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109

Challenges, Microbiology and Epidemiology of Microbial Keratitis

Loretta Szczotka-Flynn, OD, PhD

Room: Valencia 2

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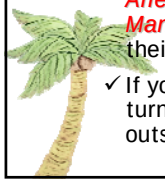

109 – Challenges, Microbiology and Epidemiology of Microbial Keratitis

Loretta Szczotka-Flynn, OD, PhD

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- Vistakon: Research Grant/Research

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Challenges, Microbiology and Epidemiology of Contact Lens Related Microbial Keratitis

University Hospitals Case Medical Center

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

LORETTA SZCZOTKA-FLYNN OD, PhD, FAAO(*dipl CL*)
Professor
Case Western Reserve University
Department of Ophthalmology & Visual Sciences

University Hospitals Case Medical Center

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

The Epidemiological Perspective

FIGURE 20–2 ▼ One view of the seemingly endless stream of reported risks confronting the public. (Jim Borgman, The Cincinnati Enquirer, 1997. Reprinted with special permission of King Features Syndicate.)

*cartoons taken from Epidemiology 3rd Edition by Leon Gordis

Annualized incidence of MK in the pre-silicone hydrogel era

Study Location	Year	Lens Type	Annualized Incidence per 10,000 wearers Daily soft contact lens wearers	Annualized Incidence per 10,000 wearers Extended soft contact lens wearers
New England	1989	Conventional Low Dk	4.1 (95 % CI 2.9-5.2)	20.9 (95% CI 15.1-26.7)
Holland	1999	Conventional and Disposable Low Dk	3.5 (2.7-4.5)	20.0 (10.3-35.0)
West of Scotland	1999	Conventional and Disposable Low Dk	2.7 (1.6-3.7)	Not available

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)

Lens Type	Any MK	Severe MK	VA loss
Daily Wear			
RGP DW	1.2	1.2	0
DW soft	1.9	1.1	0.4
Daily Disp.	2.0	0.5	0
DW Si-Hy	11.9	8.0	1.1
Overnight Wear			
EW soft	19.5	13.3	4.0
SH soft	25.4	16.9	2.8
ANY	4.2	2.7	0.6

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13.9 % of MK results in loss of VA

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Dart Case Control Study

Risk Factor	Relative Risk	P value
Planned Replacement Soft	REFERENT	
Si-Hy	1.16	0.525
Other soft	0.87	0.698
Daily Disposable	1.56	0.009
RGP	0.16	<0.001

Dart Case Control Study

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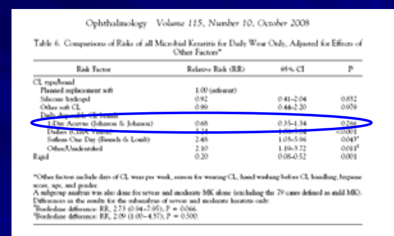
Influence of lens type



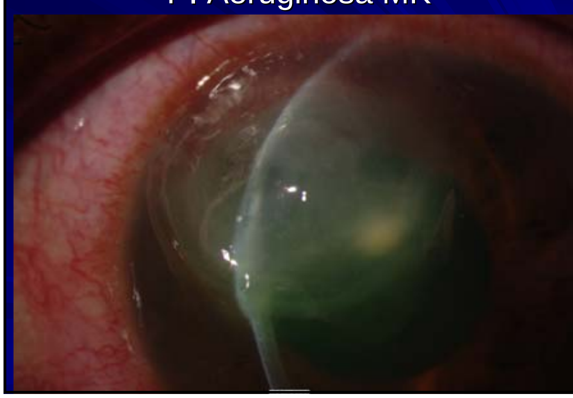
Ophthalmology Volume 115, Number 10, October 2008

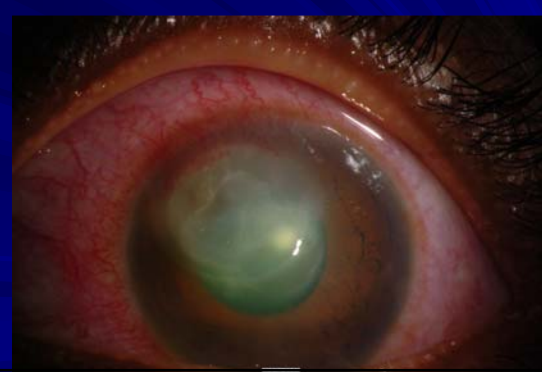
Table 6. Comparisons of Risks of all Microbial Keratitis for Daily Wear Only, Adjusted for Effects of Other Factors*

Risk Factor	Relative Risk (RR)	95% CI	P
CL type/brand			
Planned replacement soft	1.00 (referent)		
Silicone hydrogel	0.92	0.41–2.04	0.852
Other soft CL	0.99	0.44–2.20	0.979
Daily disposable CL brands			
1-Day Acuvue (Johnson & Johnson)	0.68	0.35–1.34	0.266
Dailies (CIBA Vision)	[illegible]	[illegible]	<0.001
Soflens One Day (Bausch & Lomb)	2.48	1.03–5.96	0.043*
Other/Unidentified	2.10	1.19–3.72	0.011[§]
Rigid	0.20	0.08–0.52	0.001

*Other factors include days of CL wear per week, reason for wearing CL, hand washing before CL handling, hygiene score, age, and gender.
A subgroup analysis was also done for severe and moderate MK alone (excluding the 79 cases defined as mild MK). Differences in the results for the subanalysis of severe and moderate keratitis only:
[†]Borderline difference: RR, 2.73 (0.94–7.95); P = 0.066.
[§]Borderline difference: RR, 2.09 (1.00–4.37); P = 0.500.

