Corneal infiltrates and staining with daily wear contact lenses

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Introduction

- Soft contact lenses introduced in 1970s
  - *Corneal infiltrates observed by ECPs*
- Etiology of infiltrates
  - *Hypoxia*
  - *Contamination of lenses and/or cases with bacteria*
  - *Solution sensitivities*

Dahlman CH et al. Ophthalmology 1973
Johnson DG. Canadian Journal of Ophthalmology 1973
Josephson JE and Caffery BE. Int Cont Lens Clin 1979
Mondino BJ and Groden LR. Arcg Ophthalmol 1980

Today's lenses?

- Frequent replacement
  - *1 day to 1 month*
- Wearing modality
  - *Daily, flexible, extended and continuous wear*
- Care systems
  - *No Chlorhexidine or Thimerosal*
- Materials
  - *Silicone hydrogels (SiHy)*

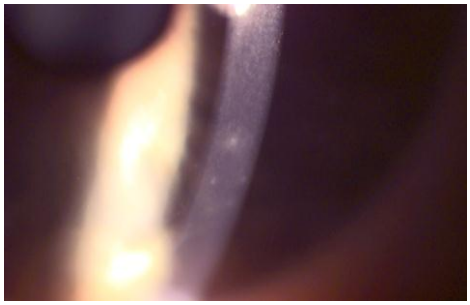
Despite these improvements, infiltrates still occur…

Definition: Corneal Infiltrates

"Small, hazy, greyish areas (focal or diffuse) located in the cornea, typically near the limbus. The adjacent conjunctiva is usually hyperemic. They appear as a result of corneal inflammation, reaction to solution preservatives and some contact lens wear (especially extended wear) which causes prolonged hypoxia"

Millidot, M and Laby D. Dictionary of Ophthalmology. 2002

Clinical appearance: Focal infiltrates

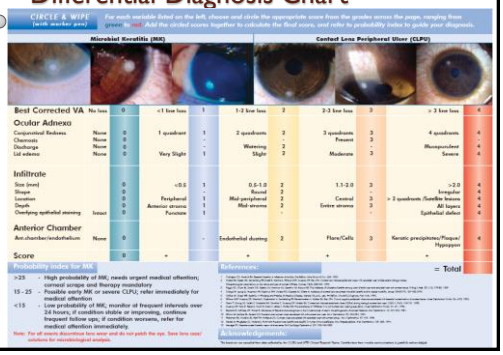


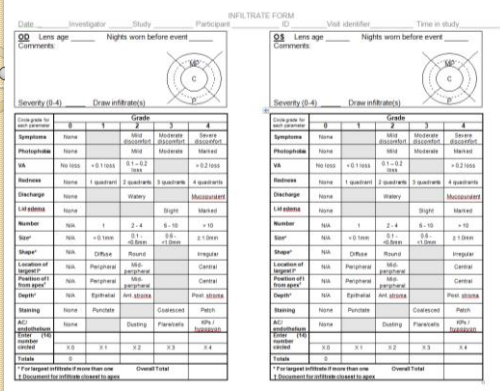
Classification

- Presumed etiology
- Severity
- "Sterile" or "Microbial"
- Clinical sub-type
  - *Serious and symptomatic* ← Microbial keratitis
  - *Clinically significant and symptomatic*
  - *Clinically non-significant and asymptomatic*

Josephson JE and Caffery BE. Int Cont Lens Clin 1979
Asauri MK et al. Eye Contact Lens 2003
Efron N et al. Optometry Vision Sci 2005
Stein RM et al. American Journal of Ophthalmology 1988
Sweeney et al. Cornea 2003

Institute for Eye Research (IER) /LVPEI Differential Diagnosis Chart



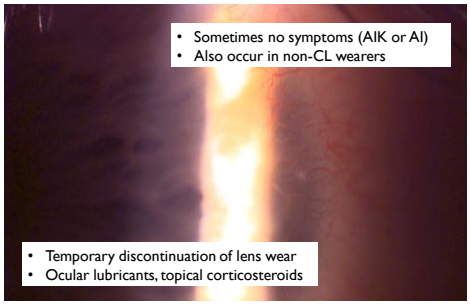


Commonly used terminology

- Infiltrative keratitis (IK)
  - *General term*
    - Infiltrates often situated peripherally
    - Limbal hyperemia
    - Epithelial staining
  - *Etiology*
    - Multifactorial
    - Gram-positive exotoxins found on or near the lid margin
  - *Symptoms*
    - Mild to moderate irritation (foreign body discomfort)
    - Mild redness
    - Lacrimation
    - Photophobia
    - Mild discharge

