The Pursuit of the Ideal Contact Lens: A 40 Year Journey

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This lecture is dedicated to my good friend and 3-decade fellow companion on the quest.

Kyoichi Tanaka
Nagoya, Japan
Infection is THE major sight-threatening complication of CTL wear........can we prevent it is the subject of this lecture.

Pseudomonas

Acanthamoeba
### Why Acanthamoeba?

- 0.2% per 10,000 contact lens wearers per year
  
  \[38 \text{ million} \times 0.2 = 109\] cases/year

- ? Increasing in frequency

- 33% of 1st 50 cases MK worldwide in orthokeratology

- Potential oral vaccine
  - Low tear IgA levels

### Why Pseudomonas?

- Pre-disposable lenses, >50% cases of lens-related microbial keratitis


- 10 years *after* disposable lenses, >50% cases of lens-related MK still

  *Pseudomonas* (Cheng; *The Lancet*, 1999).

- 52% of 1st 50 cases MK/OK
Milestones and Giants

- **1960’s**: Otto Wichterle: The hydrogel lens
- **1970’s**: John De Carle: 1st high water lens; Don Korb & Miquel Refojo: thin membrane lens
  - Holden-Mertz curve: the search for more O2 begins.....
- **1980’s**: Extended wear produces an “epidemic” of infection
  - Pure silicone lenses fail
  - The Hilton Head Conference 1986
  - Schein and Pogio papers 1989
  - Keystone Conference 1989
Milestones and Giants

- **1990’s**: Disposable lenses dominate with *LESS* O2
- **1999**: Cheng study: *Lancet*; no progress in reducing infections
- **2000’s**: Silicone hydrogels: The San Diego Conference 2003
- **Where are we now?**
Pathogenesis and Prevention of Pseudomonas Corneal Infectious Keratitis

- PA attaches to surface or deeper epithelial layer cells (pilli, LPS)…no damage, no binding; no binding, no infection.
  - Epithelial cells take up PA intracellularly by membrane lipid raft-mediated endocytosis…block with anti-cholesterol inhibitors: statins
Pathogenesis and Prevention of Pseudomonas Corneal Infectious Keratitis

- If basal lamina (BL) is intact, actual infection still may not occur in contact lens wear (Orthokeratology, filter paper damage)
- If BL is breached, infection ALWAYS occurs....“scrape/cut” injury.....
  - Is this relevant to contact lens wear?
HYPOTHESIS

• Overnight CTL-wear causes hypoxia which produces graded damage to the epithelium in inverse proportion to the Dk/L of the lens.

  and

• The amount of epithelial damage determines the amount of PA-binding, hence the risk of infection.
Pseudomonas aeruginosa American Type Culture Collection (ATCC) #27853

- 1974, selected as the world’s standard infectious test strain for antibiotic testing.¹
- Piliated, infects the cornea easily in animal keratitis models.²

QUANTITATIVE DETERMINATION OF CONTACT LENS-INDUCED DESQUAMATION BY IN VIVO CONFOCAL MICROSCOPY

Graph showing desquamation (%):
- Observer A
- Observer B

Bar graph:
- Categories: A-D, E, F, A-H, Hy-Co
- Comparison between rigid and hydrogel lenses

Scatter plot:
- Observer A (desquamation %) vs. Observer B (desquamation %)
- p < 0.01
- R = 0.919
LENSES TESTED

in vivo Rabbit Model

- 6 rigid lenses: Dk/L: 0, 10, 27, 44, 84, 97
- 4 hydrogel lenses: Dk/L: 9, 20, 39, 51*

- ALL LENSES 14.0 mm dia./0.15 mm thickness

- * Hybrid hydrogel with silicone acrylate.
Total Corneal Surface Pseudomonas Binding: Rabbit Studies

Overnight Wear

<table>
<thead>
<tr>
<th></th>
<th>RIGID</th>
<th>SOFT</th>
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<tbody>
<tr>
<td>PMMA</td>
<td>*</td>
<td>**</td>
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<tr>
<td>RGP</td>
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<tr>
<td>Hydrogel</td>
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<td>Hybrid</td>
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<td>Silicone</td>
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**p<0.01
*p<0.05

Adherent Pseudomonas (x 10^6 CFU)

Dk/L

0  27  44  97  9  20  39  62  95

In Vivo Rabbit Studies


At a fixed Dk/L value, rigid lenses produce more epithelial damage than hydrogel lenses...? Mechanical effect?

