The Epidemiological Perspective

*cartoons taken from Epidemiology 3rd Edition by Leon Gordis

Annualized incidence of MK in the pre-silicone hydrogel era

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Year</th>
<th>Lens Type</th>
<th>Annualized Incidence per 10,000 wearers Daily with contact lens wearers</th>
<th>Annualized Incidence per 10,000 wearers Extended with contact lens wearers</th>
</tr>
</thead>
<tbody>
<tr>
<td>New England</td>
<td>1989</td>
<td>Conventional Low Dk</td>
<td>4.1 (95% CI 2.9 - 5.2)</td>
<td>20.9 (95% CI 15.1 - 26.7)</td>
</tr>
<tr>
<td>Holland</td>
<td>1999</td>
<td>Conventional and Disposable Low Dk</td>
<td>3.5 (2.7 - 4.5)</td>
<td>20.0 (10.9 - 30.0)</td>
</tr>
<tr>
<td>West of Scotland</td>
<td>1999</td>
<td>Conventional and Disposable Low Dk</td>
<td>5.7 (1.5 - 9.7)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

1 in 2500
1 in 500
### Annualized incidence of MK in the Silicone Hydrogel era

- Schein et al 2005 *Ophthalmology*
  - 18 per 10,000
  - lotrafilcon A 30 day continuous wear

- Stapleton et al 2008 *Ophthalmology*
  - 11.9 per 10,000 SH daily wear
  - 25.4 per 10,000 SH extended wear

### Modern Studies Assessing Risk for MK

- Stapleton et al
  - *Ophthalmology* 2008
    - 12 month national surveillance study in Australia between 2003-04

- Dart et al
  - *Ophthalmology* 2008
    - 2 year case-control study at Moorfields in UK

### Crude Incidence for MK per 10,000 wearers (Stapleton et al 2008)

<table>
<thead>
<tr>
<th>Lens Type</th>
<th>Any MK</th>
<th>Severe MK</th>
<th>VA loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Wear</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RGP DW</td>
<td>1.2</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>DW soft</td>
<td>1.9</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Daily Disp.</td>
<td>2.0</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>DW Si-Hy</td>
<td>11.9</td>
<td>8.0</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Overnight Wear</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EW soft</td>
<td>19.5</td>
<td>13.3</td>
<td>4.0</td>
</tr>
<tr>
<td>SH soft</td>
<td>25.4</td>
<td>16.9</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>ANY</strong></td>
<td>4.2</td>
<td>2.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

13.9% of MK results in loss of VA
Crude Incidence for MK per 10,000 wearers (Stapleton et al 2008)

<table>
<thead>
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<td>2.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Dart Case Control Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned Replacement Soft</td>
<td>REFERENT</td>
<td></td>
</tr>
<tr>
<td>Si-Hy</td>
<td>1.16</td>
<td>0.525</td>
</tr>
<tr>
<td>Other soft</td>
<td>0.87</td>
<td>0.698</td>
</tr>
<tr>
<td>Daily Disposable</td>
<td>1.56</td>
<td>0.009</td>
</tr>
<tr>
<td>RGP</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Influence of lens type

Modifiable and non-modifiable risk factors for microbial keratitis

#### Australian study

<table>
<thead>
<tr>
<th>Modifiable Risk Factors</th>
<th>Odds Ratio</th>
<th>London Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occasional overnight use</td>
<td>3.96</td>
<td>1.87</td>
</tr>
<tr>
<td>Poor storage case hygiene</td>
<td>3.70 (during daily wear only)</td>
<td>2.96 (during daily wear only)</td>
</tr>
<tr>
<td>Not always hand washing before cleaning</td>
<td>1.49</td>
<td>1.49</td>
</tr>
<tr>
<td>&gt;2 days wear per week (compared to &lt;=2)</td>
<td>3.46</td>
<td>3.46</td>
</tr>
</tbody>
</table>

#### Non-modifiable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 6 months contact lens use</td>
<td>4.42 (during extended wear only)</td>
</tr>
<tr>
<td>High socioeconomic class</td>
<td>2.66 (during daily wear)</td>
</tr>
<tr>
<td>Male</td>
<td>1.48</td>
</tr>
</tbody>
</table>