Dumbleton K. Contact Lens Ant Eye 2002
Cutter GR et al. CLAO Journal 1996
Sankaridurg P et al. Silicone Hydrogels 2004
Willcox M et al. Silicone Hydrogels 2004

Infiltrative Keratitis (IK)



- Sometimes no symptoms (AIK or AI)
- Also occur in non-CL wearers

- Temporary discontinuation of lens wear
- Ocular lubricants, topical corticosteroids

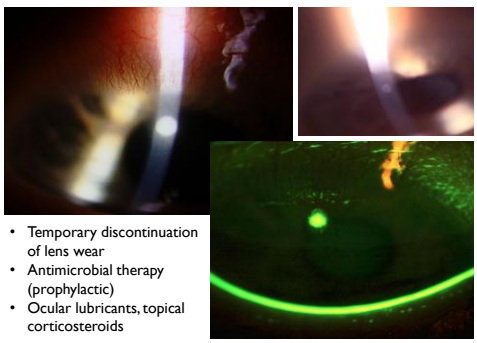
Hickson S and Papas E. Optometry Vision Science 1997
Baum J et al. Cornea 2000

Commonly used terminology

- Contact lens peripheral ulcer (CLPU)
  - *Inflammatory response*
    - Single small, circular infiltrate
    - Located in the periphery or mid-periphery of the cornea
    - Anterior stroma
    - Associated fluorescein staining of overlying epithelium
  - *Etiology*
    - Hypersensitivity reaction
    - Gram positive exotoxins released by pathogenic bacteria
  - *Symptoms*
    - Mild to moderate pain (foreign body sensation)
    - Mild lacrimation
    - Mild photophobia

Grant T et al. CLAO Journal 11998
Holden B et al. Cornea 1999
Wu P et al. Eye & Contact Lens 2003
Holden et al. Invest Ophthalmol Vis Sci 1997

Contact Lens Peripheral Ulcer(CLPU)



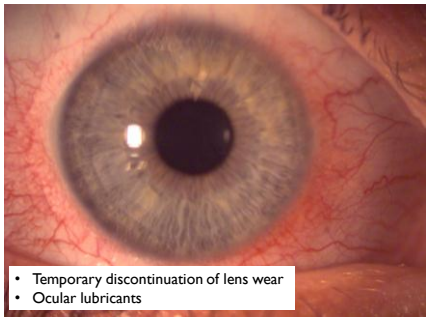
- Temporary discontinuation of lens wear
- Antimicrobial therapy (prophylactic)
- Ocular lubricants, topical corticosteroids

Commonly used terminology

- Contact lens acute red eye (CLARE)
  - *Acute inflammatory response*
    - Generally unilateral
    - Circumcorneal injection
    - Focal or diffuse sub-epithelial infiltrates close to limbus
    - No or little corneal staining of infiltrates
  - *Etiology*
    - Occurs with overnight wear (upper respiratory tract infections)
    - Gram negative organisms colonize lens surfaces and release endotoxins
  - *Symptoms*
    - Occur in early hours or on waking
    - Moderate pain (foreign body sensation)
    - Mild photophobia and epiphora

Sankaridurg P et al. Journal of Clinical Microbiology 2000
Holden B et al. CLAO Journal 1996
Sankaridurg P et al. Indian J Ophthalmol 1996
Sankaridurg P et al. Journal of Clinical Microbiology 1996

Contact Lens Acute Red Eye (CLARE)



- Temporary discontinuation of lens wear
- Ocular lubricants

Incidence of infiltrates

- Inevitably higher for symptomatic cases
- Historical comparison important
  - *0 to 41% with hydrogel lenses*
- Greatest risk with overnight wear
  - *Microbial keratitis and "sterile" infiltrates*
- Majority of clinical trials with SiHy lenses are for overnight wear
  - *Rates for sterile infiltrates*
    - 1.3 to 5.5 per 100 patient years (HEMA)
    - 2.9 to 6.7 per 100 patient years (SiHy)

Robboy et al. Eye & Contact Lens 2003
Stapleton et al. CLAO Journal. 1993
US Premarket application summaries (FDA website)
Brennan et al. Ophthalmology 2002
Chalmers et al. Optometry Vision Sci 2010
Donshik et al. Eye & Contact Lens 2007
Efron et al. Clinical and Experimental Optometry 2005
Morgan et al. Ophthalmology 2005
Radford C et al. Ophthalmology 2009