At a fixed Dk/L value, hydrogel lenses produce more bacterial binding than rigid lenses...? Stagnant tear lake – trapping effect?
Total surface corneal PA binding correlates with PA binding to exfoliated corneal epithelial cells (rabbit model) p<0.01

Ren et al. CLAO J 1997;23:63-68
Does total surface corneal PA binding correlate with PA binding to exfoliated epithelial cells in the rabbit model?

Ren et al. CLAO J 1997;23:63-68
Figure 7: The relationship between P. aeruginosa adherence to exfoliated epithelial cells and residual corneal binding ($R=0.78; \ P<0.001$).
Test lenses

- Rigid gas permeable lenses (n=3): Dk 40, 66, 146
- Soft lenses (n=7): Dk 10, 23, 33, 51, 64, 83*, 96*
- Randomized, prospective, masked clinical trial 110 patients

* Silicone hydrogel lenses

Ren et al. CLAO J 1999;25:80-100
3 Months Continuous Wear

EOP(O₂)

\[ P = 0.0084 \quad R = -0.258 \]

\[ P = 0.0132 \quad R = -0.245 \]

PA

\[ P < 0.0001 \quad R = +0.386 \]

No Correlation

DES

\[ P = 0.006 \quad R = +0.275 \]

No Correlation

SIZE
Effects of 6-hours total corneal hypoxia

- 7% corneal swelling
- No significant increase in Pseudomonas binding
- Significant decrease in surface cell exfoliation (apoptosis)

Ren et al. CLAO J 1997;23:63-68
Ren et al.  *CLAO J* 1999; 25: 80-100
Discussion & Conclusions

- Hypoxia alone produces no increased bacterial binding: presence of a lens and hypoxia are required.
- Lens $O_2$ properties drive bacterial binding: new hyper Dk lenses produced no significant increase vs no lens wear in a pilot study.

*Ren et al. CLAO J 1999;25:80-100*
Discussion & Conclusions

- All lens wear shuts down normal surface cell shedding (apoptosis)
- Cell exfoliation significantly correlates with O₂ transmission
- But: aging surface cells, gradually increasing in size do not bind more bacteria unless hypoxically challenged

Ren et al. CLAO J 1999;25:80-100
### Pseudomonas Binding Clinical Studies 1998-2002

- **Prospetive, Randomized, Double-masked, Single center, Parallel treatment groups**
- **Prior to study: 1 month no contact lens wear**
- **Prelens baseline exam (control)**
- **2,4 weeks daily wear**
- **1,3,6,9,12 months extended wear**

<table>
<thead>
<tr>
<th>Lens Type</th>
<th>N</th>
<th>Dk/L</th>
<th>Description</th>
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<tbody>
<tr>
<td>Acuvue</td>
<td>70</td>
<td>24</td>
<td>Conventional hydrogel</td>
</tr>
<tr>
<td>PureVision</td>
<td>135</td>
<td>125</td>
<td>Silicone hydrogel</td>
</tr>
<tr>
<td>Menicon Z</td>
<td>75</td>
<td>250</td>
<td>RGP</td>
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<tr>
<td>Night &amp; Day</td>
<td>98</td>
<td>175</td>
<td>Silicone hydrogel</td>
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**References**

Daily Wear

PA-binding to Exfoliated Epithelial cells

Daily Wear

Pseudomonas-binding (Bact./cell)

Baseline 2 weeks DW 4 weeks DW

Wearing Time

PA Binding

Acuvue

Pure Vision

Menicon Z

Pseudomonas binding - Daily wear

N=36

N=135

N=75

(* Statistically significant (One-Way Repeated Measures ANOVA to baseline, SNK)

Acuvue

Night & Day

N=70

N=98

(* Significant as compared to baseline, p<0.05)
Conclusions

- Physiological adaptation occurs with all lens wear
  \textit{Prediction: >6M adapted wearers should show lower MK rate}

- Lens-O$_2$ and not wearing schedule (DW, EW) regulates \textit{Pseudomonas (PA) corneal surface binding}
  \textit{Prediction: MK rates should drop or not increase significantly with EW hyper O$_2$ lenses}

- Lens-type also regulates PA-binding: RGP<SH<conventional hydrogel lens wear
  \textit{Prediction: MK rate will be the lowest for hyper RGP lens DW or EW}
Orthokeratology and Microbial Keratitis

- Of 1st 50 cases reported worldwide:
  - 26/46 cases with cultured pathogens were *Pseudomonas* (57%)
  - 15/46 cases were *Acanthamoeba* (33%)

Swarbrick, *Eye & Contact Lens*, Sept, 2005
PA vs OK

Adherent Pseudomonas (x10^6 CFU)

0 1 2

PA vs Dk/L

Dk/L (L=0.15 mm)

RGP Alignment Fit Test Lenses: Rabbit Model

Conventional

PA Binding

Rabbit Model

RGP Wear

Ortho K
The new generation of both rigid and soft hyper-O_2 transmitting lenses should replace conventional, low-\text{O}_2 lens use.