#### Demographics

<table>
<thead>
<tr>
<th>Australian study</th>
<th>London Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;=50</td>
<td>0.45 (protective)</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>1.77</td>
</tr>
</tbody>
</table>

#### Microbial contamination

<table>
<thead>
<tr>
<th>Australian study</th>
<th>London Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchase of lenses from internet or mail order</td>
<td>4.76 (during daily wear only)</td>
</tr>
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<td>1.48</td>
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</table>

#### ATTITUDE/ RISKY BEHAVIORS

<table>
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<th>Australian study</th>
<th>London Study</th>
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<td>Male</td>
<td>1.48</td>
</tr>
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</table>
Comparative Risk of Microbial Keratitis with Other Ocular Diseases

### Microbial Keratitis
- Late-ARMD
- Early ARMD
- Eye/Orbit Cancer
- Nuclear Cataracts
- PK in keratoconus
- Eye Injury
- Keratoconus
- Endophthalmitis after cataract surgery
- RD after cataract surgery
- Infiltrates with EWCL
- Loss BSCVA after LASIK

### Comparative Risks

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK</td>
<td></td>
</tr>
<tr>
<td>MK less likely</td>
<td></td>
</tr>
<tr>
<td>MK more likely</td>
<td></td>
</tr>
</tbody>
</table>

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Comparative Risk of Microbial Keratitis with Health-Related Risks

### Death: Food-born Illnesses
- TB
- Lung Cancer
- Breast Cancer

### Death: within 1 month of myocardial infarction

### Death: HIV

### Death: Breast Cancer

### Comparative Risk

- 0.10
- 1.00
- 10.00
- 100.00
- 1000.00
- 10000.00
- 100000.00

---

Comparative Risk of Microbial Keratitis with Non-Health-Related Risks

### Murder
- Death: Motor Vehicle Accident
- Forcible Rape
- Robbery
- Aggravated Assault
- Motor Vehicle Theft
- Violent Crime
- Burglary
- Mishandled Baggage
- Larceny-Theft
- Property Crime

### Comparative Risk

- 1
- 10
- 100
- 1000
- 10000
- 100000
- -100
- -50
- 0
- 50
- 100
- 150
- 200
- 250
- 300

---

Defining Infiltrates

- **By Etiology**
  - Sweeney et al
  - Infectious (microbial keratitis)
  - Non-Infectious
    - CLARE
    - CLPU
    - IK
    - AIK
    - AI

### CONTACT LENS ACUTE RED EYE (CLARE)
- Inflammatory reaction of the cornea after overnight wear
- Generalized redness and pain upon awakening
- Usually unilateral
- No corneal stain overlying infiltrates
- Has been associated with high levels of Gram negative bacteria on lens
  - Pseudomonas aeruginosa
  - Serratia marcescens
  - Haemophilus influenzae
- Has also been associated with Gram + Streptococcus pneumoniae
CONTACT LENS PERIPHERAL ULCER (CLPU)
- Acute inflammatory reaction with PMN infiltration
- Biopsies have been sterile
- Usually located in corneal periphery
- May be asymptomatic
- May scar
- Usually adherence of Gram + organisms on lens
  - Associated with S. aureus bacteria

Infiltrative keratitis (IK)
- Diffuse corneal infiltration
- Associated with
  - Pseudomonas aeruginosa
  - Serratia marcescens
  - Haemophilus influenzae
    - Often from nasopharynx

Defining Infiltrates as a continuum of disease severity

Efron & Morgan (2005)
- 10 signs & symptoms (ex. redness, infiltrate size and shape, haze, discomfort, etc.)
- Score range 2-22
- Adapted version 25 max
- If > 8: Severe keratitis (MK)

Schein et al (2005)
- Levels 1 & 2
  - Probably MK
- Levels 3-4
  - Infiltrative keratitis
- Level 5
  - Infiltrates not CL-related
### Risk (Incidence) of CIE ("significant CIE")

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daily Wear (persons)</th>
<th>Extended Wear (eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dk</td>
<td>0.14%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Silicone Hydrogel</td>
<td>0.6%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### Significant CIE