P. Aeruginosa MK





Modifiable and non-modifiable risk factors for microbial keratitis

	Australian study		London Study
	Odds Ratio		Odds Ratio
Modifiable Risk Factors			
Occasional overnight use	3.96		1.87
Regular overnight use			5.28
Poor storage case hygiene	3.70 (during daily wear only)		
Smoking	2.96 (during daily wear only)		
Purchase of lenses from internet or mail order	4.76 (during daily wear only)		
Not always hand washing before cleaning			1.49
>2 days wear per week (compared to <=2)			3.46 (3-5 days CI wear per week)
Non-Modifiable Risk Factors			
<= 6 months contact lens use	4.42 (during extended wear only)		
High socioeconomic class	2.66 (during daily wear)	2.76 (during extended wear)	
Hyperopia			1.77
Age >=50			0.45 (protective)
Male			1.48

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ATTITUDE/

RISKY BEHAVIORS

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Demographics

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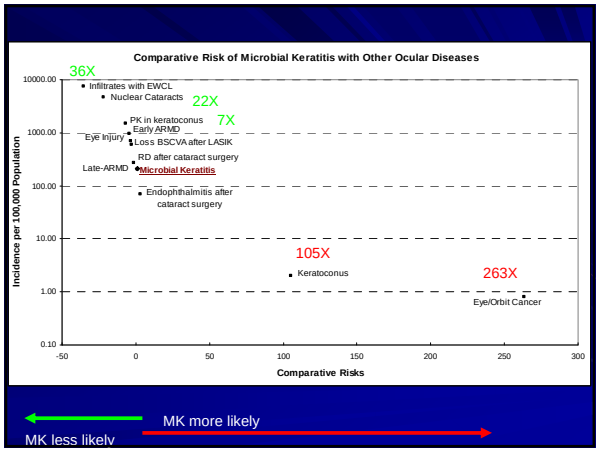
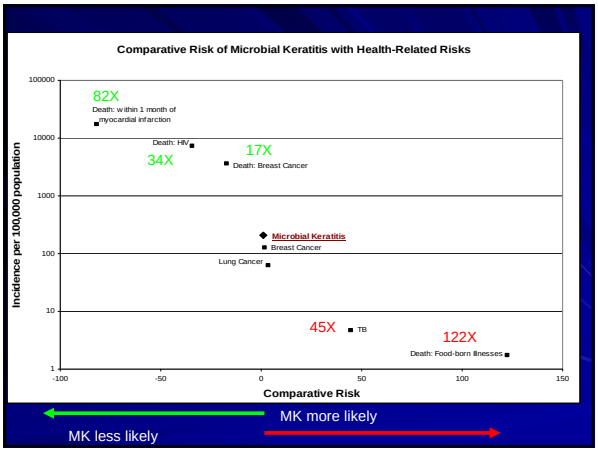
MICROBIAL CONTAMINATION



MK less likely

MK more likely



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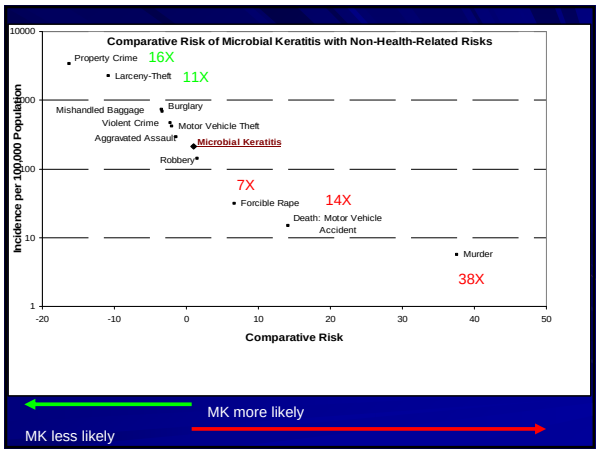
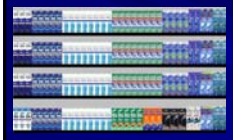


What is the rate of Lens, Case and Care System Contamination?