Caution must be exercised when mechanical compression (Ortho K) lenses are used clinically, especially in children.
A 12-Month Clinical Trial
Comparing The Effects of Wearing Modality of Hyper-Dk Silicone Hydrogel Contact Lenses with Non-preserved Solutions on Human Corneal Epithelium

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The University of Texas Southwestern Medical Center at Dallas, TX
Prerequisite for infection = Pseudomonas (PA) binding
Critical Questions Revisited

• What are the effects of long-term daily wear compared to de novo overnight (extended) wear of three hyper-O$_2$ permeable silicone hydrogel contact lenses on human corneal epithelium with non-preserved solutions?

→ Prior studies used preserved care solutions.

→ Solution effects secondary to the use of chemically preserved multi-purpose solutions?

Robertson et al., Invest Ophthalm & Vis Sci, 2008
Study Design

- Prospective, Randomized, Double-masked, Single center, Parallel treatment groups
  - National Clinical Trial (NCT00344643)
- 115 patients completed the study
- 30 day washout period prior to lens wear
- Patients were assessed at baseline, 1 week, 1, 3, 6, 9 and 12 months of lens wear
Study Design

- Lotrafilcon A
  - DW (N=31)
  - 30 N EW (N=29)

- Lotrafilcon B
  - DW (N=21)
  - 6 N EW (N=20)

- Galyfilcon A
  - DW (N=20)

- Central epithelial thickness (in vivo confocal microscopy)
- Epithelial cell exfoliation
- Pseudomonas aeruginosa binding

All patients dispensed Clear Care
Central Epithelial Thickness: 1 Month Lens Wear

- **Epithelial Thickness**
  - AA DW
  - FND DW
  - FND EW
  - O2 Optix DW
  - O2 Optix EW
  - A2 DW

- **Central Epithelial Thickness**
  - 1

- **Visit**
  - 0
  - 1m

- **Graph**
  - *NS*
  - † *p=0.026*

- **Note**
  - *Acuvue 2: historical control*
CET: 12 Months of Lens Wear

**Daily Wear**
- No Effect on CET with DW

**Extended Wear**
- CET Thinning in EW

Visit

Epithelial Thickness (microns)

- FND DW
- O2 Optix DW
- Acuvue 2: historical control

† p<0.05

* P<0.0001
Epithelial Cell Exfoliation: 1 Month Lens Wear

![Graph showing desquamation rates over time for different lens wear options.](image)

- **AA DW**
- **FND DW**
- **FND EW**
- **O2 Optix DW**
- **O2 Optix EW**
- **A2 DW**

*p < 0.0001
†p < 0.001

* Acuvue 2: historical control
Exfoliation: 12 Months of Lens Wear

Decrease in exfoliation in DW & EW during the initial 6 months of lens wear

* Acuvue 2: historical control
PA Binding: 1 Month Lens Wear

**MPS**

**NS**

*P<0.001

* Acuvue 2: historical control

Non-preserved
No increase in PA binding was seen with any hyper-Dk lens regardless of wearing modality.
Conclusions #1

- Effects of DW on CET are Independent of Lens-$O_2$.

- In EW mode, even with hyper Dk lenses, CET appears to decrease significantly, but recovers over one year (adapts).

- All lens wear (DW, EW), hyper or high oxygen transmission, decreases central epithelial surface cell desquamation with adaptive effects over 1 year.
Conclusions #2

• Binding data predict the risk for PA CTL-keratitis should be the same for DW and de novo EW silicone hydrogel lens wear over 1 year.

• Assumes NO solution-induced corneal surface damage that could increase PA binding (Clear Care used in all studies).
Chemically Preserved Contact Lens Care Solutions

- Prospective, double-masked, randomized, cross-over clinical trial.
- N=20 patients (10 male; 10 female).
- 4 lens care solutions: ReNu Multiplus; Optifree Express; Complete Blink-n-Clean, and Lens Plus Rewetting drops.
- Outcome measures: PA binding to exfoliated surface corneal epithelial cells; exfoliation rates.
All solutions decreased surface cell exfoliation (P<0.004)
All solutions raised PA binding (P<0.02)
Conclusions #3

• An ↑ in PA binding suggests an ↑ in risk of infection
• No ↑ in PA binding suggests no ↑ in risk of infection
• An optimal lens-solution combination exists