Meta analysis of corneal infiltrates

- Investigating risks of corneal inflammatory events
- SiHy and HEMA wearers (extended and continuous wear)
  - *14.4 per 100 eye years (SiHy)*
  - *7.7 per 100 eye years (HEMA)*
  - *2X greater risk for CW with SiHy (but more nights…)*
- Cumulative incidence with SiHy CW
  - *26.7% after one year*

Szczotka-Flynn L et al. Optometry Vision Sci 2007
Szczotka-Flynn L et al. Invest Ophthalmol Vis Sci 2010

But patients and ECPs are more interested in daily wear…

- Extreme variation in reported rates
  - *None or "few" cases*
  - *19.6 per 100 participant years*
  - *Study design and frequency of follow up*

Carnt et al. Archives Ophthalmol 2009
Donshik et al. Eye & Contact Lens 2007
Long B and McNally J. Eye & Contact Lens 2006
Long B et al. Eye & Contact Lens 2009

Patient related risk factors…

- Regardless of lens material
  - *Age (young and old!)*
    - Under 25 and over 50 at greater risk
  - *Peak risk for 15 to 25 year olds*
    - Lower risk for younger children
    - Physiological and behavioural differences
    - Greater propensity for risk taking…

Chalmers et al. Optometry Vision Sci 2007
Chalmers et al. Optometry Vision Sci 2010
McNally et al. Eye & Contact Lens 2003
Carnt et al. Contact Lens & Anterior Eye 2010
Chalmers et al. Invest Ophthalmol Vis Sci 2011
Carnt et al. Contact Lens & Anterior Eye 2010

Patient related risk factors…

- Gender?
  - *Men!*
    - 1.3 to 1.4 (30 to 40%) greater risk
    - Similar rate for microbial keratitis
  - *Are they different or do they perceive risk differently?*
    - Greater risk takers?
    - Hygiene
    - Diligence with lens care
  - *No differences between gender in the younger population*

Morgan P et al. Invest Ophthalmol Vis Sci 2005
Dart J et al. Lancet 1991
Flynn J et al. Risk Anal 1994
Carnt et al. Contact Lens & Anterior Eye 2010
Chalmers et al. Invest Ophthalmol Vis Sci 2011

Patient related risk factors…

- Smoking
  - *2X greater risk with hydrogels*
  - *1.4 to 4X with SiHy*
- Prior events
  - *4 to 7X greater risk*
  - *25% of EW Px with CLPU's experienced repeated events*
  - *or 1.8 X less likely?*

Morgan P et al. British Journal Ophthalmol 2005
Szczotka-Flynn L et al. Invest Ophthalmol Vis Sci 2010
McNally et al. Eye & Contact Lens 2003
Dumbleton et al. Optometry Vision Sci 2000

Modality of lens wear

- Overnight wear increases risk
  - *Regardless of material*
  - *2 to 6X greater risk*

Radford CF et al. Ophthalmology 2009
Morgan P et al. British Journal Ophthalmol 2005

Modality of lens wear

- Replacement frequency
  - *Lower risk with daily disposable lenses?*
    - 1.6X greater risk with conventional hydrogels
    - 10X lower in recent retrospective study
    - Daily disposable SiHy?

Suchecki JK et al. CLAO Journal 2000
Dart J et al. Ophthalmology 2008
Chalmers R et al. Invest Ophthalmol Vis Sci 2011

What about compliance?

- Compliance with CL wear and care is poor
  - *Only 32% compliant in US study*
- Hygiene and disinfection
  - *Failure to wash hands*
    - 1.5X for MK
    - 2X for sterile keratitis
  - *Failure to rub and rinse with MPS*
    - 40 – 75% of patients
    - Rubbing and rinsing can help reduce risk of MK
    - Infiltrates?
    - Higher rate of self reported problems
  - *Topping up*
    - Fusarium and Acanthamoeba keratitis

Bui TH et al Eye & Contact Lens 2010
Sweeney D et al Cornea 2003
Radford C et al Ophthalmology 2009
Wu Y et al. Contact Lens Anterior Eye 2010
Dumbleton K et al. Contact Lens Anterior Eye 2011
Butcko V et al. Eye & Contact Lens 2007
Chang DC et al JAMA 2006
Ingle CE et al Am J Ophthalmology 2007

Other aspects of compliance

- Lens replacement
  - *Most commonly reported aspect of non-compliance*
  - *Does failure to replace result in infiltrates?*
    - Greater risk of CL complications in general
- Lens case cleaning and replacement
  - *Poor hygiene associated with greater risk of MK*
  - *Biofilm build up with time*
    - Increased risk of infiltrates?