These are all SERIOUS and SIGNIFICANT INFILTRATIVE EVENTS OR THOSE THAT PRESENTED TO A HOSPITAL OR CLINICIAN FOR TREATMENT

### Asymptomatic Infiltrates

**What is the incidence of CIEs during daily wear?**

- **3-20%** presenting for care
- **3-20%** annualized to 1 year
- **7%** all CIEs, **2%** symptomatic

Rates of Adverse Events With Hydrogel and Silicone Hydrogel Daily Disposable Lenses in a Large Postmarket Surveillance Registry: The TEMPO Registry

- **1+DAY ACUVUE® TruEye®**
- **1+DAY ACUVUE® MOIST®**

Prospective registry of patients being fit with Daily Disposable CLs (not randomized):

- Enrolled October 15, 2011 to August 1, 2012
- 38 Sites, 83 Clinicians
- 1171 subjects over 1 year
Annual Incidence of CIES for TEMPO vs.

Other studies documenting a silicone hydrogel CIE effect during DW or EW

- Radford et al UK Case Control Study 2009
  - 1077 cases with non-ulcerative complications
  - 1340 hospital and 639 population controls
  - Si-Hy increased risk for sterile keratitis
  - Sensitivity analysis: 2.0 X
  - Si-Hy also associated with mechanical disorders
  - 1.8 X
  - Attendance with any non-ulcerative complication
  - 1.9 X

Other studies documenting a silicone hydrogel CIE effect during DW or EW

- Chalmers et al OVS 2010
  - 1276 soft lens wearers, retrospective chart review
  - 17,450 months of wear
  - 4,120 office visits
  - Silicone hydrogel lenses increased risk of inflammatory events
  - 1.8 X increased risk
  - Controlled for mode of wear
  - Age <25 also found to increase risk by 1.9 X

Other studies documenting a silicone hydrogel effect on CIES

- Chalmers et al IOVS 2011
  - CLAY Study
  - 3549 soft lens wearers, retrospective chart review
  - 187 CIEs in 168 patients
  - Silicone hydrogel lenses increased risk of inflammatory events
  - 1.85 X
  - Controlled for mode of wear

Other studies documenting a silicone hydrogel effect on CIES

- Chalmers et al OVS 2012
  - Case Control Study
  - 166 patients with symptomatic CIEs
  - Silicone hydrogel increased risk of CIE
  - 1.99 X
  - Daily wear
  - Extended wear did not find SH to increase risk
### Morgan & Efron Study

**Annualized Incidence of CIE per 10,000 wearers**

<table>
<thead>
<tr>
<th></th>
<th>Non-severe</th>
<th>Severe</th>
<th>RR Non-severe</th>
<th>RR Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>DW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RGP</td>
<td>5.7</td>
<td>2.9</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>DD</td>
<td>9.1</td>
<td>4.9</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>14.1</td>
<td>6.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SH</td>
<td>55.9</td>
<td>0</td>
<td>4.0</td>
<td>Na</td>
</tr>
<tr>
<td>EW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RGP</td>
<td>0</td>
<td>0</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>48.2</td>
<td>96.4</td>
<td>3.4 (ns)</td>
<td>15.2</td>
</tr>
<tr>
<td>SH</td>
<td>98.8</td>
<td>19.8</td>
<td>7.0</td>
<td>3.1 (ns)</td>
</tr>
</tbody>
</table>

### What about SH and solution hypersensitivity?

- Are certain solutions/lenses associated?
- What good studies are there?

### Influence of Lens Care Systems on Lens Materials and CIEs

**What about SH and solution hypersensitivity?**

- Are certain solutions/lenses associated?
- What good studies are there?