Lenses: > 50% harbor micro-organisms; 10% pathogenic

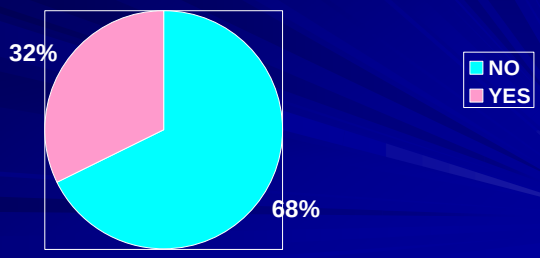


Care Systems: All can be contaminated, including up to 30% of preserved products

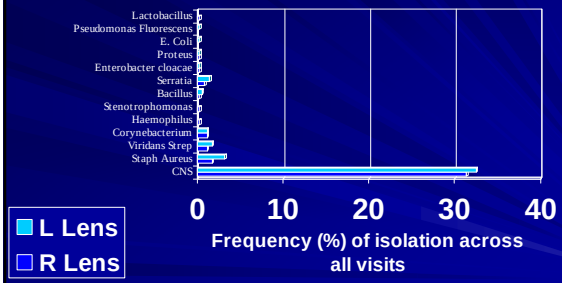
Cases: >50% contamination

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

LASH STUDY: Lens Microbiology Pathogical organisms found at at least one visit



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



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*

Bacterial Adhesion Studies

Study	Organism	Lens	SH Material vs etafilcon	Results
Willcox 2001	*Pseudomonas*	Worn	balafilcon A	**SH increased adhesion**
Borazjani 2004	*Staph. Aureus, Pseudomonas, Serratia*	Worn & unworn	balafilcon A	**No difference**
Kodjikian et al 2007	*Staph. Epi., Pseudomonas*	Unworn	galyfilcon, balafilcon, and lotrafilcon B	**SH increased adhesion**
Santos et al 2007	Normal Flora or *in vivo* contamination	Worn	balafilcon A lotrafilcon A & B, galyfilcon	**SH increased adhesion** **No difference**
Santos et al 2008	*Staph. Epi*	Worn	lotrafilcon A & B, balafilcon A, galyfilcon	**SH decreased adhesion**

Care System Contamination

Type of Care System	Rates of Contamination
Homemade Saline	100%
Unpreserved Saline	25-82%
Aerosol saline	0- 40%
Preserved Saline: New, factory sealed	0-25%
Used Preserved Saline	13-90%
Soft Lens Cleaner	6-15%
Soft Disinfecting Solution (*may include peroxide)	0-17%
Hydrogen Peroxide Soft Disinfecting Solution	4-17%
Eyedrops (artificial tears or contact lens rewetting drops)	0-9%
RGP Cleaning Solution	10%
RGP Wetting and Soaking Solution	21-41%

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

Annualized incidence of MK

Study Location	Year	Lens Type	Annualized Incidence per 10,000 wearers Daily soft contact lens wearers	Annualized Incidence per 10,000 wearers Extended soft contact lens wearers
New England	1989	Conventional Low Dk	4.1	20.9
Holland	1999	Conventional and Disposable Low Dk	3.5	20.0
West of Scotland	1999	Conventional and Disposable Low Dk	2.7	Not available
Australia	03-04	Low Dk soft Si Hy	2 11.9	19.5 25.4

1 in 2500 | 1 in 500

Studies of Microbial Colonization of Hydrogel Contact Lenses

- Sankaridurg, et al 330 subjects, 4,321 lenses cultured at LV Prasad Eye Institute
- Sterile lenses
  - 42% during "asymptomatic" wear
  - 23% during CIE
    - P<0.0001
- Gram-negative bacteria
  - 3.8% during "asymptomatic' wear
  - 23.7% during CIE
    - P<0.0001

330	Group I & IV hydrogels	Asymptomatic & infiltrative events	In CLARE and AIC, *H. influenzae, H. parainfluenzae, Haemophilus, Streptococcus pneumoniae*
1	mid-water hydrogel	CLPU	*Staph. Aureus* cultured
10	etafilcon A	CLARE	*Haemophilus influenzae* cultured
12	etafilcon A, polymacon, phemfilcon	CLARE and infiltrates	*Serratia marcescens, Pseudomonas putida, and Pseudomonas aeruginosa* inadvertently contaminated lenses

The Longitudinal Analysis of Silicone Hydrogel (LASH) Contact Lens Study

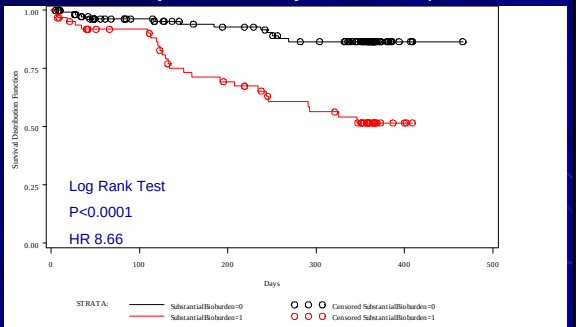
- 205 patients in lotrafilcon A 30 day CW
- Primary outcome: corneal inflammatory event (CIE)
- Main exposure:
  - Corneal staining
- Other key/interacting variable:
  - Bacterial contamination of study lenses
  - Tear immunomodulators

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

	No Infiltrative Event	During Infiltrative Event			
		Any event	Asymptomatic Events	Symptomatic Events	
Substantial bacterial bioburden	14%	65%	53%	74%	0.1365*

*p value compared to asymptomatic events

Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of substantial bioburden on study lenses over 1 year of follow-up



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

Is there any association between contact lens bioburden and discomfort?