Dumbleton K et al Eye & Contact Lens 2009
Dumbleton et al. Optom Vis Scii 2010
Yeung KK et al. Optometry 2010
Dumbleton K et al. Contact Lens Anterior Eye 2011
Stapleton F et al. Ophthalmology 2008
Dart j Contact Lens & Anterior Eye 1997
McLaughlin-Borlace L et al. J Appl Microbiol 1998
Wu YT et al. Invest Ophthalmol Vis Sci 2011

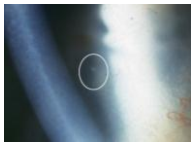
Contact lens care products

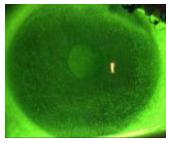
- MPS versus H_2O_2
  - *Lower rate for SiHy wearers using H_2O_2*
  - *3x higher rate of infiltrates with MPS*
- Specific combinations of SiHy and MPS?
  - *Mainly presented as series of clinical cases*
  - *No account taken for market share*
  - *No prospective, controlled studies*
  - *Retrospective study in young CL wearers (n=166 cases of corneal infiltrates) found no association between infiltrates and specific combinations of SiHy and MPS*

Carnt N et al. Archives Ophthalmol 2009
Chalmers et al Optom Vis Sci (in press)
Kislan T Optician 2011
Shovlin J Contact Lens Spectrum 2011

Contact lens care products

- Incompatibilities
- Solution induced corneal staining (SICS)
- Generally asymptomatic
- 3X higher rate of infiltrates when SICS

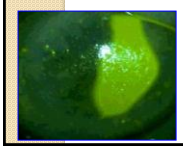
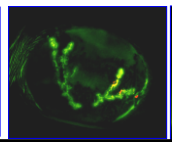
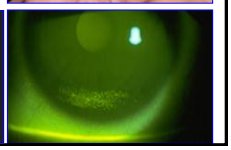




Jones L et al. Optom Vis Sci 2002
Garofalo RJ et al. Eye & Contact Lens 2005
Andrasko G and Ryen K Optometry 2008
Carnt N et al. Optom Vis Sci 2007

Corneal Staining

- Corneal staining is widely used to assess the integrity of the ocular surface
  - *disease*
  - *contact lens wear*

Initial Studies…

- 1960-1970: M.S. Norn (Denmark)

VITAL STAINING OF CORNEA AND CONJUNCTIVA*)

1962 VITAL STAINING IN PRACTICE*)
Using a Mixed Stain and Alcian Blue

1964 FLUORESCEIN VITAL STAINING
OF THE CORNEA AND CONJUNCTIVA*)
Studied by Triple Stai

1964 CONTAMINATION OF EYE DROPS USED
FOR VITAL STAINING
Bacteriological Analyses of Rose Bengal-Fluorescein,
Alcian Blue and Fluorescein-Novesin,
Instilled from a Needle-Mounted Tube.*)
1967 BY
M. S. Norn and V. Frolund Thomsen.

Review Paper

REVIEW

Superficial Punctate Fluorescein Staining of the Ocular Surface

KEITH W. WARD, PhD
Global Preclinical Development, Bausch & Lomb, Rochester, New York

ABSTRACT
Purpose. The precise mechanisms controlling the depth and extent of fluorescence signal associated with superficial punctate corneal staining remain unclear. Despite this scientific uncertainty, within the past decade there has been a shift in both medical marketing materials and in the peer-reviewed literature to attempt to extrapolate an observation of superficial punctate fluorescence to suggest compromised corneal integrity. This review presents a survey of the peer-reviewed scientific literature around superficial punctate corneal fluorescein staining.
Methods and Results. A comprehensive literature search was conducted for peer-reviewed manuscripts including data around corneal staining, and the results from this search synthesized. A brief historical review of the use of fluorescein dye as a diagnostic tool is provided. A detailed evaluation is made of the evidence supporting or refuting various proposed mechanisms for punctate corneal fluorescein staining, and the implications for corneal health and disease. Finally, future research directions in this field are proposed.

Ward KW: Optom Vis Sci 2008; 85;1: 8-16

Review Paper

Contents lists available at ScienceDirect
Contact Lens & Anterior Eye
journal homepage: www.elsevier.com/locate/clae

Review

Corneal staining: Do we really understand what we are seeing?