### Significant Multivariate Risk Factors

- Effect of care solutions, either individually or in groups (MPS or peroxide)

### Contact Lens Case Contamination during Daily Wear of Silicone Hydrogels

- Wilcox et al OVS 2010
The Longitudinal Analysis of Silicone Hydrogel (LASH) Contact Lens Study

- 205 patients in lotrafilcon A 30 day CW
- Primary outcome: CIE
- Main exposure:
  - Corneal staining
- Other key/interacting variable:
  - Bacterial contamination of study lenses
  - Indirect assessment of mucin layer/mucin balls

CONCEPTUAL MODEL FOR CIE

Microbial contamination + Presence of Ocular surface Disruption (staining or disrupted mucins) → CIE

Exam Times & Procedures

- SLIT LAMP EXAM, STAINING & CIE
- CULTURES
- 1, 4, 8, 12 weeks
- Schirmer

Risk Factor Analysis for CIE

- Corneal Staining:
  - Not associated
- Bacterial Contamination:
  - 100% increased risk
- Smoking:
  - 400% increased risk
- Mucin Balls:
  - 84% decreased risk

Unadjusted cumulative probability of remaining CIE free in the LASH Study over 1 year of follow-up

- 38 subjects experienced at least one CIE
- KM unadjusted cumulative incidence of survival = 73.3% (95% CI 65.0%-79.9%)
- KM unadjusted cumulative incidence of CIE = 26.7% (95% CI 20.1%-35.0%)

Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of at least one episode of moderate corneal staining or greater
Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of substantial bioburden on study lenses

Univariate Hazard Ratio through 12 months

4.41 (95% CI 2.21-8.79)

Percentage of subjects with culture positive lenses stratified by visit and presence of infiltrate

<table>
<thead>
<tr>
<th>Substantial bioburden</th>
<th>No Infiltrative Event</th>
<th>During Infiltrative Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any event</td>
<td>Asymptomatic Events</td>
</tr>
<tr>
<td>Substantial bioburden</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*p value compared to asymptomatic events

Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of repeated episodes of mucin ball formation

Univariate Hazard Ratio

0.17 (95% CI 0.06-0.43)

Mucin Ball Theory

- At least 4 of 19 mucin genes found on the ocular surface
- SH materials absorb very few proteins together with a depleted aqueous layer during CW and shear friction forces, the mucins present in the tear film roll up into visible balls
- Mucin balls may reflect a thicker, more concentrated, or more viscous mucus layer
- A more substantial mucus layer will envelop bacteria or bacterial byproducts, or create an impermeable physical barrier so that bacterial antigens cannot upregulate the immune response at the epithelial surface

Substantial lens bioburden is associated with at least an 8 fold (800%) increased hazard for a CIE regardless if the CIE is symptomatic or not
What is the rate of Lens, Case and Care System Contamination?

- Lenses: >50% harbor micro-organisms; 10% pathogenic
- Care Systems: All can be contaminated, including up to 30% of preserved products
- Cases: >50% contamination

From Microbial Contamination of Contact Lenses and their Accessories: A Literature Review; Szczotka-Flynn, Pearlman, Ghannoum, ECL, March 2010

Lens Organisms: Frequency (%) of isolation in LASH Study

- Lactobacillus
- Pseudomonas Fluorescens
- E. Coli
- Proteus
- Enterococcus Chaus
- Staph. Aureus
- Bacillus
- Stenotrophomonas
- Corynebacterium
- Haemophilus
- Serratia
- Enterobacter cloacae
- Staphylococcus
- Staphylococcus

LASH STUDY:
Pathogical organisms found at least one visit
32% NO
68% YES

Lens Contamination
- Over half (about 56-65%) of worn lenses are found to harbor microorganisms, almost exclusively bacteria
- Lens handling greatly increases the incidence of lens contamination
- The ocular surface has a tremendous ability to destroy organisms
- The presence of ocular pathogens is typically sporadic and unpredictable
- Lens deposits influence bacterial adherence differentially depending on lens substrate
- Variable opinions on whether silicone hydrogel lenses differ from traditional PHEMA lenses in terms of levels or frequency of bacterial colonization in vivo