- YES!
- LASH STUDY
  - Subjects that reported discomfort preventing continued EW were **4.11X** more likely to harbor substantial bioburden then subjects who did not report discomfort
  - Direction of association is unclear

The Evolving Standards of Lens Care

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University Hospitals Case Medical Center

OUTLINE

- Role of ISO, ANSI and FDA in Lens Care Standards
  - FDAs role in Safeguards for Contact Lenses and Care Products
  - Proposed Silicone Hydrogel Lens Groupings for Lens Care Product Testing
  - Recent and relevant FDA publications
- Biofilms as an example of Lens Care Efficacy Testing
  - Definition of Biofilms
  - *Fusarium* spp
  - Bacterial Biofilms

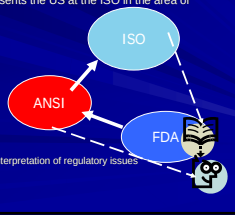
The Contact Lens Event of 2012

BY JASON J.NICHOLS, OD, MPH, PHD, FAAO

Among many other noteworthy events too numerous to mention here, one event of 2012 stood out from the rest. For several years, the United States Food and Drug Administration (FDA) has been moving toward updating the regulatory climate associated with contact lenses and lens care. To my knowledge, this public process started at an FDA-sponsored workshop in January 2009, held in response to the *Fusarium* and *Acanthamoeba* outbreaks in 2006 and 2007, respectively. In the latter half of 2012, the FDA published a series of articles in *Eye and Contact Lens*—eight in all—on this process. The issues at hand primarily include preclinical microbiological testing methodologies and classification for soft lens materials with an expansion to a fifth grouping and related rationale. While these regulatory changes have been a long time in coming, there is no doubt that the changes will impact the contact lens field in addition to the safety of our patients. Thus, we feel that the FDA's forward steps in this process are 2012's Contact Lens Event of the Year.

Role of ISO, ANSI and FDA in Lens Care Standards

- ISO (International Organization for Standardization) and ANSI (American National Standards Institute) develop industry standards that are often adopted by regulatory agencies such as the FDA
- **ISO**
  - The ISO contact lens standards committee includes representatives from approximately 20 countries
- **ANSI**
  - body accredited by the US government that represents the US at the ISO in the area of ophthalmic products (ANSI Z80 Committee)
  - ~20 members include
    - FDA
    - Contact Lens Institute
    - Contact Lens Manufacturers Association
    - American Optometric Association
    - American Academy of Optometry
    - American Academy of Ophthalmology
    - Opticians Association of America
- **FDA**
  - Part of ANSI Z80 Committee
    - Plays a role in the development of ANSI standards
    - Issues Guidance Documents which describe their interpretation of regulatory issues
      - Issue Guidance on
        - regulatory pathway
        - study design
        - data analysis



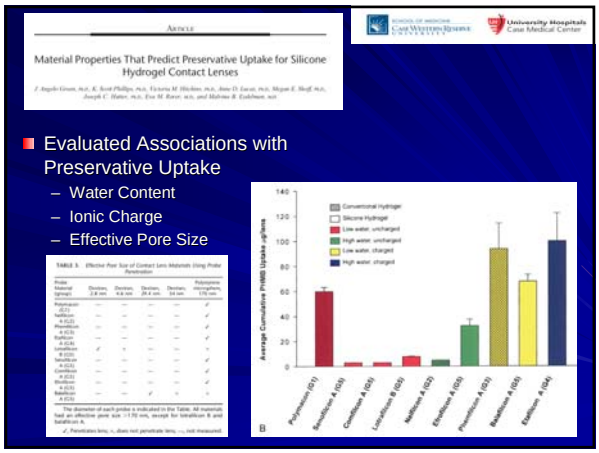
Editorial

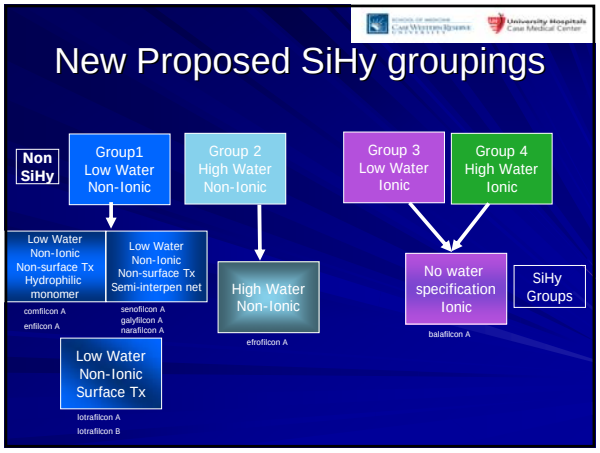
and Maintaining Safeguards for Contact Lenses and Contact Lens Care Products

