome allows for earlier intervention yet.
- Rejection episodes less likely.

Comparison of benefits

**DMEK to DSAEK**

- Refractivity close to neutral: minimal to no hyperopic shift. Minimal effect on astigmatism – no dependence on rGPS.
- Best corrected acuity as good or better than DSAEK (20/25-20/30, 20/20 outcomes relatively common).
- Very rapid recovery relative to DSAEK (~3-6 months).
- Quick recovery and strong visual outcome allows for earlier intervention yet.
- Rejection episodes less likely (only 1% risk!).
- DMEK more challenging.

**PK to DSAEK**

- Refractivity close to neutral: minimal to no hyperopic shift. Minimal effect on astigmatism – no dependence on rGPS.
- Best corrected acuity as good or better than DSAEK (20/25-20/30, 20/20 outcomes relatively common).
- Very rapid recovery relative to DSAEK (~3-6 months).
- Quick recovery and strong visual outcome allows for earlier intervention yet.
- Rejection episodes less likely (only 1% risk!).
- More stable globe than with PK.
Draw backs of DMEK

• Technically more challenging than DSAEK
• Greater risk of early graft dislocation
• Greater risk of early graft failure
• Greater risk of tissue wastage (~8%)
• Gas bubble in eye for longer than with DSAEK
  — Can’t travel over elevation with the bubble

Average Course of DMEK

• Gas bubble in eye with positioning restrictions for about twice as long as DSAEK. Early acuities are worse as the gas bubble degrades VA.
  — Greater potential for early dislocation, may require multiple re-bubbles
• As gas bubble recedes VA is often quite good
  — Even though course is quicker than DSAEK, may still seem slow to patient
• Usually stable by 6 mos post operatively
• Steroid maintained at some level for 12-18 mos

DSAEK/DMEK life expectancy

• Endothelial decompensation to the graft caused by the surgery is variable with the graft type, insertion technique and incision size
• DSAEK - 28-32% ECD loss at 6 mos
• DMEK – 34-42% ECD loss at 6 mos
• Acceleration of endothelial decompensation is about equal to that of PK
• In an uneventful recovery, life span will likely mirror that of PK
Drawback of any Endo transplant

• Not really a draw back, but visual recovery can be surprisingly slow, even with a healthy looking transplant
• Refractive effect not always predictable especially in patients with prior LASIK
• Stromal graft host interface leads to slight risk of interface problems
  — Textural Interface Opacity

Deep Anterior Lamellar Keratoplasty (DALK)

• Anterior cornea is transplanted with goal of leaving only host descemet’s membrane and endothelium
• Useful in cases of anterior stromal disease: kerato-ectasias, corneal scarring
**DALK**

- **Strengths**
  - No endothelium transplanted so risk of rejection leading to failure is low/absent
  - No/minimal effect on endothelial decompensation
  - Less long term dependence on steroids
  - Stronger tectonically than PK

**DALK life expectancy**

- In an uneventful recovery, should persist indefinitely

**DALK**

- **Weakness**
  - Astigmatism/rgp dependence
  - Prolonged visual recovery
  - Surgical complexity often requires conversion to PK
  - Greater failure rate than PK
  - Interface issues
DALK Interface Problems

- Converts to PK ~20% of the time
- Breaks and pleats in Descemet's
- Interface haze
- Interface vascularization

Quick Case: the benefit of DALK

- 69 YOM
- Ohx:
  - 2004 re-PK, 1 rejection episode in first year
  - Ongoing – severe glaucoma developed in interim
  - 2013 – DSAEK to PK – process and postop resulted in increased IOP and exacerbated glaucoma
  - Currently BSVA to 20/400

Quick Case Take home

- 100% of these problems would have been avoided with DALK
Referral Paradigms for transplant

• More options available now than ever before
• Most effective treatment is the primary consideration
• Least invasive treatment is the secondary consideration
  – Should consider both immediate and extended postoperative period

Endothelial transplant Treatment Paradigm

• All sources of endothelial decompensation are treated with PLK, including:
  – Fuch’s Dystrophy
  – Pseudo/Aphakic Bullous Keratopathy
  – ICE syndromes
  – Failed penetrating keratoplasty
• These can be treated at levels that precede substantial edema if endothelial clarity is sufficiently reduced
• My preference is DMEK whenever possible, DSAEK as second option

DALK: Treatment Paradigm

• For all scars and dystrophies: 2\textsuperscript{nd} Choice
  – Phototherapeutic keratectomy (PTK) is first choice. If opacities are too deep to make this feasible DALK is indicated
• For keratoectasias: 2\textsuperscript{nd} Choice
  – Corneal Collagen Crosslinking is the primary treatment of choice in early or mid-stage disease
  – Our goal as a profession should be to get away from transplant for ectasia
PK: treatment paradigm

- PK is indicated:
  - For scars involving the full corneal thickness, including endothelium
  - When DALK is attempted, but clean interface not achieved
  - When DALK is attempted but Descemet’s membrane perforates

- It's generally the last choice

Conclusion

- Remembering the cellular make-up of each graft type will help predict risk of complication, course of recovery and life span
- Each transplant type has its own advantages, disadvantages and characteristic postoperative course
- Being aware of typical postoperative outcomes with the various transplants can improve referral timing and add quality years of vision to our patient’s life

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