Care System Contamination

<table>
<thead>
<tr>
<th>Type of Care System</th>
<th>Rates of Contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homemade Saline</td>
<td>100%</td>
</tr>
<tr>
<td>Unpreserved Saline</td>
<td>89-94%</td>
</tr>
<tr>
<td>Aseptic Saline</td>
<td>8-9%</td>
</tr>
<tr>
<td>Preserved Saline: New, Factory</td>
<td>0-33%</td>
</tr>
<tr>
<td>Used Preserved Saline</td>
<td>13-93%</td>
</tr>
<tr>
<td>Soft Lens Cleaner</td>
<td>9-15%</td>
</tr>
<tr>
<td>Sal Veteris Disinfecting Solution (<em>may include peroxide</em>)</td>
<td>0-11%</td>
</tr>
<tr>
<td>Hydrogen Peroxide Soft Disinfecting Solution</td>
<td>6-17%</td>
</tr>
<tr>
<td>Ecolyte (solution for contact lens rewetting drops)</td>
<td>0-4%</td>
</tr>
<tr>
<td>RGP Cleaning Solution</td>
<td>10%</td>
</tr>
<tr>
<td>RGP Wetting and Soaking Solution</td>
<td>21-81%</td>
</tr>
</tbody>
</table>
Case Contamination
- The incidence of positive microbial bioburden within storage cases ranges from 24-81%.
- ¾ of studies report an incidence of greater than 50%.
- Biofilms are considered the major culprit resulting in transfer of resistant organisms from the lens case to the lens surface.
- Lens care solutions have varying efficacies against biofilm.

The Ocular Immune Response
- Two types of immune response:
  - Innate
    - First line of defense
    - Rapid onset (minutes)
    - Lacks memory
  - Adaptive
    - Humoral (antibody) and cell mediated pathways
    - Longer time frame (hours or days)
    - Three phases:
      - Antigen recognition and presentation to host T cells
      - Antigen processing and activation of T and B cells and effector lymphocytes
      - Memory: Cells react with target antigen
    - Memory: Subsequent exposure generates a more aggressive response

The Innate Response
- In the eyes: bony orbit, blink reflex, tear film with anti-inflammatory and anti-microbial proteins, commensal bacteria, tight junctions of corneal epithelium, B-defensins, alternate pathway of complement, pattern recognition receptors

Pattern Recognition Receptors (PRRs) recognize Pathogen Associated Molecular Patterns (PAMPs)
- Molecular Patterns on the surfaces of many micro-organisms can activate complement
  - Direct lysis
  - phagocyte C receptors
  - chemotactic fragments
- Phagocyte PRRs including Complement Receptors, CD14, and Scavenger Receptors recognize Micro-organism PAMPs

If microbes are present at the site of an inflammatory response, how are they recognized as “foreign”?

Innate immunity: activation
- Some components of innate host responses are constitutive and fully or partially active at all times:
  - Barrier functions of skin and mucus membranes (mechanical)
  - Lysozymes, proteolytic enzymes, acid, etc which exist in tears, and other body fluids such as in the stomach (chemical)
- Other innate defense mechanisms require short term activation........
**How can bacterial initiate the immune response?**
- We live in a virtual sea of bacteria with which we peacefully co-exist most of the time. Bacteria can cause disease by:
  - "invading" a space where they are not "normally" found
  - Producing toxins
  - Immunopathology—sometimes the immune response is the disease

**Toll Like Receptors (TLR’s) are Another Class of PRR’s**
- Signaling through various combinations of TLR’s activates the epithelial cells to produce inflammatory cytokines and chemokines
- The cytokines/chemokines recruit white blood cells (mostly PMNs) to the site of insult so they can phagocytose and kill the microbe

**TLR2 + TLR6**
- General Ligands: Peptidoglycan, Zymosan (Yeast), GPI anchor of T. cruzi, some bacterial LPS, Lipoarabinomannan and phosphotidylinositol dimanoside (MTB)

**TLR3**
- Double stranded (viral) RNA

**TLR4**
- LPS, Taxol, HSP60, fibronectin extra domain A, respiratory syncytial virus F protein

**TLR5**
- Bacterial flagellin

**TLR9**
- Hypo-methylated CpG (bacterial DNA)

Underhill & Ozinsky, Current Opinion Immunol, 14: 103-110, 2002
**Mouse model of Contact lens associated corneal inflammation**

- Epithelial abrasion
- 2 µl LPS or other microbial product added to corneal surface
  - 2mm diameter punch from contact lens placed on ocular surface
  - Or soak CL in LPS
- Lens removed, mice wake up
- Measure CXC chemokines at 6 hours
  - Dissect and ELISA
- Neutrophil infiltration to corneal stroma, corneal thickness and haze at 24 hours
  - Confocal microscopy to measure infiltrate
  - Immunohistochemistry for neutrophils

**Central corneal stroma 24h after topical exposure to LPS**

- Normal C57Bl/6
- LPS treated C57BL/6

Infiltrates evident, highly refractile cells

**Bacterial plasma membranes are surrounded by a cell wall composed of a repeating polymer of peptides and sugars (peptidoglycan).** The cell wall is relatively thin in Gram negative bacteria and thicker in Gram positive bacteria.