Philip B. Morgan, Carole Maldonado-Codina *

ARTICLE INFO
ABSTRACT
Sodium fluorescein ('fluorescein') is widely utilised for the evaluation of ocular surface integrity. It is particularly well suited to this task due to its fluorescent properties and its high visibility at low concentrations. Ocular surface fluorescence observed clinically is affected by a number of factors including concentration of fluorescein, thickness of the fluorescein layer, the wavelength of the exciting light source and whether or not a barrier filter is used as part of the viewing system. In this review we have attempted to provide a critical evaluation of the published literature relating to three potential cellular mechanisms involved in corneal surface fluorescence: surface pooling, uptake by cells and ingress around cells. Despite the widespread adoption of use of fluorescein for the assessment of the ocular surface, we contend that the clinical understanding and interpretation of corneal surface fluorescence is based upon assumption, extrapolation and clinical intuition rather than solid evidence-based science underpinning the basic causative mechanisms of this phenomenon. Further research in order to understand the basic interactions between the ocular surface cells and fluorescein should be

Morgan PB, Maldonado-Codina C: Cont Lens Anterior Eye 2009; 32;2: 48-54.

"Staining" ?

- Exact mechanism which gives rise to "corneal staining" not well understood
- Different types of "staining"
  - *pooling*
    - not really "staining"
  - *uptake by cells*
  - *ingress around cells*
- Much further work is required to elucidate what happens when corneal staining is observed

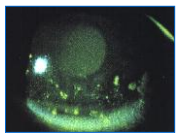
Ward KW: Optom Vis Sci 2008; 85;1: 8-16
Morgan PB, Maldonado-Codina C: Cont Lens Anterior Eye 2009; 32;2: 48-54

Corneal Staining

- Occurs in non lens wearers
  - *severe*
    - trauma
    - disease
  - *mild*
    - tear film
    - environment
- Occurs in CL wearers
  - *all above plus*
    - lens
    - care regimen

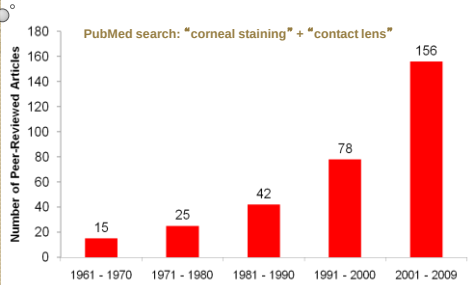
Prevalence of Corneal Staining

- In non-lens wearers:
  - *4 to 79%*
  - *typically minimal in degree*
    - <grade 1
  - *often associated with poor tear film*



Korb & Korb, JAOA 1970
Caffery & Josephson, OVS 1991
Josephson & Caffery, OVS 1992
Schwallie *et al*, OVS 1997
Dundas *et al*, OPO 2001

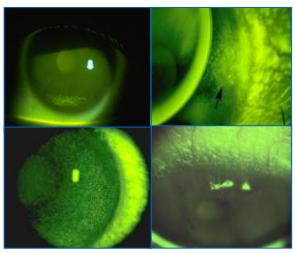
Contact lens wearers



2012: 365 publications!

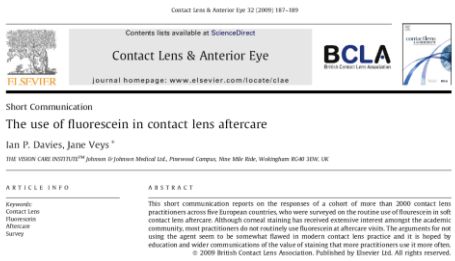
Prevalence of Staining

- In lens wearers:
  - *30 to 55%*
    - often asymptomatic
    - mainly inferior cornea
    - <grade 2
    - only 5-10% >grade 2
  - *etiology*
    - hypoxia
    - trauma
    - dehydration
    - solution toxicity



Begley *et al*, OVS 1996
Nichols *et al*, OVS 2002

Why such differences in rates?