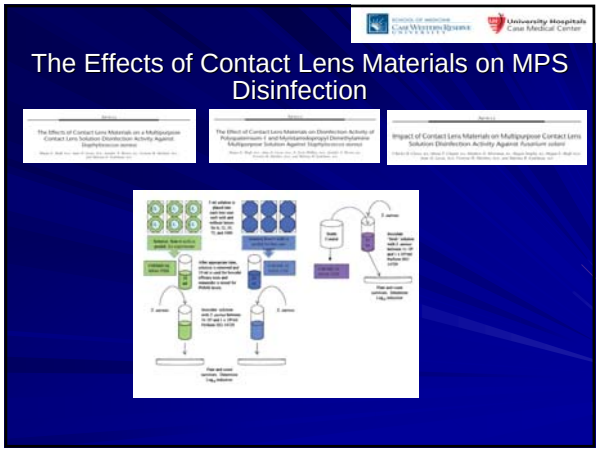
- All RGP, DW SCLs and care products are Class II Devices
  - Require 510K submissions for marketing clearance
- EW CLs are Class III
  - Require Premarket Approval (PMA)
- DW CL guidance 1994
- Contact Lens Care Products 1997
- Consumer confidence erodes in 2006 and 2007 after Fusarium and AK outbreaks
- FDA Ophthalmic Devices Panel and AK Meetings 2008 and 2009

1971 1st SCL | 1985 Draft | 1994 CL | 1997 Solutions | 1999 SH | 2006 Fungal | 2007 AK | 2012


The Food and Drug Administration's Role in Establishing and Maintaining Safeguards for Contact Lenses and Contact Lens Care Products
FDA PLAN FOR THE IMPROVEMENT OF CL SAFETY
1. Research Plan to improve Preclinical Testing
Physiochemical properties of SH lenses for better subcategorization
Antimicrobial efficacy in presence of contact lens (preservative uptake)
Acanthamoeba testing
2. Guidance to manufacturers on labeling
2012 Draft addendum to Care Products Guidance Document
Remove "No-Rub" labeling and recommend Rub-n-rinse
Topping Off Risk Warning
Tap Water Exposure Warning
Discard Date Advice
3. Education
Patient Education Video
Updating FDA CL Website
Consumer articles


Material Properties That Predict Preservative Uptake for Silicone Hydrogel Contact Lenses
Evaluated Associations with Preservative Uptake
Water Content
Ionic Charge
Effective Pore Size


New Proposed SiHy groupings
Non SiHy
Group1 Low Water Non-Ionic
Group 2 High Water Non-Ionic
Group 3 Low Water Ionic
Group 4 High Water Ionic
Low Water Non-Ionic Non-surface Tx Hydrophilic monomer
comfilcon A
enfilcon A
Low Water Non-Ionic Non-surface Tx Semi-interpen net
senofilcon A
galyfilcon A
narafilcon A
High Water Non-Ionic
efrofilcon A
No water specification Ionic
balafilcon A
SiHy Groups
Low Water Non-Ionic Surface Tx
lotrafilcon A
lotrafilcon B


The Effects of Contact Lens Materials on MPS Disinfection

The Effects of Contact Lens Materials on MPS Disinfection

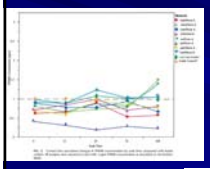
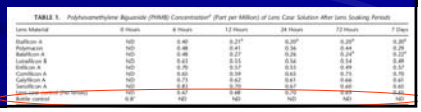


TABLE 1. *Log Kill, Significance, and Associates*

Lens Material	Log Kill	P
Control set 1	2.56	N/A
Balafilcon A	3.57	0.0029
Comfilcon A	3.28	0.0029
Lotrafilcon B	3.12	0.0006
Control set 2	2.14	N/A
Senofilcon A	2.83	0.0015
Enfilcon A	2.71	0.0104
Etafilcon	2.41	0.0415
Galyfilcon A	2.93	<0.0001

NA, not available; OD, optical density.



The Effects of Contact Lens Materials on MPS Disinfection

CONCLUSIONS

- Materials differentially affect preservative concentration
- Preservative uptake influences solution efficacy
- ISO Guidance Documents updated in 2010 to consider testing these interactions
- FDA "now recognizes" these standards

- Problems with this approach: products most affected by the preservative uptake models are not those associated with epidemiological issues
  - Ex. etafilcon A

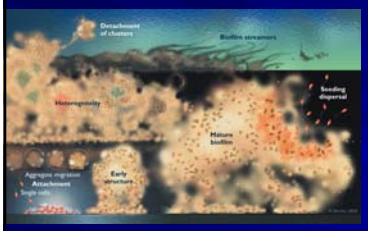
ARTICLE

Strategies to Optimize Conditions for Testing Multipurpose Contact Lens Solution Efficacy Against *Acanthamoeba*

Megan E. Shoff, M.S. and Melvina B. Eydelman, M.D.

- Suggested protocols for Acanthamoeba growth and encystment in testing methods

Biofilms as an example of Lens Care Efficacy Testing



- Identified biofilm forming ability of Fusarium outbreak clinical isolates
- Evaluated efficacy of implicated products against Fusarium outbreak isolates
- Evaluated efficacy of other MPS and peroxide disinfection on Fusarium outbreak clinical isolates
- Identified biofilm forming ability of bacterial clinical CIE isolates
- Evaluated efficacy of MPS and peroxide disinfection on bacterial CIE-clinical isolates

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Acknowledgements

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  - R01 DE017486-01A1, R01DE 13932-4 (MG)
  - K23 EY015270-01 (LSF)
  - EY14362 (EP)
  - P30 EY11373 (EP)
- Bristol Myers Squibb Freedom to Discover Award (MG)
- American Heart Association (Scientist Development Grant 0335313N) Award (PKM)
- Research to Prevent Blindness Foundation
- Ohio Lions Eye Research Foundation