**Alternative Pathway Complement Activation can Result in the formation of a Membrane Attack Complex which can lyse Gram –, but not Gram + Bacteria.**

Some Bacteria Secrete Exotoxins
Antitoxin Antibodies can Neutralize Bacterial Toxins

Treatment

- Antibiotics
- Steroids
- Removal of antigen/removal of CL

Prevention, Prevention, Prevention

- Lid Hygiene?
- Antibacterial coated lenses?
- Antibacterial coated cases?

Antimicrobial Cases

- Decreased microbial contamination of lenses stored in silver ion case

Results of Lens Storage Challenge

- For silicone and conventional hydrogels, adhesion of PAGSU3 to AQuify MPS-soaked lenses in the PRO GUARD™ case was significantly lower than adhesion to lenses soaked in all other solution and lens case systems (p-value <0.05)

- In contrast, there was generally no significant difference in adhesion between lenses soaked in ReNu and OPTI-FREE® systems and lenses soaked in AQuify MPS in standard lens cases (p-value >0.05)
Will Compliance Solve Inflammation and Infection?

  - Reinforced compliance in 65 normal contact lens wearers and assessed bacterial contamination CLs and accessories
  - Only a slight decrease in contamination rates, which did not reach statistical significance was observed
  - groups showed no significant differences in contamination rates

Lid Bioburden

- Lid bioburden 5X increased risk for CIE
- Anterior blepharitis (i.e. staphylococcal) heritability is 75%
- Patients predisposed to CIE regardless of compliance

Recurrence

- Recurrence also suggests genetic susceptibility

Genetics

- BERK, LEON, HAZLETT, INFECTION AND IMMUNITY, Dec. 1979, p. 1221-1223
  - Inbred mouse strains differ in susceptibility to intracorneal challenge with Pseudomonas aeruginosa.
  - Genetic studies indicate that resistance to corneal infection is dominant over susceptibility and is controlled by autosomal genes.
  - Resistant mice: infection remains localized and spontaneously heals vs Susceptible mice: necrosis, perforation, and phthisis
  - Response appears to be under multigenetic control
  - Suggests a relationship between the natural immune status of the eyes and the genetic background

Genetic control of murine corneal response to Pseudomonas aeruginosa.

- Resistance is dominant over susceptibility
- Inbred mouse strains differ in susceptibility to intracorneal challenge with Pseudomonas aeruginosa.
- Natural resistance to intracorneal challenge with Pseudomonas aeruginosa is controlled by two or more autosomal dominant genes, at least one of which is located outside of the major histocompatibility (H-2) complex.
- Susceptible strains they studied beared one autosomal resistance gene
- A dominant gene is required at each of the two loci involved for resistance to be expressed.
- Natural host resistance to P. aeruginosa corneal infection is regulated by three complementing dominant genes PsCR1, PsCR2, and PsCS.
- Mouse strains favoring development of a Th1-type response are susceptible (cornea perforates), whereas strains favoring Th2 response development are resistant (no corneal perforation).
Genetic Studies in Humans

  - IL-10 promoter haplotypes associated with susceptibility to and severity of bacterial corneal ulcers.
  - Carriers of IL-6 SNPs more susceptible to infection
  - Certain genotypes of IL-12 more likely to have “sterile keratitis”
  - Variation in genotype of IL-6 associated with severity of keratitis
  - Contact lens wearers carrying one copy of the SNP were 3.1 × more likely to experience moderate/severe keratitis and those with two copies, were 6.4 × more at risk compared with those without the mutation.
- Carnt, Willcox, et al. Ophthalmology 2012. Genetic variation in DEF1 that may lead to decreased protein expression of hBD-1 exhibits a tendency toward increased susceptibility and severity of contact lens–related keratitis.

Thank you