Contact Lens & Anterior Eye 32 (2009) 187–189

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Contact Lens & Anterior Eye

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Short Communication

The use of fluorescein in contact lens aftercare

Ian P. Davies, Jane Veys *

THE VISION CARE INSTITUTE™ Johnson & Johnson Medical Ltd., Pinewood Campus, Nine Mile Ride, Wokingham RG40 3EW, UK

ARTICLE INFO

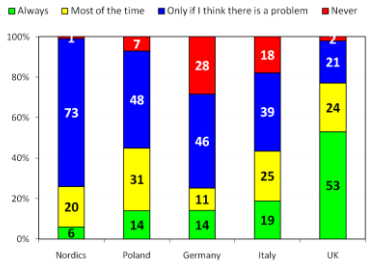
Keywords:
Contact Lens
Fluorescein
Aftercare
Survey

ABSTRACT

This short communication reports on the responses of a cohort of more than 2000 contact lens practitioners across five European countries, who were surveyed on the routine use of fluorescein in soft contact lens aftercare. Although corneal staining has received extensive interest amongst the academic community, most practitioners do not routinely use fluorescein at aftercare visits. The arguments for not using the agent seem to be somewhat flawed in modern contact lens practice and it is hoped by education and wider communications of the value of staining that more practitioners use it more often.

Davies & Veys, CLAE 2009

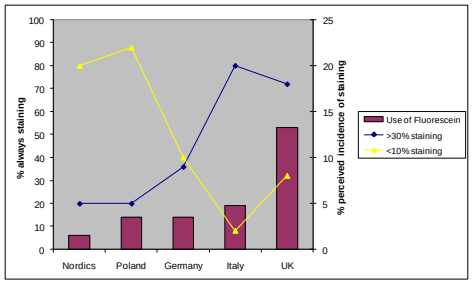
Corneal staining frequency in soft contact lens wearers (Europe) n = 2116



Davies & Veys, CLAE 2009

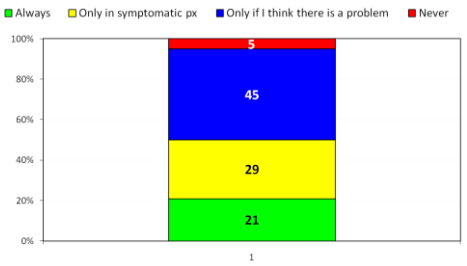
Practitioners estimated amount staining seen in soft DW CL wearers: <10%, 10-19%, 20% - 30%, > 30%

Reported incidence staining vs frequency FI used

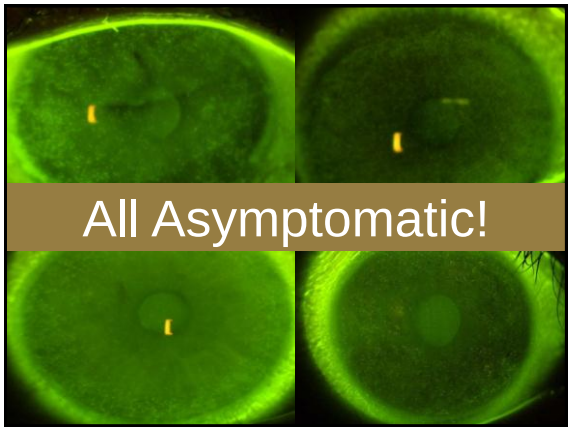


Davies & Veys, CLAE 2009

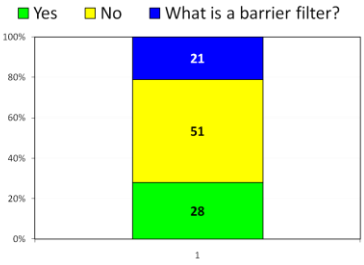
Corneal staining frequency in soft contact lens wearers (USA)



N=197 US practitioners attending CE in 2 US cities



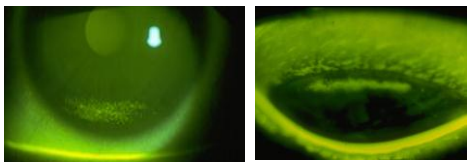
Use of a barrier filter to assess corneal staining (USA)



N=1579 US practitioners attending CE in 10 US cities

Optimization of Observation of Corneal Staining

- How much to insert?
- Instill inferior or superior?
- Observation filters



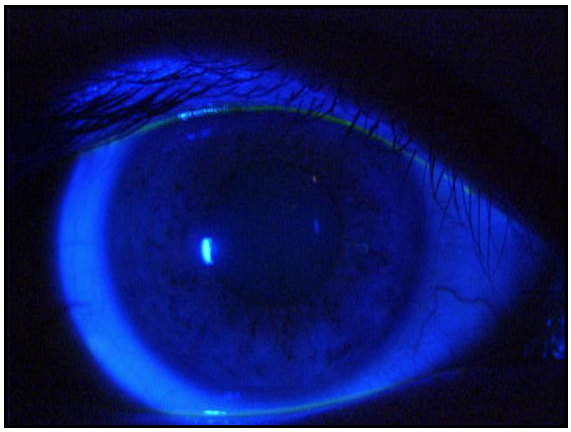
How much to insert?