Biofilms can form *in vivo*

BACTERIAL ADHERENCE AND GLYCOCALYX FORMATION ON UNWORN HYDROGEL LENSES

Fiona Stapleton, John K. Dart†, Melville Matheso*

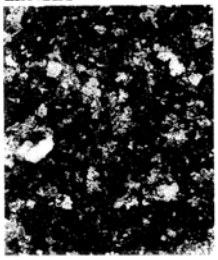
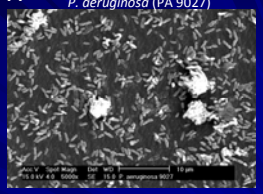


Figure 3. An electron micrograph showing an ES4 lens incubated with 3ml of 10^7 organisms ml^{-1} for 30 min, showing the distribution of organisms on the surface. Lashing marks are clearly visible. Scale: 1cm=6.6μm.

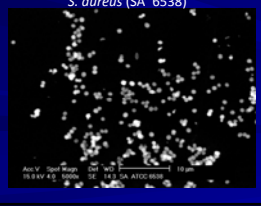
Planktonic
P. aeruginosa (PA 9027)

5000 X

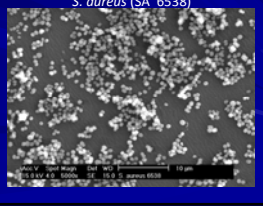
Biofilm
P. aeruginosa (PA 9027)



S. aureus (SA 6538)



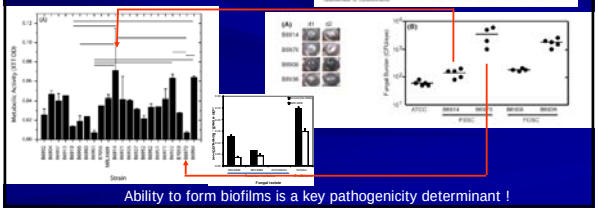
S. aureus (SA 6538)



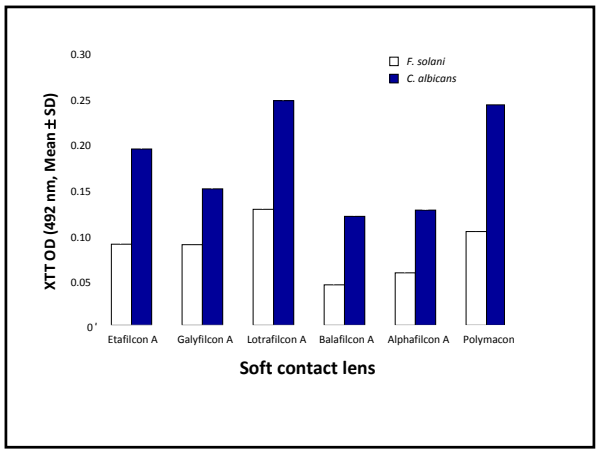
Fungal

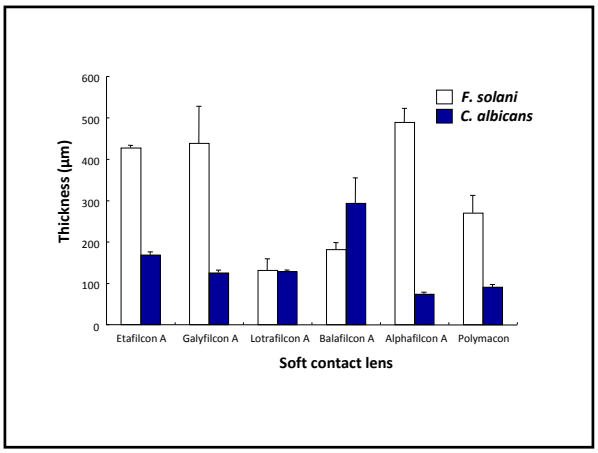
Fusarium and *Candida albicans* Biofilms on Soft Contact Lenses: Model Development, Influence of Lens Type, and Susceptibility to Lens Care Solutions

Characterization of *Fusarium* Keratitis Outbreak Isolates: Contribution of Biofilms to Antimicrobial Resistance and Pathogenesis



Ability to form biofilms is a key pathogenicity determinant !





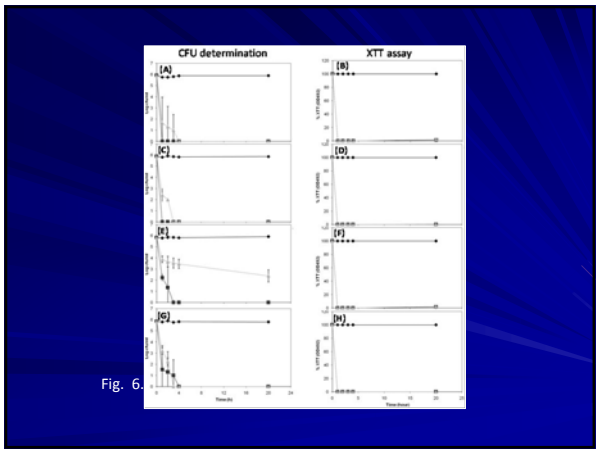


Fig. 6.

TABLE 2. Effect of MoistureLoc or MultiPlus solution on metabolic activities of biofilms formed by two species of *Fusarium* or *C. albicans* on lotrafilcon A lens[a]

Strain	Lens care solution	Activity for incubation time (h) of: 4 — Mean ± SD	4 — % Growth	20 — Mean ± SD	20 — % Growth	*P* value[b]
FSSC 1-b MRL8609	None	0.0403 ± 0.0015	100.0	0.0377 ± 0.0006	100.0	0.047
	MoistureLoc	0.0190 ± 0.0010	47.1	0.0140 ± 0.0010	37.1	0.004
	MultiPlus	0.0197 ± 0.0012	48.8	0.0093 ± 0.0006	24.7	0.0001
FOSC 3-a MRL8996	None	0.0433 ± 0.0025	100.0	0.0483 ± 0.0029	100.0	0.087
	MoistureLoc	0.0230 ± 0.0046	53.1	0.0193 ± 0.0031	39.9	0.313
	MultiPlus	0.0223 ± 0.0006	51.5	0.0263 ± 0.0023	54.4	0.044
C. albicans SC5314	None	0.1483 ± 0.0124	100.0	0.1310 ± 0.0096	100.0	0.129
	MoistureLoc	0.1787 ± 0.0119	120.4	0.1337 ± 0.0159	102.1	0.017
	MultiPlus	0.1797 ± 0.0049	121.1	0.1777 ± 0.0112	135.6	0.785

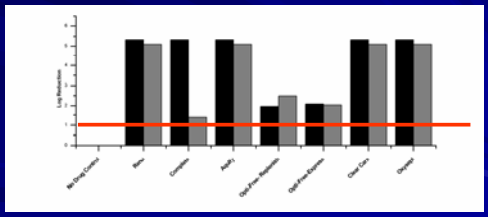
[a] Biofilms were formed using an FSSC 1-b (MRL8609), FOSC 3-a (MRL8996), or *C. albicans* SC5314 isolate on lotrafilcon A lenses as described in Materials and Methods. The effect of MoistureLoc or MultiPlus lens care solution on the metabolic activities of fungal biofilms was determined using the XTT-based metabolic activity assay. Percent growth and metabolic activity (measured as optical density at 492 nm) were calculated for each lens care solution with respect to metabolic activity of biofilms grown in the absence of the disinfectant (which was considered to be 100% activity). Data represent means ± SDs for three separate experiments.

[b] *P* values were obtained for comparison of metabolic activities of biofilms formed by each isolate with incubation with lens care solution for 4 h or 20 h.

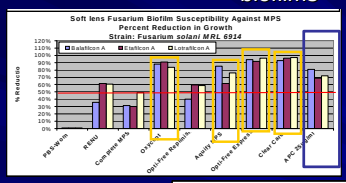
SUBJECTS & CONTACT LENS

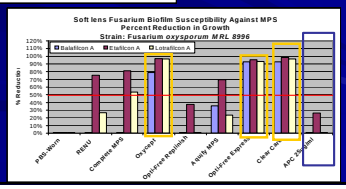
- Four subjects wore contact lenses daily for six hours
  - balafilcon A
  - etafilcon A
  - lotrafilcon A

Efficacy of various solutions against planktonic *Fusarium solani* cells



Efficacy of Various Solutions against mature *F. solani* biofilms





Increased Resistance of Contact Lens–Related Bacterial Biofilms to Antimicrobial Activity of Soft Contact Lens Care Solutions

Loretta B. Szczotka-Flynn, Yoshifumi Imamura,† Jyotsna Chandra,† Changping Yu,†‡ Pranab K. Mukherjee,† Eric Pearlman,* and Mahmood A. Ghannoum†*

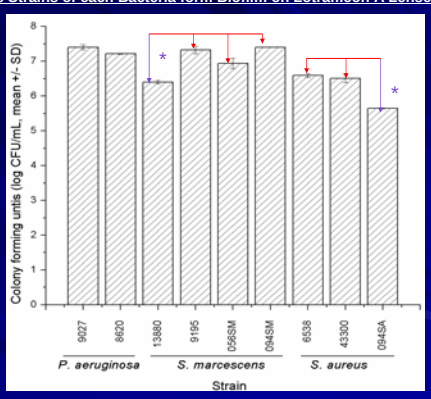
- Cornea Journal 2009
- To assess the antimicrobial activities of contact lens care solutions against bacterial cells grown under planktonic or biofilm conditions.