- Too much or too little minimizes fluorescence
  - *too much* ➡ *fluorescence quenching*
  - *too little* ➡ *insufficient to produce suitable fluorescence*
  - *optimum is at concentrations of approximately 0.1%*
- By moistened fluoret
  - *shake off any excess*
- By pipette
  - *5µl of 1% NaFl appears optimal*

Bron *et al*, Cornea 2003
Peterson *et al*, AJO 2006
Peterson *et al*, AAO 2009

Enhancing Fluorescein Appearance

- Barrier filter (yellow)
  - *reduce overlap between the absorption and excitation spectra*
  - *Wratten 12 or 15*
  - *in viewing system*
    - built in to newer models of slit lamps



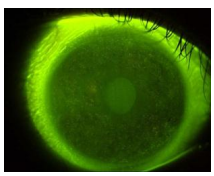
"Simple" Grading Scale

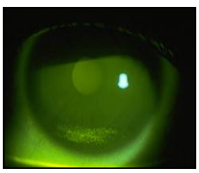
Numerical	Descriptive	Meaning
Grade 0	Normal	No action
Grade 1	Slight	Not clinically significant
Grade 2	Moderate	May require intervention
Grade 3	Severe	Requires intervention
Grade 4	Very severe	Requires medical intervention

Add ½ scales to enhance sensitivity

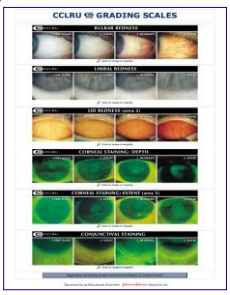
Descriptive Grading Scale
Corneal Staining

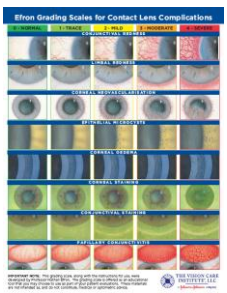
0 None
1 1-20 mild scattered punctate spots
2 21-40 punctate spots
3 >40 spots or dense confluent patch
4 Dense, confluent patch or erosion



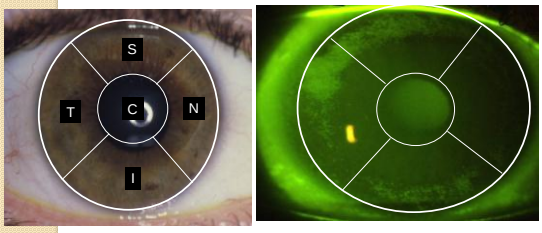


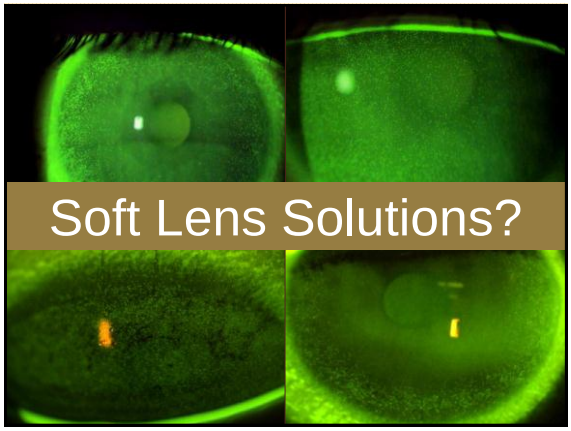
Photographic Grading Scales:
"Real" Photos or Illustrative





Location?

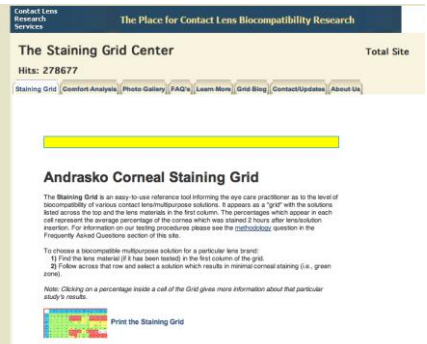




Solution Induced Corneal Staining (SICS): Material & Solution Roles?

- Highlights
  - *Influence of material?*
  - *Influence of preservative?*

www.staininggrid.com



IER, Sydney, Australia

Carnt *et al*, Mar 2008

THE IER MATRIX STUDY: CORNEAL STAINING				
*Solution-Induced Corneal Staining per month with the combination**				
Lens / Solution	CLEAR CARE®	AQuify®	OPTI-FREE Express®	OPTI-FREE RepleniSH®
ACUVUE® ADVANCE™	0.0%	0.9%	0.0%	0.0% (2W)
ACUVUE® OASYS™	0.9% (2W)	2.6% (2W)	6.2%	7.1% (2W)
O_2OPTIX™	0.5%	3.2%	5.9%	6.7%
PureVision®	0.9%	23.2%	11.3%	14.2%
NIGHT & DAY™	1.7%	0.9%	7.2%	6.7%

Lower quartile | Inner two quartiles | Upper quartile

* percentage of patients per month showing lens care related staining in the first 3 months of lens wear
2W = 2 weekly replacement

5 SH CL & 4 care regimens. N=40/cell. Followed for 3 months of DW

SICS Grids: Differences?

	Andrasko	IER
Lens types	Conventional and silicone hydrogel	Silicone hydrogel only
Solutions examined	Includes generics	No generics
# of px per combination	30	40
Duration	2hr acute exposure model	3 months of use
Methods	Lenses and cases soaked before wear	Conventional daily wear only
Assessment	1x	3x
Reporting	Average % of cornea showing any form of staining	% of patients per month exhibiting SICS

SICS Summary

- Subject dependent
  - *all products will see some staining issues*
- Material dependent
  - *FDA group II > group IV*
  - *SH > conventional*
    - varies by chemistry
- Certain combinations show increased staining
- Formulation dependent
  - *not just one particular preservative*
  - *least with peroxide by any grid or clinical study reported*
- Clinical relevance?
  - *a hot-topic in CL research today*
  - *no association with MK*

Literature review

1040-5488/07/8406-0305/0 VOL. 84, NO. 4, PP. 305–315
OPTOMETRY AND VISION SCIENCE

ORIGINAL ARTICLE

Solution Toxicity in Soft Contact Lens Daily Wear Is Associated With Corneal Inflammation

NICOLE CARNT, BOptom, ISABELLE JALBERT, OD, PhD, FAAO, SERINA STRETTON, PhD, THOMAS NADUVILATH, PhD, and ERIC PAPAS, PhD

Vision Cooperative Research Centre, Sydney, Australia (NC, IJ, SS, TN, EP), Institute for Eye Research, The University of New South Wales, Sydney, Australia (NC, IJ, SS, TN, EP), and School of Optometry and Vision Science, The University of New South Wales, Sydney, Australia (IJ, EP)

Literature review

CLINICAL SCIENCES

Contact Lens–Related Adverse Events and the Silicone Hydrogel Lenses and Daily Wear Care System Used

Nicole A. Carnt, BOptom; Victoria E. Evans, PhD; Thomas J. Naduvilath, PhD; Mark D. P. Willcox, PhD; Eric B. Papas, PhD, MCOptom, DipCL; Kevin D. Frick, PhD; Brien A. Holden, PhD, DSc, OAM

(REPRINTED) ARCH OPHTHALMOL/VOL 127 (NO. 12), DEC 2009 WWW.ARCHOPHTHALMOL.COM
1616

Literature review

- *Chalmers et al Optom Vis Sci (in press)*
- *Kislan T Optician 2011*
- *Shovlin J Contact Lens Spectrum 2011*

Management Strategies

- Temporary discontinuation of lens wear
- Ocular lubricants
- Change in care products
- Steroids

Reducing prevalence

- Instigation of eyelid hygiene for at risk patients (blepharitis and / or meibomian gland dysfunction)
- Daily disposable modality
- Careful counselling on appropriate contact lens care procedures

Summary: Infiltrates

- Overview of corneal infiltrates in SiHy wearers
  - *Not sight threatening*
  - *Inconvenience for patient*
  - *Chair time for ECPs – therapeutic management and counseling*
- Patient associated risk factors
  - *Some modifiable*
  - *Others good to be aware of…*
- ECP's choices
  - *Wearing schedule, replacement frequency, care system*
  - *Counseling important to improve compliance*

Summary: Corneal Staining

- Assessment of corneal staining is vital in assessment of contact lens wearers
- Instillation of appropriate amounts of NaFl and optimization of the observation of the staining will enhance its utilization
- Grading scales should be used to accurately record the staining

Summary

- Assessment of corneal staining is vital in assessment of both contact lens wearers and those with external ocular disease
- Instillation of appropriate amounts of NaFl and optimization of the observation of the staining will enhance its utilization
- Grading scales should be used to accurately record the staining
- Conjunctival staining is best undertaken using lissamine green

Thank you!