Product	Disinfectant
ReNu MultiPlus	DYMED® (polyaminopropyl biguanide) 0.0001%
ReNu MoistureLoc	Alexidine 0.00045%
AQuify	Polyhexanide (polyhexamethylene biguanide) 0.0001%
COMPLETE MoisturePlus	Polyhexamethylene biguanide 0.0001%
OPTI Free Replenish	Polyquad® (polyquaternium-1) 0.001%; Aldox® (myristamidopropyl dimethylamine) 0.0005%
CLEAR CARE	Hydrogen peroxide 3%

Species	Isolate	Source
P. aeruginosa	ATCC 9027	ATCC*
	MRL8620	CMM*
S. marcescens	ATCC 13880	ATCC
	MRL9195	CMM
	056SM	Contact lenses of a patient with contact lens acute red eye (CLARE) in the Longitudinal Analysis of Silicone Hydrogel (LASH) contact lens study[5]
	094SM	Contact lenses of a patient with infiltrative keratitis the Longitudinal Analysis of Silicone Hydrogel (LASH) contact lens study[5]
S. aureus	ATCC 6538	ATCC
	ATCC 43300	ATCC
	094SA	Contact lenses of a patient with infiltrative keratitis the Longitudinal Analysis of Silicone Hydrogel (LASH) contact lens study[5]

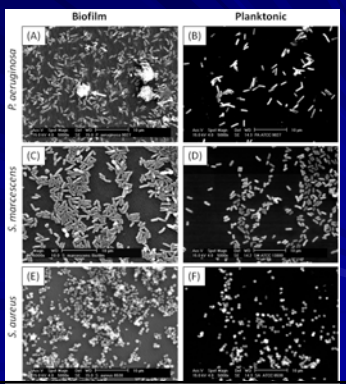
CMM: Center for Medical Mycology at CWRU

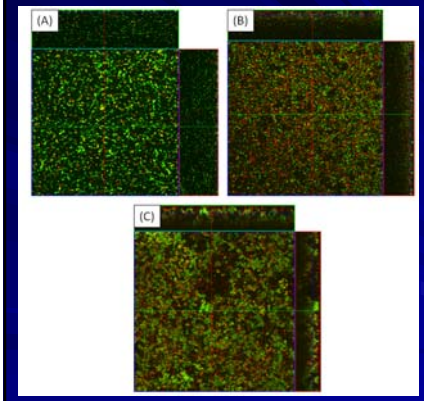
Multiple Strains of each Bacteria form Biofilm on Lotrafilcon A Lenses



*p<0.05

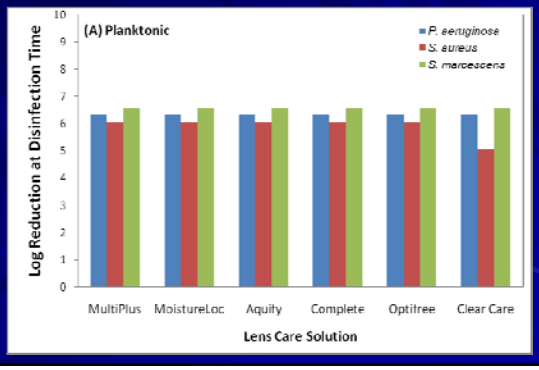
Ultrastructural/ scanning EM analysis of Bacterial Biofilms formed on Lotrafilcon A lenses

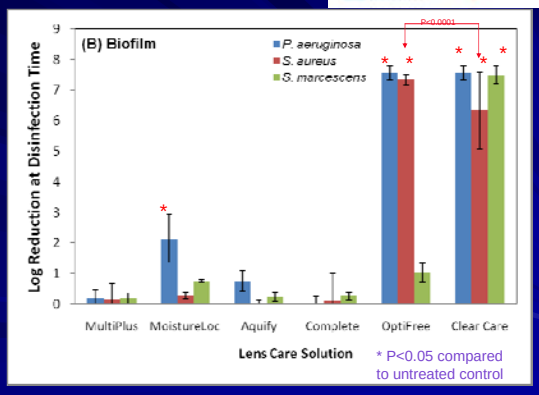




Confocal analysis of the architecture of biofilms formed by *P. aeruginosa*, *S. marcescens* and *S. aureus*. Panels show orthogonal view of biofilms formed on silicone hydrogel contact lens by (A) *P. aeruginosa*, (B) *S. marcescens*, or (C) *S. aureus*. Magnification, x40.

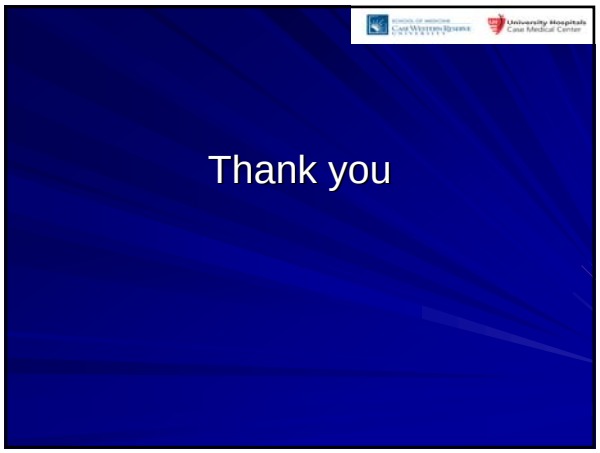
Contact Lens Solutions are Active Against Planktonic but not Biofilm Forms of Bacteria





Summary & Recommendations

- Expand SH lens groups
- Addition of lens to testing methods of solution efficacy
- Evaluation of recent, applicable clinical isolates in testing regime
- Evaluation of biofilm producing strains
- Incorporation of *Acanthamoeba* testing


Thank you